S1

Definition
Primary somatosensory cortex.

S2

Definition
Secondary somatosensory cortex.

S-100

Definition
S-100 protein is a dimer consisting of two 11-kDa subunits, alpha and beta, and is structurally related to the calcium-binding protein calmodulin, and to intestinal vitamin D-dependent calcium-binding protein. S-100 functions in calcium-dependent interactions with other proteins. S-100 is not found in Schwann cell precursors, but the protein is expressed in immature and mature Schwann cells. It is also expressed in mature astrocytes. S-100 can be used to distinguish between mature/immature Schwann cells and Schwann cell precursors or crest cells.

►Schwann Cell
►Schwann Cells in Nerve Regeneration

Saccade

Definition
►Saccade
►Saccadic Eye Movement

Saccade – Delayed

Definition
Saccades that are voluntarily withheld, after a targeting eccentric stimulus appears, until a central fixation stimulus is turned off. The temporal overlap between the time of target appearance and the turning off of the fixation point is called the delay period.

►Saccade
►Saccadic Eye Movement

Saccade, Saccadic Eye Movement

Definition
A rapid conjugate eye movement that shifts the line of sight (center of gaze) rapidly from one part of the visual field to another, mainly used for orienting towards an object of interest. It is characterized by stereotyped relationships between amplitude, duration, and peak velocity. In human subjects, peak velocity typically rises along with saccade amplitude up to a saturation level of 400–500° s^{-1} which is reached when the amplitude exceeds 10–30°, whereas duration rises linearly at a rate of 1.5–3 ms per degree starting from a minimum of 20–30 ms. Saccades are the only type of eye movements that can be readily executed at will (as when scanning a picture), but are also intimately involved in reflexive and involuntary behaviors:

Suddenly occurring visual, but also auditory and tactile, stimuli elicit reflexive saccades toward the stimulus location (visual grasp reflex), and during seemingly quiet fixation the eyes are engaged in an ever continuing series of microsaccades which go unnoticed by the individual. Saccades are thought to be essentially preprogrammed according to visual information arising at latest about 100 ms before movement onset although some possibility of "on-line" modification by concurrent sensory stimuli has been noted.

►Microsaccades

Saccade Adaptation

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Definition

Saccade adaptation is a process for maintaining saccade accuracy based on evaluating the accuracy of past saccades and appropriately correcting the motor commands for subsequent saccades. An adaptive process is required to maintain saccade accuracy because saccades have too short a duration relative to the long delays in the visual pathways to be corrected while in flight. It is a true adaptive process in that it is unconscious, accuracy improves gradually over repeated trials, and when complete, removal of the original error by experimental intervention produces a new saccadic error (dysmetria) in the opposite direction that can only be eliminated by a new process of adaptation.

The normally high accuracy of saccades is largely the product of continuous adaptation. Numerous components of the oculomotor system, such as the eye muscles, cranial nerves, and central pathways, gradually change during development and aging, and these changes would produce saccadic inaccuracy if uncorrected. Adaptation can sometimes maintain accuracy after pathological changes occurring in any of these components.

Characteristics

Methods to Measure Adaptation

Saccade accuracy is quantified by measuring the endpoint of the saccade relative to the location of the target. In a typical experimental setup, subjects fixate a small stationary target spot, and after a delay, the target jumps to a new location. Subjects must quickly shift their gaze (make a saccade) to re-fixate the displaced target. Beginning at the initial fixation point, the target displacement and the saccade are expressed as vectors in polar coordinates. Adaptation can be expressed as a decrease in saccade error, which is the angular error (difference between the angles of the target and saccade vectors) together with the amplitude error (difference between the amplitudes of the target and saccade vectors). Alternatively, it can be expressed as the amplitude of the saccade relative to the amplitude of the target displacement, with 100% being perfect. This ratio is often called ►gain, but the term has mechanistic connotations that are inappropriate for saccade adaptation.

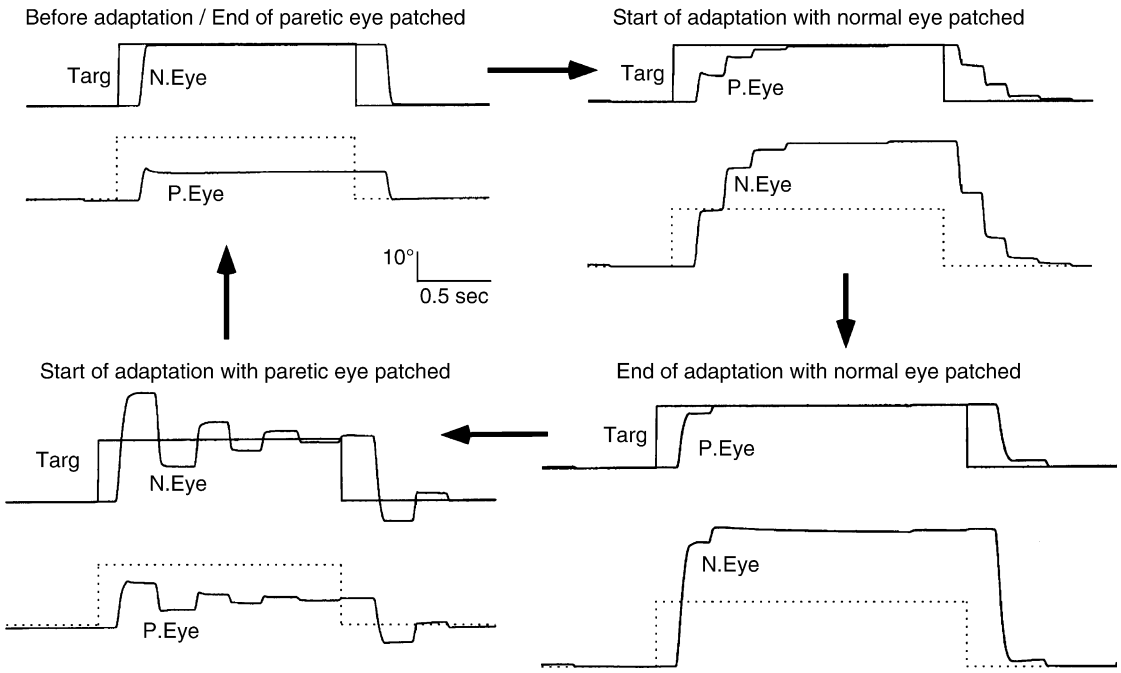
Although saccade adaptation is an everyday occurrence, an experimental intervention is usually invoked to reveal its power and features. The first experimental paradigm was modeled after human pathology. Patients who develop a ►paresis of one or more muscles in one eye produce saccades that have different amplitudes in each eye. If the patient had been using the normal eye to view the world, the normal eye would make accurate saccades, but the eye with paresis (the "paretic eye") would make saccades too short to land on the target (undershooting saccades). If an experimenter placed an opaque patch over the normal eye and forced the patient to use the paretic eye, saccades in the paretic eye would initially undershoot, but would also increase in size (adapt) over the period of about a day until they were nearly accurate [1]. Saccades in the normal eye would also increase in size so that they would overshoot the target. Of course, the normal eye is patched so that the CNS is unaware of the overshoot. Subsequently, if the patch is removed from the normal eye and placed over the paretic eye, the now viewing normal eye continues to overshoot the target. The overshoots gradually diminish until saccade metrics are restored to the state before the eye was ever patched. The paradigm has been adapted for use in animals by surgically weakening the medial and lateral rectus muscles of one eye to produce an artificial paresis [2], and an example of such adaptation is shown in Fig. 1.

In a second paradigm for producing saccadic adaptation, a target steps away from the fixation point, and while the saccade is in flight, the target is displaced again so that the otherwise accurate saccade will not land on the target [3,4]. The "intrasaccadic" target displacements can be backward relative to the first target step, forward, or to the side, and are typically 15–40% of the amplitude of the first target step. Repeated trials of the same type (e.g., all back-stepping) cause a consistent error that is gradually corrected by adaptation. Figure 2 illustrates this process for a human subject tracking a target where the initial target step of about 9° is followed by an intrasaccadic step of 3° backwards. In the space of 150 trials, the amplitude of the saccade decreases from overshooting the displaced target to essentially landing on the target. When the intrasaccadic step is discontinued at trial 375, saccade amplitude remains at its reduced value for some time even though the saccade now undershoots the target. In fact, a new gradual process of adaptation is required to increase saccade amplitude back to normal. A similar process of adaptation of saccade direction occurs if the intrasaccadic step is perpendicular to the initial target step.

Characteristics of Saccade Adaptation

A True Adaptation?

Data indicate that the above changes in amplitude are the product of a true sensory-motor adaptation rather than the product of conscious effort or some covert "strategy." First, the majority of human subjects are unaware of the intrasaccadic steps and therefore could



Saccade Adaptation. Figure 1 Adaptation of saccade size produced by patching of either the normal or the paretic eye. The four stages of adaptation are shown for typical single trials, and are in clockwise order (*large arrows*). Horizontal position is illustrated for the visible target (Targ), normal eye (N.Eye), paretic eye (P.Eye), and the unseen target for the patched eye (*dotted lines*). Initially, the patch covered the paretic eye and the normal eye viewed the target (*top left*). Adaptation was initiated by switching the patch to cover the normal eye so that saccades in the viewing paretic eye were severely undershooting (*top right*). After viewing with the paretic eye for a day or more, saccade size increased in both eyes (*bottom right*). Finally, switching the patch back to cover the paretic eye resulted in severely overshooting saccades in the viewing normal eye (*bottom left*). Long-term adaptation to this situation produced decreases in saccade size and a return to normal-sized saccades in the normal eye (*top left*).

not form such a strategy. Second, discontinuation of the intrasaccadic steps (e.g., at trial 375, Fig. 1) does not produce an immediate reversal of the change in saccade size, even though the adapted size is now an encumbrance. Third, repeated sessions of adaptation and reversal do not result in any faster changes. Fourth, when examined under similar experimental conditions, the paretic-eye and intrasaccadic-step paradigms produce similar amounts of adaptation in similar amounts of time [2].

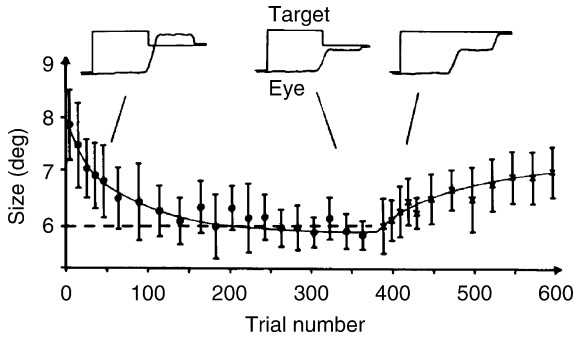
Conjugate or Monocular?

Adapted saccades are conjugate by default, even in the paretic-eye paradigm where one eye is patched. However, if disparate visual stimuli are presented to each eye, a limited ability to adapt each eye disconjugately can be demonstrated.

Time Course

The time course of adaptation varies tremendously depending on the details of the paradigm and the species. Adaptation in humans is approximately ten times faster than that in monkeys under comparable experimental conditions. Adaptation is faster (as much as two times) when decreases in saccade size are required compared to when increases are required. Adaptation is also faster when there are few potential targets (e.g., subjects saccade back and forth between two targets) than when there are many (e.g., saccades are made to an array of targets with multiple rows and columns) [2,4].

The wide range in rates of adaptation might indicate that different sites and/or mechanisms of plastic changes are invoked with different paradigms or in different species. However, these apparent differences are probably more quantitative than qualitative. For instance, a very rapid form of adaptation has been identified in both monkeys [2] and humans [4], but in the former, it accounts for only a small part (<10%) of the total possible change, whereas in the latter it accounts for 20–85%. Consequently, many human experiments are terminated before a slower (monkey-like) form of adaptation could be revealed. Similarly, the paretic-muscle paradigm produces slow adaptation when subjects view the natural world outside the laboratory. However, the rate is the same as in the



Saccade Adaptation. Figure 2 Time course of adaptation of saccade size produced by using the intrasaccadic-step paradigm. Saccade size is plotted against the number of trials. To a target step about 9°, the monkey makes a slightly undershooting saccade (*left inset*), but the 3° backward step that occurs during the saccade makes it appear to the monkey that the saccade overshoots the target. After repeated trials with backward intrasaccadic steps, the saccade declines in size so that it slightly undershoots the displaced target (middle insert, and dotted line on plot). Elimination of the backward intrasaccadic steps at trial 375 renders the newly adapted saccade to seriously undershoot (*right insert*). The apparent ►saccadic dysmetria is slowly reversed (figure adapted from Deubel [3]).

intrasaccadic-step paradigm when the number of targets is the same, indicating that the paretic-muscle paradigm does not invoke a separate mechanism of adaptation [2].

Adaptation Fields

If saccades are adapted using target steps of one size and direction, and the effects are tested using target steps of various sizes and directions, it is found that the induced change in saccade size decreases with increasing disparity between the test and adapted target step (reviewed in [5]). The range over which training transfers (generalizes) to steps of other sizes and directions is called the adaptation field. This finding explains the previous result that adaptation is slower with increasing numbers of potential targets. That is, adaptation of saccades to each target in the array occurs with incomplete benefit from adaptation to other targets in the array.

By default, adaptation fields are only weakly dependent on eye position *per se*. That is, adaptation to 10° rightward target steps at one location mostly transfers to 10° rightward target steps anywhere else in the visual field. However, adaptation can be rendered position dependent if training is position dependent [2,5]. For instance, training with backward intrasaccadic steps when looking left, and forward intrasaccadic steps when looking right, produces decreases in saccade size when looking left and increases in saccade size when looking right. Moreover, in humans with paresis of one extraocular muscle, saccadic size in the paretic eye is eye-position dependent, and adaptation is correspondingly position dependent when the paretic eye is forced view the world [1].

Transfer of Adaptation to Different Tasks

The situation in monkeys is simple; adaptation using one saccadic tracking task produces adapted saccades when measured in any other saccadic task. For instance, training using intrasaccadic steps and the simple "targeting" task described above produces comparable, or nearly comparable, adaptation of express saccades evoked in a ►gap task (very short latency reflexive saccades, see ►Saccades-Express), saccades measured in a ►memory-guided saccade task (saccades to a target flashed on and off 1 sec earlier), self-paced saccades to fixed targets, and catch-up saccades during smooth pursuit. In humans, transfer is more complicated. In general, transfer of adaptation from simpler paradigms (targeting task and gap task) to "higher-order" saccades (scanning and memory-guided) is weak, and visa-versa (reviewed in [5]). The data have been taken to mean that humans have more than one site of adaptation (see below).

Upstream Conditions

Adaptation is a process of detecting errors and incrementally correcting them in subsequent movements. Obviously, the visual error produced when the line of sight does not fall on the target is the operational error that drives adaptation. However, after the dysmetric saccade, subjects immediately make a corrective saccade to remove the visual error. The nervous system could use either a neural representation of the visual error or a copy of the efferent command for the corrective saccade to serve as the error signal to induce the synaptic changes that underlie adaptation. Experimental tricks that produce visual error without corrective saccades show that the neural representation of visual error is used as the predominant signal that drives adaptation (reviewed in [5]).

Involved Structures

A priori, any of the structures involved in generating saccades could potentially harbor the synapses that change to produce adaptation. These include the major cortical areas (►frontal eye fields, ►supplementary eye fields, and ►lateral intraparietal area), the ►superior colliculus, the midline ►cerebellum, and the burst generator itself. The characteristics of adaptation constrain the choice. The existence of adaptation fields implicates a structure whose neurons have movement fields or a structure that receives input from one with movement fields. The existence of eye-position dependent adaptation implicates a structure that is at least potentially aware of current eye position. This would

appear to rule out the burst generator per se, the collicular synapses on burst-generator neurons, and arguably the superior colliculus itself, because all three areas are thought to encode only eye or gaze displacement. These conjectures have been tested by neurophysiological experiments in the superior colliculus. Experiments using saccades evoked by microstimulation of the colliculus either during the adapting or testing phase have been inconclusive (reviewed in [5]), perhaps because microstimulation does not evoke saccades in the same way as normal targeting saccades. On the other hand, measurements of the ►movement fields of neurons in the superior colliculus show that they change minimally as a result of adaptation, indicating that the adaptation takes place downstream of the colliculus [6].

The cerebellum is downstream of the superior colliculus (see ►Cerebellum – role in eye movements) and satisfies behavioral criteria noted above. In addition, it has been strongly implicated in adaptation in other motor systems and has a wealth of identified mechanisms of synaptic plasticity. Physiological experiments in monkeys strengthen the conjecture that it has a major role in saccade adaptation. Permanent lesions of the ►oculomotor vermis or fastigial nucleus severely impair or abolish the ability to adapt saccade size using intrasaccadic steps [7]. Temporary inactivation of the caudal fastigial nuclei using a GABA agonist produces dysmetria and prevents the expression of adaptation while the drug is active, but not after the drug has worn off [8]. Presumably, plastic changes had occurred upstream of the fastigial nucleus, e.g., in the vermis. Finally, the discharges of fastigial-nucleus neurons change as a result of adaptation of saccade size in a manner adequate to have produced the changes in size [9].

Adaptive changes in humans probably also involve the cerebellum [10], but the failure of changes to transfer to saccade tasks different from the training paradigm and the predominance of a very rapid form of adaptation indicates that another site might also be involved in some tasks. Functional MRI data do not implicate another structure [10], but the data are not definitive. There are other possibilities, including that most changes could occur in the cerebellum, but separate channels from different sources (the superior colliculus or frontal eye fields) are maintained and separately adapted.

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Saccade Remapping

Definition

Saccade-related shift of visual target representation in The central nervosu system (CNS). Conceivably due to processes subsumed under the rubric "Vector-subtraction hypothesis" (see Foveation Hypothesis) it is consistent with the well documented saccade-related shift of the receptive field of neurons sensitive to a direct or memorized visual stimulation (see Lateral intraparietal area (LIP) for a description of such visual receptive fields). This observed shift, which sometimes occurs in anticipation of the actual movement of the eyes, likely contributes to the neural processes suppressing the awareness of visual instabilities caused by saccadic eye movements.

Thus by extension, saccade remapping also refers to visual stability processes and to space constancy processes which allow us to encode our environment independently of eye movements.

►Eye-Hand Coordination
►Foveation Hypothesis
►Lateral Intraparietal Area (LIP)
►Saccade
►Saccadic Eye Movement

S

Saccade-Vergence Interactions

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Definition

►Saccades are very fast (up to 700°/s) movements of the eyes which are generally employed to shift gaze from one object to another. In general, saccades are conjugate, in that the two eyes move in the same direction and by the same amount, even if only one eye is allowed to view the target. Saccades may be horizontal, vertical, or oblique. Horizontal ►vergence (Disparity dependent vergence, Radial flow dependent vergence) movements are very slow (5°/s to 50°/s) movements of the eyes in the opposite direction in the horizontal plane, and are used to transfer gaze between objects at different distances from the observer. Horizontal vergence movements are part of a near response, and are associated with ocular accommodation, which is the change in lens power needed to focus on a nearer or farther object (see ►Accommodation-vergence interaction). Saccade-vergence interaction refers to the increase in the speed of vergence observed when saccades occur during vergence movements, or alternatively, to the inequality of the sizes of horizontal saccades when they occur during vergence movements [1].

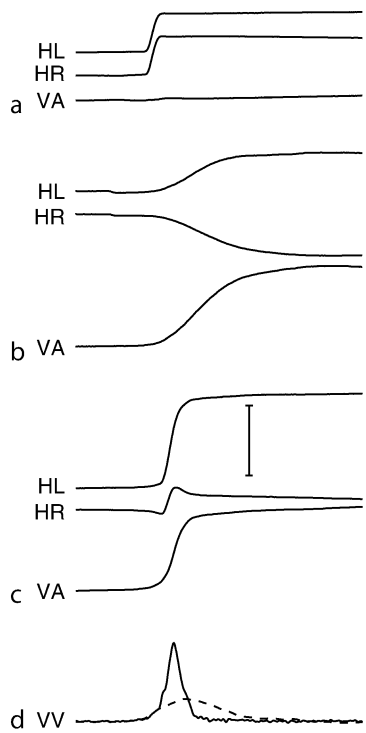
Characteristics

Upstream Events/Conditions

Saccades may be voluntary or involuntary, and are usually directed toward visual targets in the environment, or they may be spontaneous or occur in response to other (e.g. auditory) cues. Saccades between targets that are equidistant from the observer do not involve vergence movements, aside from a small rapid divergence-convergence transient (►Divergent eye movement, ►Convergent eye movement), which may be due to mechanical factors. A horizontal saccade between two targets spaced 8° apart is shown in Fig. 1a. A saccade-free, or smooth, vergence movement between a far and a near target is shown in Fig. 1b. Vergence movements occur in response to shifts in gaze between visual targets at different distances. Vergence movements can occur in the absence of saccades, but this is rare in the natural environment; to do so, the far and near targets must be aligned with a point halfway between the eyes, as was the case for this example. Vergence movements have been extensively studied in the laboratory in this situation. There is evidence that the neuronal circuits for saccades and vergence movements are somewhat independent, although utilize the same ►extraocular motoneurons [2]. Lesions of the pons and ►medial longitudinal fasciculus (MLF) may impair horizontal saccades without a major effect on vergence [3], while some midbrain lesions may impair vergence while leaving horizontal saccades relatively unaffected.

Downstream Events/Conditions

If the vergence and saccadic subsystems were essentially independent, then one might expect the eye movements produced by each to sum linearly when a saccade occurs during a vergence movement. That this is not the case can be seen in Fig. 1c and d. This can be seen by noting the relative sizes of the horizontal saccades (Fig. 1c), or by comparing the vergence velocity profile for the saccade-vergence trace with that of the similar smooth vergence (saccade-free) case (Fig. 1d). There is a rapid acceleration of vergence during the saccade, which causes vergence movements during saccades to be completed more quickly than if



Saccade-Vergence Interactions.
Figure 1 Saccade-vergence interaction. This figure shows an 8° horizontal saccade (a), an 11.5° smooth horizontal vergence movement (b), and the interaction when a saccade of this size occurs during the vergence movement (c). (d) shows the vergence velocity profiles for the saccade + vergence (solid line) compared to the vergence only (dashed line) case. Abbreviations are: *HL*, horizontal left eye position; *HR*, horizontal right eye position; *VA*, vergence angle (i.e. HL-HR); *VV*, vergence velocity (first derivative of VA). The scale bar is 10°, and the time base is 500 ms.

there were no saccades. If the saccade and the vergence events summed linearly, the vergence velocity profiles in Fig. 1d would be identical. Not only do saccades speed vergence; it appears that vergence movements slow saccades.

Involved Structures

The same extraocular motoneurons (►medial rectus for adduction, abducens for abduction) (►Ocular adduction, ►Ocular abduction) are utilized for both saccades and vergence movements, although not necessarily to the same extent. The pre-motor circuitry is quite different for the two types of eye movement. For vergence, some midbrain ►near response neurons appear to project to the medial rectus subdivisions of the oculomotor nucleus [4] and carry a signal related to vergence and accommodation but are unrelated to the conjugate movements characteristic of saccades. Most near response cells have precisely the vergence signal needed by medial rectus motoneurons, that is, they increase their firing rate linearly for convergence (convergent eye movements), and also have an appropriate vergence velocity signal. A small number of midbrain near response cells decrease their firing rate for convergence (divergence cells), and so have the appropriate signal for abducens motoneurons, but this connection has not been documented.

The pre-motor commands for horizontal saccades are organized in the pons. Two types of saccadic burst neurons (also called short- or medium-lead burst neurons) are found [5]. ►Excitatory burst neurons (EBNs) provide an excitatory burst to ipsilateral abducens neurons (motoneurons and internuclear neurons) and so provide the appropriate velocity command for the high-speed saccades. Inhibitory burst neurons show the same pattern of activity (i.e., burst for the horizontal component of an ipsilateral saccade) but inhibit the contralateral abducens nucleus during the saccade. Saccadic burst neurons are inhibited by pontine ►omnipause neurons, which are located in the nucleus raphé interpositus. Omnipause neurons are normally active during wakefulness, and must cease firing in order for a saccade to occur.

►Abducens internuclear neurons are located within the abducens nucleus but are not motoneurons. Their axons cross the brain at the level of the abducens nucleus and ascend the medial longitudinal fasciculus to provide excitatory input to the medial rectus motoneurons. To the extent that abducens internuclear neurons receive the same inputs as abducens motoneurons, the abducens internuclear pathway serves to ensure that the two eyes move conjugately in the horizontal plane. Abducens internuclear neurons do not provide a vergence signal to the medial rectus motoneurons, and damage to the internuclear pathway disrupts adduction for conjugate gaze shifts but not convergence [3]. Indeed, nearly all abducens internuclear neurons decrease their firing rate for convergence (as do abducens motoneurons) and so they provide an inappropriate vergence signal to the medial rectus motoneurons, which must be overcome by the near response cell input to these motoneurons [6].

Mechanism of the Interaction

Three mechanisms for this non-linear interaction between saccades and vergence have been proposed. The first explanation is that there is a non-linear interaction between saccadic and vergence commands at the level of the extraocular muscles, since the same extraocular muscles are used to execute both saccades and vergence movements. A strong argument against this explanation is that purely vertical saccades are about as effective at speeding vergence as horizontal saccades. This should not be the case if the interaction depended upon an interaction at the level of the extraocular muscles since different muscles are used for horizontal and vertical eye movements.

The second explanation notes that the sizes of the saccades in the two eyes are markedly different, and proposes that under the condition of shifting gaze between objects at different distances and directions, the normally conjugate saccadic system is allowed to operate in a disconjugate, or disjunctive mode (►Disjunctive eye movements), and produce different saccades for the two eyes [7]. One argument in favor of this explanation is the observation that, for unequal horizontal saccades occurring during vergence, some saccadic burst cells have activity associated with the movement of the right eye and some are associated with the left eye [8]. The possibility that saccadic pre-motor elements might command the eyes to move different distances suggests that the saccadic system is responsible for the speeding of vergence in this situation. On the other hand, there are strong arguments against this view. Studies of the activity of abducens motoneurons and internuclear neurons show that any separate right eye/left eye pre-motor signals are commingled and essentially lost at the level of the motoneurons [6]. Furthermore, it is clear that abducens internuclear neurons do not convey an appropriate vergence signal to the medial rectus motoneurons. Moreover, it is difficult to reconcile the idea that speeding of vergence is due to unequal horizontal saccades when it occurs with vertical saccades, which employ different motoneuron pools and different pre-motor circuitry.

A third view is that there is a mechanism that selectively speeds vergence during a saccade. According to this idea, the saccadic system generates equal saccades for the two eyes, but the occurrence of the saccade accelerates the vergence command, and the resulting rapid change in vergence angle, synchronized with the saccade, causes the saccade in one eye to be larger than that in the other. Indeed, it has been suggested that

pontine omnipause neurons, which inhibit saccadic burst neurons and must be turned off during saccades, also inhibit vergence burst neurons [9]. If so, then these vergence burst cells would be allowed to fire more vigorously during saccades, speeding vergence. Alternatively, some component of the saccadic burst signal could be combined with the vergence velocity signal to speed the vergence movement.

Methods to Measure this Event/Condition

Saccade-vergence interactions require methods to measure eye movements with high temporal and spatial resolution. In general, faithful recording of saccades requires a sampling rate of at least 500 samples/s and small vergence movements should be recorded to nearest 0.1°. Non-contacting infrared techniques can be used if only horizontal movements are to be recorded. If vertical saccades are to be measured, scleral search (electromagnetic) coils should be considered.

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Saccadic Burst Generator

Definition

The saccadic burst generator is a neural network in the brain stem that converts saccadic-related signals from higher level sensorimotor structures into intense bursts of activity that temporally drive the oculomotor neurons. The bursts of neural activity can be excitatory for agonist motoneurons and inhibitory for antagonists. The generator may also include gating circuits that help to control the onset and end of the bursts.

►Brainstem Burst Generator
►Saccade, Saccadic Eye Movement

Saccadic Dysmetria

Definition

Is a repeatable failure of saccadic eye movements to land on their intended target. The error can be one of saccade amplitude (either undershooting or overshooting) or one of saccade direction. Dysmetria can be produced by pathology within the orbital tissues, extraocular muscles, or in the brain. The brain has robust adaptive capabilities to make conjugate corrections for dysmetria, and limited capability to make monocular corrections.

These capabilities are thought to require the midline cerebellum, so enduring conjugate dysmetria is frequently due to pathology of the cerebellum.

►Dysmetria
►Saccade
►Saccadic Eye Movement

Saccadic Eye Movement

Definition

►Saccade
►Saccadic Eye Movement

Saccular Test

►Vestibular Tests: Vestibular Evoked Myogenic Potentials Induced by High Level Sounds

Saccule

Definition

One of two otolith organs that sense gravity and linear acceleration such as from initiation of movement in a straight line. The saccule is oriented vertically in the head, and registers accelerations in the vertical or coronal plane.

►Peripheral Vestibular Apparatus

Sacral Segment of the Spinal Cord

Synonyms

Pars sacralis medullae spinalis; Sacral part of spinal cord

Definition

Sacral cord. The segment of the spinal cord comprising the spinal nerves of the sacrum.

►Medulla Spinalis

SAGE

►Serial Analysis of Gene Expression

SAI and SAII Afferents

Definition

Slowly adapting (SA) mechanoreceptive afferents thought to be related, respectively, to Merkel cells and Ruffini corpuscles. SAI afferents have small receptive fields, and a low threshold to mechanical stimulation.

SAII afferents have larger receptive fields, appear to be absent from glabrous skin, and are especially sensitive to lateral skin stretch of the type that accompanies movement.

►Active Touch
►Cutaneous Mechanoreceptors – Functional Behavior
►Processing of Tactile Stimuli

Salivary Secretion Control

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Definition

The control of salivary secretion depends on reflex nerve impulses that involve afferent limbs, medullar salivary nuclei and an efferent limb consisting of the ►parasympathetic and sympathetic secretomotor and vascular nerves. Except for a scanty spontaneous secretion from minor salivary glands, the secretory process is elicited entirely by activity in the autonomic glandular innervation, albeit endocrine stimuli may modulate saliva composition. Also the glandular blood flow is principally controlled via the innervation with other influences, such as hormones having little effect. At rest, a small secretion normally occurs as a result of reflex glandular activation and the spontaneous secretion. Taste and mastication are important sensory inputs leading to activity in the two divisions of the ►autonomic nervous system, which act synergistically in the control of salivary secretion.

Characteristics

Quantitative Description

Saliva is produced by three pairs of major glands and a number of minor glands (labial, buccal, lingual, palatinal) [1]. The parotid (20–30 g) and submandibular glands (8–10 g) are conspicuously larger than the sublingual gland (3–5 g). The resting flow in healthy individuals usually amounts to 0.3–0.4 ml/min, which have the relative glandular contributions: submandibular 65%, parotid 20% and the sublingual and the minor glands 5–10% each. In stimulated flow of whole saliva, the parotid part may be as large as 50%.

Higher Level Structures

Anatomy [1,2]

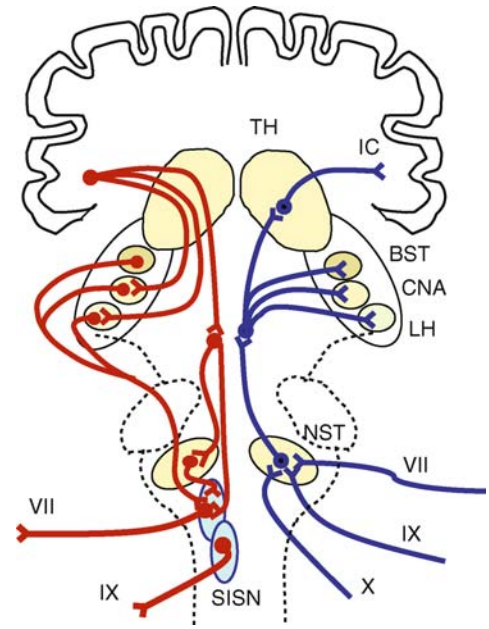
The parotid gland is located frontal and caudal to the auditory canal and surrounds the dorsal part of the mandible. On the masseter surface, close to the parotid duct, additional glandular tissue may occur (accessory parotid gland). The submandibular gland is located caudal to the parotid gland and medially to the body of the mandible, while the sublingual gland is located in the floor of the mouth cranial to the mylohyoid muscle. The minor salivary glands underlie most of the oral mucosa except the gingiva and the dorsum of the tongue, and in contrast to the major glands these glands may produce saliva spontaneously. The arterial blood flow supply is derived from various branches of the external carotid artery, and the venous drainage is provided by tributaries of the external and internal jugular veins.

Autonomic Nerves

The parasympathetic preganglionic nerve fibers leave the central nervous system via the facial and the glossopharyngeal ►cranial nerves. The fibers in the facial nerve depart the nerve within the skull and run in the chorda tympani before fusing with the lingual nerve; some fibers of facial nerve reach palatinal glands by other routes. The ►postganglionic fibers of ganglion submandibularis innervate the submandibular and the sublingual glands as well as minor lingual glands. The glossopharyngeal fibers enter the otic ganglion via n. petrosus minor, and the relatively long postganglionic nerve fibers reach the parotid gland and minor buccal glands via the auriculotemporal nerve. The postganglionic fibers of the sympathetic innervation originate in the superior cervical ganglion and follow the blood vessels to the glands.

Central Connections

Figure 1 shows a schematic illustration of taste afferents, projections to areas of the ►limbic system and cortical level and efferent system [3]. Tentatively, ►limbic areas are associated with feeding- and drinking-related behavior and the cortex with discrimination of taste intensity and quality. The salivatory centers receive impulses from other brainstem nuclei and from the forebrain, and these impulses may be modulated by ►inhibitory or excitatory synapses. The precise location of the sympathetic salivary center is not identified, but the sympathetic impulses are outflows from the upper thoracic spinal cord. Vascular nerves are a separate set of efferent nerves than the secretomotor efferents, at least sympathetic, and while the parasympathetic vascular efferents are controlled by salivatory centers, the sympathetic are under central vasomotor control.



Salivary Secretion Control. Figure 1 Schematic illustration based on studies in rats [3] of parasympathetic efferent system (facial nerve – submandibular/sublingual glands and glossopharyngeal nerve – parotid gland; to the left in illustration) and taste afferent system (facial, glossopharyngeal and ►vagal nerves; to the right). Taste information is relayed via neurons of the solitary nucleus (NST) to a second-order of neurons in the parabrachial nucleus. The dorsal ►thalamus (TH) projections of the nucleus terminate in the insular cortex (IC), while a ventral route to the limbic system terminates in the ►lateral hypothalamic area (LH), the central nucleus of the amygdale (►amygdala) (CNA) and the bed nucleus of the stria terminalis (BST). Direct and indirect descending projections reach the medullar parasympathetic superior ►salivatory center (the only one characterized). This salivatory center consists of the ►salivatory nuclei (superior and inferior salivatory nuclei) (SISN), the former connected to the submandibular and sublingual glands, and the latter to the parotid gland.

Lower Level Components

Histology [4]

The glandular parenchyma consists of secretory endpieces (acini), often capped by cells in the form of demilunes, and of ducts. The endpieces consist of serous cells, producing a protein- and enzyme-rich secretion, of mucous cells, producing a secretion rich in glycoconjugates (e.g. mucin), and of seromucous cells, sharing features of each of the other two. The human parotid gland is a homocrine serous gland, the submandibular a heterocrine (mixed seromucous), while mucous cells dominate in the sublingual gland. Minor glands are heterocrine except the mucous palatinal and the serous lingual von Ebner's glands. Contractile myoepithelial cells surround the secretory endpieces and the intercalated ducts into which the saliva produced by the endpieces drains. In the succeeding striated ducts, an active transport of electrolytes from the saliva to the bloodstream occurs. Eventually the striated ducts empty into the excretory ducts.

Innervation [4]

Generally, human salivary glands are densely innervated by ►cholinergic and ►adrenergic fibers, but the adrenergic innervation of sublingual and minor salivary glands is sparse or deficient. Fibers containing neuropeptides (►NANC transmitters; mainly ►vasoactive intestinal peptide (VIP) and ►neuropeptide Y (NPY)), also occur. The NANC transmitters often co-exist with a classical autonomic ►neurotransmitter in the same fiber. In animals, VIP and acetylcholine, and occasionally the enzyme ►nitric oxide synthase, may occur in the same parasympathetic postganglionic neuron, while NPY may co-exist with noradrenaline.

Receptors

►Muscarinic receptors, alpha- and beta-►adrenoceptors as well as NANC transmitter receptors (VIP receptors) occur abundantly on parenchymal cells and in the glandular vasculature, and moreover, muscarinic receptors and α_2-adrenoceptors occur on nerve terminals [5]. Glandular α_1- and β_1-adrenoceptors have been described in human glands. While both muscarinic M1 and M3 receptors occur in human labial glands, all five subtypes exist in the rat submandibular gland but still with M3 subtype dominance. However, receptors for a number of transmitters, hormones and factors have been described in human salivary glands (e.g. epithelium growth factor (►EGF), androgen, progesterone, aldosteron and glucagons) and considering findings in animals, the list grows even longer and includes ►tachykinin (NK1), purine, ►serotonin and ►GABA receptors.

Structural Regulation

Ontogenesis and Neuronal Trophic Effects

Salivary glands arise in the embryo from the proliferation of epithelial cells into the mesoderm, forming a cord that becomes canalized, and postnatal the terminal cells are developed into the fully mature secretory endpieces. Parasympathetic responses occur already at birth, while sympathetic appear some days later. The autonomic innervation affects size and sensibility of salivary glands, and, as shown by animal studies, loss of the parasympathetic NANC drive causes a profound atrophy and ►denervation supersensitivity [4,6]. Acetylcholine seems to be of less significance for long-term regulations, but noradrenaline have structural effects; stimulation of the β−adrenoceptor induces increase in glandular size. In addition to the neuronal structural regulation, hormones (i.e. different steroid hormones including oestrogen, progesterone and androgens) may affect cell growth and gland size.

Higher Level Processes

Activation of Reflexes

During eating, increases in efferent outflows are attributed to stimulation of different ►sensory receptors; ►gustatory receptors, ►mechanoreceptors, ►olfactory receptors and nociceptors [2]. The gustatory-salivary reflex, activated by strong sour stimulus evokes a maximal secretory response, while other basic stimuli (salt, bitter, sweet) give smaller. However, secretion elicited by sweet and salt is richer in protein, suggesting quality-specific activation of parasympathetic and sympathetic fibers. Mastication activates mechanoreceptors in the periodontal ligament (►Ruffini endings) and in the mucosa, which results in greater ipsilateral responses than contralateral. Smell may evoke secretion by chemical irritation of free nerve endings and by odorants stimulating nasal olfactory receptor neurons (olfactory-salivary reflex); the latter exists in the submandibular but not in the parotid gland. Noxious and non-noxious stimuli of oral tissues also activate salivary reflexes, while the existence of oesophageal, visual and psychic reflexes is a matter of debate. Hyposalivation during fear is, however, explained by central inhibition of salivatory centers reducing the efferent outflow.

Sensory Inputs and Efferent Impulses

In animals, the efferent outflows from the salivatory centers depend on the sensory modality and on which confined oral area is being stimulated, and preganglionic parasympathetic and sympathetic neurons respond differently to taste, tactile and noxious mechanical stimulation [3]. The preganglionic parasympathetic neurons discharged spontaneously at a low firing rate, when examined in hamsters and rats, and fired to reflex stimulation by phasic-tonic or ►tonic activity (periodically up to 30 Hz). Neurons assumed to be a vasodilator type, tended to fire at a slightly higher frequency. Nevertheless, the ganglionic transmission from pre- to postganglionic neurons varies between species. Some species (e.g. rats) have ganglion cells that are innervated by a single preganglionic axon, while others have a multiple innervation yielding discharges in postganglionic neurons in short bursts, each at a very high frequency as seen in sheep. Also, sympathetic neurons may have a spontaneous and irregular discharge, in which the number of bursts increases by a sensory input.

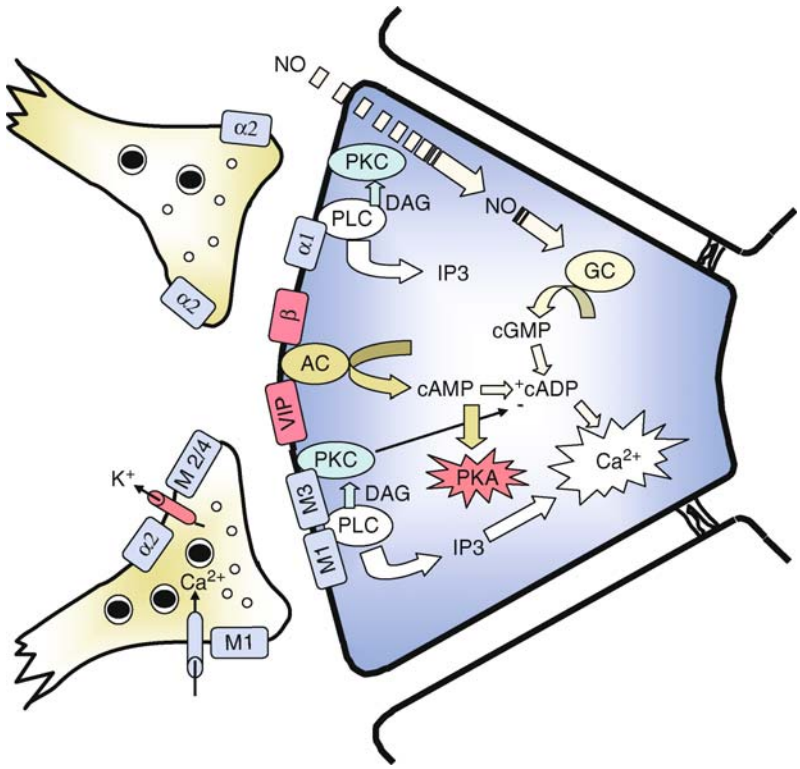
Lower Level Processes

Receptor Pathways and the Cellular Secretory Mechanisms

Saliva, containing approximately 99% water and 1% of electrolytes and proteins, is produced in two steps – first formation of isotonic primary saliva by secretion from the secretory endpieces, and second reabsorption of sodium and chloride and some secretion of potassium and bicarbonate in the ducts [5]. Since the ducts are relatively impermeable for water the secondary saliva becomes hypotonic, but less so at increasing flow rates. Receptors being preferentially hydrokinetic (muscarinic ►acetylcholine receptors and α_1-adrenoceptors (and tachykinin receptors in some species) activate the Ca^{2+}-dependent pathway, while the proteokinetic type (β-adrenoceptors and VIP receptors) activates the cAMP-pathway (Fig. 2) [4,7]).

The combined stimulation of both pathways results in ►potentiation of the responses, but responses are also modulated by prejunctional receptors that facilitate or inhibit transmitter release. The intracellular events leading to fluid secretion is elicited when Ca^{2+} rises, but how water moves is not fully clarified (Fig. 3 [7]).

Proteins are primarily secreted from acinar cells with the addition of a small proportion from ducts cells. Low



Salivary Secretion Control. Figure 2 Schematic illustration of ►G-protein-coupled receptors for principal transmitters and key molecules of the intracellular pathways in a salivary secretory cell innervated by adrenergic and cholinergic/VIPergic neurons (modified from [3]). Transmitter binding to α_1-►adrenoceptors, muscarinic M1 or M3 receptors induces via activation of phospholipase C phosphatidylinositol-4,5-bisphosphate to be hydrolyzed into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), leading to increase in the intracellular Ca^{2+} levels and to activation of ►protein kinase C (PKC). Transmitter binding to β-adrenoceptors activates ►adenylate cyclase that elevates $[cAMP]_i$ thereby activating ►protein kinase A (PKA). Nitric oxide synthesized from L-arginine by nitric oxide synthase, passes through the cell membrane and activates soluble ►guanylate cyclase leading to the formation of cGMP. cGMP may activate ADP-ribosyl cyclase, leading to the formation of cADP ribose. cADP ribose and ►IP_3 receptors induce the release of stored Ca^{2+}. The activity of ADP-ribosyl cyclase is stimulated by cAMP, while protein kinase C seems to inhibit the enzyme. The connections provide possible ways for fluid and protein secretion by activation of any pathway. ►Presynaptic inhibition by muscarinic (M2 or M4) receptors and α_2-adrenoceptors, hyperpolarizing (increased conductance of ►$K^{\pm}$ channels) the neuronal membrane, may restrain transmitter release. Presynaptic muscarinic M1 receptors may similarly affect ►$Ca^{2\pm}$ channels, thereby facilitating calcium influx and ►neurotransmitter release.

intensity of sympathetic and parasympathetic activity engage the ►regulatory and the ►constitutive route, respectively, while high parasympathetic intensity is necessary for activating the ►regulatory route [4].

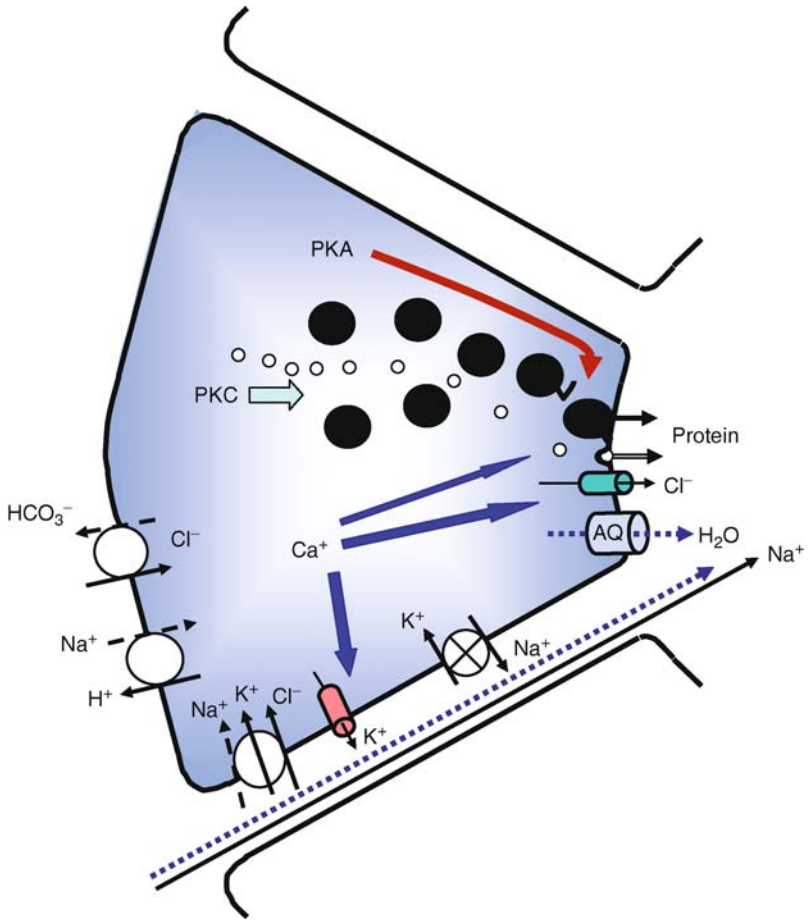
Process Regulation

Fluid Responses

The autonomic impulses evoke secretion by releasing acetylcholine, noradrenaline and neuropeptides from glandular nerve terminals [4–6]. While parasympathetic activity evokes a copious secretion relatively poor in protein, activity within the sympathetic innervation evokes a sparse but protein-rich secretion. Although α- or β-adrenoceptors evoke little fluid secretion, they are important for protein and enzyme secretion, in particular β_1-adrenoceptors. Activation of the parasympathetic muscarinic receptors, predominantly of the M3 subtype, elicits most of the fluid secretion (Fig. 4). However, muscarinic M1 receptors also contribute to the salivary response as studies in animals indicate, in particular at low intensity of nerve activity (Fig. 5 [8]). The initiation of secretion is supported by parasympathetic and sympathetic (α_1) induced contraction of myoepithelial cells [4].

Vascular Responses

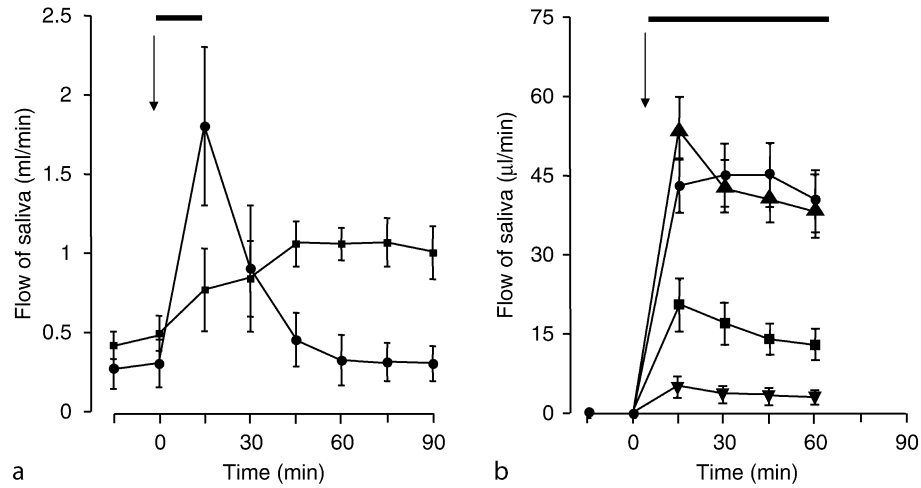
Blood flow is not a secretion-limiting factor initially, since the interstitial fluid will preserve the response. However, in short, because of increase in interstitial oncotic pressure, salivation will cease unless the blood



Salivary Secretion Control. Figure 3 Schematic illustration of key molecular events leading to fluid and protein secretion in a secretory salivary cell (drawn from data from [4]). In the resting state, the intracellular Ca^{2+} concentration of the secretory cell is low, and the Ca^{2+} activated ►$K^{\pm}$and ►Cl^- channels are closed. When the Ca^{2+} concentration increases, the K^+ and Cl^- channels open; effluxes of Cl^- and K^+ occur via luminar and basolateral membrane channels, respectively. Chloride enters the secretory cell via a sodium-chloride co-transporter (NKCCl) in the basolateral membrane, for which energy is provided by the inwardly directed electrochemical gradient for Na^+. The increase in intracellular Na^+ concentration stimulates Na^+/K^+ATPase (►$Na^{\pm}$-$K^{\pm}$ pump) to the expense of cellular ►ATP. The luminar secretion of Na^+ seems to occur via the paracellular pathway driven by the electrochemical gradient across the epithelium. Water is transported by osmosis by the paracellular pathway and/or via aquaporin channels in the acinar cell membrane. Proteins, synthesized in the rough endoplasmic reticulum are transported in vesicles from the Golgi complex either to storage in granules (regulatory route) or directly to the plasma membrane (constitutive route). In the granular exocytosis, protein kinase A plays a key role by activating binding proteins (►Docking/priming; ►VAMP2 to t-SNAREs), and Ca^{2+} seems to enhance membrane fusion. Protein kinase C has been connected to protein secretion, possibly by affecting binding proteins.

flow increases. While parasympathetic activity invariably increases it (Fig. 5), sympathetic activity exerts variable effects.

The parasympathetic-evoked increase is, as shown by animal experiments, largely mediated by neuropeptides (i.e. VIP [9]). In contrast to the cholinergic vasodilatation that occurs at low intensity of parasympathetic activity and which is partially un-dependent on nitric oxide synthesis, the atropine-resistant vasodilatation seems to be completely dependent. Also in man, VIP is a potent vasodilator and causes *in vitro* relaxation of the submandibular artery. At rest, a tonic activity within the sympathetic innervation maintains a glandular vascular resistance by α-adrenoceptor-mediated constriction, probably enhanced by NPY. However, during sympathetic activity, blood flow may still be preserved and thereby also the flow of saliva, as has been shown by animal studies [9]. Namely, after discontinuation of electrical stimulation of the sympathetic nerve, an adrenoceptor-mediated after-dilatation occurs that may be larger than the preceding vasoconstriction. Since sympathetic neurons fire in bursts during reflex-induced



Salivary Secretion Control. Figure 4 Fluid responses (means±SEM) induced by different stimulation techniques in healthy adults (A; n = 5) and in anaesthetized rats (B; n = 3–6). A) Flow of saliva, without tongue movements or mastication in response to lozenges containing malic acid placed on the tongue (*filled circle*; dissolving period indicated by horizontal bar;) and to oral pilocarpine (*filled square*; 5 mg; administration indicated by arrow). B) Flow of saliva from rat parotid glands induced by application of one drop of citric acid (*filled circle*; 5%) on the tongue every 30 s (horizontal bar), by electrical stimulation of the auriculotemporal nerve (*filled triangle*; 40 Hz; horizontal bar), by electrical stimulation of the sympathetic nerve (*filled inverted triangle*; 50 Hz 1:10 s; horizontal bar) or by pilocarpine (*filled square*; 2 mg/kg IV; arrow). The diagrams in figure 4 are drawn from unpublished material and redrawn from data in Götrick et al. (2004) J Dent Res 83:393–397; Götrick, Tobin (2004) Arch Oral Biol 49:969–973).

activity, this is likely to occur repeatedly during physiological conditions.

Transmitter Interactions

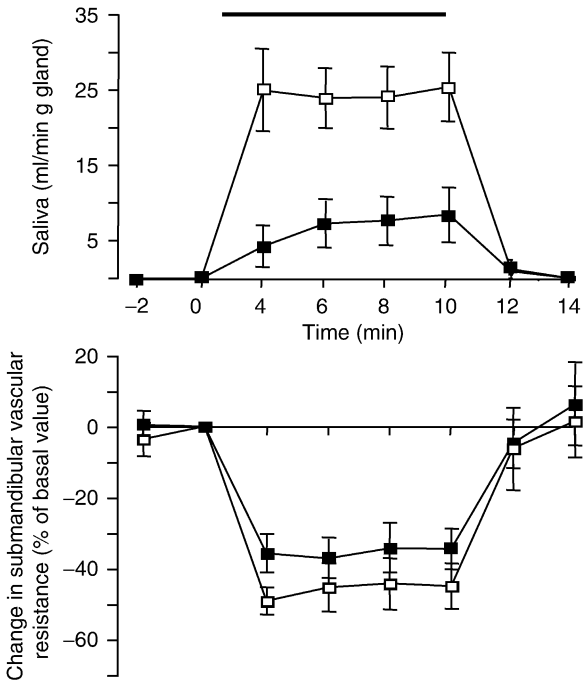
Simultaneous parasympathetic and sympathetic stimulations potentiate the responses as reflected by the fact that strong gustatory stimulations result in maximal flow rates of whole saliva (5–10 ml/min). In some species, administration of neuropeptides into the bloodstream evokes fluid and/or protein secretion; e.g. ►substance P (mainly fluid) and ►VIP (protein with or without a sparse fluid response), and when the parasympathetic nerve is stimulated electrically in these species, an atropine-resistant secretory response occurs [6]. *In vitro* examinations of the human submandibular glands do not indicate that these peptides induce any flow of saliva on their own, but VIP probably contributes by potentiating effects; muscarinic responses are potentiated by VIP (see Fig. 4 illustrating NANC + acetylcholine interaction; nerve response), and VIP elevates the content of ►cAMP in human submandibular glands. Co-localization of transmitters in single neurons implies that the relative amounts being released vary depending on the rate and pattern of the firing [9]. The release of VIP requires a high intensity of nerve activity (>10 Hz) and, as shown in animals, parasympathetic ►burst stimulation at high frequencies enhances vasodilatation and protein secretion, occasionally also salivation; *n.b.* maximal functional responses usually occur at 15–40 Hz (cf. preganglionic discharge). Furthermore, in burst patterns, the long duration effects of neuropeptides improve the prerequisites for the classical transmitters acting thereupon, and additionally, the pattern takes advantage of transient facilitation by neuronal excitatory receptors and avoids the hold back at less neuronal activity by prejunctional inhibition [10].

Function

The main functions of saliva are lubrication, protection and digestion [1]. Lubrication facilitates speaking and swallowing, the water of saliva moistens and the mucins bind food particles into bolus formation. Mucins lubricate and protect the mucosa, and salivary EGF benefits its repair. Protective roles are exerted by removing substances from the oral cavity (oral clearance), and by the buffer capacity by bicarbonate, phosphate and proteins in saliva. Salivary proteins may also protect against infections (e.g. IgA, peroxidase and lysozyme). The enzymes α-amylase (parotid) and lipase (lingual von Ebner's glands) may initiate digestion of starch and triglycerides, respectively. Saliva also fulfils a taste-aiding function by dissolving flavor compounds, a necessity for taste receptor activation.

Pathology

Salivary gland dysfunction, deleterious to oral health, could originate from primary glandular conditions (e.g. radiation, inflammatory diseases such as ►Sjögren's syndrome, duct stones, retention cysts and tumors) or could be secondary to systemic conditions (e.g.



Salivary Secretion Control. Figure 5 Flow of saliva (upper panel) and changes in submandibular vascular resistance (lower panel; perfusion pressure/blood flow; reflecting changes in glandular blood flow) in response to electrical stimulation of the chorda lingual nerve in anaesthetized sheep at 2 Hz for 10 min (indicated by horizontal bar) before (*open square*) and after (*filled square*) administration of pirenzepine (100 nmol/kg IV; "M1-selective" dose). Responses are mean±SEM (n = 4). (Redrawn from material presented at the Physiological Society, Dec 2003; Tobin and Edwards, 2004, J Physiol 555P:C19).

medications, endocrine and autoimmune diseases, neurological disorders and infections [1,5]). The conditions often result in ►xerostomia, most commonly to medication, Sjögren's syndrome and radiation towards the head and neck region. Due to the complexity of the reflexes involved in the control of salivary secretion, the targets for possible xerogenic effects are numerous, as also reflected by synergistic effects by multiple medications (polypharmacy). The principal mechanism of xerogenicity is by an anticholinergic action or by interference of central pathways.

Therapy

Salivary enhancement therapies are either topical, local therapies or systemic therapies ([5], Fig. 4). Chewing gums and flavor lozenges as well as oral rinses are pillars in the palliative therapy. Acupuncture is a suggested local therapy, assumed to cause relief of xerostomia by inducing release of neuropeptides. A number of drugs have the potential to intensify the flow of saliva. Pilocarpine causes significant increases in most patients irrespective of the cause of xerostomia, but shows the typically adverse effects of a parasympathomimetic. In order to find secretagogues with less adverse effects, agents such as ►acetylcholine esterase inhibitors, α_2-antagonists and agents up-regulating substance P have been evaluated in clinical trials.

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S

Salivatory Nuclei (Superior and Inferior Salivatory Nuclei)

Definition

A pair of nuclei (superior and inferior salivatory nuclei) located rostral to the dorsal nucleus of the vagus from where the parasympathetic preganglionic neurons of the salivary gland innervation emerge.

►Salivary Secretion Control

Salt Taste

Definition

►Taste - Salt

Saltatory Conduction

Definition

Conduction in myelinated axons depends upon a similar pattern of circular current flow. However, myelin is an effective insulator, and current flow through it is negligible. Instead, depolarization in myelinated axons jumps from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize to the firing level the node ahead of the action potential. This jumping of depolarization from node to node is called saltatory conduction. It is a rapid process, and myelinated axons conduct up to 50 times faster than the fastest unmyelinated fibers.

►Action Potential Propagation

Sampling

Definition

The process of transforming a continuous signal into discrete units.

►Signals and Systems

Sampling Density of Retinal Ganglion Cells

Definition

The density of retinal ganglion cells across the retina. The total sampling by the human retina is slightly higher than that of a megapixel digital camera (1,000 by 1,000 samples). Unlike the camera, which has constant sampling density across the photograph, the primate retina has higher density nearer the fovea. Each of the individual ganglion cell classes has its own sampling density, and most are substantially lower than a 1-megapixel camera.

►Retinal Ganglion Cells
►Visual Processing Streams in Primates

Sampling Frequency

Definition

►Nyquist sampling theorem

►Signals and Systems

Sapid Saporous, Saporific Stimulus

►Tastant

Sarco(endo)plasmic Reticulum Ca^{2+}-ATPase (SERCA)

Definition

Integral membrane proteins that catalyze the ATP-dependent transport of Ca^{2+} from the cytosol to the lumen of the sarcoplasmic reticulum (SR). In conjunction with plasma membrane Ca^{2+}-ATPases, SERCAs are responsible for setting resting cytoplasmic Ca^{2+} concentrations, and during repetitive muscle contractions, they induce muscle relaxation through the rapid sequestration of large Ca^{2+} loads from the cytoplasm into the lumen of the SR.

►Excitation–Contraction Coupling

Sarcolemma

Definition

Sarcolemma is the cell membrane of skeletal muscle fibers.

►Skeletal Muscle Architecture

Sarcomere

Definition

A sarcomere is typically considered to be the basic contractile unit of muscle. It is defined as the structural repeat element that is bordered by two neighboring Z-plates.

It contains the contractile proteins actin and myosin, the regulatory proteins troponin and tropomyosin, and a host of structural proteins, most prominently titin, nebulin, and desmin.

►Actin
►Myosin
►Sarcomere Structural Proteins
►Skeletal Muscle Architecture
►Sliding Filament Theory
►Molecular and Cellular Biomechanics

Sarcomere Structural Proteins

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Synonyms

Cytoskeleton of the sarcomere

Definition

Structural proteins are necessary to guarantee the correct assembly and maintenance of the ►sarcomere, the smallest unit of the ►myofibril. This multiprotein complex is essential for muscle contraction and mutations in structural proteins can lead to hereditary myopathies.

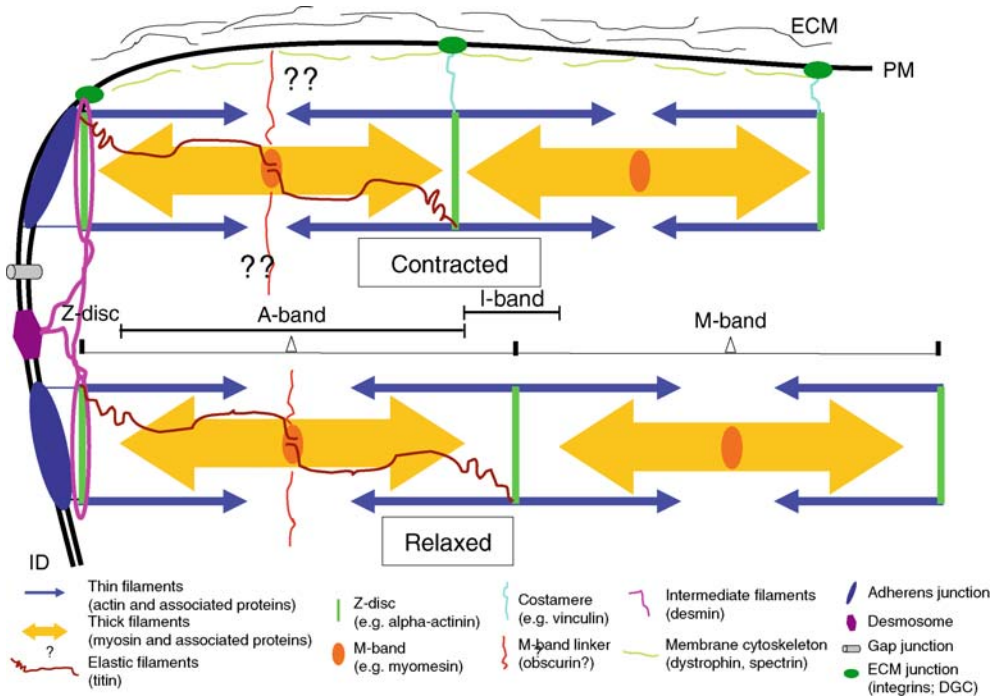
Characteristics

The sarcomere is the smallest subunit of a myofibril, the contractile multiprotein complex in striated muscle cells (Fig. 1).

It is defined as the region between two Z-discs, which anchor the thin filaments, which are composed of actin and its associated proteins. Contraction is brought about by the interaction between actin and myosin, which is organized in a bipolar fashion to the thick filaments. These are anchored in the middle of the sarcomere in the M-band, which provides connection with the third filament system in muscle, the elastic filaments composed of titin. The thick filaments are equivalent to the A-bands (anisotropic), which are seen as dark broad bands in the polarization microscope and in electron micrographs. They alternate with the I-bands (isotropic), which have the darker contrasted Z-disc as a transverse structure in their middle. To provide maximum force output the contractile filaments in muscle are arranged to paracrystalline multiprotein complexes. Despite their extremely regular appearance, sarcomeres are constantly renewed with an approximal protein half-life of about 3 days. Increased physiological demand leads to the addition of sarcomeres in a process called ►hypertrophy. Also protein isoform composition can change, depending on developmental stage, muscle fiber type and mechanical stress, which is sensed in the sarcomere itself at transverse structures such as the Z-disc and the M-band [1]. A multitude of structural proteins are needed to bring about the regular arrangement of the sarcomere during embryonic development and to maintain it during lifetime. A key role seems to be played by the Z-disk protein alpha-actinin, the M-band protein myomesin and titin filaments stretching in between, which can be considered as the "backbone" of the sarcomere.

Titin – Combining Scaffolding, Elasticity and Signaling

Titin (also called connectin) is regarded as the most important structural protein of the sarcomere since it spans throughout half a sarcomere and functions as a "molecular ruler" for the integration of most sarcomeric proteins, several signaling proteins and even metabolic enzymes [1]. Titin has a unique size with a molecular weight >3,000 kDa, leading to a single protein of about 1 μm length and lack of titin prevents the assembly of sarcomeres [1]. Titin is mainly composed of fibronectin type II and immunoglobulin modules. Its N-terminus is anchored at the Z-disk, where it interacts with actin filaments, alpha-actinin and telethonin and the protein stretches then throughout the sarcomere to the M-band, where its C-terminus overlaps with titin molecules coming from the other half sarcomere [2]. In addition to providing structural stability and functioning as a building plan, titin also contributes elasticity to the sarcomere due to the presence of inserted non-modular



Sarcomere Structural Proteins. Figure 1 Simplified schematic representation of sarcomeres and associated structural proteins. The thin (actin) and thick (myosin) filaments are represented as *solid blue* and *yellow arrows*, respectively to indicate their contractile behavior. Structural proteins can be classified according (i) to their location within sarcomeres (titin, actin-associated proteins in the thin filaments and Z-disc, myosin associated proteins in the thick filaments and M-band) (ii) by providing lateral or terminal links of the sarcomeres to contact structures at the plasma membrane (lateral: costameres; terminal: adherens junctions and desmosomes) and (iii) by integrating adjacent sarcomeres (intermediate filaments like desmin; obscurin?). Only one titin filament per half sarcomere is shown. The distance between two neighboring Z-discs is about two micrometers. *ECM* extracellular matrix; *PM* plasma membrane; *ID* intercalated disc; ►*DGC* dystrophin glycoprotein complex.

sequences mainly in the I-band region, whose length depends on muscle type and developmental stage [2]. This huge protein also possesses a kinase domain in its C-terminal region, whose activity is mechanically regulated and can trigger a signaling cascade to the nucleus [1].

Sarcomere Structural Proteins of the Z-Disc and the Thin Filaments

Z-Discs are the terminal anchorage sites of the thin filaments and are characterized by the presence of sarcomeric alpha-actinin, which is a muscle-specific isoform of the actin cross-linking protein. In addition a plethora of other proteins has been identified at the Z-discs in recent years [3]. These play mainly a structural role (alpha-actinin, actin, titin N-terminus; nebulin C-terminus, CapZ), a signaling role (MLP, calcineurin) or potentially both (FATZ/myozenin/calsarcin2, ZASP/Cypher/Oracle, ALP, myotilin, telethonin/T-cap, gamma-filamin, myopalladin, enigma, myopodin, ArgBP2). The N-terminal region of titin binds both actin and alpha-actinin and is probably essential for the formation of the first complexes to be organized in a regular pattern during ►myofibrillogenesis [4]. In mature sarcomeres the two most N-terminal domains of titin form a sandwich-like complex with telethonin to provide additional stabilization [2]. Neighboring Z-discs are linked by a cytoskeletal network that is composed of the muscle specific intermediate filament protein desmin (Fig. 1).

The thin filaments are constituted by two about one micrometer long filamentous chains composed of globular actin, which are entwined in a stretched helix. At the Z-disc end, which is also called the barbed end, they are capped by Cap-Z, at the end that stretches towards the middle of the sarcomere, the pointed end, they are capped by tropomodulin [5]. Tropomyosin dimers stretch along seven of these globular actins and interact with the troponin complex, which consists of troponin T, troponin I and troponin C. Calcium release by the sarcoplasmic reticulum triggers a conformational change in the troponin – tropomyosin complex, which makes actin more accessible for the myosin heads and eventually leads to muscle contraction.

Actin filaments have a precisely defined length that depends on the muscle fiber type. In skeletal muscle, the length regulation is mainly contributed by nebulin, a <900 kDa structural protein, whose C-terminus is

anchored at the Z-disc and which stretches through the internal groove of the helical actin filaments. Cardiac muscle expresses a shorter variant, nebulette, which is also anchored at the Z-disc, but which stretches only up to one third of the thin filament [3].

Sarcomere Structural Proteins of the M-Band and the Thick Filaments

The transverse structure in the middle of the sarcomere is called the M-band. Depending on muscle fiber type, a different number of substructures can be defined by electron microscopy, the M-lines. The most important protein of the M-band appears to be myomesin, which is present in all vertebrate sarcomeres. Myomesin provides a structural link in the form of an antiparallel dimer between the tails of the myosin filaments and the C-termini of titin [6]. Due to its biophysical properties myomesin also contributes elasticity transverse to the direction of contraction in the sarcomere [6]. The elastic properties of the M-band are fiber-type specific and depend on the molecular composition of the M-band. Fast fibers express M-protein in addition to myomesin and show a rigid three-dimensional structure, while slow fibers or embryonic heart muscle express the EH-myomesin isoform in addition to myomesin and are more compliant [6]. Further evidence for the importance of the M-band region for sensing mechanical load comes from observations that the titin kinase domain, which is localized adjacent to the M-band, can be activated by stretch [1]. This induces a signaling cascade that eventually can lead to changes in gene expression via the transcription factor SRF (serum response factor) [1]. The M-band region also serves as anchorage site for several metabolic enzymes [7], for skeletal muscle calpain and for signaling proteins such as members of the MURF family, which bind either to titin itself or to adapter proteins [1].

The precise assembly of myosin to the thick filaments and their length is under tight control of the titin A-band region, which displays a super-repeat pattern of its modular domains and also interacts tightly with myosin. It is currently estimated that six titin filaments are associated with a half thick filament [2]. The super-repeat pattern also defines the association of MyBP-C to a subset of the A-band region. MyBP-C is probably important for the maintenance of thick filament structure, but may in addition also play a role for the fine-tuning of contraction, especially in cardiac muscle.

Structural Connections Between the Sarcomere and the Plasma Membrane

Due to the considerable forces that are exerted during contraction it is absolutely essential that the sarcomeres are anchored properly to the plasma membrane and that they are also integrated between each other. The terminal anchorage sites of the myofibrils are adherens junctions at the intercalated disk in cardiac muscle and focal contacts at the myotendinous junction in skeletal muscle and involve the anchorage of actin filaments emanating from the last Z-disc. A structural protein that seems to be important in these contact sites is N-RAP, a nebulin-related protein that is also known to interact with actin and several cell junction-type proteins [5].

In addition there are lateral connections between the sarcomeres and the plasma membrane. These are present at the level of the Z-disc, where they are called costameres and are mainly composed of vinculin and integrins, which mediate the contact to the extracellular matrix that surrounds muscle cells laterally [5]. By electron microscopy also filamentous connections between the M-band and the plasma membrane were observed, which may be based on obscurin, another high molecular weight modular protein of the sarcomere [6]. Additional structural stabilization is contributed by spectrin, which connects the edges of the Z-disks to membraneous compartments such as the sarcoplasmic reticulum as well as to the plasma membrane itself and by dystrophin, which via the dystrophin glycoprotein complex (►DGC) links the muscle cell cytoskeleton to extracellular laminin filaments [5].

Links between neighboring myofibrils are mainly mediated via the intermediate filament cytoskeleton, which is composed of desmin in muscle and which is concentrated at the level of the Z-disk. Currently it is unclear whether and how myofibrils are integrated at the level of the M-band. Among the currently identified proteins in this region, myomesin and obscurin are the most likely candidates for this role [6].

Pathology

In the last decades mutations in structural sarcomeric proteins could be linked to different types of muscle disease [3], ranging from congenital myopathies (e.g. actin, tropomyosin, troponin T, gamma-filamin, myotilin, nebulin) and muscular dystrophies (e.g. titin, myotilin, telethonin, ZASP, desmin, nebulin, myosin heavy chain, dystrophin) to hereditary cardiomyopathies such as hypertrophic cardiomyopathy (titin, actin, MLP, troponin T, troponin I, troponin C, tropomyosin, myosin heavy chain, myosin light chain, MyBP-C) or dilated cardiomyopathy (titin, alpha-actinin, MLP, ZASP, actin, troponin T, tropomyosin, desmin, MyBP-C, myosin heavy chain, metavinculin, dystrophin). These myopathies can be clinically heterogeneous with a significant variability in severity and time of onset and a type of muscle disease is also not always strictly linked to a mutation in a particular protein. The position of the mutation in the respective molecule and its effect on protein stability and interaction with other proteins may define the final phenotype of the disease.

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Sarcopenia

►Muscle: Age-Related Changes

Sarcoplasma

Definition

Intracellular fluid within a muscle fiber.

►Membrane Potential: Basics

Sarcopterygians

Definition

Sistergroup of actinopterygians, include lobe-finned fishes, i.e., Latimeria (actinistians) and the lungfishes (dipnoi), and all land-vertebrates (tetrapods).

►Evolution of the Brain: In Fishes
►Evolution of the Telencephalon: In Anamniotes

Satellite Cells in Muscle

Definition

Satellite cells are located between the sarcolemma and the basal lamina of the muscle fiber, and remain in a non-proliferative quiescent state. They represent undifferentiated myogenic precursor cells, which have the ability to re-enter the cell cycle either in order to generate new muscle fibers or to provide new myonuclei to the parent fiber. Unlike myonuclei, satellite cells retain their ability to divide following myotrauma or exercise, and therefore have a unique role in the regeneration and growth of adult skeletal muscle that cannot be fulfilled by the post-mitotic myonuclei.

►Muscle – Age-Related Changes

Sauropsids

Definition

The diapsid radiation of amniote vertebrates, i.e., those with two bony fenestrae in the temporal region of the skull. Extant sauropsids include lizards, snakes, the tuatara Sphenodon, turtles, crocodiles, and birds.

►Evolution and the Concept of Homology
►The Phylogeny and Evolution of Amniotes

Saxitoxin (STX)

Definition

Saxitoxin (STX) is a paralytic toxin in marine dinoflagellates that, in some seasons, “bloom” and discolor the seawater (“red tide”). The shellfish feeding on them become contaminated and are highly dangerous to eat. Through the marine food chain, it can poison humans. The mechanism of toxicity is very similar to that of Tetrodotoxin (TTX). Saxitoxin binds from the outside of the cell membrane to various forms of Voltage-dependent Na^+ Channels and blocks the channel in an activation-state-independent manner.

►Action Potential
►Sodium Channels

SC – Buildup Neurons

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San Francisco, CA, USA

Synonyms

Prelude neurons

Definitions

►Saccade-related neurons in the superior colliculus (SC) that display extensive low frequency discharge, well before the onset of a saccade into the ►movement field (►of a neuron) of the cell have been called buildup [1] or prelude [2] neurons.

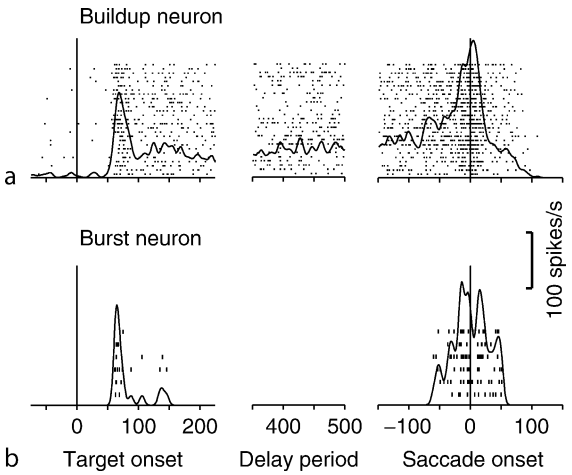
Characteristics

History and Function

Saccade-related neurons in the superior colliculus (SC) in the alert monkey, which displayed a long buildup of low frequency discharge well before the onset of optimal saccades, were first described by Sparks et al. [3] and Mohler and Wurtz [4]. Sparks et al. [3] called cells that began a buildup of discharge approximately 80–100 ms before saccade onset in a ►reaction time task, class II neurons. They contrasted the gradual buildup of this type of SC neuron with another class of collicular neuron, which showed only a discrete high-frequency burst of activity that commenced about 20 ms before saccade onset. They argued that these two classes of collicular neurons formed separate classes. In contrast, Mohler and Wurtz [4] emphasized the earlier discharge of cells before saccade onset as a function of the depth of the neuron's location below the superficial layers of the SC. Deeper cells tended to have earlier discharge, but the amount of pre-saccadic lead varied gradually with depth into the SC. Based on their observations, the latter authors did not attempt to assign SC neurons into two separate classes, and did not assign a name to the deeper cells with longer pre-saccadic discharge. They also noted that deep cells tended to have larger movement fields.

Glimcher and Sparks [2] subsequently called a group of SC neurons with long-lead discharge before saccades into their movement field, prelude bursters. They distinguished this group of neurons in a cued, movement-selection task in which activity of prelude bursters began soon after a central visual cue indicated which of two potential eccentric targets was to be the goal of a delayed saccadic (►Saccade – delayed) response. This pre-saccadic activity was present when the cue required a saccade to the target located in the cell's movement field. They hypothesized that prelude bursters participate in the process of movement goal selection.

Munoz and Wurtz [1] identified delay-period activity in a group of SC neurons in a ►delayed saccade task and codified the name "buildup neurons" for these cells, which they argued formed a separate class of SC neurons that discharged (for movements into the center of the cell's movement field) at rates >30 spikes/s during the 100-ms period of time ending 100 ms before saccade onset. They showed further that neurons in this class tended to be located more ventrally in the intermediate and deep layers of the SC than the other class that they called "burst neurons", neurons that began their discharge just before saccade onset. Finally, they stated that buildup cells displayed ►open-field response characteristics because they discharged for all saccades (in the preferred direction) larger than the center of the cell's response field. Based on this last characteristic and the timing of buildup cell discharge, they suggested that buildup neurons form a functional group of cells in which a rostrally spreading wave of activity codes the dynamic progression of a saccade, which ends when the wave of activity in buildup cells reaches the rostral pole of the SC. Figure 1 shows examples that contrast the difference of discharge patterns in SC buildup and burst neurons in a delayed saccade paradigm. In this paradigm, a monkey continued to fixate a centrally located visual spot when an



SC – Buildup Neurons. Figure 1 Examples of the discharge patterns of a buildup and a burst cell recorded in the monkey SC during a delayed saccade paradigm. Each dot in the raster plots shows an individual discharge of a cell. Each row in the rasters shows a single trial. The curves in each plot show the average spike density of the cell's activity for the set of illustrated trials (Gaussian smoothing parameter = 4 ms). Plots on the left are aligned on the appearance of the target, those in the center are aligned on the end of the delay period when the fixation spot goes off (500 ms), and those on the right are aligned on saccade onset. (Modified by permission from [5]).

S

eccentric target appeared near the center of the cell's movement field. The two plots on the left, which are aligned on the appearance of the target, show that both cells have a brisk visual response that begins about 50 ms after target onset. The animal was required to maintain fixation at the central location after the appearance of the target until the fixation spot was extinguished. When the fixation spot was extinguished, the animal made a saccade to the location of the target. The two plots in the center show the activity in the two neurons aligned on the end of the delay period at 500 ms. Only the buildup cell shows activity in the delay period. The two plots on the right show the activity of the two cells aligned on the initiation of the saccade to the target. The buildup neuron shows a substantial amount of irregular activity in the period well before saccade onset, and exceeds the criterion used by Munoz and Wurtz [1] in the period of time ending 100 ms before saccade onset to be classified as a buildup neuron. The burst neuron shows a more discrete burst of activity that begins about 50 ms before saccade onset, and no activity in the period of time earlier than 100 ms before saccade onset.

Anderson et al. [6], using a delayed-saccade task, showed that SC saccade-related cells form a continuum in the level of their pre-saccadic discharge in a delayed-saccade task. They argued that cells like those shown in Fig. 1 formed the end points of such a continuum. In order to compare their cells sampled over a broader anatomical extent of the SC to those recorded by Munoz and Wurtz [1], they used a similar pre-saccadic level of discharge measure to arbitrarily define buildup cells. The later authors also provided evidence, using a two-dimensional estimation of the spatiotemporal population discharge in the SC, against the hypothesis that buildup cells participated in an organized, rostrally progressing wave of activity that controlled saccade duration during saccades. Instead, they hypothesized that buildup cells participated in saccade control in a similar fashion to burst cells, with population activity that peaked just before saccade onset and declined during saccades. However, neither burst cell or buildup cell discharge could command saccade end because considerable population activity remained at saccade end, particularly in buildup cells. Anderson et al. [6] confirmed the earlier observation [1] that SC cells with larger relative levels of pre-saccadic activity tended to be located more ventrally in the SC and to have open-field response characteristics. A subset of buildup cells have been reported to continue to discharge during the period of time when saccade trajectory was interrupted by electrical ►microstimulation in the rostral SC or the ►omnipause neuron area in the brain stem [7,8]. Since most SC neurons (both buildup and burst neurons) are silenced during the interrupted period, this subset of buildup cells may serve as the functional source that rekindles SC discharge at the active cite in the SC as the saccade resumes and ends on target.

Dorris et al. [9] also found that buildup and burst neurons overlapped in the level of their pre-saccadic buildup of discharge in a delayed saccade task. They proposed that two classes of neurons in the SC could better be distinguished based on the level of discharge present at the end of the gap period in a ►gap-saccade paradigm. Cells with significant prelude activity in the gap period were defined as buildup neurons. As the prelude activity occurred in the gap period before the location of the target for the saccade was known, and was correlated with saccade latency and the occurrence of express saccades, these authors hypothesized that buildup cell activity was related to the function of motor preparation for saccades.

Basso and Wurtz [10] defined a group of SC cells they called buildup neurons that showed significant discharge in the delay period in a memory-guided, delayed-saccade task. In their definition, the criterion level of activity that distinguished buildup neurons was determined by a metric aligned to the end of the delay period, in contrast to most previous measures that were aligned on saccade onset. In additional experiments, they manipulated the number of potential targets present as the animal maintained fixation on a central visual target before signaling goal location by dimming one of the potential targets (a target pre-specification period). Based on their observation that the discharge of buildup cells in the pre-specification period showed an inverse level of activity in relation to the number of potential targets, they hypothesized that buildup cells signaled the establishment of a motor set before target selection was possible.

The rostral region of the SC has neurons that decrease their discharge during saccades rather than show a saccade-related increase. Cells located in this region of the SC that pause for most saccades have been called fixation neurons [11]. Anderson et al. [6] argued that these cells, although they paused for most saccades, showed a burst of activity for very small contralaterally directed saccades. Thus, they hypothesized that fixation cells formed a rostral extension of the caudal buildup cells, with movement fields that became smaller and smaller and ever closer to the fovea for more rostral locations on the SC. Krauzlis et al. [12] recorded from these rostral SC cells under a wider range of experimental conditions, including smooth pursuit movements, small saccades and fixation. They found that these cells displayed increased discharge during small saccades, for small fixation errors and during smooth pursuit, when small errors between the target and the eyes existed. They hypothesized that the discharge of these rostral cells best signified the existence of near foveal position errors between the target and eye position, regardless of the type of eye

movement (saccade or pursuit) or lack of an eye movement (fixation) that might be used to correct the error.

McPeek and Keller [5] found that SC saccade-related cells displayed activity that was consistent with a role in target selection in a reaction time, popout visual search task. They found no difference in the behavior of buildup neurons and burst neurons in this task. They identified buildup cells in a manner similar to that used by Basso and Wurtz [10]. McPeek et al. [13] also found, in a reaction time, popout visual search task, that the pre-saccadic discharge of SC cells located at the collicular image location of visual field distractors was correlated with the amount of curvature present in saccades. They found no difference in the behavior of buildup or burst neurons in their results. Buildup cells were identified in a manner similar to that used by Basso and Wurtz [10].

In conclusion, a wide ranging succession of experiments have consistently identified SC neurons called buildup or prelude neurons that show considerable amounts of low level, pre-saccade discharge that can lead saccade onset by 100 ms or more. It has not been conclusively established if the cells with buildup discharge form a discrete subset of SC saccade-related neurons or whether they are better described as one end of a continuum of cells with respect to pre-saccadic discharge behavior. The method of Basso and Wurtz [10], which defines cells as buildup cells based on significant delay-period discharge relative to resting discharge, suggests a subset of SC cells may be distinguishable statistically. Cells that display higher amounts of pre-saccadic discharge also tend to be located more ventrally in the SC and have larger movement fields than cells with less pre-saccadic discharge. In particular, the outer edge of the movement field of many of these buildup cells may extend beyond the limit of the oculomotor range. It is also not clear if buildup cells, as discriminated by the Basso and Wurtz [10] criterion, have a separate functional role in the saccadic system. Separate roles in motor set, target selection or motor preparation have been suggested as the functional role of buildup neurons. Reaction time tasks tend to show no difference in the functional role of buildup and burst cells.

Higher Order Structures

Buildup neurons are found in the intermediate and deep layers of the superior colliculus. They form part of the descending oculomotor saccadic system.

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SC – Interlayer Neurons

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Definition

Neurons of the superficial SC layers *strata griseum superficiale* and *opticum* which project to the deeper SC layers.

Characteristics

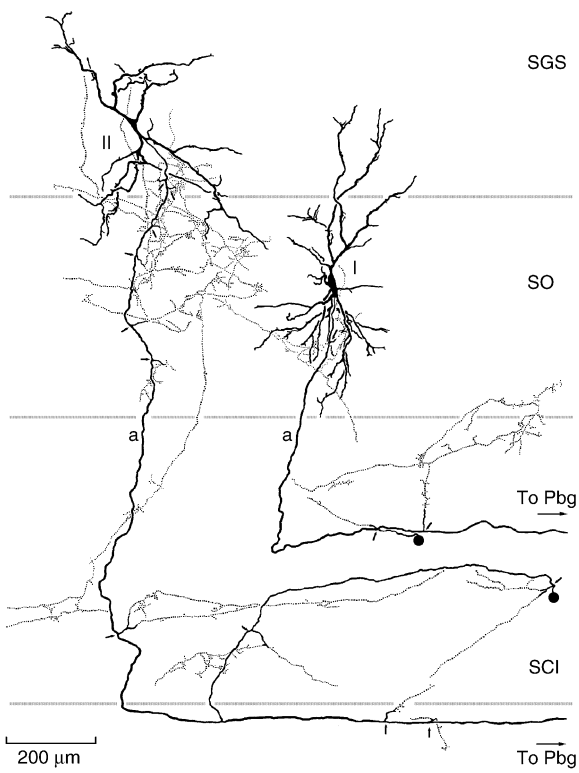
Higher Order Structure

Interlayer neurons are crucial components of the sensorimotor interface implemented inside the superior colliculus.

S

Parts of the Structure

In primates, the projection from the superficial to the deeper SC layers largely originates from a particular class of neurons, designated L [1,2]. Fig. 1. provides two typical examples and illustrates the range of their morphological characteristics. Typical of such cells is the fact that one of them is located in the superficial gray layer (SGS) and the other in the stratum opticum (SO). Also typical of such cells is their somatodendritic morphology, which can be characterized as narrow field vertical in the case of cell I and wide field vertical in the case of cell II. Finally, typical of L cells is the fact that one of their axonal branches projects to the parabigeminal nucleus and even beyond it, presumably to the dorsolateral pontine gray. Fig. 1. also illustrates the considerable number of collaterals arising from the axons of L neurons. Some of them deploy terminal fields in the neighborhood of the soma they originate from in the SGS and SO, while others deploy terminal fields in the intermediate gray layer (SGI).



SC – Interlayer Neurons. Figure 1 Complete camera lucida reconstruction of the dendritic (*solid*) and intratectal axonal termination patterns (*dotted*) of two primate L neurons in the frontal plane (modified from [2], with permission). The solid line indicates the surface of the superior colliculus and the stippled lines indicate borders between its layers. Small arrows point to the origin of intrinsic collaterals. Solid circles indicate the point where major axonal branches assume rostral trajectory. Abbreviations: *Pbg*, parabigeminal nucleus; *SGI*, stratum griseum intermediale; *SGS*, stratum griseum superficiale; *SO*, stratum opticum.

The origin of superficial to deeper collicular projections from cells displaying the somatodendritic features of L neurons (i.e. narrow and wide-field vertical cells) has been corroborated in other mammalian species. Narrow field vertical neurons of the SGS and SO of the rabbit were known to Cajal who was able to follow their axons to their bifurcation in the deeper tectal layers (Fig. 119 of [3]), but was unable to ascertain if they deployed any boutons. Examples of narrow and wide field vertical cells of the SGS and SO and their extensive axonal arborizations in the SGI have been documented in the hamster [4,5] and the rat [6]. However, L neurons are not the only ones to relay information from the superficial to the deeper SC layers. In both the monkey and the cat, the axons of tectotectal neurons of the SO (T neurons) also issue collaterals ramifying in the deeper tectal layers [7,2]. Additionally, axons of upper SGS neurons emit collaterals distributing terminals in the SGS, the SO, and the SGI in the neonate cat [8]. Unlike those originating from L or T neurons, the fairly long dendritic arbors of the feline neurons were seen to originate only from the dorsal pole of the soma and to branch profusely towards the surface of the SC. Axons of wide and narrow field vertical cells of the SGS and the SO, projecting to the nucleus lateralis posterior, have been also shown to deploy terminal fields in the deeper tectal layers of the hamster [9]. The axons of marginal, stellate, horizontal and unclassified cells of the superficial SC layers of this species have also been shown to deploy terminal fields in the deeper SC layers [5].

Function of the Structure

In the rhesus monkey, the information carried from the superficial to the deeper SC layers can be surmised from the response properties of tectoparabigeminal cells; often these are directionally selective and respond with sustained discharges to stimuli crossing the center of their receptive field [10]. More varied information is conveyed from the superficial to the deeper SC layers in the hamster: the cells it originates from can respond to stationary flashed stimuli or not, they can be directionally selective or not and they can be sensitive to stimuli moving at high or low speeds [5]. Its importance is demonstrated by the fact that the visual responses of almost 90% of deeper SC neurons are reduced or abolished after injection of $CoCl_2$, which blocks synaptic transmission near the injection site in the superficial SC layers of the hamster [11]. The pattern of their projections to the deeper SC layers can have

important implications for the therein represented map of visual space. For example, in the hamster, visual receptive fields of deeper SC layer neurons are shifted laterally together, with the lateral shift of the projection from the superficial to the deeper tectal layers relative to projection lines normal to the SC surface [12].

Activation of the superficial layers (with brief electrical pulses) suffices to evoke excitatory postsynaptic potentials (EPSPs) in neurons of the deeper layers of frontally cut slices of the SC of young (8–28 old) tree shrews; their minimal latencies are monosynaptic but they can have multiple peaks and their duration, which can outlast the duration of the stimuli by 100-fold or more, is not related to the duration or the intensity of the stimulus [13]. Work in slices has been crucial in elucidating their pharmacology. Evoked EPSPs are glutamatergic [6,14,15] and are strongly enhanced when the target neurons are depolarized (either through activation of nicotinic ACh receptors or blockade of $GABA_A$ mediated inhibition).

The long bursts evoked in deeper SC neurons in response to electrical stimulation of the superficial SC, could be due to the reverberatory engagement of groups of deeper SC neurons mutually activated through their recurrent collaterals (described in the entry devoted to ►SC – tectal long-lead burst neurons). They could also be due to the reverberatory engagement of groups of superficial SC neurons contacted by the recurrent collaterals of their neighbors, which may or may not project directly to the deeper tectal layers. The density of the terminal fields deployed by axons of superficial SC neurons in the vicinity of the some they originate from can be appreciated from the examples shown in Fig. 1. Recurrent networks of similar complexity have been documented in several other mammalian species, i.e. cat [8,7], hamster [4,5], monkey [1,2] and the rat [6]. It is, therefore, hardly surprising that some of the deeper SC projecting superficial SC cells display similar long bursts of discharge in response to electrical stimulation of the superficial SC [14]. The multi-step projection of the superficial tectal layers to the deeper through several synapses may be the dominant path in some species. For example, small injections of biocytin in the SGS of the tree shrew (*Tupaia belangeri*) demonstrated the existence of a strong SGS projection to the SO, but not to the deeper layers [16].

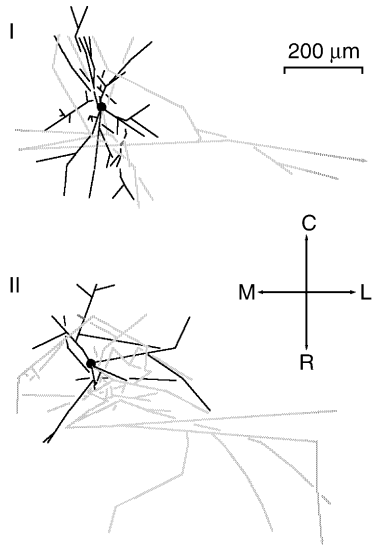
Higher Order Function

Relatively direct relay of visual signals from the superficial to the deeper SC is implicit in the ►foveation hypothesis proposed by Schiller and Koerner [17] (see the entry devoted to the foveation hypothesis for a discussion of this, at one time dominant, account of information flow through the SC). Despite early efforts to determine its existence [18], the projection from the superficial to the deeper SC remained controversial until the mid-1980s. In a seminal review written in 1984, Chalupa [19] ranked this at the top of several questions that remained to be answered regarding the physiology of the SC. Soon after this review appeared, conclusive evidence of its existence began to appear, much in the manner that he had envisioned, i.e. with use of the intracellular HRP technique. This was accomplished first in the neonate [8] and adult [7] cat, and then in quick succession the adult hamster [4,5] and monkey [1,2]. Bulk tracer injections of an anterograde tracer generally thought not to be taken up and transported over significant distances by fibers of passage (*Phaseolus vulgaris* Leucoagglutinin, in short PHAL) were later employed to show that it exists on a larger scale in the hamster [12], and cat [20]. In ferrets, there is morphological evidence to suggest that its targets in the deeper tectal layers include cells of origin of the predorsal bundle [15].

The entry devoted to the foveation hypothesis also includes a summary of the reasons to doubt that transmission of visual information from the superficial to the deeper SC layers always suffices to accurately specify the metrics of saccades towards visual targets. Instead, relatively direct relay of visual signals from the superficial to the deeper SC could underlie the short latency of "express" saccades [2,21], as described in the entry SC-sensorimotor integration. Consistent with this notion, and the acetylcholinergic modulation of the efficacy of signal transmission along this route, injection of nicotine in the SC of the monkey increases the frequency of express saccades [22].

Quantitative Measure for this Structure

About 40% of the neurons in the superficial SC have axons that deploy terminal fields in the deeper tectal layers [5]. Of the cell classes that participate in this projection, it is the primate L neurons whose appearance has been the object of detailed quantitative analysis [2]. Besides providing information about the range of values obtained by several morphological features (e.g. 3-D orientation of the dendritic tree, complexity of its branching pattern, etc.) this analysis allowed the formulation of canonical discriminant functions, which can objectively differentiate L neurons from other classes of SC cells. Moreover, given the manner in which visual space is represented in the superficial SC (along the mediolateral and rostrocaudal extent of the nucleus), the location and spatial distribution of the somatodendritic processes of L neurons on horizontal maps of the SC must have important implications for the size of their receptive fields, and thus the graininess with which they can represent the visible world. Examples of such horizontal rotations of camera lucida reconstructions of primate L neurons are shown in Fig. 2. The same figure also



SC – Interlayer Neurons. Figure 2 Reconstruction of the primate L neurons of Fig. 1 in the horizontal plane (modified from [2], with permission). Stippled lines indicate the neurons' axonal systems.

illustrates the region occupied by their axonal terminations in the deeper layers of the SC. Consistent with their columnar arrangement, the fairly large number of *boutons* they deploy (sometimes more than 3,000) is largely confined to a cylinder that measures somewhat less than 1 mm in diameter, underlies the territory occupied by the dendrites of the same neurons, and is oriented normally to the surface of the SC.

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SC – Local Feedback

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Synonyms

Efference copy; Corollary discharge feedback

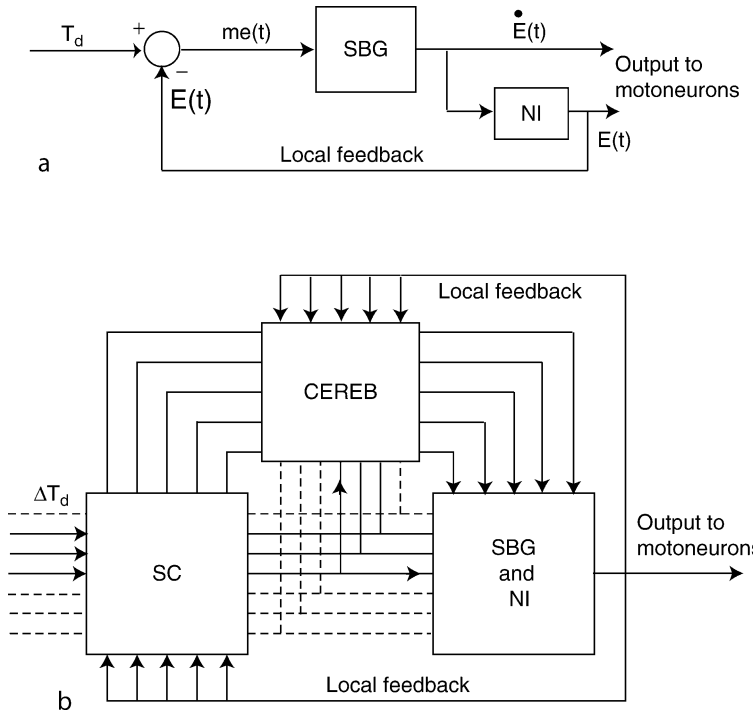
Definitions

►Saccades are rapid eye movements that normally are very accurate. Their accuracy under varying conditions suggests that this class of movements is controlled by feedback mechanisms in contrast to a preprogrammed control. However, feedback of afferent visual information about the progression of the movement that could be used to control and adjust saccade trajectory in flight is not possible, due to the short temporal duration of saccades and the long latencies required to process visual input. Following theoretical ideas derived from the study of other movement control systems [1], Robinson [1] proposed that saccades were controlled by feedback information derived from the ►efferent motor commands. Such internal or local signals, as opposed to afferent feedback from the visual system, could continuously encode the current eye position during saccades with only minimal delay (►delayed saccade), and thus, play a role in controlling their accuracy.

Description of the Theory

In Robinson's theory [3], a copy of the efferent saccadic motor command was integrated to produce an eye position signal. This signal was directed centrally (the local feedback signal) and was compared to a neural representation of the goal or target of the saccade (Fig. 1). The difference between the local feedback signal, which represented current eye position during the saccade, and the desired goal was a dynamic motor error signal that in turn continuously updated the motor command until the error signal dropped to zero and the eyes arrived on target. Since the local feedback signal was derived from neural signals very close (in a synaptic sense) to the motor outflow, delays (in the feedback loop could be very short and performance, in terms of terminal accuracy, was optimized [2]. As evidence for the existence of a local feedback loop in the saccadic system, van Gisbergen et al. [2] cited the results of perturbation experiments in which the normal stereotyped trajectories of saccades were halted in mid-flight by electrical ►microstimulation of the omnipause neuron region (►omnipause neuron area) in the brainstem. Such interrupted saccades resumed their trajectory and ended on target [3,4], and thus, were compensated for the trajectory perturbation. Robinson and his colleagues [2] hypothesized that the ►comparator that generated the dynamic motor error signal was located at the level of the ►saccadic burst generator in the brainstem, and further that the eye position local feedback signal used to close the feedback loop was generated by a ►neural integrator located in the brainstem close to the saccadic burst generator.

The concept of saccade control by local feedback remains a central hypothesis in all saccade system models, but the original model of Robinson has undergone considerable debate and modification since its promulgation. Jürgens et al. [5] argued that the desired saccade goal (desired target location) should be specified in retinotopic coordinates, not absolute position in head-centered coordinates as posited in the Robinson model. Implementation of this suggestion requires that the local feedback signal is displacement of eye position during the current saccade. An eye displacement signal could be generated by a separate neural integrator from the integrator that controlled the static, eye-position related discharge of oculomotor neurons. This second integrator would have to be reset after the end of each saccade. Scudder [6] proposed a model that posited that the superior colliculus was the source of the retinotopically coded desired target signal. In his model he integrated the difference between the SC input signal and a local feedback inhibitory signal from the saccadic burst generator that carried an instantaneous eye velocity signal in a group of brainstem neurons called long-lead bursters. Such an arrangement operated in displacement coordinates and avoided the specification of a resetable integrator by the incorporation of the inhibitory eye velocity signal. The output of the integrator in the Scudder model first increased in magnitude in the pre-saccadic period as the SC signal increased, but then declined in magnitude as the saccade progressed and returned to a zero level by saccade end under the influence of the inhibitory (negative sign in the model) eye velocity signal. No physical dynamic motor error signal exists in this model. Figure 1a shows a Robinson type local feedback model which specifically defines the signals discussed above: desired goal position (T_d); local feedback of eye position (E(t)); and dynamic motor error (me(t)). The inclusion of the time variable (t) in some model signals indicates that signal is updated continuously during a saccade. The schematic version shown here provides a lumped representation of the neural operations that are hypothesized to occur when saccades are generated. All the dynamic elements in the models described so far have single-input, single-output signals and well defined variables with exact physical meaning (e.g. motor error). These model elements (e.g. the comparator which computes the difference between the final goal and instantaneous eye position and outputs dynamic motor error) appear at discrete locations in the model topography, and



SC – Local Feedback. Figure 1 Examples of models of saccade control that utilize local feedback to ensure movement accuracy. (a): Lumped model utilizing eye position feedback. A comparator continuously computes the difference between the saccade goal (T_d) and the local feedback signal (E(t)). The difference signal is dynamic motor error (me(t)). Dynamic motor error controls the activity of burst neurons in the saccadic burst generator (SBG) which produce an eye velocity ($\dot{E}(t)$) command signal to ocular motoneurons. The local feedback signal is current eye position that is computed by a neural integrator (NI) that also controls the eye-position related tonic discharge of ocular motoneurons. (b): A distributed model of saccade control. The boxes labeled SC and CEREB represent recurrent neural networks of the superior colliculus and the cerebellum, respectively. The box labeled SBG and NI represents the saccadic burst generator and a neural integrator. The saccade goal (ΔT_d) is represented with a space code by which input lines to the SC are active (shown by solid lines). Dashed lines indicate inactive input lines. Spatiotemporal discharge in SC and CEREB are produced by interconnected feedforward and feedback lines between the two structures and each structure's own pattern of recurrent connections (not shown). Both structures control the activity of the SBG in parallel through spatially weighted input lines. Local feedback is derived from the SBG and NI and may include both eye position and eye velocity signals. Combinations of these latter signals are fed back in a spatially weighted, distributed fashion to all the units in SC and CEREB. Dynamic motor error is represented in the distributed activity of the units in both SC and CEREB. Not all known connections are shown, e.g. CEREB may receive a spatially distributed input of ΔT_d that is separate from that to SC.

hence the term "lumped model" that is used to classify this type of model. The single signal lines should not be confused to represent single neurons, rather they posit the existence of a group of neurons that carry a single physical signal with a temporal rate code.

More recently, several attempts have been made to represent the organization of the saccadic system and the local feedback concept with distributed models of signal processing (see [7] for a review). Biologically realistic models of this system require that at least the source of the desired goal, which originates in structures like the SC and the ►cortical frontal eye fields (FEF), be modeled in a distributed fashion. This is because these higher level sensorimotor structures primarily represent the desired target (saccade goal), with a space code in which a target position is represented by the discharge of a population of cells centered at a specific location in the SC and the FEF. The temporal discharge pattern of the activated population of cells may be the same for very different saccade goals. Only the anatomical location of the activated population changes with target location.

Figure 1b is a schematic model which illustrates that most of the structures involved in the control of saccades are interconnected with multiple distributed feedback loops. Each of the structures shown by box elements: the SC, the cerebellum and the saccadic burst generator (SBG and NI) are themselves dynamic, recurrent neural networks. Saccade-related neurons in the SC and cerebellum display both place and temporal

coding. A local feedback signal still exists, but it may consist of both eye displacement and eye velocity signals, and it is distributed in a weighted fashion to all the spatially distributed neurons in the SC and the cerebellum. There is no single place in the model where a physical signal coding dynamic motor error exists. Instead, error is represented in a distributed fashion as a property of the whole network.

Specific implementations of distributed control have focused on the SC or the cerebellum.

Depending on the symmetry and the parameters used to model the lateral interconnections in either of these two structures, two quite different types of distributed control mechanisms may be generated. In one type of distributed model, eye velocity local feedback drives a moving wave of activity from an originally active site in the SC or the cerebellum [8]. This original locus of activity codes the desired saccade vector. When the spreading activity reaches the rostral pole of the colliculus (in the SC model) or the mirror symmetric location in the opposite cerebellum (in the cerebellar model), the movement ends. The rate of movement of the wave is controlled by the local distributed feedback of eye velocity, so that at any time during the saccade the distance from the wave front to the end-point location in either colliculus or cerebellum spatially codes motor error. In this form of local feedback control, the distributed structure performs a spatial integration of the eye velocity feedback and represents motor error in a distributed spatial location.

In the other type of control scheme, a distributed population of cells in the SC becomes activated by spatially coded visual input and recurrent, excitatory connections among SC cells themselves [9, 10]. In the Arai [10] model, and to a lesser extent in the Bozis and Moschovakis [9] model, feedback of eye velocity and/or eye displacement to the SC drives the discharge of SC cells originally active down at a rate coupled to the progression of the saccade. Additional local feedback to the brainstem SBG or the cerebellum is needed to make either model function in an accurate fashion.

In conclusion, some type of local feedback about the ongoing eye movement during saccades controls saccade trajectory, and hence the accuracy of these rapid movements. The feedback signal may involve instantaneous eye displacement or eye velocity variables or both. Both the superior colliculus and the cerebellum are involved in the control of saccades, and both receive extensive inputs from brainstem structures that carry eye velocity and position signals. Both structures are themselves recurrently connected, distributed dynamic neural networks. Therefore, control by local feedback is certain to involve highly distributed control processes. With present day neuroscience recording techniques it will be difficult to isolate the location of, and the precise mechanisms, underlying local feedback control in this distributed system. Instead, local feedback and the motor error signals generated by local feedback are likely to be distributed properties of the entire network. Modern imaging techniques may be able to advance our knowledge of the mechanisms involved in the distributed control of saccades by local feedback.

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S

SC – Motor Map

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Definition

The term motor map refers to a very general neuroscience concept in which movements with specific

spatial characteristics are represented topographically within a neural structure. The exposition here will be limited to gaze shifts (movements of the head and eyes) directed to targets presented in the visual surround of a subject. With this restriction, the topographical arrangement of movements on the map may be retinotopic or spatial. In a retinotopic motor map, the movements represented on the map are independent of the initial eye position in space, but vary smoothly in amplitude and direction as a function of the location of the target with respect to the fovea (the current line of sight). In a spatially coded motor map, specific locations in space are represented topographically in the neural structure. In this type of motor map, gaze comes to rest after a movement at a fixed location in space regardless of the initial position of gaze. For retinotopically coded motor maps, gaze shifts may be represented as movement vectors directed between the initial gaze position and the position of the target with respect to the fovea. Retinotopic movement vectors remain invariant for any initial position of gaze. In spatially coded maps, the movement is directed from any initial gaze position to an invariant point in the visual surround. Retinotopic motor maps in the SC are considered in detail below, but an example of a spatially coded map in SC in the cat is also described. Neurons in several gaze-related regions of the brain have a preferred movement vector for which they show the most vigorous peri-movement discharge. The level of their discharge declines systematically for movement vectors that are different in direction or amplitude from the preferred vector. Movement vectors are defined by the polar coordinates of movements to point targets in visual space, and therefore, can be alternately described as coordinates in a foveally centered visual space. If the movement-related neurons in a structure are organized in a topographical manner such that nearest neighbors anatomically also have nearest neighbor preferred vectors in the visual field, the structure contains a motor map. That is, neighboring points in the visual field (the movement vectors) are mapped to neighboring points in the motor map. In such motor maps, the amplitude and direction of the preferred movement vector in individual cells changes in a smooth manner as the anatomic locations of the cells being recorded are systematically altered within the neural structure. When the preferred movement vectors are plotted on an anatomical representation of the structure, a vector field emerges on which the preferred vector changes smoothly in direction and amplitude as a function of anatomic location.

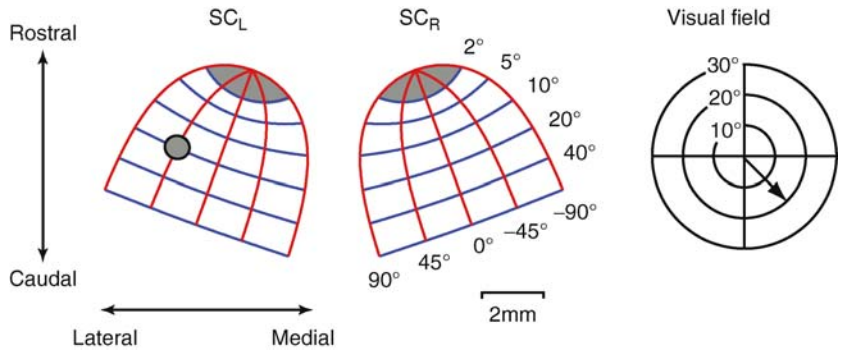
Description of the Theory

A variety of techniques have shown that several structures in the brain contain retinotopically coded motor maps for saccadic eye movements. The two most thoroughly studied structures with ►saccade motor maps are the superior colliculus (SC) and the ►cortical frontal eye fields (FEF). The motor map in the SC will be described in detail in this exposition. The motor map in the SC has been well described because this midbrain structure is approximately flat and is not located in a cortical sulcus, which has allowed recording and electrical ►microstimulation experiments to more precisely characterize the topographical arrangement of saccade vectors in this structure. In initial studies of the motor map in the SC, the animals' heads were mechanically restrained so that only eye and not combined eye and head (gaze) movements were recorded.

The saccadic eye movement fields of neurons in the intermediate and deep layers of the SC were determined by recording their discharge during a temporal window aligned on saccade onset. The activity of cells was determined for a succession of targets presented at different positions in the animal's visual field. In a manner similar to that found for the visual response of cells in visual structures of the brain, these response fields contained a central location (a saccade of a fixed amplitude and direction) which was associated with the most intense saccade-related discharge. The saccade vector with the largest discharge was called the preferred vector. By recording this preferred vector for cells encountered at different locations in the SC, a retinotopically organized map of the contralateral visual field was found [1]. The horizontal meridian of the contralateral field was represented by cells located along a rostral to caudal strip of the middle portion of one colliculus. Cells with preferred movement vectors with small amplitudes were located at rostral locations on this medial strip, and cells with large-amplitude preferred vectors were located caudally. Cells that coded movement vectors with down components were located laterally on the colliculus, and cells with up preferred vectors were located near the midline. The motor map found in the deeper layers of the SC is in spatial register with the sensory map of visual cell responses found in the upper layers of the SC.

A more precise specification of this collicular motor map of preferred saccade vectors was provided by an electrical microstimulation study [2]. In this study, the colliculus was sampled with sufficient density of stimulation sites to show that the motor map was logarithmically warped, so that the space allotted to the representation of small saccades in the rostral SC was greatly magnified with respect to that allotted to large saccades in caudal SC.

Ottes et al. [3] used Robinson's stimulation data [2] to construct a set of equations that converted saccade vectors in visual space into location in collicular space. The motor map defined by their equations is shown in Fig. 1. This motor map in SC space can be quantified by



SC – Motor Map. Figure 1 Motor map for saccadic eye movements in the monkey superior colliculus. The plot on the right shows a representation of the visual field in polar coordinates. An example of one saccade vector is shown by the arrow in this plot. The plot on the left shows the left superior colliculus (SC_L) and the right superior colliculus (SC_R) with inscribed saccadic isoamplitude curves (blue) and isodirectional curves (red). When the saccade vector shown in the visual field plot is made, the greatest activity will appear in the SC_L at the location of the small gray disk. The gray sectors at the most rostral extent of both colliculi show the location of a hypothesized fixation zone.

a logarithmic transformation of amplitude coordinates in visual space along rostral to caudal strips (blue curves in Fig. 1) in SC space, and by an inverse tangent transformation of directional coordinates in visual space along the medial to lateral strips (red curves in Fig. 1) in SC space. Figure 1 shows that the conformal transformation of the coordinates of the saccade vector in visual space into rostrocaudal and mediolateral coordinates of associated activity in collicular space is single valued. That is, each saccade vector in retinotopically centered visual space maps to a unique point in collicular space. One example of the mapping is shown by a vector in visual space (black arrow) which illustrates a desired saccade goal with an amplitude of 20°, and a direction to the right and down at 45°. This goal is represented in the motor map of the left SC at the location of the small gray disk where activity would be the greatest during this particular saccade. However, the motor map in one colliculus represents only contralateral visual space, so the map has discontinuities along its medial and lateral edges that represent saccades with pure up (medial edges) or down (lateral edges) directions. The exact pattern of discharge in the SC for nearly vertical saccades has never been studied quantitatively, but most likely pure vertical saccades are coded by activity in both colliculi.

Another irregularity has been reported to exist in the SC motor map. Instead of the map representing progressively ever smaller saccades as the most rostral region of the colliculus is traversed, a rostral region called the fixation zone is found that codes instead the suppression of saccades [4]. This zone, as defined by these investigators, is shown in Fig. 1 as the gray-shaded sectors at the rostral poles of both colliculi. Gandhi and Keller [5] stimulated this rostral region of the SC, and showed that progressively smaller saccades could be evoked as the anatomic location of the stimulation site was moved further in the rostral direction. The direction of the small saccade evoked by stimulation at a particular rostral site with the animal fixating was first determined. They next stimulated with a short pulse train at the same site at the onset of large visually triggered saccades. If the direction of the small evoked saccade and the large visually guided saccade were the same, only a momentary interruption of the ongoing saccade occurred. This result would be expected if the site in the rostral SC were part of a fixation zone. In contrast, when the direction of the small evoked saccade was orthogonal to the direction of the large visual saccade, they found that, in addition to the slowing of the ongoing saccade, a spatial deviation of the two-dimensional trajectory of the ongoing saccade was produced. The direction of the deviation was consistent with the direction of the small saccade evoked by stimulation in the absence of an ongoing movement. The latter observation would be expected if the rostral region of the SC coded small saccade vectors that were averaged with the trajectory of the ongoing saccade during stimulation. Thus, although the rostral SC appears to play a role in maintaining gaze fixation (through the high level of tonic activity of cells located there and their connections to the omnipause cell region in the brain stem), it also plays a role in coding for smaller and smaller saccade vectors as location on the map is moved more rostral.

It is instructive to compare the single-valued transformation that characterizes the motor map in the SC with the motor map that exists in the FEF, in which the mapping from visual space to FEF space is not unique [6]. The precise form of this FEF map, which exists in the anterior bank of the arcuate sulcus, has not been quantified as well as that in the SC, but larger

amplitude saccades are represented dorsomedially and smaller saccades ventrolaterally. The representation of saccade direction changes systematically on radial penetrations down the anterior bank, but a given direction in visual space is often represented at multiple locations along the penetration.

Recently, movement mapping studies have been repeated in the SC of the monkey with its head unrestrained so that the possible representation of both head and eye movements could be ascertained. Both single-neuron recording studies [7] and microstimulation studies have demonstrated that the retinotopically organized motor map in the SC codes gaze (the sum of eye and head motion) instead of eye saccades. Based on their data from the head-unrestrained monkey, Freedman and his colleagues have suggested that the saccadic eye movement motor map shown in Fig. 1, which was obtained from recording and stimulation data in head-fixed animals, is badly distorted.

A motor map also exists in the SC of the cat as determined by electrical microstimulation experiments [8]. These investigators stimulated the deeper layers of the SC in the head-restrained cat, and reported that a map similar to that found in the monkey existed in the rostral half of the SC. Small saccades were presented rostrally and larger movement caudally, while saccades with a downward component were represented laterally and those with an up component were found medially. However, in contrast to the map found in the monkey, the map in the posterior half of the cat SC appeared to have a goal-directed (spatially coded) organization. Saccades evoked at a given site in this portion of the SC invariably ended at a fixed orientation in space, regardless of the initial position of the eyes at the start of the movement. Thus, the evoked saccade vector was highly dependent on the initial position of the eyes just before the saccade was initiated. The limited oculomotor range of the cat made the differentiation between goal-directed behavior and saturation effects near the limits of the oculomotor range difficult to make. Roucoux and Crommelinck [8] repeated the electrical stimulation study in the SC of the head-unrestrained cat and reported that a topologically organized gaze motor map existed throughout the structure. Small, eye only saccades were evoked from the rostral SC, while large gaze shifts that were composed of both eye and head movements were evoked from the caudal SC. The apparent goal-directed map found previously in the cat SC was apparently an artifact produced by restraining the head. A more recent study suggests that the rostral most portion of the cat SC contains a fixation zone [9] which codes for the suppression of saccades rather than smaller and smaller gaze vectors. Additional studies are required to check this suggestion against the conflicting results found in the monkey [5].

The movement fields of SC neurons can be quite large, i.e. these neurons discharge with the greatest intensity for a particular saccade vector, but also display significant activity over an extended range of neighboring saccade vectors. The result of this behavior in single cells is that a large population of cells in the SC will be active for any saccade. The location of this population of active cells shifts within the SC as a function of saccade vector [3,10]. The locus of population activity on the SC is an alternative way to describe the motor map for saccadic eye movements in the SC. Anderson et al. [10] estimated the two-dimensional loci of activity in the SC for a variety of saccades made to an extended region in contralateral visual space. The spatial extent of the population activity involved nearly 50% of the contralateral colliculus for any saccade. The spatial extent of the population activity was rather invariant with saccade size or direction, and the center of mass of this activity fit well with the motor map for saccades shown in Fig. 1, which was based on electrical microstimulation studies [2].

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SC – Place Code

Definition

A theoretical term used to refer to the fact that the SC specifies the metrics of saccades in terms of the anteroposterior and mediolateral location of the SC area activated when the nucleus is projected onto a horizontal plane.

►Eye Movements Field

SC – Saccade Related Burst Neurons

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Definition

►Saccade related burst neurons (SRBNs) of the ►superior colliculus (SC) are characterized by a high frequency burst that begins about 20 ms before ►saccades of appropriate amplitude and direction. In addition to the burst, some SRBNs have low frequency prelude activity preceding the burst. Although the onset of the burst is tightly coupled to the onset of the upcoming saccade (see below), the duration of the prelude activity varies from trial to trial and its onset is neither tightly coupled to the onset of the saccade nor to the onset of the target [1].

Characteristics

Higher Order Structures

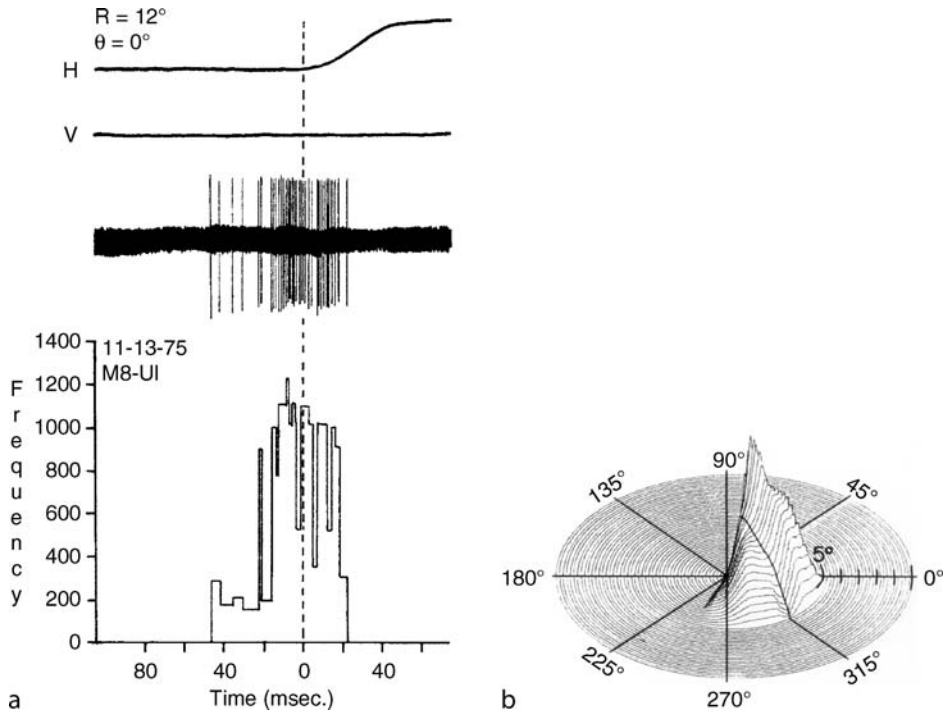
SRBNs are located in the deeper layers of SC and each of them has a movement field (each SRBN discharges optimally before saccades of a specific amplitude and direction, see below). They are organized topographically according to their movement fields. Neurons discharging before small saccades are found in the anterior part of SC, while those firing before large saccades are found in the posterior part of SC. Cells discharging before saccades with a downward component are located laterally in SC and those firing before saccades with an upward component are located medially [1]. In general, the distribution pattern of SRBNs movement fields in SC corresponds to the motor map obtained by microstimulation studies [2].

Parts of This Structure

The deeper layers of SC receive inputs from cortical and subcortical regions serving both sensory and motor functions. For example, the frontal eye fields (FEF), the posterior parietal cortex and inferior colliculus project extensively to this part of SC. These signals are processed and integrated into motor commands here and outputted downstream for the control of orienting behavior of the animal. Converging lines of evidence indicate that the axons of SRBNs are an important component of SC efferent pathway. Keller [3] reported that 10 out of 10 SRBNs recorded in SC could be antidromically activated by stimulation of the ►paramedian pontine reticular formation (PPRF) and the area that contains ►omnipause neurons (OPNs). Only 1 of 12 non-burst SC neurons, which displayed saccade related activity but lacked the high frequency burst, was activated. In another experiment, Moschovakis et al. [4] recorded from the SC of squirrel monkeys making spontaneous eye movements and grouped the recorded neurons into different functional classes. One class, named vectorial long-lead burst neurons, has properties that are very similar to those of the SRBNs. Those vectorial long-lead burst neurons have a motor field, display very little spontaneous activity and burst intensively before saccades made into their motor field. Like SRBNs, the burst preceded saccade onset by about 20 ms. The axons were filled with HRP after the recording, permitting their morphological identification. In addition to projecting to the contralateral SC, axons of those vectorial long-lead burst neurons bifurcate in the midbrain. One branch crosses the midline and joins the predorsal bundle, which terminates in, among other targets, PPRF, the horizontal burst generator. There is evidence indicating that these axons of the vectorial long-lead burst neurons actually make synaptic connections with neurons in PPRF [5]. The other branch joins the ventral ascending efferent bundle (AV). The vertical burst generator, the rostral interstitial nucleus of the median longitudinal fasciculus (riMLF), is one of the targets of the AV pathway [6].

Functions of This Structure

As mentioned above, SRBNs have movement fields. The SRBN shown in Fig. 1 is an example. This cell discharges before a range of saccades (amplitude < 5°) aimed to the right and down region in the visual field. As the positions of the saccadic end points in the movement field varies, a systematic change of the discharge rate and duration can be observed. Saccades directed to the center of the field are preceded by



SC – Saccade Related Burst Neurons. Figure 1 (a) Discharge pattern of a typical SC saccade related burst neuron (SRBN). Top graph: horizontal eye position (H) and vertical eye position (V) as a function of time. Middle graph: Action potentials of the cell. Bottom graph: instantaneous firing rate as a function of time. Vertical dotted line: the onset of the saccade. (b) A 3D plot of the movement field of this cell. The optimal amplitude is 1 degree at an angle of 320 degree (Courtesy of Sparks and Jay, 1986).

more vigorous discharges with longer durations, while saccades deviating from the optimal direction and amplitude are accompanied by less vigorous discharges with shorter durations. In addition to this spatial gradient, the movement field is also characterized by a temporal gradient. The time between the onset of the burst and the onset of the saccade is longer for those movements to the center of the field than those to the periphery. The size of SRBNs' movement fields tends to increase with eccentricity. That is, neurons that discharge before small saccades have small and sharply defined movement fields, while those firing before large saccades have large and coarsely tuned fields [1,7].

SRBNs discharge before saccades of specific directions and amplitudes regardless of initial eye position. Therefore, the collicular command is not to move the eye to a particular position in the orbit, but to displace the eye in a specific direction and amplitude [1]. Unlike the motor neurons and excitatory burst neurons (EBNs) in the brain stem, SRBNs do not code the direction and amplitude of an upcoming saccade by firing rate. Identical bursts may occur in association with many saccades of different directions and amplitudes. Moreover, there is no distinguishable difference among the discharges of different SRBNs preferring different saccade sizes [7]. Thus, it is the location of the activated SRBNs in the SC motor map that determines saccade amplitude and direction. In other words, the direction and amplitude of a saccade are spatially coded in SC.

There is strong evidence indicating that the high frequency burst of SRBNs plays an important role in saccade initiation. First, the onset of the burst is tightly correlated to the saccade onset ($r = 0.99$). Second, when the experimental parameters are setup in such a way that sometimes the visual target elicits a saccade and sometimes does not, the occurrence of the burst of a SRBN is almost perfectly correlated with the occurrence of the saccade. Although SRBNs sometimes discharge a few spikes in the absence of a saccade, this kind of activity is far less vigorous than the least vigorous ones that accompany appropriate saccades [8]. A more recent experiment, in which the monkey was required to cancel an on going visually guided saccade in one third of the trials, also showed that SC neurons

play an important role in the decision process regulating whether a saccade is to be made [9]. In addition to initiating the normal visually guided saccade mentioned in the above two experiments, the burst of SRBNs could also serve as the trigger signal in express saccades (saccades that have very short latency, ranging from 80 to 100 ms). Under the "gap" condition in which express saccades are often observed, the interval between the onset of the visual target and onset of the burst is shortened and, as a result, the saccadic latency is shortened [10].

Higher Order Function

The deeper layers of SC in which the SRBNs are located are an important component in a circuit transforming signals from different sensory and motor areas into motor commands that initiate and guide the ►orienting responses of the eyes, head and pinnae.

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SC – Sensorimotor Integration

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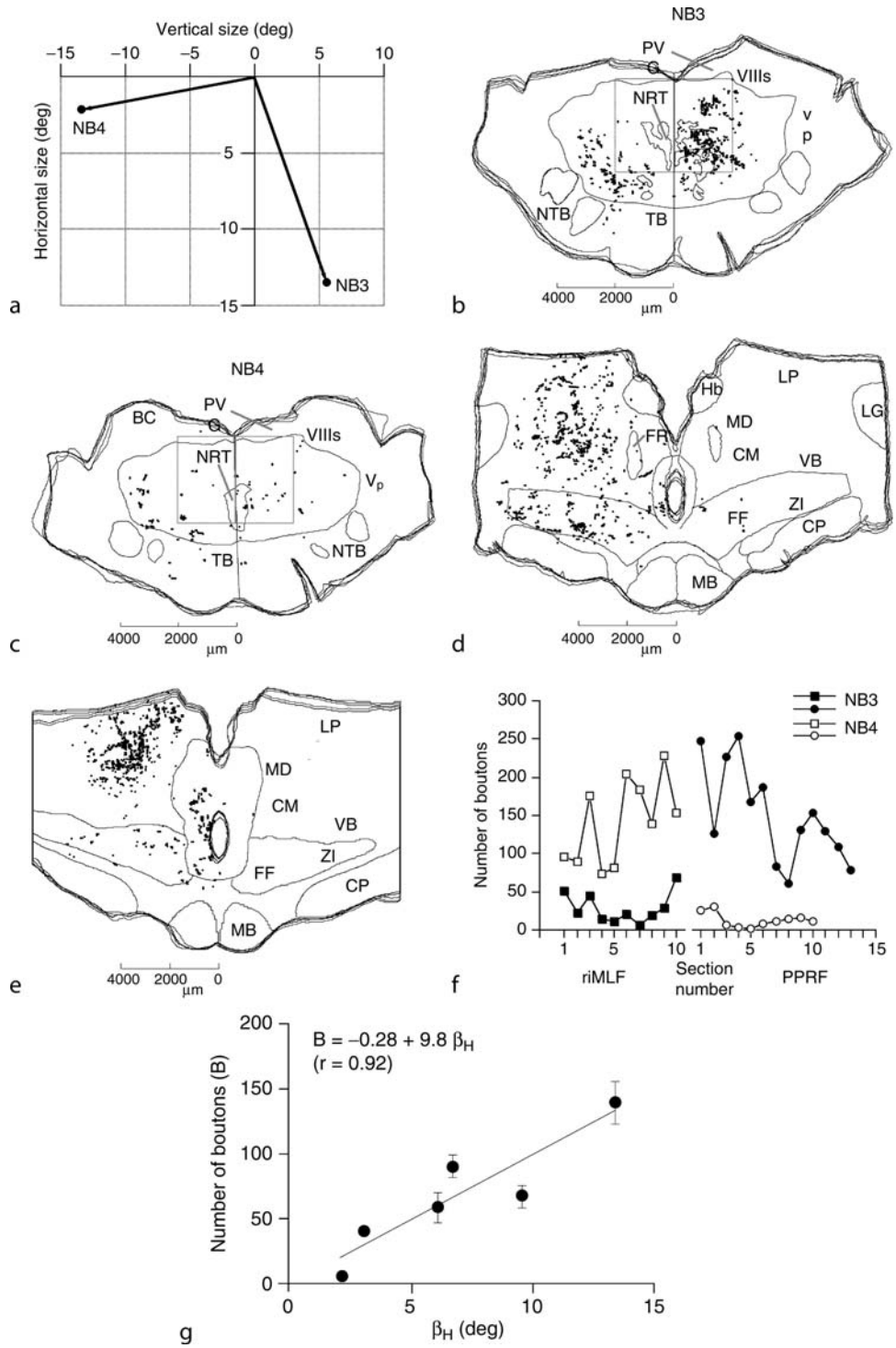
Definition

The sequence of neural processes that enables the SC to use information about world events in order to issue motor commands guiding orienting responses to these events.

Characteristics

Description of the Theory

The front stage of the sensorimotor interface contained in the SC devotes neural space to represent the location of sensory stimuli. The neural mechanisms employed to this end are considered in some length in the entry ►SC – sensory maps. Since the SC uses different frames of reference to encode the spatial location of stimuli of different modalities, the sensorimotor interface must use coordinate transformations to bring them in register to one another, as well as to the frame of reference used to encode movement metrics. Further, because sensory information reaches the SC from a multitude of stimuli while orienting movements can be executed one at a time, the sensorimotor interface must also include a mechanism to decide when to launch a movement and which of several targets to favor with it. Once the decision to launch the appropriate movement is reached, a command that specifies its amplitude and direction is issued in the form of presaccadic bursts of SC neuron discharges. As the SC uses a place code, and premotoneuronal interneurons use a time code to specify these parameters, the movement related commands must be decomposed and spatio-temporally transformed. The coordinate transformations used in the SC are briefly considered in the entry devoted to the ►foveation hypothesis, while the representation of movement metrics is considered in some length in the entries ►SC – motor map, ►SC – role in eye movements, ►SC – saccade related burst neurons (SRBNs) and ►SC – tectal long lead burst neurons (TLLBs). The present entry is devoted to the following issues: (i) Transmission of sensory information to movement related cells of the SC; (ii) Decision processes; (iii) Burst generation; and (iv) Vector decomposition and spatiotemporal transformation.



SC – Sensorimotor Integration. Figure 1 (a) 2-D plot of the amplitude and direction of saccade vectors (abscissa: horizontal, ordinate: vertical) evoked from two SC sites in cats NB3 and NB4. Consistent with the motor map of the SC, the horizontal contraversive component was big (13.5 deg) in the case of NB3 and small (2.1 deg) in the case of NB4. Similarly, a conspicuous difference in the size and direction of the vertical components (5.6 deg upward in NB3 and 13.4 deg downward in NB4) agreed well with the location of the stimulus sites on the motor map. (b, c) Distribution of *boutons* in five consecutive sections, at the level of the rostral border of the nucleus reticularis pontis caudalis (NRPc), after biocytin injections in areas of the feline SC encoding saccades with a big horizontal and a small vertical component (NB3, b), or saccades with a small horizontal and a big vertical component (NB4, c). (d, e) Distribution of

Transmission of Sensory Information to Movement Related Cells

The classes of cells that convey visual information from the superficial to the deeper SC layers and the role they play in generating bursts of discharge in deeper SC layer neurons are examined in the entry devoted to ►SC – interlayer neurons. The direct superficial to deeper visual information transfer is supplemented by a massive cortical projection of visual information to the deeper SC. Information of other modalities (e.g. auditory or somatosensory) is similarly funneled to the deeper SC layers, as described in the entry SC – sensory maps. The intensity of SC neuron discharge depends on the properties of the stimuli employed. For example, moving stimuli are particularly effective in driving SC cells [1]. Moreover, multimodal stimuli are more efficient in driving SC neurons than unimodal ones; the vast majority (84%) of deeper SC cells respond much more strongly to stimuli involving two or more sensory modalities than would be expected on the basis of their responses to unimodal stimuli [2]. It also depends on the context in which such discharges are emitted. For example, visual responses of primate superficial SC cells can be enhanced if stimuli in their receptive fields are used as targets for saccades [3], and the same is true of the visual responses of deeper SC movement related cells for rewarded movements [4].

The biological means that the SC employs to encode the location of visual targets and match it to the metrics of the saccade related motor commands it sends to its targets are examined in the entry devoted to the foveation hypothesis. As discussed there, use of raw sense data to represent stimulus location does not always suffice to accurately specify the discharge of presaccadic SC neurons, and therefore the metrics of ensuing saccades. Instead, stimulus location must sometimes be reevaluated through the use of coordinate transformations; subsumed under the heading "vector subtraction hypothesis" they are also described in the entry foveation hypothesis, while neurons crucially relevant for its implementation are described in the entries devoted to the ►reticulotectal long-lead burst neurons and the ►SC – quasivisual neurons.

Decision Processes

There is considerable evidence to suggest that the SC participates in processes which determine whether a saccade needs to be produced and if so when. Saccade reaction times offer a convenient means to assess the neural mechanisms leading to such a decision, in particular since their range can be readily influenced by experimental manipulation. For example, the latency of ►express saccades (often evoked with the use of the gap paradigm, in particular in trained subjects) is shorter than that of regular saccades [5]. Conversely, saccades to auditory [6] and somatosensory targets [7] and saccades away from targets (antisaccades [8]) take longer to initiate. Several parameters of the discharge of deeper SC neurons reflect these reaction time differences. For example, the number of deeper SC layer neurons bursting for saccades is larger [9], and the intensity of their discharge is greater [10], when saccade targets are visible rather than when they are not (such as in the case of antisaccades or spontaneous saccades). Also, the bursts of discharge of SC motor cells for longer latency saccades (e.g. to somatosensory targets) are delayed relative to those for saccades to visual targets [11].

It might be argued that the phasic sensory responses reaching the deeper SC layers are automatically translated into executable movement related phasic commands leading to quick decisions and early movements. This is probably not always the case, as indicated by the fact that ►tectoreticulospinal neurons (TRSNs) of the deeper SC of the cat emit short latency bursts of discharges for visual stimuli, yet these bursts do not accompany saccades [12]. Further, the motor responses of primate buildup neurons, which accompany correct anti-saccades of appropriate metrics, are weaker than their sensory responses to visual stimuli into their receptive field which are not followed by saccades (these would be erroneous prosaccades towards the stimulus rather than the correct anti-saccades away

boutons in five consecutive sections at the level of the rostral border of the Fields of Forel (FF) and, more precisely, their medial portion traversed by the retroflex bundle (homologous to the riMLF of the monkey) in the same cases (NB4, d; NB3, e). (f) Number of *boutons* that were recovered in the ipsilateral riMLF of NB3 (*solid squares*) and NB4 (*open squares*), and the contralateral PPRF of NB3 (*solid circles*) and NB4 (*open circles*) in several individual consecutive sections through these nuclei. (g) Plot of the average number of *boutons* deployed in the feline PPRF per 100 fibers per section (B; *ordinate*) from each one of several SC injection sites versus the size of the horizontal component of the characteristic vector (i.e. the saccade vector that would have been evoked had the eyes started from a straight ahead position) of the saccades evoked from the same site (β_H; *abscissa*) after bulk injections of a tracer in collicular microzones of the cat. Error bars indicate the standard error of the mean. The solid line is the linear regression line through the data and obeys the equation displayed. Abbreviations: *Vp*, principal sensory nucleus of the trigeminal nerve; *VIIIs*, superior vestibular nucleus; *BC*, brachium conjuctivum; *CM*, central median nucleus; *CP*, cerebral peduncle; *FF*, fields of Forel; *FR*, fasciculus retroflexus; *Hb*, habenula; *LG*, lateral geniculate nucleus; *LP*, lateral posterior complex; *MB*, mammillary bodies; *MD*, mediodorsal nucleus; *NRT*, nucleus reticularis tegmenti pontis; *NTB*, nucleus of the trapezoid body; *PVG*, periventricular gray; *TB*, trapezoid body; *ZI*, zona incerta.

from the stimulus which are actually executed [10]). Conceivably, the visual responses of omnipause neurons [13] transiently raise the threshold for initiating eye movements and thus bursts exiting the SC shortly after the appearance of salient stimuli are rendered ineffective. The notion that the visual bursts of deeper SC neurons could elicit saccades at least in some circumstances, such as those favoring express saccades (visuo-motor hypothesis [14]), has been explored, and shown to be unlikely in monkeys executing saccades of a particularly wide range of reaction times (engendered by interleaving trials in which target onset preceded -delayed saccade task, coincided with -step task, or followed -gap task, fixation target offset). Most SC cells emit only one burst which is tightly coupled either with the appearance of the target (visual cells) or with the onset of the saccade (movement cells). However, visuo-motor cells of the deeper SC generate two bursts of discharge, an early visual one and a second, motor one. The interval between the two decreased with the latency of the saccades until extremely short latencies were reached, in which case the motor burst fused with the visual one. The tight coupling between the onset of the motor burst and the onset of saccades extended into the express saccade range for both the visuo-motor and the motor cells, while no range of saccade reaction times was found in which visual rather than motor responses were tightly coupled to saccade onset [15].

A large range of reaction times can also be found in experiments employing a two choice discrimination task in which subject decision is declared by making a saccade in one of two directions. In such experiments, the latency of the movement varies almost continuously with task difficulty (a function of the separability of the cues employed to instruct movements in one or the other direction). Of the models proposed to account for the variability of saccade reaction times, diffusion models have been particularly useful in that they capture essential features of both subject performance and of cell discharge. Such models assume that to initiate a saccade, information starts from a baseline and drifts over time until it reaches a boundary [16]; reaction time (as well as the number of correct and erroneous responses) could in principle depend on the baseline, boundary and rate of the drift values. Indeed, the post-target presentation rate of rise of the firing of prelude neurons has been shown to reflect the dynamics of the decision process [16]. Moreover, there is some evidence to suggest that when the discharge of saccade related SC neurons exceeds a certain intensity (threshold), saccades in their movement field must be executed [17]. Finally, the intensity of discharge of prelude neurons, before target presentation (baseline), is influenced by the probability of reward [4] and of a target present in their receptive field [18], increases in the gap period [10], and is inversely correlated with the latency of saccades [18]. It also determines whether a correct or erroneous movement will be executed in the anti-saccade task; high level prestimulus activity of prelude cells located near the SC site where visual stimuli are represented gives rise to reflexive saccades towards them [10]. Apparently, several factors can increase the excitability of deeper SC neurons; whenever this is the case, and depending on the strength and timing of superimposed sensory signals, SC cells can emit motor bursts leading to extremely short latency and maybe even inappropriate movements.

Burst Generation

To some extent, the saccade related bursts of SC neurons are due to movement related signals they receive from the ►frontal and ►supplementary eye fields. However, since saccades can still be executed after lesions of the frontal lobes, the SC must be able to generate presaccadic bursts from signals which need not be either phasic or saccade related. Here, we consider two mechanisms: (i) synaptically modulated non-linear responses of deeper layer SC neurons, and (ii) the recurrent excitatory network deployed by TLLBs.

Under certain circumstances, the synaptic influence of fibers carrying sensory information to the deeper SC layers might evoke intense bursts in their targets. For example, application of the GABAergic antagonist bicuculline can evoke prolonged bursts of action potentials, which ride on top of large amplitude EPSPs produced in deeper SC neurons in response to electrical stimulation of the superficial layers of rat SC slices [19,20]. These are presumably due to NMDA receptor mediated regenerative processes switched on by the depolarization of the deeper SC cells due to the removal of synaptic inhibition. The source of GABA in such preparations is probably local interneurons [21], but the SC of intact animals has several additional ones. The best studied of these is the pars reticulata of the substantia nigra, and is examined in detail in the entry ►Substantia nigra – role in eye movements.

The recurrent plexus of TLLBs is described in the entry devoted to the ►SC – Tectal Long Lead Burst Neurons. The notion that it mediates excitatory synaptic influences between adjacent TLLBs is consistent with the fact that the main axon of such neurons joins the predorsal bundle [22] and the fact that predorsal bundle fibers are glutamatergic [23]. It is also consistent with the fact that brief inward currents superimposed on long-lasting ones can be recorded from SGI neurons in response to the photorelease of caged glutamate [24]. Similar bursting discharges of SGI neurons in rat slices could not be accounted for by the relationship between the firing rate and the intensity of the current injected into the neurons studied. Instead, consistent with the above described network of interacting TLLBs, they could be reproduced (abolished) by NMDA receptor activation (block) [25].

Spatiotemporal Transformation and Vector Decomposition

As with other motor systems, the saccadic one is characterized by a profound transformation of its signals as they pass from higher order supranuclear structures to motoneurons. The "place" code used by the motor SC to specify saccade vectors is described in the entry devoted to ►SC – tectal long lead burst neurons. Its adoption makes eminent sense, as it allows the front end of the saccadic system (the motor SC) to use a code favored by sensory systems. However, because neural circuits interposed between the SC and the extraocular motoneurons use a time code to specify the same parameters (considered in the entries devoted to the ►horizontal and ►vertical medium lead burst neurons), this choice engenders two transformations of the movement related commands exiting the SC. Firstly, the vector of saccadic displacement represented in the SC must be "decomposed" into the vertical and horizontal saccadic components specified by the burst generators. Conceivably, this could be implemented by the Av and PDB branches of the axons of single TLLB neurons (described in the entry ►SC – tectal long lead burst neurons) which target the ipsilateral riMLF (the Av branch) and the contralateral PPRF (the PDB branch), respectively. The differential weighing of the simultaneous projections of single SC sites onto the vertical and horizontal burst generators could provide an anatomical substrate for "vector decomposition". Consistent with this scheme, and as documented in Fig. 1b–f, collicular regions encoding saccades with a big horizontal and a small vertical component project strongly upon the horizontal burst generator and weakly upon the vertical burst generator, while regions encoding saccades with a small horizontal and a big vertical component give rise to the opposite pattern of projections [26].

Following vector decomposition, the spatial code employed by the SC must be further transformed to obtain a matching temporal code at the level of the burst generators. Such a "spatio-temporal" transformation could rely on the graded strength of anatomical projections of distinct SC sites onto the burst generators. Figure 1g illustrates experimental evidence consistent with this scheme [27]. As shown here, the number of *boutons* that tectal efferent fibers deploy within the confines of regions housing the horizontal burst generators (B) increases in proportion to the amplitude of the horizontal component of the saccade vector (β_H) encoded by the collicular sites from which they originate. The relation between the two variables obeys the expression indicated on the figure. Its slope is equal to about ten *boutons* per degree of horizontal eye displacement per 100 fibers per section, while the high correlation coefficient ($r = 0.92$) indicates that about 85% of the variance of the dependent variable (number of *boutons*) can be accounted for by the independent variable (saccade size).

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SC – Sensory Maps

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Definition

A topographic arrangement of visual, somatosensory, and auditory signals can be found in the ►superior colliculus. When the eyes are centered in the orbits, these maps lie approximately in spatial register with each other, and with saccade-related motor maps. When the eyes are not centered in the orbits, however, a map organized in body or head-centered coordinates will provide an inappropriate input to the oculomotor system, which requires that target position be specified in ►motor coordinates (i.e. the change in eye position required to look to the target). Consistent with this view, the spatial alignment of sensory maps in superior colliculus appears to shift with changes in the orientation of the eyes, head, and body.

Characteristics

Higher Order Structures

The superior colliculus is a layered structure in the midbrain, consisting of three cellular layers, alternating with four fibrous layers. Layer II contains the cell bodies of visual neurons, arranged in a topographic map of the contralateral visual hemifield. Multimodal sensory and motor signals are found in the intermediate and deep layers.

Parts of This Structure

Topographic maps have been identified in the superior colliculus for several sensory modalities. Visual, somatosensory, and auditory maps lie approximately in register when the eyes are centered in the orbits.

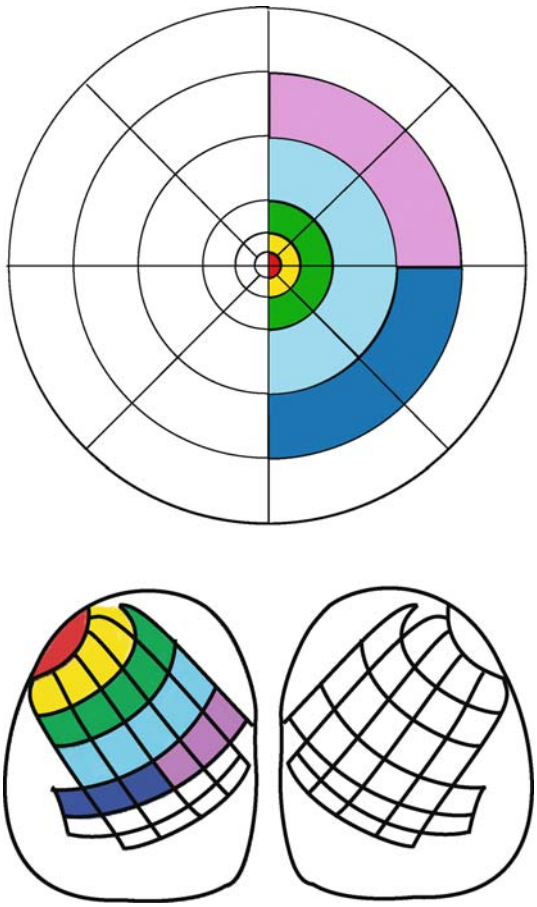
Functions of This Structure

Sensory Maps and Map Alignment

The ease with which we can reach out and grab our morning cup of coffee belies the complexity of the neural processing required to compute the location of the coffee cup in space. Cells in a specific region of the retina will be activated by light reflected from the cup, but there is not a one- to-one correspondence between which region of the retina is activated and the location of the cup in space. The positions of the eyes in the orbits, the position of the head, and the position of the body all affect the region of retinal activation. Thus, the location of a visual target cannot be computed using only signals that reach the brain through the optic nerve: localization requires that visual signals be combined with information about eye, head, and body positions. Localization of somatosensory and auditory stimuli also requires complex neural computations.

The superior colliculus (SC) provides an excellent model system for studying the neural processing involved in spatially-directed action. Signals from several sensory modalities converge in the deeper layers of SC, a region that also contains cells generating commands for orienting movements of the eyes, head, and pinnae. In mammals, many neurons residing in the deep division of SC are responsive to auditory, somatosensory and/or visual stimuli. Each sensory cell has a spatial receptive field and the sensory cells are organized according to the location of their receptive fields, thereby forming topographical sensory maps.

Visually responsive cells are activated by stimuli appearing in the contralateral visual field. Neurons with receptive fields in the upper visual field are located medially; those with receptive fields in the lower visual field are found laterally. Cells with receptive fields near the center of the visual field reside anteriorly; those responsive to peripheral stimuli are located posteriorly (Fig. 1). Tactile receptive fields are also organized topographically in the SC [1,2]. In each colliculus, representation of the contralateral forelimb and head is extensive, whereas only a small part of the colliculus is allocated to representation of the large cutaneous surface area of the trunk and hindlimb. The acoustic receptive fields of collicular neurons are large, but each



SC – Sensory Maps. Figure 1 Top: color coded diagram of visual space. Bottom: schematic diagram of superior colliculus, showing the representation of the contralateral visual hemifield. Colors on the SC map correspond to the colors in the top panel. The area of visual space near the fovea is represented near the rostral end of superior colliculus; peripheral locations are represented caudally. Note that the area of visual space near the fovea is represented by a disproportionately large area of the SC map.

cell has a "best area," defined as the range of stimulus locations which elicit responses greater than 75% of maximum. The best areas of cells vary systematically with cell location, forming a map of auditory space in the SC [3].

Thus, cells responsive to each modality are organized in an anatomical map and in anesthetized or paralyzed preparations; the visual, somatosensory, and auditory maps appear to be aligned. For example, in the paralyzed cat, collicular neurons responding to both auditory and visual stimuli have visual and auditory receptive fields that overlap spatially. For cells responding to auditory but not to visual stimuli, the location of the auditory receptive field is correlated with the spatial location of the receptive fields of nearby visually responsive neurons. Observations such as these led to the assumption that the SC contains a general, modality independent map of the external environment. In such a map, stimuli originating from a particular region of the external world (regardless of sensory modality) would activate a particular subset of multimodal neurons (neurons that respond to visual, auditory, or tactile stimuli). The activation of these sensory neurons, in turn, could initiate ►orienting responses by exciting adjacent cells with movement- related activity organized in a motor map aligned with the multimodal map of sensory space.

But what happens to the alignment of the visual and somatosensory maps in the unanesthetized, freely moving animal when the direction of ►gaze and the position of the limbs in space do not maintain a fixed relationship, or to the alignment of the visual and auditory maps when the positions of the eyes change, with respect to the head? Jay and Sparks [4] noted that collicular neurons with saccade-related activity are organized topographically and it is the location of active neurons within the topographical map of movement fields that specifies the change in eye position required to direct gaze to the target location. They reasoned that the task of sensory systems is to specify the change in eye position required to look to a target, not merely the location of the target in head, body or ►retinal coordinates. Consider, for example, a monkey with the head positioned "straight ahead" but with gaze directed 24° to the left of center. When an auditory stimulus is presented 10° to the right of center, interaural cues are used to localize the acoustic target in ►head coordinates ("target is 10° right"). However, since the eyes are directed 24° left of center, a 34° rightward saccade is required to look to the target, and neurons in caudal regions of the left SC must be activated to produce this movement. If an auditory target is presented in the same location on another occasion with gaze directed 24° to the right of center, cells in the right SC must be activated to produce the 14° leftward saccade required to look to stimulus. Based upon these observations, they hypothesized that the maps of sensory space observed in the deeper layers of the SC were not static, and that the activity of the cells are encoded in motor, rather than sensory, coordinates.

To test this hypothesis, Jay and Sparks [4] plotted the receptive fields of neurons responsive to auditory and visual stimuli while the eye position of trained, alert monkeys was systematically varied. If auditory signals are organized in head coordinates, then in these experiments in which the head is fixed, the discharge of acoustically responsive neurons should be independent of initial fixation position and depend entirely upon the azimuth and elevation of the sound source. However, if auditory signals have been translated into motor coordinates, then the response of collicular

neurons to acoustic stimuli should be sensitive to both the position of the speaker in space and the position of the eyes in the orbits. They found that the auditory receptive fields shifted with changes in eye position and that, in the monkey, the map of auditory space in the deeper layers of the SC is not static. With each change in eye position, the site of neural activity induced by a fixed auditory stimulus shifts to a new location – a location that specifies the metrics of the movement that would direct gaze to the target location. A similar effect of eye position on the responses of collicular neurons to acoustic [5–7] and somatosensory [8] stimuli has been observed by other researchers.

Multimodal Interactions

Many cells in the intermediate layers of SC respond to sensory stimuli of more than one modality. In anesthetized animals, dramatic enhancement and inhibitory effects on the responses of multimodal cells have been reported to occur when combinations of visual, somatic and auditory stimuli are presented to cat [2]. These interaction effects depend upon the spatial and temporal overlap of the multimodal stimuli. Enhancement usually occurs if each stimulus is in the center of its receptive field and if the two stimuli are temporally contiguous. Response depression occurs most commonly when one of the two stimuli is outside or on the fringe of the cell's receptive field, or if there is a large temporal disparity in the onset of the two stimuli [9]. A reasonable hypothesis is that ►multimodal enhancement, assumed to occur when two stimuli from the same region in external space appear simultaneously, facilitates orienting movements to that part of the environment. The physiological studies describing bimodal enhancement were performed in anesthetized animals. Populin and Yin [7] tested for bimodal enhancement in the superior colliculus of behaving cats trained to orient to acoustic, visual, and bimodal stimuli. They failed to observe the large enhanced responses reported in anesthetized animals, even when the time between presentation of the visual and acoustic stimuli was varied systematically and/or the relative intensity of the two stimuli was varied. They did, however, observe prominent depressive effects when the cats were required to fixate a visual target during presentation of an acoustic stimulus. Much remains to be learned about the role of multimodal cells in SC in the initiation and guidance of orienting movements of the eyes, head, and external ears.

Higher Order Function

Although most neuroscientists studying sensory processing view the problem from the perspective of perception, perception is not the only end point of sensory processing. Movements are often initiated by and guided by sensory signals. Studies of the sensory maps in SC have been influenced by the realization that the format of the motor command imposes constraints on the types of sensory processing that must occur. In the case of orienting movements of the eyes, the motor map in the SC is organized in relative coordinates – the signals specify the change in eye position required to look to a target. Thus, input signals that initiate a movement must also specify the location of the target with respect to the current gaze position, not the location of the target in body or head coordinates. According to this view, the sensory maps are dynamic and the receptive fields of collicular neurons shift with relative movements of the eyes, head, and body. A dynamic mapping of sensory space is required because of constraints imposed by the organization of the motor map. It seems likely that other motor systems will require specialized sensory processing to transform sensory signals into the format of the motor commands.

Quantitative Measure for This Structure

Approximately 50% of neurons in the intermediate layers of SC are multisensory. Visual responses in superior colliculus occur at latencies of approximately 70 ms, and auditory responses occur at latencies of 20 ms or less [7]. In anesthetized cats, bimodal enhancement can exceed 300%; bimodal suppression can be nearly a complete suppression (99%) [2]. However, in the awake animal, Populin and Yin [7] reported that the responses to bimodal stimuli approximated, but generally did not exceed, the sum of the responses to the two single modality stimuli.

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SC – Tectal Long-Lead Burst Neurons

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Synonyms

TLLBs

Definition

The best studied saccade related efferent cells of the primate SC. They emit high frequency bursts for all saccades in their ►movement field (of saccade related neurons), including spontaneous ones. Their medium size somata occupy fairly superficial locations in the deeper layers of the SC, and give rise to vertically oriented dendritic fields of average complexity. Finally, their rather delicate axons deploy recurrent collaterals and participate in several tectofugal fiber bundles reaching a multitude of brainstem oculomotor related nuclei. Due to their pattern of discharge, TLLBs can be thought to correspond to the saccade related burst neurons (SRBNs), a subclass of SC movement cells described in detail by Sparks and his colleagues [1]. Also, due to their rather short lasting bursts, TLLBs cannot correspond to the ►SRBN type II neurons also first described by Sparks and his colleagues [2] and more recently by Wurtz and his colleagues [3] (the build-up neurons of these authors). The same is true for visually triggered movement cells, and ►fixation neurons.

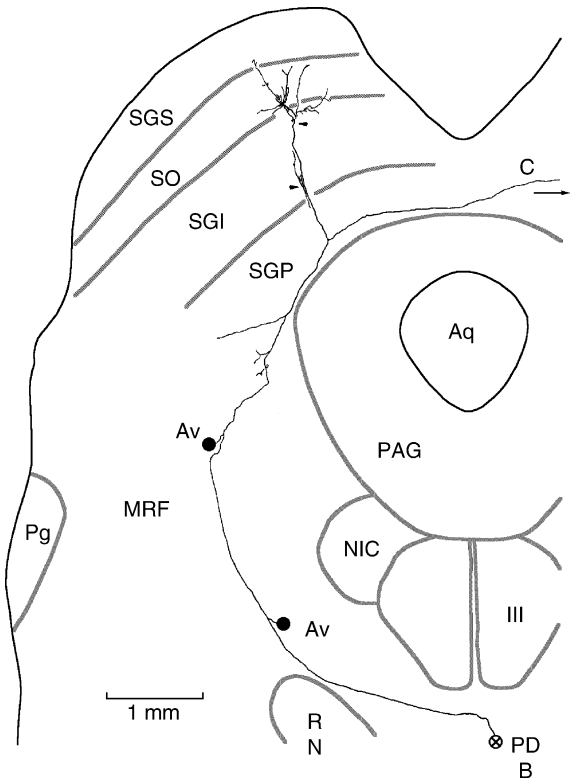
Characteristics

Higher Order Structure

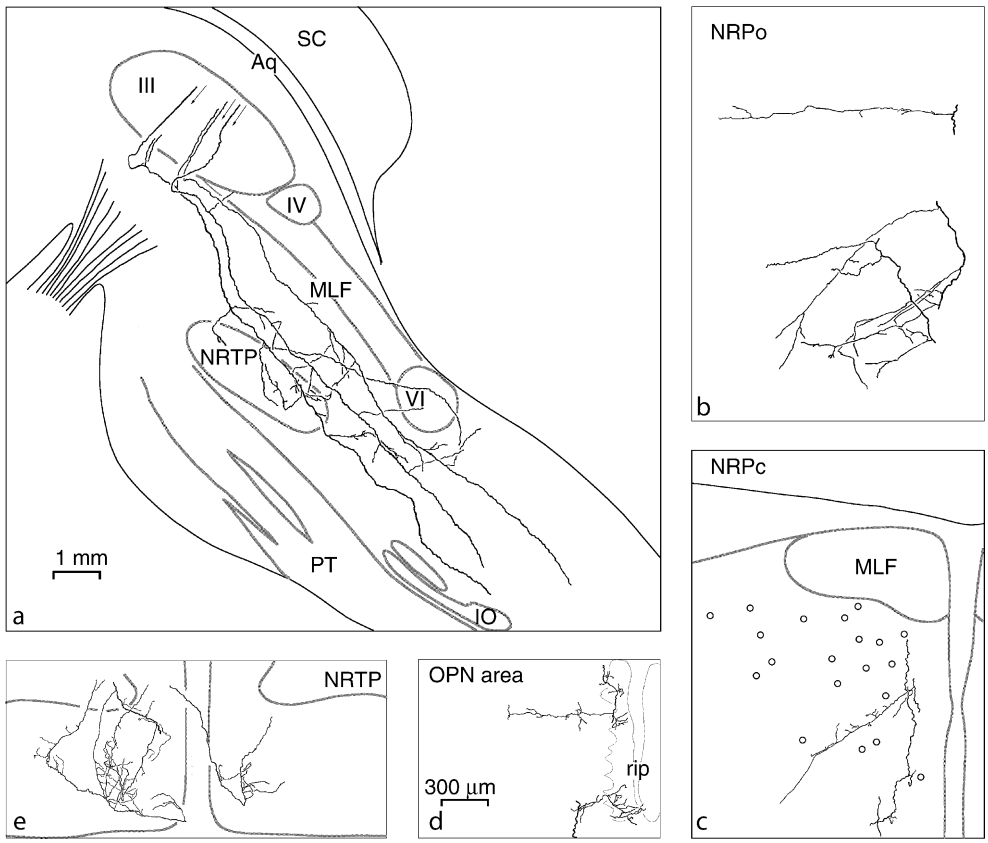
The TLLBs are crucial components of the metric computer in the superior colliculus, the output of which they convey to the burst generators.

Parts of this Structure

The morphological features of TLLBs were elucidated after recording their discharges intraaxonally in alert behaving monkeys and then injecting them with HRP [4]. A typical example is illustrated in Fig. 1. The shape and small or medium size of TLLB somata allows their assignment to the T class of tectal efferent neurons. This identification is consistent with their fairly superficial location in the SC, namely in the ventral stratum opticum and the dorsal stratum griseum intermediate. Further, it is consistent with the moderate complexity of their dendritic trees, which are oriented normally to the surface of the SC. Finally, it is consistent with the fact that their axons are rather thin (2.5–3.5 mm) and give rise to recurrent (Fig. 1, arrowhead) and commissural (Fig. 1, arrow) fibers. The axonal system of TLLBs participates in several efferent systems of the SC. As shown in Fig. 1, their main axon travels along the borders of the periaqueductal gray and crosses to the



SC – Tectal Long-Lead Burst Neurons.
Figure 1 Camera lucida reconstruction of the somatodendritic and proximal axonal system of a TLLB (modified from [4], with permission). Arrowheads point to recurrent collaterals. Abbreviations: *III*, oculomotor nucleus; *Aq*, aqueduct of Sylvius; *Av*, ventral ascending fiber; *C*, commissural fiber; *MRF*, mesencephalic reticular formation; *NIC*, interstitial nucleus of Cajal; *PAG*, periaqueductal grey; *PDB*, predorsal bundle; *Pg*, parabigeminal nucleus; *RN*, red nucleus; *SGI*, stratum griseum intermediale; *SGP*, stratum griseum profundum; *SGS*, stratum griseum superficiale; *SO*, stratum opticum.

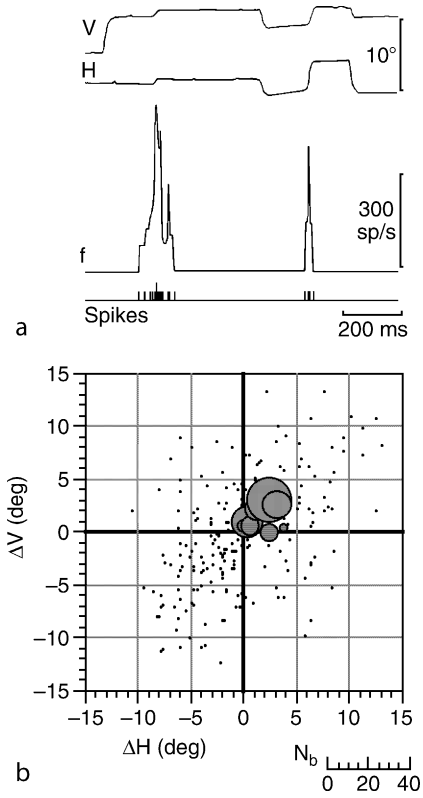


SC – Tectal Long-Lead Burst Neurons. Figure 2 Distal pattern of axonal trajectory and projections of TLLBs (reproduced from [5], with permission). (a) Composite camera lucida reconstruction of the axonal system of three TLLBs in the sagittal plane. (b–e) Composite camera lucida reconstruction of the axonal system of two TLLBs in the frontal plane. Calibration bar in (d) applies to (b–e). Open circles in (c) indicate the location of functionally identified EBNs that were intracellularly injected with HRP by Strassman et al. [6]. Abbreviations: *IV*, trochlear nucleus; *VI*, abducens nucleus; *IO*, inferior olive; *MLF*, medial longitudinal fasciculus; *NRTP*, nucleus reticularis tegmenti pontis; *PT*, pyramidal tract; *rip*, nucleus raphe interpositus. Other abbreviations as in Fig. 1.

opposite side in the dorsal tegmental decussation of Meynert. Before crossing, it emits one or two major branches that follow the ventral ascending (Av) tectofugal fiber bundle on its way toward the riMLF. It also emits several thin collaterals which deploy terminal fields in the mesencephalic reticular formation. Fig. 2 illustrates the distal trajectory and patterns of termination of PDB branches of single identified TLLBs [5]. Their distal targets include the nucleus reticularis tegmenti pontis (NRTP), the nuclei reticularis pontis oralis (NRPo) and caudalis (NRPc), the nucleus paragigantocellularis dorsalis, and the nucleus raphe interpositus (rip).

Functions of the Structure

TLLBs emit high frequency bursts for contraversive spontaneous saccades of the appropriate metrics (Fig. 3a). As the latency of their bursts is in the long lead range (21–46 ms on the average), such SC cells are called tectal long lead burst neurons (in short TLLBs). Saccades preceded by TLLB discharges collectively define the cell's movement field; in the case of the neuron illustrated in Fig. 1, it encompasses small (about 3°) right-up saccades (Fig. 3b). It is via their movement fields that TLLBs can encode the vector (amplitude and direction) of desired saccade displacement. As expected of cells causally relevant for saccades, TLLBs are generally silent both between saccades and for saccades outside their movement field (Fig. 1a). Nevertheless, the relationship between cell discharge and the execution of saccades is not as obligate as originally thought. For example, cell discharge does not reflect the actual displacement of the eyes during saccades that have been adapted, are executed toward remembered targets, or participate in gaze shifts accomplished through a combination of eye and head movements. In all these cases, TLLB discharge is better related to the distance between target and fovea (i.e. the metrics of saccades that would have foveated the target had they been executed) rather than to the metrics of the saccades that are in fact executed.



SC – Tectal Long-Lead Burst Neurons.
Figure 3 Salient physiological features of TLLBs (modified from [4], with permission). (a) Neuronal discharge pattern in relation to saccades. (b) Bubble diagram of the neuron's movement field. Circles are centered over the end points of saccades (in retinotopic coordinates) and their diameter is proportional to the number of spikes in the accompanying burst (N_b). Dots indicate saccades not accompanied by spikes. Abbreviations: *f*, instantaneous firing rate; *H, V*, instantaneous horizontal (H) and vertical (V) eye position.

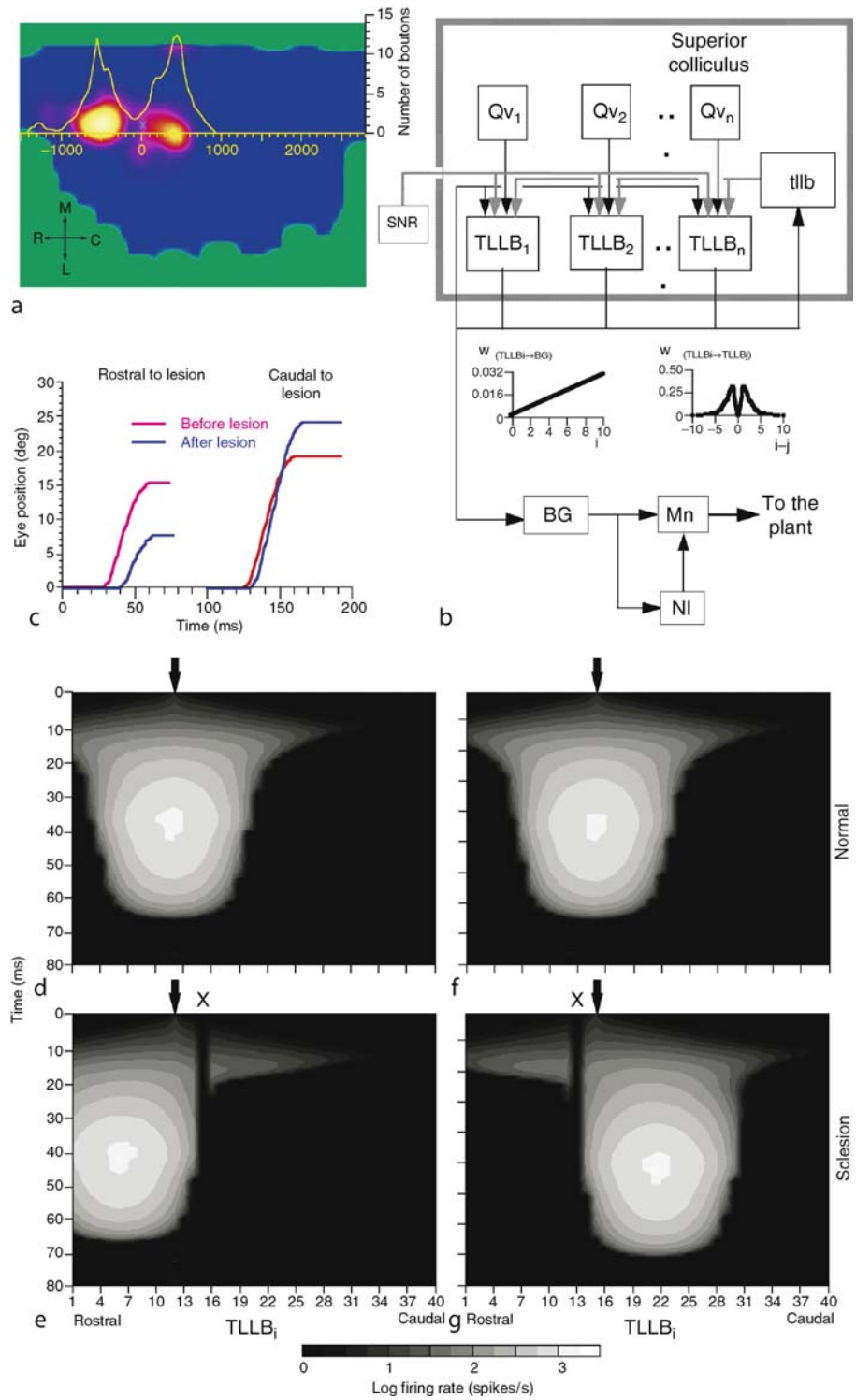
The highly distributed axonal system of TLLBs is eminently suitable for conveying a saccade related command to targets of the SC. Firstly, the terminal fields they deploy in the central mesencephalic reticular formation occupy a region housing the somata of ►reticulo-tectal long-lead burst (RTLLB). Moreover, the nuclei targeted by Av and PDB fibers contain most of the premotoneuronal interneurons that comprise the burst generators: the Av branch supplies an area that houses ►vertical medium lead burst neurons (VMLBs), while the PDB branch supplies an area that houses ►horizontal ones (HMLBs). In this manner, each TLLB can simultaneously influence both the vertical and the horizontal burst generators. Also, the commissural collaterals of TLLBs could couple the two colliculi in a push-pull fashion so that saccades in opposite on-directions are not programmed simultaneously. This is consistent with the observation that cells of the feline SC, which burst before saccades in one direction, are inhibited during saccades in the opposite direction [7]. Finally, as discussed in the entry ►SC – sensorimotor integration, the plexus of recurrent connections deployed by TLLBs could ensure the reciprocal excitation of neighboring TLLBs and give rise to their intense bursts.

Higher Order Function

As different TLLBs encode different saccade vectors, the SC can be thought to implement a labeled line code. Moreover, TLLBs are topographically organized over the mediolateral and rostrocaudal extent of the SC, such that cells preferring small saccades are located in the rostral SC, while cells that prefer big saccades are located more caudally. Also, cells that discharge before upward saccades are located medially in the SC, whereas cells that discharge before downward saccades are located laterally [4]. It is for this reason that the SC is said to also use a place code to specify movement parameters. Adoption of a code generally preferred by sensory systems (the "place" code), provides an elegant biological solution to the problem of how to interface the front end of the saccadic system (the motor SC) with systems carrying sensory information about outside world events.

Quantitative Measure for this Structure

The appearance of the class of primate collicular efferent neurons (T neurons) to which TLLBs belong has been the object of detailed quantitative analysis [8]. Besides providing information about the range of values obtained by several morphological features (e.g. 3-D orientation of their dendritic tree, complexity of its branching pattern, etc.), this analysis allowed the formulation of canonical discriminant functions that can objectively discriminate T neurons from other classes of collicular efferent cells. Moreover, there is some quantitative information regarding the differential strength of descending projections of intraaxonally labeled TLLBs to several of their target nuclei [5]. Due to the important role it could play in the generation of TLLB bursts, the spatial distribution of the boutons they deploy inside the SC has also attracted quantitative attention. Figure 4a illustrates the spatial distribution of the recurrent terminal field of one TLLB that was intraaxonally injected with HRP following its functional identification in an alert behaving squirrel monkey [9]. As shown here, TLLB recurrent projections (plotted in the inset of $w_{(TLLBi \rightarrow TLLBj)}$ versus i–j; Fig. 4b) cover a considerable proportion of the ipsilateral SC, and are spatially distributed in a bi-lobe fashion centered around the cell body they originate from. Such information has been used to generate a computational model of the SC, (schematically illustrated in Fig. 4b) that accounts for several counterintuitive results [9]. Firstly, it accounts



SC – Tectal Long-Lead Burst Neurons. Figure 4 (a) Horizontal spatial distribution of terminals deployed in the deeper layers of the primate SC by a single functionally identified TLLB that was intraaxonally injected with HRP (reproduced from [9], with permission). Colors range from dark to light in proportion to the small or large number of boutons deployed in the corresponding point of the horizontal map of the SC. The yellow line is a plot of the number of boutons (*ordinate*) within 80 μm of a plane through the soma and normal to the SC surface as a function of the rostrocaudal distance from the soma (*abscissa*). (b) Model of distributed population coding of saccade metrics in the motor layers of the SC (modified from [9], with permission). Solid lines indicate excitatory connections.

for the fact that simultaneous electrical stimulation of two collicular sites generates saccades equal to the average of the saccades that are generated when the two sites are stimulated separately, rather than to their sum. Further, it provides an intuitive understanding of why this is so, in that the spatial distribution of its engaged TLLB units shifts to a site intermediate between those activated when the two sites are stimulated separately. It also accounts for the fact that saccades can be hypermetric as well as hypometric after lesions of the superior colliculus (Fig. 4c), and demonstrates that the spatiotemporal profile of TLLB activation shifts in the requisite manner depending on the relative location of the stimulus and lesion sites (Fig. 4d–g). Finally, it accounts for the generation of staircases of saccades in response to long trains of constant stimulation, thus implying that the superior colliculus contains a biological oscillator. Evidence consistent with the involvement of a recurrent network of mutually excited TLLBs in burst generation is considered in the entry SC – sensorimotor integration. The same entry also includes a description of quantitative estimates of the spatial distribution of *boutons* deployed by efferent neurons of the SC in regions housing the burst generators and their implications for the "spatio-temporal transformation."

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SC – Tectoreticulospinal Neurons

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Synonyms

X neurons, TRSNs

Definition

"Tectoreticulospinal neurons (TRSNs)" are large or medium-size superior colliculus (SC) ►projection neurons. Their long axons cross the midline in the dorsal tegmental decussation, descend in the ►predorsal bundle (►tectobulbospinal tract) and make extensive connections with the midbrain, pontobulbar ►tegmentum (Midbrain, Pontobulbar) and the spinal cord by virtue of multiple axon collaterals. TRSNs are a subset of a larger class of the SC projection neurons, called "X neurons" [1] (Figs. 1 and 2).

Characteristics

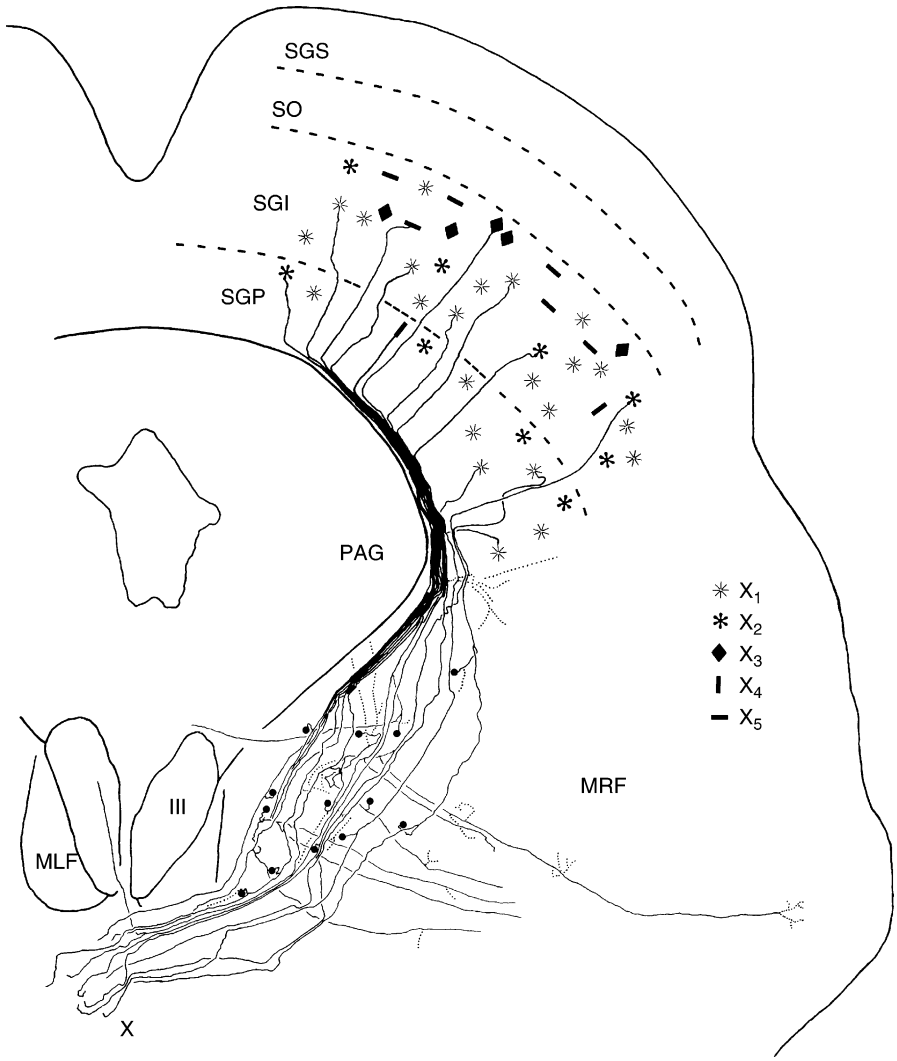
Higher Order Structures

The Superior Colliculus: An Overview

Cell bodies (somata) of TRSNs are located in the deep division of the SC, a laminated structure (Fig. 1)

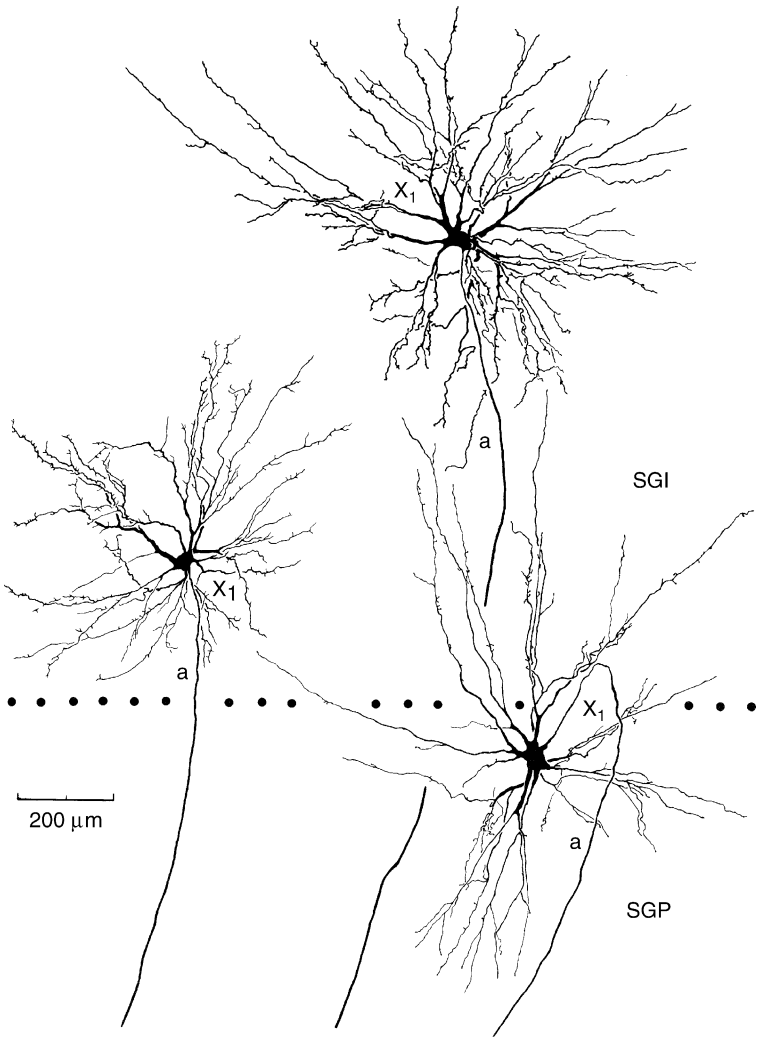
All other connections are inhibitory. Numbers indicate connection strengths. Insets indicate spatially varying connection strengths (w), plotted as a function of the location of source (i), or the target (j) neurons within their respective arrays, or in terms of the distance between them (i–j). (c) Two examples of saccades produced before (blue) and after (red) simulated focal TLLB "lesion" experiments in response to activation of the same Qv unit. (d–g) Gray scale contour plot of the spatio-temporal profile of all TLLB units employed in the model as a function of their index (*abscissa*) and time (*ordinate*) for saccades evoked from a normal (d and f) or a "focally lesioned" (e and g) SC. Small index numbers correspond to rostral SC sites and big index numbers correspond to caudal SC sites. The gray scale is proportional to the Logarithm of the TLLB activation function. In (d) and (e), the stimulation point (*arrowheads*) is rostral to the lesion (x), while in (f) and (g), the stimulation point is caudal to the lesion. Abbreviations: *BG*, burst generator; *C*, caudal; *L*, lateral; *M*, medial; *Mn*, motoneuron; *NI*, neural integrator; *R*, rostral; *SNR*, neuron of the substantia nigra pars reticulata that pauses for saccades; *Qv*, quasivisual neuron; *TLLB and tllb*, excitatory and inhibitory tectal long-lead burst neurons.

S



SC – Tectoreticulospinal Neurons. Figure 1 Tracing of a representative coronal section through the midbrain to show the location of the superior colliculus, its principal layers, and the distribution of different subclasses of X neurons ($X_1 - X_5$, as indicated by symbols in the *inset*). Also shown are the initial axon trajectories till the decussation and proximal axon collaterals supplying the central mesencephalic reticular formation. (from [1], with permission of the Authors and Wiley & Sons, Inc.). Abbreviations: *MLF*, medial longitudinal fasciculus; *MRF*, mesencephalic reticular formation; *PAG*, periaqueductal gray substance; *SGS*, superficial gray layer; *SO*, optic layer; *SGI*, intermediate gray layer; *SGP*, deep gray layer; *X*, dorsal tegmental decussation; *III*, oculomotor nucleus. The fiber rich intermediate white layer in the lower SGI and the deep white layer in the lowermost SGP are not labeled. The latter can be recognized as the site of collection of outgoing X neuron axons on their course along the border of the periaqueductal gray.

occupying the anterior portion of the roof of the midbrain, the tectum. Its superficial layers (SGS, SO, Fig. 1) receive a direct pathway from the retina and contain a topographic map of the contralateral visual hemifield. The deeper SC is subdivided in the intermediate and deep layers (SGI, SGP, Fig. 1), which differ in their cell composition and afferent connections. Common to them is the convergence of afferent pathways from a great number of sources, including both higher order structures, such as the cerebral cortex and basal ganglia, and ascending sensory pathways. Besides their well established role in the ►visuomotor transformation, the deeper layers are thus also the site of ►multisensory (convergence, integration). Besides neurons with local connections inside the SC, all layers contain projection neurons which form several pathways with different trajectories and different combinations of target regions. TRSNs are one of the classes of projection neurons. They send their axons in the predorsal bundle and establish the most extensive extrinsic connections.



SC – Tectoreticulospinal Neurons. Figure 2 Reconstruction of somatodenritic profiles of HRP-labeled X_1 neurons. These exemplary neurons illustrate common features of X_1 subclass (large dendritic extension, central position of the cell body with respect to radially oriented dendrites, approximately symmetrical dendritic field). Also the range of variation of soma size and dendritic extension can be readily recognized. See Table 1 for a summary of morphometric data. (from [1], with permission of the Authors and Wiley & Sons, Inc.).

S

Morphology of TRSNs

Laminar Location

A majority (66% [2] to 73% [1]) of TRSN cell bodies are located in the intermediate gray layer of the SC (SGI), the remaining ones being found in the deeper layers (Fig. 1). They are distributed over the entire rostrocaudal and mediolateral extent of the SC, but their density is somewhat higher in the caudolateral quadrant. The complete ►motor map of the SC can therefore gain access to the downstream areas contacted by TRSN axons, with some bias in favor of the representation of the lower half of the visual field.

Size and Dendritic Pattern

X neurons (see Definition "Tectoreticulospinal Neurons (TRSNs)") intracellularly labeled with ►horseradish peroxidase (HRP) have been subdivided in five subclasses (X_1–X_5), based on the size of cell bodies and the shape and orientation of the dendritic trees [1]. Some morphometric data underlying the classification are summarized in Table 1 (see ►Quantitative measures). The first three subclasses (X_1–X_3) comprise medium-size and large cells, and correspond best to TRSNs identified by their crossed projection to the lower brainstem and to the spinal cord, and by their firing patterns during ►orienting movements [2,3]. Smaller neurons (X_4, X_5) with vertically or horizontally oriented dendritic trees are unlikely to be present in the TRSN population. Judging from their spherical dendritic fields, a great majority of TRSNs belong to the X_1 subclass (Fig. 2), characterized as "large multipolar wide field neurons" in preceding studies with

Golgi method in the cat. Typically, they have 5–10 stem dendrites arranged radially and occupying an approximately spherical space of considerable size (800–1,400 µm) (Table 1). Distal portions of dendrites often cross the borders of collicular layers, which explains the capacity of TRSNs to sample and integrate ascending, descending and interlaminar inputs to the deeper layers of the SC.

Parts of this Structure

Main Axons, Axon Collaterals and Termination

Morphometric data on TRSN fiber system are summarized in Table 2 (see ►Quantitative measures). To-date, only a qualitative description of target areas is available for midbrain portions of TRSN axons [1,2]. In the pontobulbar tegmentum, the anatomical strength of connections could be evaluated for a few orienting-related TRSNs [3]. These data are collected in Table 3.

Midbrain

Axons of TRSNs, at their exit from the SC, range 3–8 µm in diameter but more than 90% are thicker than 4 µm. They course along the border of the periaqueductal gray substance (PAG) (Fig. 1), cross the midline and join the contralateral predorsal bundle (PDB). Before crossing, all TRSNs emit a long "main ascending collateral" that goes rostrally and reaches the field of Forel (FF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). TRSNs have no recurrent collaterals terminating in the SC but they do issue several ipsilateral collaterals which supply with terminals the central mesencephalic reticular formation (cMRF) (Fig. 1). Other tegmental regions are "facultative" targets of TRSNs, supplied by some but not all TRSNs. The supraoculomotor region of the PAG receives projection from about one third of TRSNs, whereas collaterals terminating in the interstitial

SC – Tectoreticulospinal Neurons. Table 1 Morphometric data of TRSN cell bodies and dendrites

	TRSN	X_1	X_2	X_3	X_4	X_5
As	1,060–2,075	1,025–2,315	1,400–2,880	1,310–2,850	745–1,250	700–1,200
N-dd	7–10	5–7	4–7	5–7	4–6	5
D-dd	9–16	3–23	6–22	4–23	4–14	3.5–15
dd-shape	Spherical	Spherical	Vertical	Vertical	Vertical	Horizontal
Ext-dd M-L	800–1,400	640–1,200	750–1,000	500–800	400–500	1,000–1,250
Ext-dd A-P	*Idem*	540–1,100	700–1,000	560–900	300–500	500–700
Ext-dd D-V	*idem*	630–1,400	820–1,300	1,150–1,400	1,100–1,500	600–750

As, soma surface area (µm^2); *N-dd*, number of dendritic trunks; *D-dd*, diameter of dendritic trunks (µm); *dd-shape*, shape and orientation bias of the dendritic field; *Ext-dd*, maximal extension of the dendritic field (µm) in mediolateral (M-L), anteroposterior (A-P) and dorsoventral (D-V) cardinal directions of the stereotaxic coordinate system.

SC – Tectoreticulospinal Neurons. Table 2 Morphometric data on TRSN axons and collaterals

	Midbrain	Pons-Medulla
Diametres of axons and collaterals (µm)		
Main axon (X1 neurons)	4.5–7.5[a]	7.0–10.0[a]
Main axon (visuomotor TRSNs)	–	4.6–9.3[b]
Main ascending collaterals	1.0–3.5[a]	[c]
Other first order collaterals	1.5–2.6[a]	1.5–3.7[a]
Intensity of collateral branching		
Number of first order collaterals	8–15[a]	7–21[b]
Distance between origins of collaterals (µm)	500–1,500[a]	110–1,975[b]
A-P extension of innervation domains[d] (µm)	–	350–3,500[b]
Number of terminal boutons per collateral	–	11–2,180[b]

[a]Data from TRSNs intracellularly labeled with HRP in acute experiments, without behavioral identification.
[b]Data from identified visuomotor TRSNs HRP-labeled in alert cats.
[c]Main ascending collaterals are present in the midbrain only; – quantitative data not available.
[d]Longitudinal space along the antero-posterior (A-P) axis of the brainstem occupied by second and higher order branches of individual collaterals and by terminals.

SC – Tectoreticulospinal Neurons. Table 3 Quantitative data on the terminations of visuomotor (vm)-TRSNs in different regions of the pontobulbar reticular formation

		TRSN "S"		TRSN "A"		TRSN "K"	
Length of axon used for bouton counts (μm)		6,000		6,000		4,800	
Total number of boutons over analyzed axon length		3,270		6,261		924	
		nB	D	nB	D	nB	D
RPc Rostral half	Total innervation area	679	110	3078	208	118	85
	EBN area	352	160	980	371	72	112
RPc Caudal half	Total innervation area	833	252	1,858	215	650	108
	Abducens nucleus	145	207	331	473	108	154
RGc Rostral one third	Total innervation area	1561	295	1,325	270	156	143
	IBN area	442	224	460	383	173	98

Bouton numbers (nB) and bouton densities (D = nB mm^{-3}) from three TRSNs labeled with HRP in alert cats and identified as visuomotor by their firing patterns. Complete reconstruction of the axonal branching of TRSN "A" is shown in Fig. 3a. *RPc*, nucl. reticularis pontis caudalis; *RGc*, nucl. reticularis gigantocellularis; *EBN*, excitatory saccadic burst neurons; *IBN*, inhibitory saccadic burst neurons.

nucleus of Cajal (INC) are rare and no terminations have been traced in the oculomotor nucleus. Some fibers enter the nucleus of the posterior commissure (NPC) and other pretectal nuclei. From the functional point of view, it is important to note that all cells of this class project not only in the contralateral PDB but also to midbrain regions containing the vertical saccade generator (riMLF, INC, NPC), some intermediate circuits involved in horizontal saccades (cMRF, supraoculomotor PAG), and neurons projecting to the spinal cord and participating in the control of ►head movements in the vertical plane (FF).

Pons and Medulla

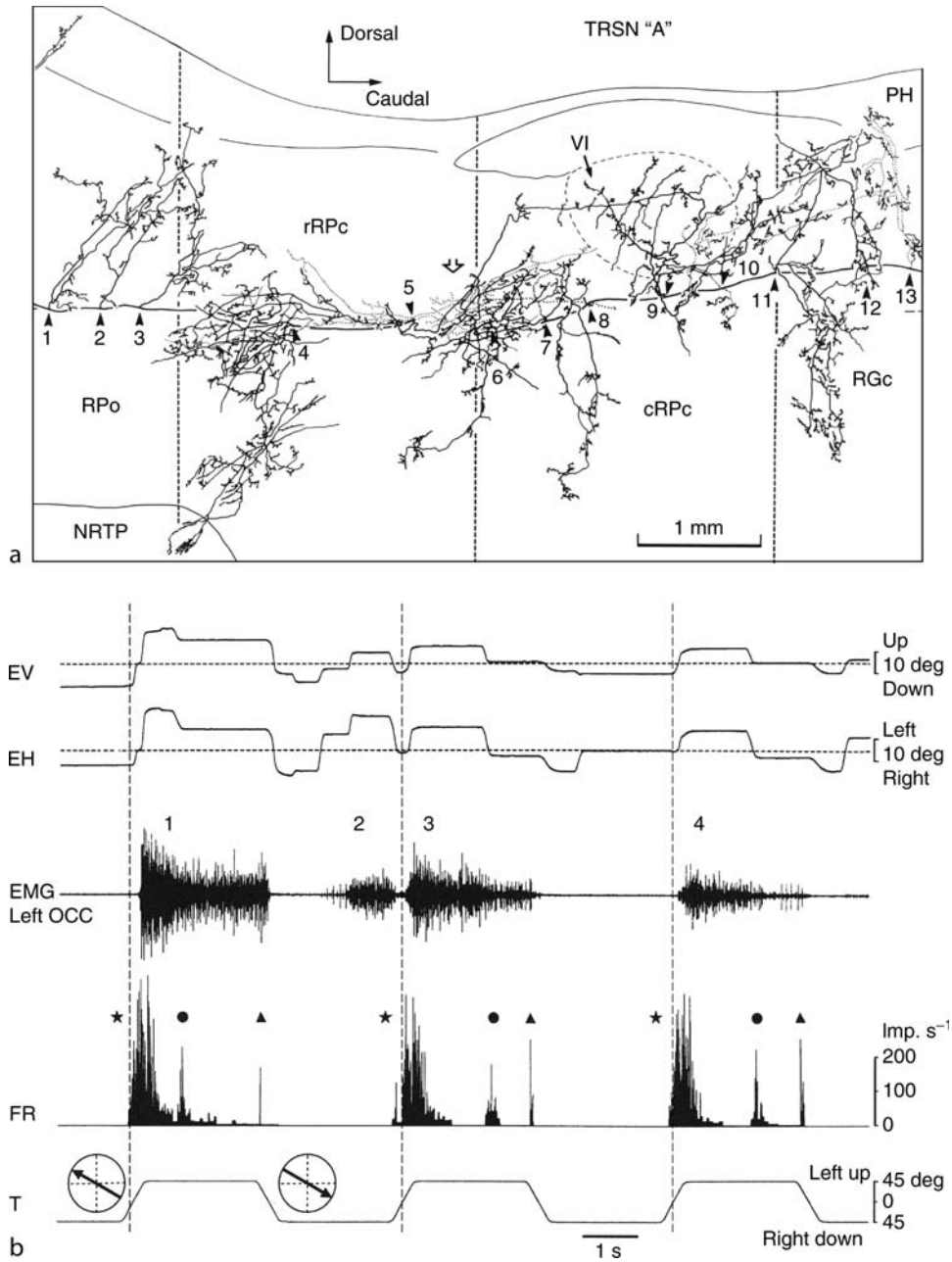
"Visuomotor TRSNs" (vm-TRSNs, see below) labeled by intra-axonal HRP injections [3,4] have axons of 4.6–9.3 μm in diameter. Collaterals are issued at all levels of the pons and medulla at variable inter-collateral distances, but their branching domains usually overlap along the longitudinal axis of the brainstem tegmentum (Table 2). The neuron illustrated in Fig. 3a is representative because the regions of its densest ramifications correspond to common terminal regions of all studied vm-TRSNs. The first of them (collateral 3 and 4) is in the rostral pole of the caudal pontine reticular nucleus (RPc), with a denser innervation of its central portion. The second (collaterals 5–8) is just rostral to the AbdN. The third one (collaterals 9, 10) corresponds to the caudal extremity of the dorsal RPc, where the terminations of vm-TRSNs become particularly dense near the border of the AbdN before entering in this nucleus as well. In the medulla, axons of vm-TRSNs ramify and terminate in the gigantocellular reticular nucleus (RGc) (e.g., Fig. 3a, collaterals 11–13). Superposition of terminal domains makes it clear that, taken together, vm-TRSNs make connections with the entire medial reticular formation in the pons and in the rostral medulla. Besides this termination domain in common, individual neurons make selective connections with some but not other areas. Among such facultative targets are the precerebellar nucleus reticularis tegmenti pontis (NRT), nucleus prepositus hypoglossi (PH) and the motor nucleus of the facial nerve (VII). The strength of projections to the areas containing excitatory and inhibitory ►burst neurons (Saccadic, Excitatory, Inhibitory) of the ►horizontal saccade generator also differs between the vm-TRSNs (Table 3). Differences in local connection strengths between TRSNs may suggest that they fulfill specialized tasks in the selection of neural populations controlling different moving segments, e.g., eyes, head, spine and limbs, during complex orienting movements (synergies).

Spinal Cord

Compared to pontobulbar axons of vm-TRSNs, spinal portions of axons, presumably originating from X neurons, have sparser collaterals and a smaller number of boutons per collateral in the spinal grey of C1 and C2 segments [6]. Although terminals in the motor nuclei of neck muscles have been previously reported, no terminations of X neurons have been found on retrogradely labeled motoneurons [6]. This latter study demonstrated an indirect connection through interneurons in the laminae V–VIII. Some electrophysiological studies affirmed, others denied, a direct SC connection with neck motoneurons, so that the question remains unresolved [5]. There is a general agreement, however, as to a powerful disynaptic tecto-reticulo-spinal connection through the caudal pontine (RPc) and rostral bulbar (RGc) reticular formations, as well as through spinal segmental interneurons.

Summary

Connections of individual TRSNs in the brainstem are very extensive, suggesting, at a first glance, a fairly unspecific function. On the other hand, when regarded



SC – Tectoreticulospinal Neurons. Figure 3 Axonal morphology and discharge patterns of a "visuomotor" TRSN recorded and labeled in alert cat. *A*, Reconstruction in the parasagittal plane of axon collaterals in the pons and in the rostral medulla. Open arrow indicates the point of intraaxonal HRP injection. Quantitative data on terminations within three segments of the pontobulbar tegmentum (vertical interrupted lines) are presented in Table 3 (TRSN "A"). Abbreviations: *NRTP*, nucl. reticularis tegmenti pontis; *RGc*, nucl. reticularis gigantocellularis; *RPc*, nucl. reticularis pontis caudalis (*r*, rostral; *c*, caudal halves); *RPo*, nucl. reticularis pontis oralis; *VI*, abducens nucleus. (modified from Grantyn et al. (1993), Multisensory Control of Movement, Oxford University Press, pp. 185–200, with permission). *B*, Discharge pattern of the same neuron during tracking of a moving target. From *top to bottom*: vertical (EV) and horizontal (EH) eye position, electromyogram (EMG) of the left m. obliquus capitis cranialis (OCC), instantaneous firing rate (FR) of the neuron and position of the target (T). *Insets* show the direction of target motion. Stars: "visuomotor" bursts during target motion in the neuron's preferred direction, associated with tracking saccades, slow drifts (event 4) and neck muscle contractions. Vertical interrupted lines are drawn through the onset of high frequency firing before the saccades. Note weaker bursts of visual origin during return saccades (*circles*) and at the onset of target motion in the direction, opposite to the preferred one (*triangles*). Event 2 demonstrates the absence of discharge during spontaneous gaze shift in the preferred direction of the neuron. (Modified from [5], with permission).

as a population, they supply with terminals all areas known to harbor premotor neurons controlling eye and head movements toward the contralateral visual field. In the lower brainstem, terminals are distributed to the regions of long-lead and medium lead excitatory burst neurons of the horizontal saccade generator (RPc). Caudal RPc and RGc contain reticulospinal neurons (RSNs) controlling horizontal head movements, and strong monosynaptic connections of TRSNs to such cells have been proven by intracellular recordings (►intracellular labeling). In the midbrain, TRSNs distribute terminals in the region of the vertical saccade generator (riMLF) and in the field of Forel, the site of location of RSNs controlling vertical components of head movements. TRSNs contact directly not only premotor areas but also motor nuclei participating in orienting movements. Monosynaptic excitatory effects of TRSNs on abducens (eye muscle), facial (ear muscles) and neck motoneurons are admittedly weak. Nevertheless, it is worth underscoring such a divergence to motor nuclei, all participating in complex orienting synergies, but very different according to biomechanical properties of moving organs (effectors) they control.

Higher Order Function

The Role of the Superior Colliculus in the Control of Gaze Shifts–An Overview

The role of TRSNs is to transmit output signals of the SC to premotor structures of the brainstem tegmentum. The SC is commonly referred to as a subcortical "center" controlling orienting movements. Under orienting movements we understand rapid ►gaze shifts toward novel or otherwise biologically significant events in the surroundings. Under natural conditions, such changes of gaze direction are achieved by coordinated saccadic movements of the eyes and rapid head movements. When large gaze displacements are required, movements of the trunk and of extremities do participate in orienting synergies. The most studied function of the SC consists of providing an output signal specifying the desired direction, amplitude and, to some extent, the speed of gaze shifts. These parameters are encoded in the location of the active population of SC output neurons with respect to coordinates of the motor map, as well as in the size and the level of excitation of the population. For a detailed description of neural processes underlying the control of gaze by the SC see ►SC – Role in eye movements, ►SC-Motor map, ►SC-Sensorimotor integration.

Physiology of TRSNs

Visuomotor Properties

Typical activity pattern of a morphologically identified (Fig. 3a) visuomotor TRSN (vm-TRSN) [3–5] is shown in Fig. 3b. This TRSN generated the strongest activity during ►tracking of a target when it moved in the direction, opposite to the side of the cell's location in the SC. Preferred directions of other TRSNs are usually within 50–60° from horizontal, but a few cells respond stronger to nearly vertical target motion. The earliest portions of the bursts (Fig. 3b, stars) are visual responses to the target, when it is close to entering the contralateral visual hemifield. Increments of the spike rate to 150–200 s^{-1} precede first tracking saccades by about 100 ms but bursts continue beyond the saccade ends. They often coincide in time with sequences of saccades (Fig. 3b, event 1) or post-saccadic slow eye movements (e.g., Fig. 3b, event 4). Burst duration is similar to the duration of the dynamic component of the electromyogram (EMG) of neck muscles participating in an attempted head movement.

Discharge characteristics of vm-TRSNs, illustrated by an individual example of Fig. 3, vary in a broad range. Bursts start in advance of the onsets of gaze movement or EMG activation with lead times as short as 30 ms in some neurons and as long as 200 ms in others. Some cells generate bursts of relatively short duration (50–400 ms) and terminating before the end of eye saccades, others are able to generate sustained bursts in the range of 0.5–2.0 s. Temporal relationships of bursts with motor events of different duration (saccades, slow eye movements, activation of neck EMG) differ accordingly. Firing rate within the bursts is maximal in association with saccades in the neuron's preferred direction and, particularly, when movements are very fast, as it happens when the level of the animal's motivation for visual "capturing" of the target is high. However, the maximum firing rates vary considerably among vm-TRSNs (100–500 imp s^{-1}), even when tested in neuron's optimal behavioral conditions. The differences in burst durations, spike frequency during visuomotor bursts, and the probability of neuron's recruitment during the movement can be explained by the differences in membrane excitability of TRSNs [7].

The above description, based on experiments on cats with immobilized heads, is in perfect agreement with the results obtained in head-free cats [8,9]. The study clearly demonstrated the contribution of TRSN discharges to the generation of eye and head components of the orienting synergy. In particular, there exists a tight temporal coupling between increments of the firing rate and accelerations of eye (delay 10–12 ms) and head (delay 24–32 ms) movements. Using stationary instead of moving targets for orienting, Munoz and coworkers [9] were able to further analyze spatial properties of movement-related TRSN discharges. They found that maximal firing rates are always associated with a particular vector of gaze shifts, corresponding to the optimal ►gaze motor error (of a

neuron). However, all neurons will produce some firing for smaller or larger gaze displacements. Besides burst-like (phasic) movement-related discharges, about 75% of TRSNs generate sustained discharges during preparation of gaze shifts toward the location in space roughly corresponding to the location of neuron's visual receptive field. The size of the field is large (up to 70° horizontally and 40° vertically). The strongest preparatory firing is observed when target location corresponds to the optimal gaze motor error (►Gaze Motor Error-Static) of the neuron.

Multisensory Properties

Practically all TRSNs tested in alert animals with visual, auditory and somesthetic stimuli display a multisensory convergence [8,10]. Visual responses to stationary targets have mean latencies of 50–95 ms, but the majority of neurons respond at less than 60 ms. Such responses usually consist of a few spikes, and they are weaker than responses to moving targets. Different sensory modalities interact on TRSNs in a complex way. Although the most consistent excitatory effects are provided by vision, via the retinotectal connections, auditory and somesthetic modalities can enhance or suppress visual responses, depending on the spatial coincidence or disparity of the stimulus sources in the surrounding space. Such interactions are considered as a part of the processes underlying the selection of targets for orienting movements [10].

Summary

TRSNs identified both by morphological and by behavioral criteria in head-fixed cats have the following properties: (i) Broad spatial tuning of visual and movement-related discharges; (ii) Responsiveness to sensory stimuli of different modalities and a superposition of sensory (predominantly visual) and motor components in their bursts; (iii) Unequal capability to generate high frequency firing; (iv) Broad range burst durations, such that discharges of some neurons coincide in time with saccades only, while discharges of other neurons can contribute to all dynamic components of orienting synergies (saccades, slow eye drifts and contractions of neck muscles); (v) Nonobligatory association of vm-TRSN bursts with gaze shifts: they discharge only when the animal moves its gaze toward an object of its choice, but not during scanning gaze movements across a uniform visual background or in darkness. They also generate visual responses when a moving target is neglected and not tracked. By their location on the collicular motor map, TRSNs encode the gaze motor error and they also contribute to the control of dynamic parameters of both eye and head movements (►eye-head tracking). Considering the behavioral properties of individual TRSNs, their function should be defined as a fairly generalized facilitation of premotor extracollicular circuits, whose activation is required to realign the head and the eyes to a relatively large albeit circumscribed area of the environment. This conclusion is well corroborated by the broad divergence of TRSN projections to the brainstem tegmentum. More specific functions of individual TRSNs are suggested by anatomical data, such as regional differences in the strength of connections and differences in patterns of multisensory integration. This aspect of "specificity" has, however, not been sufficiently studied.

Quantitative Measure for this Structure

Cell Bodies and Dendrites

Table 1 presents a selection of morphometric characteristics compiled from references [1,2]. TRSNs and X neurons have similar trajectory and branching patterns of axons in the midbrain, but the definition of TRSNs is further restricted by adding an identified descending projection to the lower medulla and to the spinal cord. According to their size (As) TRSNs are well comparable to X_1–X_3 neurons. It should be noted that X_2 and X_3 neurons have a vertical orientation of dendritic fields, whereas radially symmetrical fields have only been reported for TRSNs. The available sample of completely reconstructed TRSNs is, however, smaller than that of X neurons, and it is premature to affirm that all of them belong to the X_1 subclass. On the other hand, all X neurons, including TRSNs, can be clearly distinguished from another class of SC neurons projecting in the PDB, the T neurons [1]. Firstly, T neurons are of consistently smaller size and, secondly, they emit recurrent collaterals passing to the opposite SC in the collicular commissure. Such collaterals have not been observed, either on X neurons or on TRSNs.

Axons and Axon Collaterals

Table 2 summarizes quantitative data on axons and collaterals of TRSNs [2,3]. A broader range (3.0–8.0 μm) has been reported for the whole population of X neurons [1], but the thinnest axons (3.0–4.5 μm) were not observed among TRSNs. An HRP study of TRSN axons in the pontomedullary region of anesthetized cats suggested an increase of axon diameters on their descending course to the spinal cord [2]. The range of behaviorally identified visuomotor TRSNs also includes, however, smaller diameters. Conduction velocities of TRSN axons between the SC and the pons are in the range of 35.7–57.2 m s^{-1} whereas the range of ponto-spinal portions of axons is broader (39.0–80 m s^{-1}). Axon diameters and the related parameter, conduction velocities, are appropriate for a rapid and fairly synchronous transmission of spike volleys to target areas separated by long distances. Intracellular recordings have indeed demonstrated that minimal latencies of synaptic responses to SC stimulation are

0.5–1.0 ms in the pontine reticular formation neurons, 0.8–1.0 ms in abducens motoneurons and 1.4–1.6 ms in motoneurons of neck muscles in the upper spinal segments.

The presence of axon collaterals along the total length of main axons is common to all TRSNs. The richness of the collateralization varies between individual neurons, as shown in Table 2 by the numbers of collaterals issued over axon segments of a comparable length. Although some inter-collateral distances are quite long, termination domains of successive individual collaterals show practically no gaps. This is due to a great antero-posterior extension of collateral trees formed by second and higher order branches. The number of terminals issued by each collateral is variable and depends on the profuseness of branching which, in turn, is related to the diameter of collaterals at their origin.

Topographic Distribution of Terminal Boutons in the Pontobulbar Tegmentum

The numbers of terminals and, in particular, their regional densities serve as a measure of the anatomical strength of connections. To obtain reliable data, the labeling of collaterals must be complete, i.e., one should be able to identify terminal boutons on all preterminal fibers. Table 3 shows bouton counts from three behaviorally identified vm-TRSNs [3]. To satisfy the above criterion of labeling quality, only a limited length of axons has been used for counts. Similar data are not available for the midbrain portion of TRSN axons.

Table 3 includes three well known areas involved in the control of saccadic eye movements which represent common targets of TRSNs. It can be seen that, in spite of considerable differences in local bouton numbers, their densities in the area of excitatory saccadic burst neurons are consistently higher than over the total innervation domain at the same brainstem level. It is not so in the case of the Abducens nucleus for which only TRSN "A" shows a high selectivity while it is small for TRSN "K", and absent for TRSN "S". Finally, TRSN "S" is the only one showing an over-proportional density of terminations in the region of inhibitory saccadic burst neurons.

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SC – Visually Triggered Movement Cells

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Definition

Visually guided saccades (►saccade, ►saccadic eye movement) are those rapid eye movements that direct the eye to a visual target. This is in contrast to saccades occurring under other conditions, such as those made without any overt target termed spontaneous saccades or those made to targets that are no longer present, which are referred to as memory guided saccades. Neurons in the brain of a monkey that are active *only* when the saccade is made to a visual target that is present in the field of view are visually triggered movement cells. Neurons of this type were first identified in the ►superior colliculus (SC) and study of them has concentrated on that structure.

Characteristics

Higher Order Structures

The inputs to the superior colliculus that could contribute to the activity of the visually triggered

movement cells include large regions of cerebral cortex, but several areas in particular have neuronal responses to visual stimuli and increased activity before saccadic eye movements [1]. Neurons in the lateral intraparietal area of parietal cortex have strong responses to visual targets for saccades and are modestly active before saccades, while neurons in the frontal eye field area of frontal cortex have both visual responses to targets and clear bursts of activity before saccades. For the visually triggered movement cells in the superior colliculus, it may well be the nature of the visual activity in the cortex that is most important for understanding their function. Both cortical areas have strong direct projections to the superior colliculus, and the frontal eye field has an indirect pathway through the basal ganglia.

Parts of This Structure

The superior colliculus has multiple layers including the superficial layers in which all of the neurons have visual responses, and the intermediate layers in which the neurons have not only visual responses but many also have a burst of activity preceding the saccadic eye movement [2]. The visually triggered movement cells lie in the intermediate layers and generally have both increased activity in response to the stimulus and the burst of activity before the onset of the saccade.

Functions of This Structure

The visually triggered movement cells were first identified by comparing their activity when the monkey made a saccade to a visual target, with the activity before a saccade of the same amplitude and direction made in total darkness [3]. The visual response was of course absent in the dark, but the burst before the saccade was also absent even though the saccade in the dark and the saccade to a visual target were nearly identical. Such an absence of presaccadic bursts of activity were subsequently seen in experiments in which the monkey made a series of two saccades [4], or in which it made an anti-saccade away from a visual target [5]. More recently, the role of the visual target has been investigated systematically, and the presence of a visual target was found to alter the presaccadic burst of many collicular neurons [6]. In these tasks, monkeys made saccades to visual targets, to the location of remembered visual targets, and to locations where the targets had not appeared at all (a task referred to as the anti-saccade task). What these experiments showed was that the collicular neurons fell along a continuum, from those at one end that only showed the burst of activity before saccades to visual targets to those at the other end where the burst was the same whether or not the saccade was to a visual target. The visually triggered movement cells were simply those lying at one end of a continuum, not a unique class of neurons. It should be emphasized that this effect of the visual target was independent of the intensity of the visual response of the neuron; weak visual responses could be followed by strong potentiation of the burst before the saccade. The strength of the visual effect on the presaccadic burst tended to decrease over several hundred milliseconds after the visual target had disappeared. Even though the velocity of the saccades in the absence of a visual target is lower, this variable did not fully account for the reduced presaccadic burst in the absence of the visual target. In net, the presence of the visual target seemed to have an effect on the vigor of the presaccadic burst that was second only to the effect of the amplitude and direction of the saccade to be made. Furthermore, at the same time as the presence of a visual target increased the presaccadic bursts, the presence of the target also reduced the scatter in the saccadic end points around the target, which is consistent with a contribution of the increased bursts to the greater precision of the saccades to visual targets.

Higher Order Function

The superior colliculus is a homologue of the optic tectum found in other vertebrate animals, and across species these structures are clearly related to the control of eye and head movements. As the eyes are shifted to more frontal positions in the head and the high resolution fovea develops in the retina, the need for greater precision in directing saccades to visual targets becomes more critical for the animal's survival. It has been suggested [6] that the enhanced burst of activity in the superior colliculus that accompanies saccades to visual targets is part of this adaptation for greater precision in the visual guidance of saccades.

Quantitative Measure for This Structure

Progress on the nature of the effect of the visual stimulus on neuronal activity has been made possible by the use of tasks that separate out the variables that alter the neuronal activity. A second critical factor in studying the awake monkeys results from the accurate recording of movements using the magnetic search coil method, which gives precise indication of eye position, velocity, and acceleration. The entire experiment is controlled by online computer systems that also collect and store all the data from the experiments.

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Scaffold Protein

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Synonyms

The words "adaptor" and "linker" are sometimes used to mean a scaffold protein; Although scaffold proteins have more varied functions than adaptor and linker

Definition

Scaffold proteins are proteins that simultaneously bind two or more other proteins, and organize binding partners into a functional unit to enhance signaling efficiency and fidelity.

Signaling molecules interact with each other to form large complexes, and most of those complexes do not diffuse in the cytoplasm, but rather are attached to cell membranes. The complex is called signalsome or transducisome. Among components of a signalsome, a protein that binds to more than one protein and has no enzymatic activity is defined as a scaffold protein, because the primary function of such a molecule is to provide other components with a framework on which they efficiently work.

Characteristics

Higher Level Structures

As biological signals come from outside a cell, many signalsomes are localized under the plasma membranes with receptors for the external signals. In the field of neurobiology, scaffold proteins at synapses are the most extensively studied. However, scaffold proteins can also form signalsomes in other subcellular structures including the nucleus, the Golgi apparatus, mitochondria, and centrosome.

Lower Level Components

Scaffold proteins are composed of multiple protein modules. Modules are compact folded portions of proteins with 30–200 amino acids that recognize short continuous peptide sequences in their binding partners. ►PSD-95/Discs large-A/ZO-1 (PDZ), Src-homology (SH) 2, SH3, WW, and phosphotyrosine binding, and guanylate kinase homologue domains are frequently recognized in scaffold proteins. Sterile alpha motif (SAM), WASP homology 1, ARM, and LIM domains are also detected in scaffold proteins. L27 and protein kinase A anchor domains are present in scaffold proteins binding to Lin-2/Lin-7 and protein kinase A, respectively. Scaffold proteins often have sequences involved in multimerization such as a coiled-coil domain and leucine-rich repeats. Furthermore, some scaffold proteins have short target motifs that bind to modules of other scaffold proteins.

Structural Regulation

Alternative splicing is a source of diversity of scaffold proteins. Variants with different combinations of modules and motifs mediate distinct protein–protein interactions. Synapse-associated protein 97 (SAP97) has alternatively spliced insertions in the N-terminal domain, and in the region (HOOK domain) between the SH3 and the GK domains. The N-terminal insertions determine the ability of SAP97 to cluster potassium channels. The interaction of human Discs large (hDLG; human homologue of SAP97) with protein 4.1 depends on the insertion in the HOOK domain, and is involved in the localization of hDLG at cell junctions in epithelial cells. SAP97 with the same insertion is targeted to synapses in neurons, and delivers AMPA receptor subunit GluR1 to the cell surface. Posttranslational modifications also contribute to diversity and regulation of scaffold proteins. Phosphorylation regulates the interaction of the AMPA receptor subunit GluR2 with ►Glutamate Receptor Interacting Protein (GRIP) and PICK1. Phosphorylation by cyclin-dependent kinase 5 regulates the clustering (►receptor regulation, clustering) of PSD-95. Phosphorylation by calcium/calmodulin-dependent kinase II (CaMKII) induces synaptic targeting of SAP97. Palmitoylation is involved in synaptic targeting and interaction with ion channels of PSD-95 and localization at spine heads of GRIP. Axin needs sumoylation to activate c-Jun N-terminal kinase. Finally, activity-dependent polyubiquitination regulates the amount of scaffold proteins in neurons.

Higher Level Processes

Scaffold proteins function in a wide variety of receptor, channel, and cell adhesion molecule signalings. Major research efforts by neurobiologists have been made to demonstrate that synaptic activity modulates protein-protein interactions mediated by synaptic scaffold proteins. For instance, activity-dependent phosphorylation of NMDA receptor subunit 2B disrupts the interaction with PSD-95. Activation of NMDA receptors induces

redistribution of A kinase-anchoring protein (AKAP) 79/150 through calcium signaling and F-actin organization. Studies on PSD-95 suggest that higher level processes may regulate the amount of scaffold proteins at translation and transcription levels. Estrogen stimulates translation of PSD-95. Activation of type I metabotropic glutamate receptors induces translation of PSD-95. Neuronal depolarization of spiral ganglion cells upregulates transcription of PSD-95 through neuregulin-1. Activity-dependent protein degradation also regulates the amount of synaptic scaffold proteins.

Lower Level Processes

Scaffold proteins are involved in many biological processes including cell proliferation, apoptosis, endocytosis, and regulation of cytoskeletons. In neurons, scaffold proteins are involved in membrane traffic and endocytosis of neurotransmitter receptors, accumulation of synaptic components, and regulation of actin cytoskeleton. Researchers consider that scaffold proteins play roles through these processes in synaptogenesis and synaptic plasticity.

Function

Function of Scaffold Proteins in Signaling

Scaffold proteins form signalsome to enhance signaling efficiency, ensure signaling fidelity, increase signaling sensitivity, and coordinate different signaling pathways. These biological advantages of signalsome were first delineated for *Drosophila* INAD. INAD is a multivalent PDZ protein that functions as a scaffold in the phototransduction pathway. It assembles TRP, protein kinase C, and phospholipase C, and promotes signaling specificity and speed. The importance of scaffold proteins in mitogen activated protein kinase (MAPK) and cyclic AMP-dependent signalings is well documented.

Scaffold Proteins in MAPK Pathway

In yeast, Ste5 assembles components of MAPK including Ste11 (MAPK kinase), Ste7 (MAPK kinase), and Fus3 (MAPK) so that the kinases are efficiently activated. Another MAPK, Kss1, is also activated by Ste11 and Ste7. However, Ste5 only weakly binds Kss1, so that Fus3 is preferentially activated in response to pheromone. In other animals, Kinase suppressor of Ras (KSR) is a well-characterized scaffold in MAPK cascade. KSR has a multiple modular structure and binds many proteins, for example, Raf, MEK, ERK, and others. Although KSR has no kinase activity, loss-of-function studies in *Drosophila* and nematode indicate that KSR is a positive component of Ras/MAPK pathway. Gene targeting in mice supports that KSR is a requirement of the MAPK pathway in mammals. The connector enhancer of KSR (CNK) is a potential scaffold in MAPK pathway, and has SAM, PDZ, and pleckstrin homology domains and interacts with Ras, Raf, and Rassf1. Synapses have a neuronal isoform of CNK named MAGUIN/CNK2. MAGUIN/CNK2 interacts with Raf and is necessary for NGF-mediated MAPK signaling. Jun-N terminal kinase (JNK)-interacting proteins (JIPs) are scaffold proteins for JNK and bind JNK, MKK7 (MAPK kinase), and MLK (MAPK kinase) [1].

Scaffold Proteins in cAMP Signaling

As its name implies, AKAP family proteins anchor PKA at specific subcellular structures, and regulate the temporal and spatial organization of signalings mediated by PKA. AKAP79/150 directly binds to PSD-95 and SAP97 in neurons, and forms a PKA-containing macromolecular complex that is associated with NMDA and AMPA receptors. Moreover,AKAP79/150 binds PKA, PKC, and calcium/calmodulin-dependent phosphatase, and provides a platform on which different signaling pathwayscross-taf [2].

Scaffold Proteins Associated with Membrane Receptors

Scaffold proteins modulate receptor-dependent signaling in two ways: by clustering of receptors and through the assembly of signalsome physically associated to receptors. Scaffold proteins often cluster different categories of membrane proteins such as receptors, channels, and transporters. Na^+/H^+ exchanger regulatory factor (NHERF) binds to β_2-adrenergic receptor in an agonist-dependent manner and mediates the change of cellular pH after stimulation of adrenergic receptor. Likewise, synaptic scaffold proteins link different receptors. PSD-95 directly binds to NMDA receptors, and indirectly associates with AMPA receptors through its interaction with stargazin. NMDA receptors are also linked to metabotropic glutamate receptors by sequential interactions of PSD-95, GKAP/SAPAP, Shank, and Homer/Vesl. PSD-95 also links β_1-adrenergic receptor to NMDA receptors. GRIP binds AMPA receptors and Eph receptor kinases by different PDZ domains. Moreover, GRIP binds EphrinB, a transmembrane ligand for Eph, and LAR family of receptor tyrosine phosphatase *via* liprin-α proteins. Tamalin interacts with metabotropic glutamate receptors and $GABA_{B2}$ receptor. As tamalin was also identified as a GRIP-associated protein, it may interact indirectly with AMPA receptors. In Purkinje cells, Shank that is associated with metabotropic glutamate receptors through Homer/Vesl directly binds glutamate receptor delta2. Although it needs to be determined which interactions can occur simultaneously, synaptic scaffold proteins may form a functional unit composed of various membrane proteins on specific cell surface domains.

As receptor density affects receptor properties, scaffold proteins can directly modulate receptor functions by cluster formation. For instance, NEHRF and cystic fibrosis transmembrane conductance regulator (CFTR)-associated protein 70 both interact with CFTR, and

directly affect CFTR gating using tandem PDZ domains. In contrast, precise details of synaptic scaffold proteins on neurotransmitter receptors are not clear enough. NHERF binds platelet-derived growth factor receptor (PDGFR) and potentiates autophosphorylation of the receptor by oligomerization. PSD-95 induces clustering of ErbB4 and enhances ErbB4-mediated ERK signaling, although it is not shown whether PSD-95 affects autophosphorylation of ErbB4.

In addition to receptor-level regulation, scaffold proteins facilitate signal transduction through tethering signal molecules to physical proximity of receptors. β–Arrestin is a scaffold protein in G protein-coupled receptor (GPCR) signaling. The list of β-arrestin-interacting molecules includes JNK signaling molecules, tyrosine kinase, and components involved in endocytosis. β-Arrestin binds to GPCR phosphorylated by GPCR kinase and recruits interacting molecules to activated receptors. Recent intense studies have revealed that PSD-95 and other synaptic scaffold proteins bind various signaling proteins implicated in synaptic plasticity. PSD-95 interacts with GTPase-activating protein for Rap1 (synGAP-α), GDP/GTP exchange factors for Rap1 (SPAR) and Rac (Kalirin-7), tyrosine kinase fyn, and Rho target protein (Citron kinase). GRIP, tamalin, and ▶gephyrin bind GDP/GTP exchange factors for Ras (GRASP-1), ARF (ARNO), and CDC42 (collybistin), respectively. GRIP also interacts with GAP for ARF (GIT1) through liprin-α. Studies using mutant mice support that synaptic scaffold proteins are crucial for signaling of synaptic plasticity. Collectively, the data suggest that signaling molecules, only when assembled by scaffold proteins, can respond quickly to receptor activation, interact with each other efficiently to produce down-stream signals, and modulate receptor functions through the regulation of cytoskeleton and phosphorylation of receptors. A recent study has demonstrated that MUPP1 directly binds synGAP-α and CaMKII, and that CaMKII phosphorylates synGAP and suppresses its activity. Upon NMDAR stimulation, the elevation of calcium ions induces dephosphorylation of synGAP and dissociation of CaMKII from MUPP1. synGAP is then activated and inhibits p38 MAP kinase by inactivation of Rap1. The authors have demonstrated that synGAP-α phosphorylation requires the binding to MUPP1. Although how CaMKII regulates the activity of synGAP is not free of controversy, this report depicts the function of a scaffold protein in signaling well [3,4].

Function of Scaffold Proteins to Organize the Molecular Architectures in Cells

Scaffold Proteins and Cell Polarity

Scaffold proteins are important to establish, maintain, and remodel the molecular architecture of specific membrane domains. Three complexes composed of scaffold proteins and their binding partners are essential for cell polarity in epithelial cells. The first complex is Par3/Par6/aPKC. The second and the third complexes are Crumb/Pals1/PATJ and Scrib/Dlg/Lgl. Par3 have three PDZ domains, whereas Par6 has one PDZ domain and a CRIB motif to bind CDC42. PATJ is similar to MUPP1 and has L27 and thirteen PDZ domains. Dlg is SAP97 orthologue. Pals1 has L27, SH3, PDZ, and guanylate kinase domains. Scrib has a leucine-rich repeat and one PDZ domain. All these proteins function as scaffold proteins. The first and the second complexes are essential for proper formation of tight junctions in epithelial cells. The third complex is involved in the establishment of basolateral membranes. These polarity complexes link to each other. Par6 directly binds to Pals1. aPKC phosphorylates Lgl. In neurons, Par complex is involved in axon specification. The complex is localized at the tip of a newly formed axon depending on PI3-kinase, Rap1B, and CDC42, and interacts with kinesin [5].

Scaffold Proteins and Receptor Localization

Scaffold proteins regulate receptor localization on the cell surface. Receptor trafficking has been investigated most extensively for AMPA receptors. Newly synthesized AMPA receptors interact with scaffold proteins when they are still present at the ER. GluR2 interacts with PICK1, and this interaction is necessary for the export of GluR2 from the ER to the Golgi apparatus. Trafficking from cell bodies to dendrites is also regulated by scaffold proteins. GRIP binds to kinesin heavy chain and KIF5 transports GluR2 to dendrites. Although the precise details are unknown, SAP97 binds GluR1 and regulates the synaptic delivery. Stargazin and its isoforms are tetraspanins and bind all AMPA receptors. Stargazer mice, which do not have AMPA receptors on the cell surface in cerebellar granule neurons, support the essential role of stargazin in AMPA receptor trafficking. Furthermore, stargazin mediates synaptic targeting of AMPA receptors through binding to PSD-95. Additional factors that regulate synaptic targeting and clustering of AMPA receptors are cytoskeletal protein 4.1N, nPIST, and RIL. Among them, nPIST and RIL are regarded as scaffold proteins. nPIST binds to NMDA receptor subunit 2A by a PDZ domain and to stargazin by a different region. RIL binds to α-actinin by a PDZ domain and GluR1 by a LIM domain. LTP correlates with the insertion of AMPA receptors into the cell surface membranes, while LTD involves the retrieval of receptors by endocytosis. The phosphorylation state of GluR1 is important for LTP and LTD, but the effect of phosphorylation and dephosphorylation of GluR1 on the interaction with SAP97 is not well characterized. In terms of GluR2, it is proposed that dephosphorylation following the modest elevation of calcium ion triggers dissociation of GRIP

from GluR2, so that GluR2 binds to PICK1 and is removed from the cell surface. Recent studies have shed light on NMDA receptor trafficking. NMDA receptor subunit 2B is transported to dendrites by a cargo composed of CASK/Lin-7/Lin-10 that binds to KIF17. The complex of Sec8 and SAP102 is important for NMDA receptor trafficking. NMDA receptors are internalized by clathrin-coated pits. This internalization is inhibited by PSD-95 and its isoforms. Activity-dependent serine phosphorylation of NMDA receptor subunit 2B by casein kinase II inhibits the interaction with PSD-95 and SAP102, and decreases the number of receptors on the cell's surface. Tyrosine dephosphorylation is also reported to regulate the endocytosis of NMDA receptors. At inhibitory postsynaptic sites, gephyrin plays a key role in the localization of glycine and $GABA_A$ receptors. Deletion of gephyrin reduces clusters of both receptors. Gephyrin interacts with tubulin and $GABA_A$ receptor-associated protein (GABARAP) that binds to γ2 subunit. The later protein is small and does not fit the criteria of a scaffold protein, but is involved in the intracellular transport of the receptor [6–8].

Scaffold Proteins and Membrane Transport

Scaffold proteins are implicated in the transport of other proteins besides receptors. The presynaptic active zone is the membrane domain specialized for vesicle release. The active zone is composed of the matrix proteins (Bassoon, Piccolo, CAST/ERC) and functional units implicated in exocytosis (RIM, Munc13, Munc18). Most of them have modular structures and interact with each other in multiple ways. For instance, Piccolo has a PDZ domain and C2 domains, and interacts with signaling molecules (GAP for ARF (GIT1), and cAMP-GEF), a cytoskeleton-related protein (profilin and Abp), and other scaffold proteins (liprin-α, RIM, and CAST/ERC). In the synapse formation, vesicles containing scaffold proteins like Bassoon and Piccolo transport components of the active zone as packets to a nascent synapse. Furthermore, some scaffold proteins interact with motor proteins. Liprin-α has coiled-coil and SAM domains and interacts with LAR, Piccolo, RIM, CAST, GIT1, and GRIP. It also interacts with KIF1A that transports synaptic vesicles. JIPs bind to kinesin light chain and link amyloid precursor protein and ApoER2 to KIF5. Thereby, scaffold proteins may be important to ensure that distinct combinations of proteins are delivered efficiently to a specific membrane domain [9,10].

Scaffold Proteins and the Cytoskeleton

One of the major outputs of signal transduction is the morphological change of cells. As mentioned above, synaptic scaffold proteins assemble various regulator proteins for the actin cytoskeleton, and are directly or indirectly associated with the cytoskeleton. For instance, AKAP79/150 directly binds F-actin. Shank binds α-fodrin, βPIX (GEF for Rac and CDC42), and cortactin (regulator for the cortical actin cytoskeleton). RIL binds α-actinin. Cupidin, an isoform of Homer/Vesl, directly interacts with F-actin and CDC42. These scaffold proteins are positioned to transmit signals from receptors to the cytoskeleton and modify the receptor activity through the remodeling of the cytoskeleton.

Pathology

As scaffold proteins have various functions in neurons, they should be implicated in the pathophysiology of many neuronal diseases. However, to date, the number of reports is still limited. Human DLG3 encoding SAP102 was recently identified as a nonsyndromic X-linked mental retardation gene. Filamin is a scaffold protein associated with cortical actin and interacts with a large number of proteins including receptors and kinases. Filamin comprises of three members. One of the filamin genes, *FLNA*, is X-linked and its mutations cause brain malformation. Several mutant mice generated by gene targeting show phenotypes similar to human congenital diseases. The mutation of GRIP1 alters the localization of ECM protein, Fras, in keratinocytes, and leads to a phenotype that is reminiscent of Fraser syndrome with the blistered skin. Future studies may uncover mutations of scaffold protein genes in human diseases.

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Scalar

Definition
A quantity described by a single number.

►Neural Networks for Control

Scale of Nature

►Evolution and the Scala Naturae

Scent, Aroma

►Odor

Schizophrenia

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Synonyms
Schizophrenic psychosis; Morbus Bleuler

Definition
The term "schizophrenia" was introduced in 1911 by E. Bleuler meaning a splitting of emotional and cognitive functions in the affected patients. Today the international classification systems ICD-10 and DSM IV-R provide consensus criteria on symptom constellations required for this diagnosis. Leading symptoms in the acute periods of the disease are

1. Reality distortions such as hallucinations (mainly auditory and somatosensory)
2. Delusions and paranoid symptoms such as feelings of being observed or persecuted often associated with anxiety
3. Disorganization of thinking and behaviour

These symptoms are summarized as so-called ►positive schizophrenic symptoms.

Patients can also suffer from ►negative schizophrenic symptoms such as

1. Emotional flattening
2. Loss of drive and initiative
3. Social withdrawal
4. Depression

as well as from psychomotor alterations such as stupor and mutism (inability to move or to speak). Positive and negative symptoms can occur alternatively during the course of the disease or simultaneously in acute stages. Symptom constellation and the long term course of the illness vary considerably. If hallucinations and delusions prevail, the paranoid-hallucinatory subtype (reality distortion subtype) of schizophrenia has to be diagnosed, if psychomotor symptoms (often combined with anxiety) dominate, the catatonic subtype (►catatonia), if affective flattening and avolition are the leading syndrome, the hebephrenic subtype (►hebephrenia), if disorganization of thinking and behaviour are the prominent clinical signs the disorganized subtype has to be diagnosed.

There are persons – often close relatives of schizophrenics – with eccentric behaviour and anomalies of thinking and emotions that have some similarities with schizophrenia but do not reach the extent of a real schizophrenic psychosis. Such very weak forms of positive or negative symptoms are usually diagnosed as ►schizotypal personality disorder.

The typical "positive" symptoms usually start in young adulthood or late adolescence, males in general earlier and more severely affected then females. Hebephrenia often becomes obvious during or shortly after puberty. With regard to the long term course, about one third of the patients show a rather benign outcome, i.e., symptoms disappear after one or two episodes; one third has an unfavourable outcome with progressive impairment of psychotic or residual symptoms (worsening of cognitive and emotional functions) and one third has a fluctuating course with exacerbations and remissions.

It should be emphasized that the enormous variety of psychopathological alterations summarized under the term "schizophrenia" do not represent a disease entity, but rather a hypothetical construct that was created many decades ago by leading authorities in the field and is now defined by international classifications committees, whose inclusion criteria changed from issue to issue, there are moreover differences between schizophrenia definitions in ICD and DSM criteria.

Characteristics
Epidemiology and Genetics, Risk Factors
About one percent of the world's population has a lifetime prevalence of schizophrenia, this is independent from the cultural or geographical background.

Schizophrenia very seldom begins during childhood on beyond the forth decade of life. The disease has a strong genetic component. Monozygotic twins have a concordance rate of about 50%, even if they grow up in different families, first degree relatives have a concordance rate of 10–20%. This indicates that genetic and non-genetic components play an essential role in pathogenesis of schizophrenia.

Several research groups recently demonstrated that polymorphisms in the neuregulin-1 gene (chromosome 8p12) and dysbindin (DPNBP, chromosome 6p23.3) predispose to the disease. Because of the clinical complexity of psychotic symptoms, other genes might also have a pathogenetic significance. Neuregulin is important for neurodevelopmental processes, myelination and for NMDA-neurotransmission, Dysbindin is localized in the postsynaptic membranes and plays a role in neuronal signal transduction. All of these functions are believed to be disturbed in schizophrenia [1,2].

The following risk factors for later development of schizophrenia are now well established:

1. Genetic disposition (50% concordance in monozygotic twins)
2. Prenatal neurodevelopmental disorder (as indicated by, abnormal cytoarchitecture in frontal and temporal cortex) [3]
3. Birth complications (obstetric complications, hypoxia during birth)
4. Winter birth (increased risk of viral infections)
5. Chronic cannabis consumption
6. Migration (increased frequency in first and second generation Afro-Caribbean immigrants) [3]

In contrast to earlier psychodynamic oriented opinions, parental influences during childhood or educational styles do not predispose to later development of schizophrenic psychoses.

Changes in Brain Structure of Schizophrenics

Numerous structural imaging studies by computed tomography (CT) or magnetic resonance imaging (MRI) reported a broad variety of subtle structural alterations in the brains of schizophrenics. The most consistent statistical findings are [4,5]:

1. Lateral ventricular enlargement (by about 20%)
2. Enlargement of frontal, temporal and parietal sulci
3. Smaller volume of hippocampus and parahippocampal gyrus (by about 10%)
4. Decreased thickness of frontal, temporal and parietal association cortex (by 5%)
5. Reduced asymmetry between right and left hemisphere

Post mortem studies also found changes at the microscopical level [4]:

1. Cellular disarray and abnormally positioned neurons in entorhinal cortex, hippocampus and prefrontal brain, as an indicator of a prenatal disorder of neurodevelopment
2. Reduced neuropil and synaptic markers, while the number of nerve cells is unchanged
3. Alterations in myelin and oligodendroglia components [6]
4. Reduction of inhibitory interneuron terminals [7]

While cellular disarray in limbic mesiotemporal structures and frontal cortex as well as reduced cortical asymmetry are a strong argument for a prenatal developmental disorder, several MRI-studies could demonstrate a progressive loss of cortical tissue in the first years after the onset of clinical symptoms. This points to an additional degenerative component that adds to a primary neurodevelopmental disorder [3].

Neurotransmitter Theories

Dopamine

The most prominent theory on neurotransmitter dysfunctions causing schizophrenic symptoms is the dopamine theory, according to which dopaminergic functions are in some way overactive in the schizophrenic brain. This theory is essentially based on the observation that antagonists on the D2-receptor have antipsychotic properties and that dopaminergic substances like amphetamine, cocaine or L-DOPA can induce a schizophrenia-like psychosis. However, earlier reports of increased concentration of dopamine receptors in the schizophrenic brain proved to be an artefact of antipsychotic treatment. On the other hand there are reports that schizophrenics have increased dopamine release after application of amphetamine and animal models after lesions in prefrontal and limbic structures show changes in dopamine turnover similar to those observed in psychotic patients [8,9].

Glutamat

The best drug induced model for schizophrenic symptoms is the phencyclidin-(PCP)-psychosis. After PCP consumption, the full spectrum of schizophrenic symptoms (hallucinations, paranoid ideas, catatonia, disorganized behaviour) can occur. PCP, like ketamine, is an antagonist of the NMDA-subtype of glutamate receptors. Several postmortem studies found a decreased concentration of the NMDA-subreceptor NR1 in temporal cortex or thalamus. Thus, a hypofunction of NMDA-linked neurotransmission can be postulated. The glutamate agonists Glycin and D-Serine are reported to have moderate antipsychotic effects [9].

GABA

Inhibitory interneurons containing GABA as neurotransmitter are another important candidate in current neurotransmitter theories of schizophrenia. GABA-cells are responsible for the bulk of neuronal inhibition in all cortical and subcortical structures. There are

several clinical indicators of disturbed neuronal inhibition in schizophrenic patients; these are:

1. Deficits in sensory gating
2. Hallucinations (explainable as dysinhibition of sensory cortical areas)
3. Reduced latent inhibition
4. Reduced prepulse inhibition

Some studies showed decreased mRNA for the GABA-synthesizing enzymes GAD65 and GAD67 in hippocampus and frontal cortex and of the GABA-transporter GAT in inhibitory cortical synapses. The peptides parvalbumin and reelin, that are co-localized in special subclasses of GABA-interneurons, are also diminished in frontal and temporal cortex [7].

Therapy

After treatment with ►antischizophrenic drugs (synonyms: antipsychotic drugs, neuroleptics), acute symptoms usually improve within a few weeks. In many patients, prophylactic long term treatment with these drugs over years is necessary to prevent relapses.

Antipsychotic drugs or neuroleptics are dopamine antagonists whose therapeutic efficacy correlates essentially with their affinity to the Dopamine-2 (D2) receptor.

Antipsychotics can be divided into first generation or typical neuroleptics (prototype: haloperidol) and second generation or atypical neuroleptics (prototype: clozapine). The first generation neuroleptics block D2 receptors in all dopaminergic brain systems. By D2-receptor antagonism in the nigrostriatal system they often cause their "typical" extrapyramidal side effects like Parkinson symptoms and other forms of abnormal movements (dyskinesias), while their action in the mesolimbic and mesocortical dopamine system is believed to be responsible for the antischizophrenic properties. The second generation (atypical) neuroleptics have a higher affinity to the mesolimbic than to the nigrostriatal dopamine system, therefore they have much weaker or no extrapyramidal side effects, but they have antipsychotic actions that are comparable to that of the typical antipsychotics [8]. However, some of the second generation antipsychotics have other unfavourable side effects such as weight gain and other signs of a metabolic syndrome. This could be due to their affinity to multiple receptors including the histamine and serotonin receptors

Beside pharmacological treatment and after remission from acute psychosis, additional psychotherapeutic and psycho/socioeducational treatment strategies are helpful.

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Schizophrenic Psychosis

►Schizophrenia

Schizotypal Personality Disorder

Definition

Behavioural abnormalities in thinking and emotions that resemble very weak schizophrenic symptoms but do not reach an extention to be diagnosed as schizophrenia.

►Schizophrenia

Schwann Cell

Definition

Schwann cells are a type of peripheral nerve glial cell that surround axons. A Schwann cell can enclose a

number of individual axons (ensheathment), or surround a single axon with a compact spiraled sheet of its own plasma membrane (myelination). Myelination enables saltatory action potential propagation.

►Action Potential Propagation
►Myelin

Schwann Cell Column

Definition

►Schwann Cell

►Regeneration

Schwann Cell Precursor

Definition

Schwann cell precursors differentiate from migrating crest cells to become immature Schwann cells. They display a large number of phenotypic differences from both migrating crest cells and immature Schwann cells.

The majority of the cells in the embryonic day (E-)14 and E15 rat (mouse E12 and E 13) are Schwann cell precursors, and by E17 nearly all cells present in the peripheral nerve have differentiated into Schwann cells.

The survival of the precursors depends on axonal survival signal, neuregulin-1.

►Schwann Cell
►Schwann Cells in Nerve Regeneration

Schwann Cells in Nerve Regeneration

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Definition

The Schwann cell is a type of peripheral nerve glial cell that surrounds and interacts with axons. There are two types of Schwann cells: myelinating and non-myelinating. Whereas myelinating Schwann cells form myelin around fast-conducting, large-diameter axons, non-myelinating Schwann cells surround smaller-diameter axons without forming a myelin sheath.

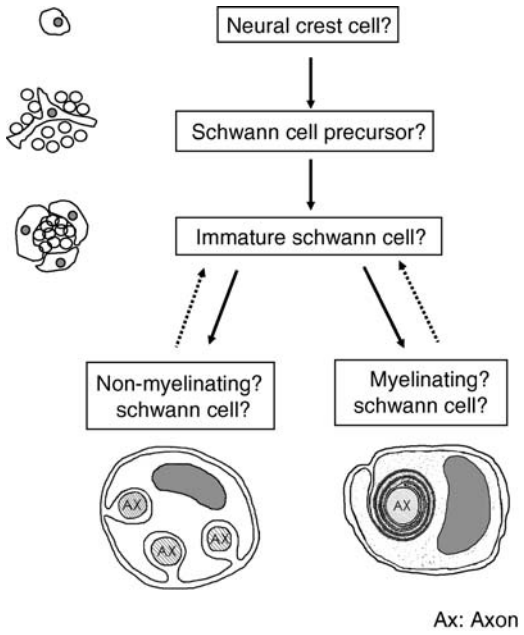
Characteristics

Development and Classification of Schwann Cells

Studies in rats and mice have led to an understanding of the process of Schwann cell maturation. Most Schwann cells develop from cells derived from the ►neural crest. The neural crest is a transient group of cells that delaminates from the dorsal part of the neural tube during embryonic development. In the trunk region, cells of the neural crest give rise to glial cells, neurons of sensory, sympathetic, and parasympathetic ganglia, chromaffin cells, and melanocytes. Between undifferentiated migrating crest cells and mature Schwann cells lie three main developmental transitions: first, the formation of ►Schwann cell precursors; second, the formation of immature Schwann cells; and lastly, the reversible generation of myelinating and non-myelinating cells (Fig. 1).

Schwann cell precursors are the most prevalent cell type in peripheral nerves at embryonic day (E-) 14/15 in rats (E12/13 in mice), and by E17/18 in rats (E15/16 in mice), nearly all cells resident in peripheral nerves are Schwann cells or their precursors. Immature Schwann cells differentiate into myelinating Schwann cells initially, and form mature non-myelinating cells as development progresses. These Schwann cells regulate the development of the three main components of peripheral nerves – the neurons, connective tissue cells, and the Schwann cells themselves – to construct the peripheral nervous system (PNS).

Various proteins are markers of Schwann cell differentiation during embryonic development [2]. Use of these markers has been crucial for the characterization of the differentiation of Schwann cells from precursors to mature myelinating or non-myelinating cells, and for defining the roles of Schwann cells in the developing and adult PNS. The markers can be classified into four categories. The first category consists of markers that are found on embryonic PNS glia, but do not differentiate between developmental stages as these proteins are also expressed at later stages of Schwann cell development. An example of this type of marker is the cell adhesion molecule ►L1. A second class of markers are those that are found on crest cells and Schwann cell precursors but at very low levels on immature Schwann cells, including N-cadherin and the transcription factor ►AP2α. The third class of markers includes proteins that allow for the differentiation of Schwann cell precursors and immature Schwann cells from crest cells. This class is comprised of fatty acid binding protein ►B-FABP, ►protein zero (P0) and desert hedgehog (►Dhh), which are also not found on



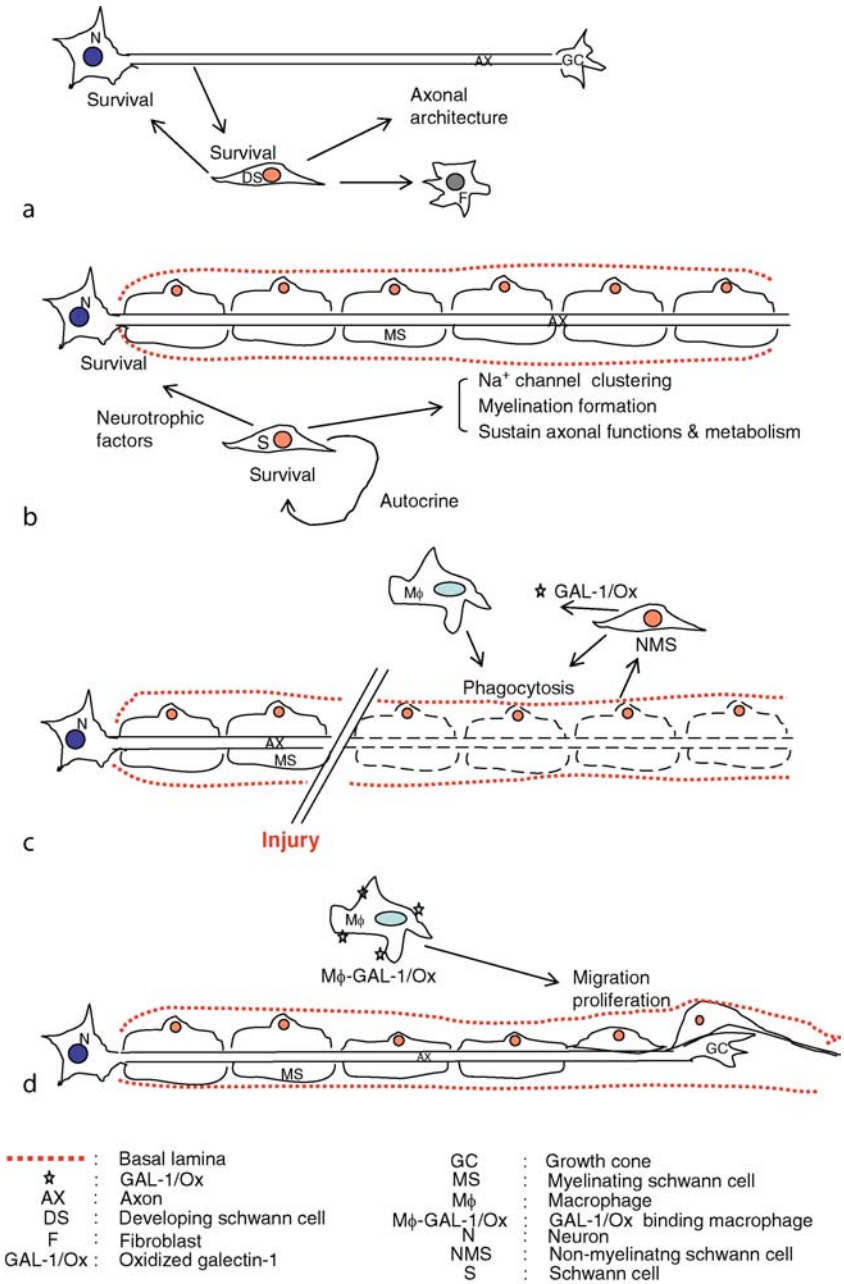
Schwann Cells in Nerve Regeneration. Figure 1 The Schwann cell lineage in the rat and mouse. Most Schwann cells develop from cells derived from the neural crest. Between migrating crest cells and mature Schwann cells lie three main developmental transitions: first, the formation of Schwann cell precursors; second, the formation of immature Schwann cells; and last, the reversible generation of myelinating and non-myelinating cells [1]. The Schwann cell precursors are always in close apposition to axons that are of similar size. They possess extensive sheet-like processes that contact and form junctions with processes from neighboring cells, thereby surrounding large groups of axons. These precursors differentiate into immature Schwann cells which display a large number of phenotypic differences from the precursor cells. The immature cells subsequently differentiate into two kinds of mature Schwann cells, myelinating and non-myelinating. Whereas myelinating Schwann cells associate with large diameter axons (Ax) in a 1:1 ratio, non-myelinating Schwann cells loosely ensheath numerous small diameter axons. Since Schwann cells are labile throughout their life cycle, differentiation into myelinating Schwann cells and non-myelinating Schwann cells is reversible [1].

early developing neurons and therefore provide a distinction between the neuronal and glial lineage at an early stage. The fourth group of markers consists of those that are found exclusively on immature and mature Schwann cells, and can therefore be used to distinguish these cells from Schwann cell precursors or crest cells. Markers in this class include calcium binding protein ►S-100 and glial fibrillary acidic protein (GFAP). Studies on the expression patterns of the aforementioned markers have led to the conclusion that immature Schwann cells reversibly differentiate into two types of cells, myelinating Schwann cells and non-myelinating Schwann cells. Both of these cell types closely associate with axons in mature PNS, and they have essential roles in maintaining the appropriate structure and function of the PNS. They are also critical players in the processes of degeneration and regeneration following nerve injury.

Function

Schwann cells have been implicated in the development of various components of the peripheral nerve. Factors secreted by Schwann cells are important in the survival of immature neurons, and in the development of the connective tissues that provide protection and mechanical support for peripheral nerves (Fig. 2a). Schwann cells and their precursors regulate nerve development actively through their interactions with axons. Likewise, axons release factors that have effects on the survival and development of immature Schwann cells. One example of this reciprocal interaction is provided by mice that lack the neuregulin-1 receptor. Neuregulin-1 is the major axonally derived Schwann cell mitogen and survival factor, and it supports the survival of Schwann cell precursors [3]. Schwann cells and their precursors are severely depleted in peripheral nerves of mice lacking the receptor for neuregulin-1. Another phenotypic abnormality is also apparent in these mice: most sensory neurons and cervical and lumbar motoneurons are lost during the second half of embryonic development [4]. This suggests that Schwann cells and their precursors act as a source of developmental signals that are crucial for the survival of peripherally projecting neurons and the generation of peripheral nerves. Recent research has also implicated Schwann cells in the formation of the connective tissue structure of the nerve, which includes the endoneurium, perineurium, and epineurium. These act as protective diffusion barriers [5]. Thus, Schwann cells and their precursors have key roles both in the survival of developing neurons, and in the production of the connective tissue sheaths of peripheral nerves (Fig. 2a).

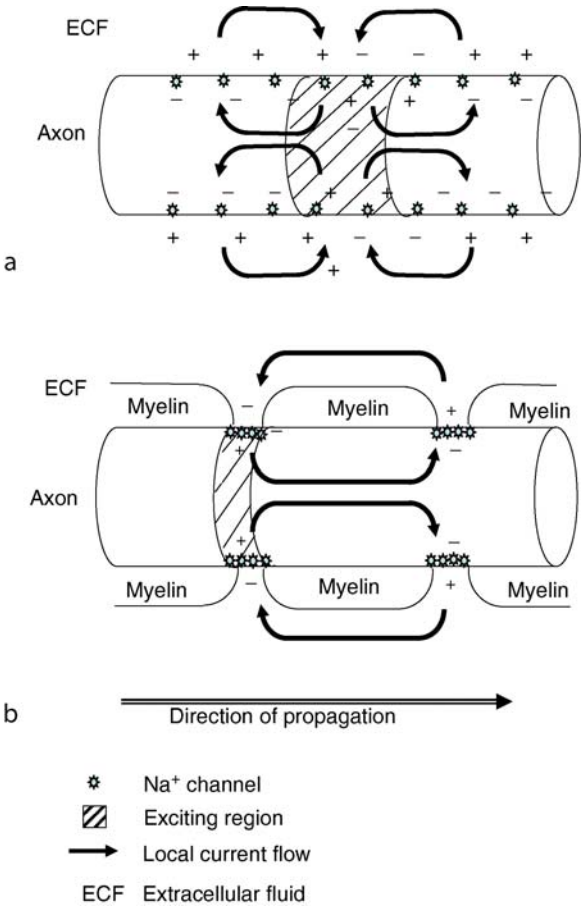
As mentioned above, myelinating and non-myelinating Schwann cells represent the terminal step of Schwann cell differentiation. These cells express distinct sets of proteins involved in cytoskeletal dynamics, associate with different sizes and numbers of axons, and have some disparate effects on the axons that they ensheath. Non-myelinating Schwann cells express high levels of the neural cell adhesion molecule (NCAM) and L1, modest levels of the neurotrophin receptor ►$p75^{NTR}$ and the growth-associated protein-43 kDa (GAP-43), and contain a distinct set of cytoskeletal proteins including glial GFAP. These cells do not express myelin-related proteins. In contrast, myelinating Schwann cells express little or no NCAM, L1, $p75^{NTR}$, GAP-43, and GFAP. Instead, these cells express high levels of the structural components



Schwann Cells in Nerve Regeneration. Figure 2 Roles of Schwann cells in peripheral nerve during development, in the adult animal, and following nerve injury (Wallerian degeneration and subsequent axonal regeneration). (a) Developmental stage; (b) Mature stage; (c) Degeneration; (d) Regeneration. During developmental stages (a), Schwann cells and their precursors provide survival signals to neurons, and contribute to constructing the connective tissue sheaths of the nerves. Their survival is supported by axons via neuregulin-1. Upon maturation of the nerve and its cells (b), Schwann cells can survive by themselves and support neurons via neurotrophic factors. At this stage, Schwann cells have also formed myelin sheath around axons to propagate action potentials more quickly via saltatory conduction. After nerve injury, Wallerian degeneration (c) occurs distal to the site of axotomy. Axons and myelin sheaths are fragmented into debris and are phagocytosed by cells in the local microenvironment. Denervated myelin-forming Schwann cells de-differentiate into immature Schwann cells. The debris is phagocytosed in part by Schwann cells, but mainly by invading hematogenous macrophages. The Schwann cells secrete GAL-1/Ox. During the regeneration phase (d), the secreted GAL-1/Ox binds to macrophages and induces the release an unidentified factor that promotes Schwann cell migration. Regrowing axons from proximal stumps can then extend their processes along migrating Schwann cells towards their peripheral targets.

of the myelin sheath, including P0, myelin basic protein (MBP), peripheral myelin protein 22kDa (PMP22), connexin32, myelin-associated glycoprotein (MAG), and ►periaxin [2]. Both types of Schwann cells surround axons to support neuronal survival by supplying trophic factors; however, unlike developing Schwann cells, mature Schwann cells can survive without support provided by axons (Fig. 2b).

Whereas non-myelinating Schwann cells loosely ensheath and support numerous small-diameter axons, myelinating Schwann cells surround large-diameter axons to furnish the myelin sheaths that insulate specific axonal populations in the PNS. Each individual myelinating Schwann cell forms a segment of myelin sheath about 1mm long on a single axon. The sheath assumes its form as the inner tongue of the Schwann cell and turns around the axon several times, wrapping it in concentric layers of membrane (Fig. 1). The intervals between segments of myelin are known as nodes of Ranvier. Myelination increases the diameter of axons and helps to direct Na^+ channels to the ►node of Ranvier [6]. Na^+ channels, which homogeneously distribute in the axonal membrane of unmyelinated axons (Fig. 3a), accumulate at these nodes. This accumulation essentially enables action potentials to "jump" from one node of Ranvier to the next (Fig. 3b). This jumping of action potential from node to node is called ►saltatory conduction. It is a rapid process, as it allows myelinated axons to conduct up to 50 times faster than the fastest unmyelinated fibers. Myelination results in significant increases in the total number of neurofilaments and the proportion of phosphorylated neurofilaments, which comprise the majority of the axonal cytoskeleton [7].



Schwann Cells in Nerve Regeneration. Figure 3 Local current flow (movement of positive charges) around an impulse in unmyelinated and myelinated axons. (a) Unmyelinated axon, (b) myelinated axon. Na^+ channels, which distribute homogeneously in the membranes of unmyelinated axons, cluster at nodes of Ranvier in myelinated axons. Action potentials are transmitted differently in the two axons. Unmyelinated axons propagate action potentials by electronically depolarizing the membrane directly ahead of the charge. In contrast, myelinated axons propagate the signal by depolarizing the membrane present in the next node of Ranvier, effectively allowing the charge to "jump" down the axon at high velocity (saltatory conduction).

Pathology

Two basic pathologies can occur in the PNS: Wallerian degeneration resulting from nerve injury and segmental demyelination caused by autoimmunity to peripheral nerve myelin. Wallerian degeneration refers to all of the events that occur distal to the site of axotomy, and is a feature of any insult that causes axonal degeneration. During the first week post-axotomy, axons fragment and disappear, and the myelin sheaths separate at incisures, breaking up into debris. Both myelinating and non-myelinating Schwann cells are denervated and are affected significantly by nerve injury. Denervated myelinating Schwann cells are plastic and change to become immature Schwann cells (Fig. 2c). Over the next few weeks, this myelin debris is phagocytosed in part by Schwann cells but mainly by macrophages that invade the degenerating nerve from blood vessels. The clearance of myelin debris, which contains proteins that inhibit axonal regeneration, is required for regenerating axons to enter and grow into the degenerated nerve. Schwann cells undergo extensive proliferation between 3 and 5 days post-axotomy, and those that phagocytose myelin are activated to produce factors that promote axonal extension. The basal lamina persists and surrounds the column of denervated Schwann cells. Denervated, previously myelinating Schwann cells express many of the proteins that are characteristic of non-myelinating Schwann cells such as NCAM, L1, $p75^{NTR}$, and GAP-43, and dramatically decrease their synthesis of myelin-related proteins and glycolipids. These observations indicate that axonal signals are required to maintain the phenotype of mature Schwann cells.

Autoimmune demyelinating peripheral neuropathies, like ►Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), are characterized by local inflammation and demyelination of peripheral nerves. Both sensory and motor axons are often affected, resulting in acute motor weakness affecting at least one limb associated with areflexia. Since most patients respond well to treatment with high dose intravenous immunoglobulin G or to plasma exchange [8], circulating self-recognizing antibodies are presumably involved in these disorders.

Therapy

Schwann cells play essential roles in the regeneration of peripheral nerves, and have been used as a cellular source for factors that promote the regeneration and remyelination of injured axons in the central nervous system (CNS) [9]. Successful peripheral nerve regeneration requires the concerted interplay of non-neuronal cells, growth factors, cell adhesion molecules, extracellular matrix components, regenerating axons, and recruited macrophages [10]. In the past, initiation of axonal outgrowth after axotomy was thought to be regulated mainly by neurotrophic factors; however, more recent studies have identified another factor that is important in this process. This factor is the oxidized form of ►galectin-1 (GAL-1/Ox), which has been shown to increase the rate of initial axonal regrowth by facilitating the interaction of neuronal and non-neuronal cells after injury [11].

The pattern of expression of GAL-1 in cells of the peripheral nerve is consistent with its potential role in enhancing axonal regrowth following insult. A common model for peripheral axotomy involves injury to the sciatic nerve, which contains axons projecting from dorsal root ganglion neurons and motoneurons. These axons, along with Schwann cells, express the reduced form of GAL-1 (GAL-1/Red) and subsequently release these molecules into the extracellular space via a non-classical pathway. After sciatic nerve injury, axons are damaged and Schwann cells become reactive. Axons in the proximal nerve stump are sealed at the injury site. The secretion of GAL-1/Red is increased by these injured axons, especially from their growth cones. Reactive Schwann cells likely secrete GAL-1/Red in the same manner following axotomy. The GAL-1 molecules that are released into the extracellular milieu have two potential fates. First, some GAL-1/Red will bind to β-galactosides located on cell surfaces. A second event may also occur: some GAL-1/Red molecules may not interact with carbohydrate moieties and can enter the extracellular space, where they could be oxidized in the presence of agents such as NO that are induced by injury. Oxidation of GAL-1 involves the formation of three disulfide bonds and the loss of lectin (carbohydrate-binding) activity. It is this form of GAL-1 that has been shown to enhance initial axonal outgrowth following peripheral nerve injury.

The major cellular target of GAL-1/Ox appears to be macrophages, and it is through events downstream of this interaction that axonal regrowth is accelerated. Target macrophages include those endogenous to the nerve itself, and those that are recruited from the blood in response to injury. The binding of GAL-1/Ox to a specific receptor on the plasma membrane of macrophages initiates a signal transduction cascade that leads to the secretion of an unidentified factor, which has been shown to promote axonal regrowth and Schwann cell migration after nerve injury. Migration of Schwann cells and fibroblasts from both proximal and distal stumps is important for the formation of cellular scaffolds that support regenerating axons. Treatment with GAL-1/Ox promotes Schwann cell migration from both stumps and accelerates axonal extension following injury, resulting in the promotion of functional recovery (Fig. 2d) [12]. Thus, GAL-1/Ox promotes the initiation of axonal regeneration in the PNS in animal models of neuropathy, suggesting that the factor may be useful therapeutically to enhance peripheral nerve regeneration.

The interaction between injured axons and cells in their microenvironment, including denervated Schwann cells, is critical for the successful regeneration of these axons. After injury and axonal sealing, growth cones are produced at the node of Ranvier located close to the proximal stump of the lesion. They must reach the distal nerve stump, which is possible even if there is a small gap between the proximal and distal nerve stumps. Upon arrival at the distal nerve stump, growth cones enter "Schwann tubes" (bands of Büngner), which consist of ordered columns of Schwann cells and their basal laminae. These bands provide the sole pathway for growth of regenerating axons in the distal nerve stump. Subsequent axon-Schwann cell interactions during nerve regeneration are fundamentally similar to those that occur during development. During early stages of regrowth, Schwann cells surround bundles of regenerating axons. As regeneration progresses, myelinating Schwann cells segregate with larger fibers into a 1:1 relationship, elaborate new basal laminae, and form new myelin sheaths. Much of the cholesterol and even a portion of the phospholipids of the original myelin sheaths are reincorporated into these new myelin sheaths. Macrophages and endoneurial fibroblasts are the key to this process, as they secrete lipoproteins that contain the recycled cholesterol and fatty acids, which are taken up by Schwann cells via low-density lipoprotein receptors [13]. With time, remyelinated axons may enlarge to nearly normal diameter, but the thickness of myelin sheaths and length of the myelin internodes do not recover to their uninjured sizes [14].

The pathway taken by regenerating axons to the targets depends largely on the nature of the lesion. After crush or freeze injury, the basal laminae of the Schwann cells remains intact at the site of injury. Growth cones usually remain within their basal lamina tubes, which guide them to their original targets. In contrast, nerve transection disrupts the continuity of the basal laminae. In this situation, axons usually do not enter their original Schwann tubes, and therefore do not reinnervate their original targets selectively. During the final stage of axonal regeneration, growth cones of regenerating axons passing through the distal nerve are guided to their targets by Schwann cells, resulting in the formation of functional neural networks.

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Schwannoma

Definition

Tumor of the ►myelin sheath built by ►Schwann cells.

►Myelin
►Schwann Cell

Sciatic Neuritis

►Neural-Immune Interactions: Implications for Pain Management in Patient with Low-Back Pain and Sciatica

Sciatica: Radiculopathy

►Neural-Immune Interactions: Implications for Pain Management in Patient with Low-Back Pain and Sciatica

SCN

►Suprachiasmatic Nucleus

SCN9A

Definition

Na^+ channel gene that encodes Nav1.7, in patients with inherited erythromelalgia (IEM).

►Sodium Channels
►Voltage-gated Sodium Channels: Multiple Roles in the Pathophysiology of Pain

Scolopidium

Definition

The individual mechanosensory receptor unit of an insect auditory organ that consists of a linear chain of four cell types: (i) one or more bipolar neurons, (ii) a scolopale cell that forms a lumen around the cilium of the neuronal dendrite and whose cytoplasm contains electron dense scolopale rods, (iii) attachment cells that mechanically anchor and support the scolopale cell, and (iv) accessory cells that envelop and provide nutritive and mechanical support to the neuronal soma.

►Invertebrate Ears and Hearing

Scotoma

Definition

A scotoma is an area within the visual field in which a person is blind. Scotomata may be caused by damage to the retina or damage to visual areas within the brain.

When a scotoma is relatively small patients may not even notice that they have a visual defect (just as we do not typically notice that we have a blindspot in the region of the retina where the optic nerve leaves the eye).

►Blindsight
►Vision

Scotopic

Definition

Night condition or vision.

Scratch Reflex

►Scratching

Scratching

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Synonyms

Scratch reflex; Wiping reflex

Definition

Scratching is a motor behavior elicited by tactile stimulation of a site on the body surface [1–10]. During a scratch, a nearby limb reaches towards and rubs against the stimulated site.

An organism can scratch using a variety of strategies, or forms, according to the biomechanical demands of the task [10]. A human can use an elbow-over-the-shoulder strategy to scratch a site on the person's upper back and an elbow-under-the-shoulder strategy to scratch a site on the person's lower back. While only one strategy may be used to scratch each site on the back, a site located elsewhere may be scratched using more than one strategy. Either the hand or the elbow can successfully rub against a lateral site on a person's thorax. This is an example of motor equivalence.

A vertebrate with a complete transection of the spinal cord, termed a ►spinal vertebrate, may produce successful scratching [7]. Supraspinal neuronal structures are not required for the generation of scratching behavior in these spinal vertebrates. Scratching has been studied in several spinal organisms: frog, turtle, cat, and dog. The spinal cord can select the appropriate strategy or form required to rub against a specific site.

For hindlimb scratching in frog [3] and in turtle [5,10], rostral scratching is used to rub against sites anterior to the hip in the midbody, lateral or pocket scratching is used to rub against sites near the hip, and caudal scratching is used to rub sites posterior to the hip near the anus.

A ►motor pattern is a specific sequence of motor neuron and/or muscle activations that occur during a behavior. In response to tactile stimulation of a site on the body surface, scratch motor patterns have been obtained with ►electromyographic recordings (EMGs) of muscle action potentials from specific muscles [5], as well as with ►electroneurographic recordings (ENGs) from nerves innervating these muscles [4,6,8]. For each scratch form, there is a specific motor pattern [4–6].

Movement-related sensory feedback can strongly modulate the characteristics of scratch motor patterns; such feedback is not required for the production of a scratch motor pattern, however. In an immobilized spinal vertebrate with all movement-related sensory feedback removed following blockade of neuromuscular synapses with a nicotinic acetylcholine receptor antagonist such as curare or gallamine, tactile stimulation evokes an excellent scratch motor pattern of ENG activation [4,6,8]. In response to stimulation of a specific site, the ENG motor pattern in the immobilized spinal preparation is an excellent replica of the EMG motor pattern in the spinal preparation with movement.

The neuronal networks in the spinal cord that produce scratch motor patterns in the absence of movement-related sensory feedback are termed ►central pattern generators (CPGs). Since these ENG motor patterns are produced in the absence of actual movements, they are termed "►fictive" motor patterns.

Characteristics

Quantitative Description

Scratching is often rhythmic. The rhythmic scratch motor pattern can be generated by a spinal CPG without movement-related sensory feedback; this establishes that the spinal CPG network is a neuronal oscillator.

The specific phase of the rhythmic scratch cycle during which a portion of the limb rubs against the stimulated site is a key feature of the scratch cycle [10]. The position of a toe in space as a function of time can be used to measure the scratch rhythm. The angles of several joints, e.g. hip and knee, are additional measures of the rhythm. The relative timing of knee angle in the cycle of movement of hip angle is a sensitive measure of the specific form of the scratch. In the turtle, the timing of the knee angle in the cycle of the hip is distinct for each form. The hip motor rhythm, the timing of activation of hip flexors and hip extensors as measured with EMGs or ENGs, is an important measure. The relative timing of knee extensor activity in the hip motor rhythm is distinct for each form of the scratch in the turtle [4–6].

Higher Level Structures

Scratch motor patterns are produced by CPGs. CPG neuronal networks are found in many organisms and produce a wide variety of rhythmic behaviors such as breathing, ►scratching, stepping, and swimming [9]. Current research programs in many laboratories include studies designed to reveal characteristics of these neuronal networks.

Lower Level components

Tactile stimulation of a site on the body surface activates cutaneous afferent neurons whose axons enter the spinal cord via dorsal roots. Cutaneous afferents activate cutaneous interneurons. The scratch CPG includes the spinal cord interneurons that generate the scratch motor pattern. CPG interneurons are activated by cutaneous afferents and cutaneous interneurons. Some CPG interneurons have outputs that synapse upon limb motor neurons. These limb motor neurons synapse in turn upon the specific muscles of the limb that are activated during a scratch.

Structural Regulation

Stimulation of a distinct set of cutaneous afferents activates the scratch CPG to generate a specific scratch motor pattern. The dynamic physiological structure of the scratch CPG is regulated by the activation pattern of tactile afferent inputs.

During the normal pattern of scratching, each agonist at a joint rhythmically alternates between activation and quiescence. During a normal scratch, each antagonist at a joint is active during agonist quiescence. During an antagonist deletion variation of scratching, the antagonist is quiet and there is no quiescence between successive bursts of agonist activation. The best-studied deletion is the hip-extensor deletion variation of rostral scratching in the turtle [6,8]. Knee-related deletions have also been described in the turtle. The occurrence of deletions demonstrates considerable flexibility in the dynamic structure of the scratch CPG.

Higher Level Processes

CPGs for rhythmic scratching have properties shared with CPGs for other rhythmic behaviors, e.g. breathing, stepping, or swimming. What the neuronal mechanisms are that are responsible for generation of the motor rhythm and the specific sets of motor patterns is a fundamental issue for all CPGs.

Lower Level Processes

Intracellular recordings from motor neurons and extracellular single-unit recordings from spinal interneurons during fictive scratching have provided important insights into the processes responsible for the production of the scratch motor pattern [1,2,4,6,8]. These recordings provide support for a modular organization of the scratch CPG.

Some studies of CPGs have focused upon evidence for a half-center modular organization; other studies of CPGs have focused upon evidence for a unit-burst-generator modular organization [6,8,9]. In the hypothesis of a half-center organization of a CPG, all the flexors of a limb are active at one phase of the cycle and all the extensors of a limb are active at a different phase of the cycle. Reciprocal inhibition between the flexor half-center and the extensor half-center is postulated to be the sole basis for CPG rhythmicity. This half-center organization does not apply to the rostral scratch in the turtle, since monoarticular knee-extensor motor activity is active during the latter portion of hip-flexor motor activity.

In the hypothesis of a unit-burst-generator organization of a turtle rostral scratch CPG, there is a hip-flexor ►module, a hip-extensor module, a knee-flexor module, and a knee-extensor module, etc. Reciprocal inhibition between agonist and antagonist modules at the hip joint is postulated to be one of the bases for CPG rhythmicity. Additional bases for CPG rhythmicity are reciprocal inhibition between agonist and antagonist modules at each other joint of the limb. Still other bases for rhythmicity are the intrinsic oscillations of each module (="unit-burst-generator"), e.g. the hip-flexor module is postulated to be rhythmogenic even when the hip-extensor module is quiet.

Studies of normal rostral scratching as well as deletion variations of rostral scratching provide support for the unit-burst-generator hypothesis of CPG organization [6,8,9]. During normal rostral scratching, hip-extensor interneurons are active during hip-flexor motor neuron quiescence. During the hip-extensor deletion variation of rostral scratching, hip-extensor interneurons as well as hip-extensor motor neurons are quiet [8]. This supports the concept that hip-extensor interneurons belong to a hip-extensor module that acts in concert. These interneurons are active during hip-flexor quiescence of normal rostral scratching, and these interneurons are quiet during the hip-extensor deletion variation of rostral scratching. In addition, these results provide support for the idea that the hip-flexor module is rhythmogenic and its rhythmicity does not depend upon interneuronal activity in the hip-extensor module. Further support for the unit-burst-generator concept of the scratch CPG has been obtained with intracellular recordings from hip motor neurons during normal rostral scratching and during the hip-extensor deletion variation of rostral scratching [6]. There is also support for rhythmogenic knee-flexor and knee-extensor modules.

Process Regulation

Scratch CPG interneurons are broadly tuned [4,9]. They fire with maximal frequency in response to stimulation of a specific site on the body surface. For example, a rostral-tuned interneuron fires with maximal frequency in response to stimulation of a site in the rostral scratch receptive field. The interneuron responds with lower frequencies in response to stimulation of other sites on the body surface. Many scratch CPG interneurons are active during more than one form of the scratch. For example, many rostral-tuned interneurons are also activated in response to stimulation of a site in the pocket scratch receptive field. This suggests that the CPG interneurons for one form of scratch are also members of the CPG for other forms of scratch. Selective output of broadly tuned interneurons has been proposed as a mechanism that contributes to the production of specific scratch forms. In this hypothesis, the outputs of rostral-tuned interneurons support the co-activation of knee extensors and hip flexors that occurs during rostral scratching.

There are multisecond excitability changes that occur in the scratch CPG in response to tactile stimulation of a site on the body surface. In response to a brief stimulus, there is often a motor after discharge that outlasts the stimulus by several seconds [1]. After the motor after discharge has ended, there may also be activation of long afterdischarge interneurons in the spinal cord that fire for many seconds after the motor afterdischarge has ended. The firing of these interneurons may be a basis for a multisecond "memory" of cutaneous activation in the spinal cord. Intrinsic modulation of voltage-gated calcium channels in spinal circuitry may also occur following the activation of metabotropic glutamate receptors in response to a tactile stimulus [1]. Future experiments are needed to understand the roles of this intrinsic modulation in the production of scratch motor patterns.

Function

Scratching serves to generate force against a site on the body surface that has received a tactile stimulus. One function of a scratch is to remove the object that has generated the tactile stimulus. For scratching to be successful, the nervous system must be able to calculate the location in space of the stimulated site on the body surface, and control the musculature of a limb so that a portion of the limb is moved to that same location in space. Scratching is an example of a ►sensorimotor transformation. Since scratching can be produced in animals with a complete transection of the spinal cord, spinal structures can perform sensorimotor transformations without neuronal interactions with supraspinal structures.

Therapy

Studies of scratching provide support for the concept that spinal cord CPGs have considerable complexity. Rehabilitation strategies for spinal-injured humans based upon the assumption of spinal CPGs show considerable promise.

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Seasonal Affective Disorder (SAD)

Definition

Seasonal affective disorder (SAD) is another term for winter depression. SAD occurs in the same person every fall/winter and remits every spring. The treatment of choice is bright light exposure scheduled in the morning. However, low-dose melatonin administration in the afternoon/evening may also be effective. For some patients, bright light should be scheduled in the evening and melatonin should be taken in the morning.

SAD is the most common affective disorder unremittingly experienced year after year in women of childbearing age living at temperate latitudes.

►Circannual Rhythm
►Circadian Sleep Phase Syndromes
►Melatonin

Seasonality

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Definition

Seasonal changes that animals undergo in order to adapt to environmental circumstances as they vary across the year.

Characteristics

Species from temperate zones experience considerable seasonal variation in their environments and many have developed complex adaptations to match their physiology and behavior to particular seasonal demands and opportunities. In mammals, the most prominent seasonal changes are seen in systems devoted to the control of energy balance and reproduction, but some species also show seasonality in non-reproductive social behaviors [e.g., aggression [1]] and immune competency [2], among other traits. There are many cues that animals can use to synchronize their seasonal cycles to environmental changes; fluctuations in average ambient temperature, rain fall and food availability are all possible candidates, but none of these is as reliable as progressive changes in daylength in predicting the flow of the seasons. Given this fact, it is perhaps not surprising to find that many species use daylength (►photoperiod) to phase their seasonal rhythms.

Photoperiodism

The term ►photoperiodism has been adopted to refer to the use of daylength by a species to orchestrate seasonal cycles in physiology and behavior. Although the vast majority of the mechanistic studies on mammalian seasonality has focused on photoperiodic species such as hamsters, sheep and ferrets, there are examples of seasonal rhythms that are independent of photoperiod and which continue with a period close to a year under constant laboratory conditions. The annual cycle of body weight and body adiposity displayed by ground

squirrels is an example of an endogenous, ►circannual rhythm that does not depend upon photoperiod [3].

Among the traits that show photoperiod-dependent seasonal cycles, reproductive physiology has received preferential attention. Work with a variety of animal models show how the shortening of the photoperiod, which signals that winter is approaching, and its lengthening in early spring can suppress gonadal function in spring and autumn breeders, respectively. Interestingly, this suppression is not maintained indefinitely, even if the animals are kept under the same daylength; after several weeks gonadal function returns to the level seen before the exposure to the non-stimulatory photoperiod. This rebound of reproductive competence is known as spontaneous recrudescence. That label implies that the recrudescence depends upon an endogenous mechanism but it also reflects our current lack of a mechanistic explanation for this phenomenon. The fact that there is a relatively fixed amount of time between gonadal regression and spontaneous recrudescence points to the existence of an ►internal interval timer that is set by exposure to a non-stimulatory photoperiod (i.e., short days for spring breeders) or by a physiological change triggered by such photoperiod (e.g., a drop in the levels of gonadal or pituitary hormones).

Photoperiodic Time Measurement and Melatonin

Pineal ►melatonin has been shown to play a central role in the transduction of photoperiod into a physiological signal. Regardless of the species-specific distribution of sleep and wakefulness across the day–night cycle, the secretion of melatonin shows a nocturnal elevation that matches the length of the dark period. The duration of this nocturnal melatonin pulse is used by photoperiodic species to measure daylength and with very rare exceptions, ►pinealectomy renders these animals insensitive to changes in photoperiod. The data from experiments with timed infusions of melatonin delivered to pinealectomized animals provide compelling evidence that the duration of the melatonin pulse drives the photoperiodic responses of the reproductive system. In hamsters relatively long-duration melatonin infusions result in gonadal regression regardless of the length of the prevailing photoperiod or the phase of the timed infusion with respect to the light dark cycle [4].

Light has two separate effects on the ►pineal gland. It ►entrains the ►circadian rhythm of melatonin secretion to the light dark cycle and it can acutely suppress melatonin production during the night. The mammalian pineal gland is not itself photosensitive. It depends upon neural inputs for its responsiveness to light. The pathway that conveys both circadian and photic information to the pineal has been described in detail in several species. It starts in the retina where a set of retinal ganglion cells that express the ►photopigment melanopsin give rise to the ►retino-hypothalamic tract, which projects preferentially to the ►suprachiasmatic nucleus (►SCN). The SCN is the main ►circadian pacemaker in mammals and it influences the pineal via a multisynaptic pathway that includes the hypothalamic ►paraventricular nucleus and its long descending projections to pre-ganglionic sympathetic neurons of the spinal cord, which in turn contact the sympathetic units of the ►superior cervical ganglia (►SCG). Axons from the SCG reach the pineal and via the release of ►norepinephrine regulate the synthesis and secretion of melatonin. Removing the eyes or transecting the optic nerve is equivalent to placing animals in short photoperiods or constant darkness. However, just like a pinealectomy, interruption of the pathway from the SCN to the pineal abolishes photoperiodic responses of most photoperiodic traits [2]. Notable exceptions are the short-day reduction in sexual behavior [5] and prolactin secretion [6] in female hamsters. These responses continue to be seen after the interruption of projections from the SCN to the paraventricular nucleus of the hypothalamus and may represent pineal-independent effects of photoperiod.

Reading and Responding to the Melatonin Signal

Even though there is universal agreement that the length of the melatonin pulse serves to encode information about daylength in photoperiodic species, there is no consensus about where in the brain this signal is read and interpreted to induce remarkable changes in multiple systems. Brain lesions in several hypothalamic sites and central infusions of melatonin directed at specific targets have identified possible candidate sites for melatonin action. However, that literature features many species differences and contradictory results even within the same species. Often the effects of central melatonin infusions are specific to a particular trait, which indicates that there may be multiple sites that respond to melatonin in parallel for the photoperiodic control of specific systems. That the critical amount of daylength necessary to support summer like features differs for different traits in the same individual [7], also argues for multiple melatonin sensitive substrates with different thresholds.

Although there is no consensus about where melatonin acts in the brain to induce gonadal regression in spring breeders such as hamsters, it is clear that part of the cause for the collapse of the reproductive system is an increase in the effectiveness of gonadal hormone inhibition of ►gonadotropin release from the anterior pituitary. This increased sensitivity to the negative feedback of gonadal steroids is a central effect, which results in diminished stimulation of the pituitary by ►gonadotropin releasing hormone (GnRH). In short

days, the pituitary remains sensitive to GnRH stimulation as shown by the activation of gonadotropin release when gonadally regressed animals receive injections of the peptide. The recently discovered brain peptide kisspeptin, which directly stimulates GnRH neurons, may also play a role in the photoperiodic regulation of the reproductive system. In hamsters seasonal gonadal regression is correlated with a reduction of kisspeptin content in the anteroventral periventricular nucleus [8].

While the central sensitivity to the negative feedback of gonadal hormones increases in short days, male and female hamsters show a partial refractoriness to the activational effects of testicular and ovarian hormones on reproductive behavior. Thus, gonadectomized male hamsters treated with identical doses of exogenous testosterone only show full activation of the male copulatory pattern when exposed to long days [9]. Similarly, ovariectomized female hamsters treated with estradiol and tested with sexually active male hamsters rarely show ►lordosis if they are kept in short days [10]. Therefore, in at least this species, seasonal infertility is achieved by suppressing the hormones of reproduction and by reducing the behavioral responsiveness to hormones that stimulate sexual behavior.

Summary and Significance for Humans

The study of seasonality and particularly photoperiodic seasonality has identified a system that extends from the ►retina to the pineal and that appears to serve as a transducer of information about daylength. This information, in the form of a nocturnal melatonin pulse, is used in a multitude of ways to produce seasonally appropriate adaptations, which increase survival and reproductive efficacy. All the components of this system have been conserved in humans, and there is evidence that humans show seasonality on a variety of traits and that these seasonal changes are driven by photoperiod. Some of us show seasonal changes in physiology and behavior, but for a few individuals these changes are extreme enough as to be considered a form of seasonal depression or ►seasonal affective disorder (►SAD). Knowledge derived from work with photoperiodic animal models is informing therapeutic interventions for SAD patients and is providing insights about milder forms of seasonal cycles in our species.

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Second Messenger

Definition

When a signal (protein hormones, growth factors, etc.) is received at the cell surface, second messengers are molecules that relay signals to target molecules inside the cell.

Second Messenger Cascade

Definition

Cascade of biochemical reaction activated by membrane receptors via trimeric G-protein leading to the generation of intracellular messengers, which in turn activate effector systems. Often mediate a considerable signal amplification.

Second Messenger Pathway

Definition

A general term indicating any of a number of intracellular signaling pathways activated by G protein-coupled receptors.

►G Protein-Coupled Receptor (Metabotropic Receptor)
►G-Protein Coupled Receptors (GPCRs) in Sensory Neuron Function and Pain
►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages

Second Somatosensory Cortex

►Somatosensory Cortex II

Secondary Hyperalgesia

Definition

Hyperalgesia at sites surrounding injured or inflamed areas.

►Hyperalgesia and Allodynia

Secondary Motor Areas

Definition

Motor areas of the cerebral cortex, other than primary motor cortex, located in the frontal lobe. These areas all contain corticospinal neurons and make synaptic connections with primary motor cortex. Six areas have been identified in primates including two areas on the lateral surface of hemisphere (dorsal premotor area, PMd and ventral premotor area, PMv) and four areas on the medial wall of the frontal lobe including supplementary motor area (SMA) and three cingulate motor areas (CMAr, CMAd, CMAv).

►Corticospinal Neurons
►Motor Cortex: Output Properties and Organization
►Primary Motor Cortex (M1)
►Visual Space Representation for Reaching

Secondary Neurodegeneration

Definition

Progressive post-injury degenerative damage or death of neural tissue that escaped primary damage. It is mediated by many compounds and processes: for example, increased content of excitatory amino acids in the extracellular milieu; deprivation of growth factors; impairment of blood supply; increase in reactive oxygen species; and general ionic imbalance. The process is common to many neurodegenerative disorders and acute injuries of the central nervous system (CNS).

Secondary Neurogenesis

►Adult Neurogenesis

Secondary Prosencephalon

Definition

Rostral subdivision of the embryonic forebrain that gives rise to the hypothalamus (ventrally), the telencephalon (dorsally) and the eye vesicle (laterally).

►Evolution and Embryological Development of the Forebrain

Secondary Receptor Cell

Definition

Specialized, non-neural sensory cell.

►Electroreceptor Organs

Secondary Reinforcer

Definition

Initially neutral sensory stimulus that obtained rewarding properties by previous association with a primary reinforcer.

►Operant Conditioning

Secondary Sensory System

Definition

►Sensory Systems

Secondary Somatosensory Cortex (S2)

Definition

A higher order sensory area, located within the depths of the lateral sulcus. Its inputs arise from a variety of sources, including S1 cortex and regions of the posterior parietal cortex. Receptive fields are often bilateral; inputs can be cutaneous or deep. There appear to be two body representations here: S2 proper is located caudally, while PV (parietal ventral area) is located rostrally.

►Primary Somatosensory Cortex (S1)
►Somatosensory Cortex, Plasticity

Secondary Structure of Proteins

Definition

The tendency of certain amino acid sequences to form ordered structures such as alpha helices or beta sheets. The amino acid sequence of an entire protein may be analyzed to determine those segments having a high probability of forming such structures (e.g. using the method of Chou and Fasman). For transmembrane proteins such as transmitter receptors or ion channels, these predictions may be combined with those of hydropathy analysis to identify regions that might form transmembrane pores or gating structures.

Secondary Vestibular Circuitry

►Vestibular Secondary Afferent Pathways

Secretomotor Neuron

Definition

Motor neurons of the enteric nervous system that innervate and evoke activity in the secretory glands of the digestive tract.

►Autonomic/Enteric Reflexes

Seeing

►Vision

Segment in Body Structure

Definition

Many animals are organized with repeated body units called segments. In annelid worms, like the leech, each segment is much like the next, both in its external features, musculature, and internal organs. In vertebrate animals, the segments are not so recognizable externally or in visceral organs, but are easily seen in the organization of the musculature, in the spinal cord and its peripheral nerves, and in the pattern of their sensory and motor innervation. In fishes, the chevron-shaped bands of axial muscle that flake when we cook their flesh are called myotomes and correspond to segments.

Each myotome receives its motor (and sensory) innervation from a different spinal segment via it associated segmental nerves.

Segmental Reflexes

Definition

A short-latency electromyogram (EMG) response to muscle stretch or cutaneous stimulation that depends on rapid transmission of the sensory volley and evoked motor volley and involves monosynaptic or oligosynaptic pathways within the spinal cord. Also known as spinal reflexes.

►Electromyography
►Electric Fish

Segmentation

Definition

Segmentation is characterized by closely spaced contractions of the circular muscle layer, dividing the small bowel into small segments adjacent each other. Since these movements rhythmically alternate the sites of contractions (alternating contraction), the segmentation effectively mixes and circulates chyme.

Segmentation of the Small Bowel

Definition

Segmentation is characterized by closely spaced contractions of the circular muscle layer, dividing the small bowel into small segments adjacent each other. Since these movements rhythmically alternate the sites of contractions (alternating contraction), the segmentation effectively mixes and circulates chyme.

►Bowel Disorders

Seizure

Definition

Paroxysmal, abnormal, often excessive, repetitive, stereotypical pattern of brainwave activity. Can be provoked by fever, infection or other metabolic derangement or happen spontaneously as in epilepsy.

►Anticonvulsants
►Epilepsy

Selective Feature Enhancement

►Contrast Enhancement

Selective Vulnerability

Definition

Selective vulnerability refers to the susceptibility of particular groups of neurons in the central and peripheral nervous system to age-associated neurodegeneration and death.

Selective Working Memory

Definition

Allows the formation of working memory, where task-relevant information is maintained in mind over a delay period while task-irrelevant information is filtered out through an attentional mechanism.

►Vision – Computational Approaches

Selectivity

►Ion Channels from Development to Disease

Self

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Synonyms

The term 'self' is often used interchangeably with the term 'I' and 'person' to refer to human beings by characterizing the special epistemic or normative status of human beings.

Definition

The self can be defined as the bearer of self-conscious states. From a naturalistic view the self is a cognitive system that enjoys some form of self-consciousness. Self-consciousness can be defined as the ability to consciously represent one's own states, especially (but not only) mental states, *as one's own* (Newen & Vogeley 2003). In the case of competent speakers this involves an indexical representation typically expressed by the word "I". If the relevant representation of my own states does involve neither language competence nor consciousness then we still have to presuppose a characteristic immediate self-representation. While "self" is mainly used to characterize the epistemic dimension of self-consciousness, i.e. the capacity to grasp first-person thoughts, "person" is used in debates searching for criteria of being a person which could serve as a basis for having rights and duties in society. From a linguistic point of view the term "self" is an artificial term which was constructed by nominalization of variants of the first-person pronoun "I" in natural language. We use expressions like "It's me," "myself," "she herself/he himself." "Self" was introduced to denote the bearer of the mental states of a self-conscious human being.

Description of the Theory

We can distinguish four central questions concerning self-consciousness:

The epistemological question: Do we have a privileged access to our own mental phenomena such that only we can know with certainty which mental phenomena we have?

The ontological question: Is there a self as an ontologically nonreducible entity or can we explain all phenomena of self-consciousness without presupposing a self as a nonreducible entity?

The Cognitive question: How can we investigate the natural basis of self-consciousness with the methods of empirical psychology and cognitive neuroscience?

The question about personal identity: What is the criterion of being a person and of remaining the same person?

Philosophical thinking about self-consciousness was not invented by Descartes – as often stated or implicitly presupposed – but is already present in ancient philosophy. The first book discussing important aspects of a theory of self-consciousness is Platon's early dialogue *Charmides*. Since the history of self-consciousness is already presented in other overviews, let me illustrate these three dimensions of self-consciousness while concentrating mainly on the modern discussions:

1. The epistemological dimension: Do we have self-knowledge on the basis of a privileged access? The philosophers of the period from Descartes to Kant took two claims to be evident: the transparency and the infallibility of the mind. If someone is in the mental state M then he/she knows that he/she has that state (transparency). If someone believes that he himself/she herself is in the mental state M then he/she knows that this is so (infallibility). Both claims are no longer acceptable as general claims. Given that mental phenomena can be divided into mental dispositions, (mental traits like being jealous, being anxious etc.) on the one hand and mental events (occurrences of thinking, feeling or perception) on the other, the transparency of the mind is undermined by several systematic observations. It is obvious that my mental dispositions can often be more reliably evaluated by other persons observing me than by myself. Furthermore, there is evidence that the same is also true for certain occurrences of my beliefs and desires, namely unconscious ones (as e.g. presupposed in Freud's psychoanalysis). Unconscious occurrences of feeling and perception are presupposed in modern theories of selective attention. But not only the transparency thesis, also the infallibility thesis has to go: There are cases in which we consciously think that we are in a certain mental state M1 when in fact we are in a different state M2. Concerning feelings psychological studies show that we can characterize a special class of people (repressors) who systematically misclassify their own feelings when they are in situations which make them feel personally concerned (Weinberger & Davidson 1994). In such situations repressors report being perfectly calm even though their palms are sweating, their hearts are racing at 180 beats per minute etc. This demonstrates that one can have a basic emotion while lacking a conscious representation of it. Furthermore, there is a general argument against the infallibility of self-knowledge, which shows that even basic perceptual impressions can be misclassified and that we therefore do not always enjoy self-knowledge of these impressions: In order to have self-knowledge we must classify our mental states on the basis of concepts. If

there are circumstances in which I have partially inadequate concepts or in which I may misuse my correct concepts due to psychological disorders or mental traits, I will misclassify my own mental events. Self-knowledge of our own mental states presupposes a correct classification on the basis of our concepts and this is not infallible but only *de facto* often given under normal circumstances. By the way, it should have become clear that we do not enjoy any privileged access such that only we know with certainty which mental state we have. The only privilege we enjoy concerning our mental states is called familiarity (Ryle 1949): We have much more information about ourselves than other people because we recognize a lot of our mental states during our life while other people only share a part of it. But such a situation of familiarity has to be learned: Parents often are more familiar with their children's mental states then the children themselves. Presupposing that we have standard conceptual competence and psychological conditions, there is one further principal challenge to the possibility of self-knowledge. This challenge is mainly based on the claim that the content of our thought is partly dependent on the environment. Putnam's famous thought-experiment distinguishes Tom who lives on earth and Twin-Tom, a psychophysical *Doppelgänger* living on Twin-earth. The only difference between earth and Twin-earth is that in using the word "water" on earth we refer to the well-known substance H_2O while Twin-Tom using the word "water" on Twin-earth refers to a substance which has the same superficial properties but nevertheless is chemically based on molecules XYZ. Independent of the question whether this difference in the essential properties is known to the speakers, the reference of "water" is a different substance. Therefore, if Tom utters "Water is a tasteless liquid" he is expressing a thought about H_2O while Twin-Tom using the same words expresses a thought about XYZ. The conclusion of this thought experiment is that the content of thoughts is dependent on the environment. This is called externalism of thought. The challenge to self-knowledge is produced by the following claims: (a1) Self-knowledge about the content of our thoughts is only based on introspection and therefore is independent of the environment. (a2) The content of our thoughts is dependent on the environment (externalism).

The conclusion is: Either self-knowledge is impossible or externalism is wrong. Which part of the conclusion is the correct one is still part of the recent debate, but, the problematic preaise is the externalism of thoughts while the externalism of utterances is widely accepted (Newen & Vogeley 2007).

2. The ontological dimension: Is there a self as an ontologically nonreducible entity? The *locus classicus* for a positive answer is the work of Rene Descartes. He claims that a person is constituted by a self as a purely mental entity (*res cogitans*) and a distinct body as a purely material entity (*res extensa*). An alternative traditional view was developed by David Hume. According to his view the self is nothing but a bundle of impressions (or ideas) such that there is no nonreducible entity in addition to the impressions which are the basic entities in his framework. A third important traditional view is that of Immanuel Kant. He claims that the self is not an entity at all but only a condition of the possibility of experience, i.e. the self is something that has an important status, but it can only be characterized negatively and as a consequence of conceptual considerations: There has to be a self as a precondition of experience, because otherwise we do not have an explanation for the unity of our experiences.

We have thereby already outlined the three vivid options which still dominate the recent debate in the twentieth century. Thomas Nagel argued for the Cartesian view that any person has an objective self as a nonreducible entity, because he claims that without such a presupposition we could not account for the first-person-perspective which is characteristic for our experiences. Dennett, in the spirit of the Kantian strategy, developed the view that the self is a special abstract entity: It is the centre of gravity of the stories which a person tells about herself, because we have to account for the self-ascription of beliefs and desires in our autobiographical memory. The special status of the self is then parallel to the special status of the centre of gravity which a bike has: It is a theoretical abstract entity which is a consequence of physical theory in the case of the bike and theory of mind in the case of the self. Since this analogy is rather unspecific it remains unclear what status the self has in more detail.

Furthermore, there is a modern radicalization of the Humean view, the claim that the self is not an entity at all: According to Wittgenstein and Anscombe the self is nothing but a fiction we introduced because of grammatical fallacies: In natural language we use sentences like "I am in pain" which express the fact that we are suffering from pain. Wittgenstein insisted that we would express exactly the same just by uttering the vowel "AUA!". Since it does not even make sense to ask what the reference of such vowels is, Wittgenstein concludes that the impression that there is a reference of "I" is just a consequence of drawing wrong conclusions from the grammatical surface structure of natural language to the ontological structure of the world. Although this argument – relying on the synonymy of vowels and normal utterances – is very weak (because such a synonymy exists only in some special cases), the general position that the self is only a fiction has become supported by new arguments. Metzinger (2003) presented the self-model theory of self-consciousness, claiming that the human being is a neural machine which is able to construct a self-model.

The self-model is nothing but all the contents of the stream of consciousness a human being experiences at one moment. Since the self is identified with a *content*, i.e. the content of our phenomenal consciousness, it is just a fiction, an epiphenomenal product of our neural machinery. Theories which claim that the self is a content cannot account for the basic fact that we use the word "I" to talk about persons as human beings. Therefore, there is still the option of identifying the self with the person as human being. According to Peter Strawson the self is nothing but a person, i.e. a primitive natural entity which has both mental and physical properties. In this framework self-consciousness is not explained away as a fiction but treated as a special property of human beings. According to the philosophy of language we know that uttering I-sentences is a standard way of expressing self-conscious thoughts. The property of expressing self-conscious thoughts is closely connected to the so-called essential indexicality of the first-person pronoun "I" (Perry 1979): The thought expressed by uttering an "I"-sentence (e.g. "I am hungry" uttered by Ernst Mach) is different from the thoughts expressed by utterances in which only the word "I" is substituted by a term having the same reference (e.g. "Ernst Mach is hungry") because only I-thoughts can have special motivational role. I will start to search for food only if I think that I am hungry. "I"-sentences have the feature of essential indexicality which is based on a property of self-conscious thoughts, namely the property of an immediate self-representation. The challenge for this common sense view is to explain the property of having an immediate self-representation.

3. The cognitive diveasion: There are atleast two ways of investigating this core property, taking an ontogenetic perspective, on the one hand, and measuring neural correlates, on the other. Developmental psychologists started to investigate the development of human self-consciousness (Neisser 1998). This led to different models of distinguishing types of self-consciousness (e.g. Bermúdez, 1998). The challenge is that there are several intuition-based distinctions on the market, but what we need is a systematically founded typology (Newen & Vogeley, 2003). The general line of this research is to understand full-fledged self-consciousness by understanding the way it is developed in human ontogenesis and in principle also in evolution. A presupposition of these investigations is an analysis of the complex phenomenon self-consciousness into several cognitive competences which are necessary to have self-conscious thoughts. We can distinguish (i) perspectivity, (ii) agency, and (iii) mineness. Perspectivity includes the first-person-perspective we have in human perception but also in the case of self-ascribing beliefs. Agency means the feeling that we are causing an action, the feeling that the action is performed because we want to perform it. Mineness can be characterized as the feeling that a bodily part (an arm, a leg) belongs to me, but also the feeling that a thought is *my* thought. The aim is to understand these fundamental cognitive capacities by investigating their development and explaining cases of malfunction in the case of mental diseases.

The second line of research aims at discovering the neural correlates of human self-consciousness. To measure neural correlates the general strategy runs as follows: On the basis of the conceptual analysis distinguishing perspectivity, agency and mineness, experimental paradigms to investigate different types of each capacity have to be developed. If an experimental design is validated then it can be used to measure the neural correlates. The first measurement of cognitive first-person-perspective was done by Vogeley, Bussfeld, Newen et al. (2001) measuring the neural correlates of the capacity to self-ascribing beliefs. There are further measurements of neural correlates of first-person-perspectives (Newen & Vogeley 2003, Ruby & Decety 2001 & 2003, Vogeley & Fink 2003).

Concerning the general strategy to naturalize human self-consciousness there is one basic argument which shows that we have to account for nonconceptual self-consciousness as a form of basic self-consciousness which is independent of and prior to linguistic competence. The argument is called the paradox of self-consciousness. It consists in the following incompatible propositions (Bermúdez 1998):

1. The only way to analyze the capacity to think a particular range of thoughts is by analyzing the capacity for the canonical linguistic expression of those thoughts (the Thought-Language-Principle).
2. The key to analyzing self-consciousness is to analyze the capacity to think "I"-thoughts.
3. "I"-thoughts are canonically expressed by means of the first-person pronoun and mastery of the first-person pronoun requires the capacity to think "I"-thoughts.
4. A noncircular account of self-consciousness is possible.

There is the additional background assumption that the capacity to think "I"-thoughts meets the Acquisition Constraint which says that if a given cognitive capacity is psychologically real, then there must be an explanation of how it is possible for an individual in the normal course of human development to acquire that capacity. If we accept that self-consciousness is independent from language competence (by denying 1) then we have to account for nonconceptual as well as conceptual forms of self-representation (Newen/Vogeley 2003).

4. Personal identity: Self-consciousness is closely related to the debates on personal identity. The question

"What are the criteria of individuating a person?" was introduced by John Locke and he claimed that the person, which he identifies with the self, is defined by the continuation of the content of the memory the human being ascribes to itself. This criterion can be called the demand of psychological continuation. It means that if a human being loses his memory then he no longer remains the same person. Modern thought experiments can illustrate another consequence of this criterion (Parfit 1984): If the content of the memory is represented in the brain and the brain of Peter is transplanted into the body of Karl, then the body of Karl including the brain of Peter will be the person Peter. Psychological continuation only demands a partial overlap of the memories to individuate a person. One problematic consequence of this criterion is that it can easily be imagined that there are several human beings fulfilling the criterion of partial overlap of memories with the content of the self-ascribed memories of Peter at the time t0. Presupposing that the memories of Peter at t0 are represented in his brain, we can make the following thought experiment: One half of Peter's brain is transplanted into the body of Jo and the other half of Peter's brain is transplanted into the body of Sam. It is presupposed that in both cases a significant part of Peter's memories was transferred to Jo as well as to Sam. If this scenario seems too unrealistic then think of the brain as a piece of hardware. Then the same result of having a significant overlap with Peter's memories at t0 can be produced by whatever method leads to copying or transferring a large part of Peter's memories to Sam's brain and to Jo's brain. In both varieties of thought transfer the intuitive result is that Sam and Jo both have a significant overlap with Peter's memories at t0. Who then is the person Peter at t1, after the transplantation of his brain partly into Sam and partly into Jo? The criterion says that there cannot be two persons which are both Peter and in the scenario of copying the memories of Peter into another brain, provided it happens without harming Peter, we would even have three persons Peter, the original one being identical with Sam and Jo. This leads us to an unacceptable violation of our intuitions concerning the principle of identity: Because of the normal change of a human being over time we have to accept that human beings differing in their material constitution can be the same person at different times. We cannot however accept that different human beings are the same person at the same time. Modern views of personal identity try to combine a criterion of space-time continuation with the demand of psychological continuation.

The modern debates in philosophy and cognitive science about the self are characterized by a lot of different scientific approaches – partly mentioned above – which aim at naturalizing the self and self-consciousness in all its facets, on the one hand, and some new considerations which try to present principle reasons for the thesis that this aim can never be reached (Baker 1998, Bealer 1997), on the other.

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Self-administration

Definition

In a behavioral experiment the animal may be awarded. If the animal is allowed to administer the award by itself, we speak of self-adminstration. This way of award is often used to study the addictive potency of a drug.

Self-antigen

►Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens

Self-appraisal

Definition

Self-appraisal refers to the process of self-reflecting on and evaluating own meta-cognitive knowledge and strategies (i.e., declarative) (e.g., what strategies are relevant), procedural (e.g., how to apply them), and conditional (e.g., why they are effective and when they should be applied).

►Metacognition

Self-consciousness

Definition

A person has self-consciousness when she has a thought that she can express in the first person singular. In a supermarket, one may be well aware that the person with the torn sugar bag is making a mess without realizing that it is oneself who is making a mess.

Realizing this, one lives through an episode of selfconsciousness expressible by "I am making a mess." Sometimes only an introspective awareness of one's own consciousness is called "self-consciousness."

►Argument
►Logic

Self-management

Definition

Self-management refers to the dynamic process of translating metacognitive knowledge adaptively to the task performance, and can be described as metacognition in action. It includes at least the three processes for actions: Planning, on-going evaluation by monitoring, and regulation by modifying plans and changing/adjusting strategies, and these three processes recur repeatedly depending upon situations.

►Metacognition

Self-motion Cues

Definition

Self motion cues are derived directly from locomotion and provide feedback information about speed and direction of motion. Self motion cues are egocentric.

Therefore, in order to provide information to update a location on a map, self motion cues must be accompanied by a sighting, which positions and orients the traveler on the map. Self-motion cues include proprioception (sensations from the body), optic flow, and feedback from motor commands – also called an efference copy. A synonym for self motion is idiothetic.

►Navigation

Self-perception

Definition

A concept in spatial cognition that involves mentally representing one's own action, other's action, and observation of action. Representations between self and others are shared, but not identical, influencing processes of empathy and social interaction.

►Spatial Cognition

Self-renewal

Definition

Ability to go through numerous (virtually-indefinite) cycles of cell division while maintaining the undifferentiated state. To ensure self-renewal, stem cells undergo two types of cell division: symmetric cell division gives rise to two identical daughter cells both endowed with stem cell properties, while asymmetric

cell division produces only one daughter stem cell and one progenitor cell with limited self-renewal potential.

One theory claims that the molecular distinction between symmetric and asymmetric cell division in neural stem cells lies in differential segregation of certain cell membrane proteins (such as receptors) between the daughter cells. An alternative theory – the cell non-autonomic regulation of stemness during adulthood - is that stem cells remain undifferentiated from environmental cues in their particular germinal niche. Stem cells eventually differentiate once they leave that germinal niche or no longer receive those environmental regulators.

►Autoimmune Demyelinating Disorders: Stem Cell Therapy

Self-sustaining Oscillation

Definition

One can imagine at least two starkly different mechanisms for keeping track of the passage of time. On the one hand are timekeeping mechanisms like hourglasses, which only encode the passage of time relative to an external triggering event, and can only keep time continuously if that external triggering event repeatedly occurs. On the other hand are self-sustaining oscillators like pendulum clocks, which encode the passage of time relative to an internally determined repeating interval of time, in this case the 12-h half-day, and keep time over multiple intervals without requiring external triggers.

Circadian clocks are all self-sustained oscillators, as demonstrated by the continuation of circadian rhythms of various biological functions when organisms are maintained in environments that are devoid of any external cues to the passage of time.

►Cellular Clock
►Circadian Rhythm
►Morning/Evening Oscillators
►Oscillator Versus Hourglass Timers

Self-synapse, Recurrent Synapse

►Autapse

Semantic Memory

Definition

Semantic memory refers to knowledge of the world. This system processes, stores and retrieves information about the meaning of words, thoughts,concepts, objects, actions, and facts.

►Amnesia
►Long-Term Memory
►Memory and Dementia

Semantic Priming

Definition

A form of priming in which the prime is semantically related to a subsequent test word.

►Latent Learning

Semantical Behaviorism

►Behaviorism, Logical

Semantical Physicalism

Definition

The view that every mental sentence (or predicate) can be translated without loss of meaning into a non-mental sentence (or predicate).

►Behaviorism
►Logic

Semantics (Two-Dimensional)

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Definition

"Two-dimensional semantics" denotes a family of semantic theories rooted in intensional semantics, held together by shared general ideas, yet divided by deep divergences in semantic aims and philosophical aspiration. Two-dimensional theorists agree that our sentence's truth-values vary with what the facts are, as well as with what the sentences mean. To model this twofold dependence of truth on fact and meaning, 2D semantics assigns our expressions intensions of more than one kind. The resulting formal framework, common to all 2D semantics, distinguishes one dimension of actual worlds and primary intensions from a second dimension of counterfactual worlds and secondary intensions (hence, two-dimensionalism). These formal similarities often obscure the deep conceptual rifts between different interpretations of the 2D framework. Kaplan interprets it to capture context-dependence; Stalnaker understands it to model meta-semantic facts, and Chalmers construes it to display the epistemic roots of meaning.

Description of the Theory

Fundamental Ideas of Two-Dimensional Semantics

Traditional intensional semantics assigns a sentence a single intension. This intension captures how the truth of the sentence depends on, and varies with, the respective facts. Two-dimensional semanticists draw our attention to another dependence. A sentence's truth-value also depends on, and varies with, what the sentence means. Two-dimensional semanticists agree that our semantics has to account for this twofold dependence of truth-value on meaning and fact, and they agree that we can capture both dependencies relying on the apparatus of possible worlds and intensions familiar from intensional semantics. We just need to add the distinction between counterfactual and actual worlds, and we have to make use of the threefold distinction of kinds of intension this effects.

The twofold dependence noted is most pronounced in sentences containing indexicals. Whether "I am in *Milano*" is true in some possible world depends on the facts in that world, and it depends on who utters this sentence in the first place. If Pavarotti utters it, the sentence is true in a possible world if in that world, Pavarotti is in Milan. If someone else utters it, the sentence has different truth-conditions. Put generally, the truth of an indexical sentence in some counterfactual world depends on what is the case in that world, and it depends on what is the case in the actual world it is uttered in. This inspires a general way to analyze the twofold dependence noted. We can hold that whether a sentence is true in some counterfactual world depends on the facts, depicted by what is the case in that world, and it depends on what the sentence means, determined by what is the case in the actual world. The counterfactual and actual worlds set apart here are not different entities. What gets discriminated are two different roles the very same possible worlds can play (assuming that we specify for worlds considered as actual a center consisting of a speaker, a place, and a time).

The distinction between counterfactual and actual worlds allows 2D semanticists to distinguish three different kinds of intensions. An expression's *primary intension* assigns it an extension in every *actual* world, determining a function f: $W_A \rightarrow E$ from actual worlds to extensions. An expression's *secondary intension* assigns it an extension in every *counterfactual* world, determining a function f: $W_C \rightarrow E$ from counterfactual worlds to extensions. An expression's *two-dimensional intension* assigns it for any actual world a secondary intension, determining a function f: $W_A \rightarrow (W_C \rightarrow E)$ from actual worlds to secondary extensions that portray how the expression's primary and secondary intensions interlock.

Assigning these different intensions to a sentence allows 2D semantics to capture the way its truth-value varies with the actual and counterfactual world and, hence, depends on fact and meaning. A plausible assignment of intensions to "I am in *Milano*" is this: the primary intension of "I am in *Milano*" yields varying extensions across actual worlds depending on who utters the sentence. The secondary intension yields varying extensions across counterfactual worlds, depending on whether or not the one having uttered "I" is in these counterfactual circumstances in Milan. The 2D intension combines these two, capturing for each actual world which secondary intension an utterance of "I am in *Milano*" in this actual world effects.

The resulting formal structure (see Fig. 1), comprising two dimensions of worlds and three kinds of intensions, is common to all 2D semantics. Two-dimensional semanticists agree that we can model all representational properties of our language by assigning primary, secondary, and/or two-dimensional intensions to our terms and sentences. This consensus extends to the dimension of counterfactual worlds and secondary intensions. Two-dimensional semanticists agree that this dimension captures how an expression's extension depends on the facts, and they take these worlds and intensions to be the possible worlds and

	Dimension 2 counterfactual worlds →		
Dimension 1 actual worlds →	W1	W2	W3
W1*	W	W	f
W2*	f	W	W
W3*	W	W	f

Semantics (Two-Dimensional). Figure 1 A 2D matrix displaying a sentence's intensions for a small sample of worlds. The diagonal displays a single primary intension. Each row displays a secondary intension. The whole matrix displays a single two-dimensional intension.

standard intensions familiar from traditional intensional semantics. There is no consensus on the understanding of actual worlds and primary intensions. Two-dimensional theorists agree that this dimension captures how an expression's extension depends on what it means. This claim is open to interpretation, and the paradigmatic interpretations put forth by Kaplan, Stalnaker, and Chalmers exhibit deep divergences in semantic aim and philosophical aspiration. They even yield different answers to the questions (i) "What are actual worlds?" and (ii) "What precisely do we need actual worlds and primary intensions for?"

Kaplan: Actual Worlds as Contexts of Use

Kaplan [1,2] propounds a semantic interpretation of the 2D framework. He holds that (i) actual worlds are contexts, or possible occasions expressions can be used in, and he (ii) maintains that we need actual worlds and primary intensions to model the context dependence of language.

Kaplan detects an asymmetry between indexical tokens and indexical types. Indexical tokens have reference but no descriptive meaning. An utterance of "I" in a context refers to an individual. This fact exhausts its meaning. Pavarotti's utterance "I am in *Milano*" thus expresses a proposition about *him*, i.e., Pavarotti. Indexical types, on the other hand, have descriptive meaning but no reference. The type "I" does not refer. It still has a descriptive meaning any competent speaker must know. This meaning consists in a conventionally assigned rule dictating that any utterance of "I" refers to whoever produces the token in the respective context. Thus, the sentence type "I am in *Milano*" does not express a proposition, but any competent speaker will know which proposition a token of this type expresses *if* it is uttered in a context.

Kaplan concludes that we must distinguish two kinds of meaning. Linguistic tokens have *contents*. The content of a term captures what it refers to, and the content of a sentence is the proposition it expresses. Linguistic types have *characters*. The character of an expression is a conventionally determined rule dictating which content a token of that expression expresses if it is uttered in a context. The characters of terms like "grandmother" will assign all tokens the very same content. By contrast, the characters of indexicals and demonstratives will assign their tokens varying contents, depending on the respective contexts.

It is this dependence of token meaning (or content) on type meaning (or character) cum context that Kaplan captures by means of a 2D framework. He models contents as secondary intensions. He models characters as two-dimensional intensions. The character of a sentence type specifies a secondary intension for each actual world, and thus captures how the proposition expressed by a token of that sentence varies with the context the token occurs in.

Stalnaker: Actual Worlds as Means for Reinterpretation

Stalnaker [3,4] offers a meta-semantic interpretation of the 2D framework. Stalnaker's holds (i) that actual worlds are possible alternative environments we might have introduced our terms in, and he (ii) distinguishes the subject matter of the 2D framework from its application: we need the apparatus of actual worlds and primary intensions to describe meta-semantic facts, but we put it to a pragmatic use.

Endorsing (i)–(iii), Stalnaker finds himself in a quandary: (i) Being necessarily true, the proposition expressed by "Hesperus = Phosphorus" does not exclude any possibility. (ii) A sentence can be used to communicate contingent information about the world only if the proposition it conveys excludes some possibility. (iii) "Hesperus = Phosphorus" can be used to communicate contingent information about the world. To resolve the puzzle, Stalnaker distinguishes the proposition *conveyed* with an informative use of "Hesperus = Phosphorus" from the proposition *expressed* in that use. The latter is determined by the standard semantic rules for the sentence, and it is necessarily true. The former is inferred from the speaker's pragmatic communicative intentions, and it is contingent. Reinterpreting the speaker's utterance to convey this contingent proposition allows the hearer to make sense of his utterance.

Reinterpretation is a familiar pragmatic procedure. If the standard semantic content of an utterance manifestly violates a conversational maxim, we assign it a different content by drawing on the speaker's communicative intentions. This is what the hearer of "Hesperus =

Phosphorus" does, noticing that the standard proposition expressed is ill-fit to convey information. The hearer reasons thus: (i) "Hesperus" has been introduced as a name for the brightest star in the evening, and "Phosphorus" has been introduced as a name for the brightest star in the morning. (ii) Which objects these introductions did yield depended on astronomical facts in our actual world. If the astronomical facts in the actual world had been relevantly different, "Hesperus" and "Phosphorus" would name two different objects. (iii) What the speaker intends to convey is that our world is one where this is not so. He wants to convey that our world conforms to the proposition *that the brightest star in the evening = the brightest star in the morning*.

It is this dependence of semantic meaning on introductory procedure cum actual world that Stalnaker captures by a 2D framework. He models standard semantic meanings as secondary intensions. Stalnaker models the propositions assigned in reinterpretation as primary intensions (which he calls, in line with Fig. 1, *diagnonal propositions*). By displaying how an expression's extension varies with the respective actual world, a primary intension captures how a term's standard semantic meaning varies with the circumstances under which it is introduced.

Chalmers: Actual Worlds as Epistemic Possibilities

Chalmers [5–8] offers an *epistemic* interpretation of the 2D framework. Chalmers (i) maintains that actual worlds are epistemic possibilities, and he (ii) holds that we need actual worlds and primary intensions to capture the epistemic dependence of meaning.

Chalmers draws on two ideas. His one idea is that reference and truth are *scrutable*. Given a description of our world cast in neutral terms, a speaker can (in principle) *a priori* infer what her expressions refer to, and which of her sentences are true. From a description of the appearance, make-up, and behavior of chemical substances that makes no use of the term "gold," she can *a priori* infer the truth of "Gold is the chemical element with atomic number 79." Chalmers' other idea is that of epistemic modality. Epistemically possible hypotheses depict ways our world might be for all we can (in principle) *a priori* know, and a complete epistemic possibility depicts an epistemically possible world. For all we can know *a priori*, gold could be the chemical element with atomic number 55. A world in which this is true, hence, is an epistemic possibility. Chalmers merges these ideas in his thesis of *generalized scrutability*. Given a description of any epistemically possible world phrased in neutral terms, a competent speaker can (in principle) *a priori* infer what her terms refer to in that world, and which of her sentences are true in that world. This ability reveals that speakers associate epistemic intensions – i.e., functions from epistemically possible worlds to extensions – with their terms and sentences. The epistemic intension associated with an expression is fundamental to the expression's significance. For one thing, it captures cognitive significance. If a term plays a cognitive role for a speaker at all, she associates an epistemic intension with it that reveals what the term means for her. Secondly, the epistemic intension determines an extension in the actual world. For the actual world simply is the actualized epistemic possibility. Thirdly, the epistemic intension will ground the counterfactual intensions of all terms whose counterfactual intension depends on actual world extension.

It is this dependence of truth and reference on our ability to determine *a priori* extensions in epistemically possible worlds that Chalmers captures by means of a 2D framework. He identifies secondary intensions with standard truth-conditional meanings, and he employs two-dimensional intensions to model the dependence of secondary intensions on primary ones. Chalmers identifies primary intensions with epistemic intensions. By displaying how an expression's extension varies with the respective actual world, a primary intension captures how a term's actual extension varies with the respective epistemic possibility that is realized in our world.

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Semaphorin

Definition

Family of secreted or cell surface-bound guidance molecules with attractive and repulsive actions mediated by receptors comprising plexin proteins and,

in certain cases, neuropilin. Semaphorins mainly act as short-range signals (semaphor is the Greek word for signal) to deflect growing axons from innervating inappropriate regions.

►Growth Inhibitory Molecules in Nervous System Development and Regeneration

Semaphorin-3A

Definition

Semaphorins constitute a family of secreted and transmembrane signaling proteins.In the nervous system, members of this family have been shown to play a role in axon pathfinding, branching and targeting. Some members of this family, including semaphoring-3A, function as chemorepellents of specific growth cones.

►Axon Pathfinding
►Growth Cone
►Semaphorin

Semicircular Canals

Definition

Parts of the membranous labyrinth in the form of semicircular ducts that stem from a structure of larger diameter (utriculus). There are three for each side, oriented along three different, roughly orthogonal planes and contain labyrinthine (ampullar) receptors located in an enlargement at the base of each canal (ampulla). Angular acceleration in space induces motion of endolymph within the canals, which is maximal when the plane of rotation corresponds to that of the canal and absent when the two planes are perpendicular. The central axons of the primary afferents from the vestibular system (vestibular nerve) run with the VIIIth cranial nerve and terminate in the vestibular nuclei.

►Peripheral Vestibular Apparatus
►Utriculus
►Vestibular Nuclei
►Vestibular Primary Afferent Pathways in Mammals
►Evolution of the Vestibular System

Semicompatibilism

Definition

The thesis that free action is compatible with the truth of determinism even if the ability to have acted otherwise than one in fact acted is incompatible with the truth of determinism.

►Freedom of Will

Semi-intact Preparations

Definition

Typically refers to in-vitro preparations in which some part of the body is kept intact in addition to the nervous system. For example, semi-intact preparations of spinal cord along with attached hindlimbs can be used to record muscular contractions in response to stimulation of the spinal cord tissue. These preparations provide opportunities to better approximate in vivo conditions while retaining the ability to control the external environment.

Sender

Definition

In communication theory the partner that emits a signal.

Senescence

►Olfaction and Gustation Aging

Senile Dementia

►Alzheimer's Disease – Oxidative Injury and Cytokines

Senile Dementia of the Alzheimer's Type

►Alzheimer's Disease – Oxidative Injury and Cytokines

Senile Plaque

Definition

A characteristic feature of the brains of Alzheimer's patients. It consists of a core of amyloid fibrils surrounded by dystrophic neuritis and is accumulated in the extracellular region. A principal component in senile plaques is amyloid fibrils, which are derived from the amyloid precursor protein (APP).

►Alzheimer's Disease
►Neuroinflammation: Chronic Neuroinflammation and Memory Impairments

Sensation Level (SL)

Definition

The decibel level expressed relative to some other level measured in an experiment.

►Acoustics

Sense Data (Singular: Sense Datum)

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Synonyms

Sensa (singular: sensum)

Definition

One of the central debates in the philosophy of perception deals with the question of what we are immediately aware of in perception. According to sense-datum-theories the objects of this immediate awareness are sense data. A typical example for a sense datum is the more or less round, red, bulgy expanse you are immediately aware of when you see a ripe tomato during normal daylight. At first, one might think that sense data are identical to those surfaces of physical objects facing us in a perceptual situation. In this case the claim that, in perception, we are immediately aware of sense data would just spell out our common sense assumption that, in perception, we are immediately aware of the facing surfaces of physical objects. But sense data should to be distinguished from these surfaces for the following four reasons: (i) certain changes in the perceptual situation lead to changes in our sense data, whereas the features of the surfaces of the perceived physical objects are not affected by these changes: if you change your perspective on the tomato in the right way you will become aware of a new sense datum which is not round but elliptical; the surface of the physical object, however, won't undergo any such change. Likewise, with a change of the lighting-conditions you might become aware of a sense datum showing a different color, whereas the surface doesn't change. Finally, drugs, impairments of sense organs or psychological factors like expectations or prejudices concerning the object of perception may influence what kind of sense data we will have without any change in the perceived physical objects. (ii) Sense data are generally taken to be private, that is, they are accessible only to one perceiving subject and not to other subjects. Physical objects, on the other hand, are taken to be publicly accessible to many perceiving subjects. (iii) Most defenders of sense data take them to exist only when we are aware of them. Physical objects are generally supposed to continue to exist when nobody is aware of them. (iv) In cases of hallucination where no physical object is present at all (think of the rats hallucinated by the delirious drinker or the dagger that appears to Macbeth in Shakespeare's play), there is nevertheless a sense datum present which we are aware of. The same holds in cases of illusions where we are aware of a sense datum with properties differing from those of the physical object present in that perceptual situation (when you immerse a straight oar into water you will be aware of a sense datum which is bent).

These four points lead on the one hand to the question of how sense data are related to the physical objects of our environment and on the other hand to the question of how they are related to our perceptual awareness. To the first question the two main sense datum theories, ►phenomenalism and ►indirect or representative realism, give radically different answers explored in the next section. To the second question a certain version of the so called "act-object analysis" of perceptual awareness has been customarily presented as an answer. According to this analysis, perceptual states consist of two parts which have to be distinguished:

an act of awareness (sometimes called the "act of sensing" or just the "sensation") and a sense datum which is the object this act is directed upon [1]. Since sense data form a part of a mental state, they have to be seen as something mental and therefore cannot exist unperceived.

Description of the Theory

Sense data have been given two roles in the literature: (i) they have been taken as necessary for an adequate account of what we are immediately aware of in perception. (ii) They have been seen as the secure base of our empirical knowledge because it has been held that we cannot err with respect to their character: if a sense datum appears to you red it has to be red. You might mistake a white plate during sunset to be pink but you cannot mistake the pink expanse you experience in this situation for something else. It is important to note that one can give sense data the first role without putting any weight on the second role. The motivating idea behind the second role is the claim that empirical knowledge needs a secure fundament. One might refuse this idea, however, without giving up the claim that sense data play an indispensable role as immediate objects of perceptual awareness, because physical objects, as they are conceived by common sense, cannot play this role. Most of the more recent defenses of sense data theories lay their emphasis only on the first role. Therefore, this essay will concentrate on this point.

Historically, sense data can be seen as the heirs of the "ideas" or "impressions" of the epistemology of the seventeenth and eighteenth century, since the latter also had to play the two mentioned roles. The heyday of sense-datum-theories was the first half of the twentieth century [2–5]. For more recent defenses see [1,6–8].

According to common sense we are in perception immediately aware of the physical objects we perceive and these objects share the characteristics given in the four distinctive features above. Therefore, a defender of sense data has to give up either the claim that we are in perception immediately aware of physical objects or the claim that they share all of these features. Indirect realism follows the first route and phenomenalism the second one.

According to indirect realism, our perception of physical objects is only indirect because it is mediated by the immediate awareness of sense data in the following way: in the case of veridical perception a physical object will initiate a causal chain which leads via an affection of our sense organs and respective processes in the brain to the appearance of a sense datum (or a collection of sense data, for that matter). Such a sense datum serves the perceiver as a representation or sign of the physical object. In cases of illusion and hallucination the causal chain leading to the appearance of the sense datum doesn't start with the same kind of object as in the case of veridical perceptions. In the case of hallucinations it starts in the brain, because no external object is present. In the case of illusions it starts with an object that has properties which are different from those the object of your immediate awareness has. Indirect realism can admit that we perceive physical objects, but it claims that we have to distinguish between the objects of our immediate perceptual awareness (sense data) and the objects of perception (physical objects). Phenomenalism, on the other hand, does not distinguish between sense data and physical objects in that way. According to this theory physical objects are nothing but complex sequences of actual and possible sense data. A tomato is then nothing but the complex sequence of actual sense data I have at the time of seeing and touching it now and the sequence of possible sense data I would have if I changed my perspective relative to it, cut it into pieces and so on. If sense data exist only when we are aware of them, this leads to the consequence that physical objects cannot exist independently of the fact that we are aware of them. The common sense assumption that a rock in the desert also exists when no one perceives it becomes, in the hands of phenomenalism, the claim that one would be aware of the required rock-like sense data if one went to the relevant place in the desert. (For more on phenomenalism and indirect realism see the essay "perception.")

But why adopt any sense-datum-theory at all? Several arguments in favor of the existence of sense data have been put forward. The general idea behind these arguments is always the same: First it is argued that there is a certain class of cases where it is impossible that we are immediately aware of physical objects, so that at least in these cases we have to be aware of something different. Then it is claimed that only by supposing our immediate awareness of certain objects of another kind, namely sense data. Can we do justice to these cases in the next step it is claimed that there is no sensible argument which allows us to restrict the result to these special cases, so we finally have to admit that we are in all cases of perception immediately aware of sense data.

The most famous of these arguments is probably the ►Argument from illusion. The conclusion that we are in perception always immediately aware of sense data is reached here in four steps. The first step consists of the observation that in perception things sometimes appear to possess sensory qualities (colors, forms, felt temperatures etc.) then they don't possess. The second step is the claim that in all cases where something appears to a subject to possess a sensory quality, there is something of which the subject is aware which does possess that quality. The third step, an application of a logical principle known as Leibniz' law, holds that if an object *a* possesses a sensory quality that an object *b* lacks, then *a* is not identical to *b*. According to the fourth step there is such continuity between those cases

in which objects appear other than they actually are and cases of veridical perception that the same analysis of perception must apply to both. An example may be helpful for illustration: A straight oar immersed in water will appear bent. Therefore, what we are immediately aware of can't be the straight oar, but must be a sense datum which is bent. And because of the continuity of the perceptual situation we will also be aware of a sense datum when we remove the oar from the water. But then we may conclude that we are always immediately aware of sense data.

Well known arguments coming to the same conclusion as the Argument from Illusion by more or less similar routes include the following: The ►Argument from perspectival variation: Objects appear different to us from different perspectives although the objects themselves don't change. Therefore, we have to be aware of different sense data in order to explain these changes. The ►Argument from hallucination: In cases of hallucinations where no object is present at all we are nevertheless aware of something which has certain sensory qualities, and therefore we are aware in these cases of certain sense data which are the bearers of these qualities. Since hallucinations and veridical perceptions are indistinguishable for the perceiving subject we can conclude that we are also aware of sense data in the latter case. The ►Argument from science: Science tells us that nothing has the properties it appears to have in perception. For example, nothing is colored in the way it appears colored to our eyes and what appears a grainless solid structure may in reality be a swarm of molecules. Therefore, perception we have to be aware in of something other than physical objects, namely sense data which are literally colored and appear grainless and solid. The ►Time gap argument: Our perceptual awareness is restricted to the present, we can't be immediately aware of things existing at earlier or future times, and all perception requires the transmission of information from the perceived object. These processes need time (as is most obviously the case when light from long ago extinct stars reaches our eyes), therefore, what we are immediately aware of in these cases can't be the physical object but has to be a sense datum. For a detailed critical discussion of these and related arguments compare [8,9].

Criticisms of sense-datum-theories take generally the following forms: (i) the validity or soundness of the aforementioned arguments is questioned. (ii) It is augued that a conception of sense data as special kinds of mental objects leads to difficulties better of avoided. (iii) Phenomenalism and indirect realism being, It being the relevant theories are supposed to have general implications which are utterly implausible or even disastrous. (For a discussion of this point see the essay on ►perception).

Concerning (i) only two prominent criticisms concerning the refusal of the second premise of the Argument from Illusion can be briefly noted here. This premise has been criticized as fallacious in a variety of ways but the most common strategy is just to deny that in cases of illusory perception there has to be something which possesses the sensory qualities the physical object lacks. If we erroneously believe that our neighbor has got a new car, the possibility of this false belief doesn't presuppose that we are aware in this case of someone else, possibly existing only in our mind, who his a new car. Indeed, such a supposition would be a mistake, because then our belief wouldn't be about our neighbor but about this other person. If this is true in the case of belief why should we invoke special objects as bearers of sensory qualities in the case of perception? Defenders of the Argument from Illusion typically retort that perception forms a special case here, because the appearant features of objects we are presented with in perception are present in one specially vivid way lacking in the cases referred to in this criticism. In the case of illusions we not only take the physical object to be different from the way it actually is, the illusory feature (e.g. a color the physical object lacks) is vividly present in perceptual consciousness as a property of the object of awareness [8].

In order to avoid the introduction of sense data at this point the so-called adverbial theory of experience has held that the phenomenal aspect of our sense experiences can be analyzed in the following way: a vivid conscious experience of something red (be it veridical or not) can be understood as a certain way of perceiving; that is, we are not conscious of something instantiating the property which is responsible for the character of our conscious experience (a sense datum), but our perceptual state itself is characterized by that property, in the case of a experience as of something red we "sense in a redly manner" as it has been put [10]. It has been claimed, however, that this account cannot deal adequately with situations where we have an awareness of a manifold of different items with different colors and forms because this seems to require being aware of different items instantiating these properties [1].

Concerning (II) the following problems have been prominent in the debates: if sense data are something mental how can their existence be accommodated within the most widely shared metaphysical position of today, physicalism, which holds that everything is physical? Defenders of sense data can try here to refute physicalism [8], or they can try to reduce the data to physical phenomena along the lines of an identity of theory [7]. A related difficulty concerns the question where sense data have to be located, if they are to be distinguished from physical phenomena. Sense data possess extension (an expanse is at least two-dimensionally extended; there is no unanimity among the defenders of sense data whether they are three-dimensional or not), which seems to require that they are located in space. But can we locate them in physical space? They are private in the sense that

only the person who experiences them has access to them. Objects in physical space are not private in that way, however. One might introduce here private spaces but such a proposal leads to further difficulties, in particular of the question how these private spaces are related to each other and how they are related to public physical space. And this is not the only problem with respect to the claim that sense data are private: The claim also seems to be at odds with the common sense claim that different persons can be, in perception, immediately aware of the same object. This seems to be a presupposition of the idea that it makes sense at all to dispute the way things appear to us in perception. Furthermore, it has been contested whether the conception of a private object makes any sense at all.

Generally, sense data have been taken to be the way they appear to the perceiver. This was why they were introduced them in cases of illusion etc. While the straight oar immersed in water isn't bent there is another object which really is as it appears: the bent sense datum. But this claim leads to the following difficulty: sometimes the features of objects we are aware of will appear indeterminate; e.g. when we see a speckled hen the number of its speckles will appear indeterminate. If we are aware of a sense datum in this situation, and sense data are exactly as they appear, the sense datum in question would have an indeterminate number of speckles. But this is a logical impossibility. At least one defender of sense data has simply contested the applicability of this logical principle to sense data [2]. But defenders of sense data might try to solve the problem by claiming that the number of speckles is only indeterminate in the sense that we are unable to determine it by counting the speckles in the given amount of time. This is compatible with the idea that the sense datum has a determinate number of speckles we are all perceptually aware of.

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Sense of Agency

Definition

The sense of being the owner of one's own actions.

►Action Representation

Sense of Balance

►Evolution of the Vestibular System

Sense of Effort

Definition

This sense refers to the perceived motor command associated with voluntary movements and muscle contractions. It is generated by sensory signals from muscles and by central signals related to the motor command required for the movements or muscle contraction.

Sense of Equilibrium

►Evolution of the Vestibular System

Sense of Smell

►Olfactory Sense

Sense of Uprightness

►Verticality Perception

Sensitive Period

Definition

In the life span of an animal, the ability to react to environmental changes is not constant. There is a period during which exposure to abnormal conditions leads to abnormal function. This period is called sensitive period. The sensitive period has to be discriminated from the critical period. The latter describes the time during which an organism acquires normal function if it is exposed to normal conditions (see also Critical Period).

Sensitivity of Sensory Receptors

Definition

In regard to the physiological characteristics of a sensory receptor cell, sensitivity is defined in relation to two variables: threshold and steepness (gain) of the relationship between stimulus intensity and receptor response. The detection sensitivity is inversely related to the detection threshold, while the gain sensitivity is related to the steepness in a static or dynamic gain curve. Corresponding Definitions hold for central neurons.

►Sensory Systems

Sensitization

Definition

Sensitization is a type of non-associative learning that results in an increase in responses in general (increase in arousal and enhancement of all reflexes) or responses once habituated. Sensitization typically occurs when noxious or fearful stimuli are presented to an animal.

►Learning
►Sensory Plasticity and Perceptual Learning
►Startle Response
►Learning and Motivation

Sensitization in Nociception

Definition

►Hyperalgesia and Allodynia

►Pain

Sensor

Definition

A sensor is a device with the capability of transforming one type of energy into another. Sensor differs from actuator in the way it is used. The sensor is used to transform physical system variables into signals readable by the user.

►Control

Sensor Fusion

►Posture – Sensory Integration

Sensorimotor

Definition

Animals register external events by their sensors and they act by their motor system. In general, the sensory information is represented in a different coordinate system than that of the motor system. Thus, the information has to be transformed from one code in the other. The processes underlying this transformation happen in sensorimotor areas and may be called sensorimotor transformations.

Sensorimotor Integration

Definition

The process of generating appropriate motor outputs, based on sensory inputs. In order to efficiently move in the world, we must integrate incoming sensory signals with each other and with motor commands. For example, to reach for a visual object, one must integrate visual representations of the object and its location with proprioception from the moving arm and hand, together with motor commands that appropriately project the arm in space. For many behaviors, motor actions and sensory processing are so tightly woven together that the two processes become inseparable.

Sensorimotor Learning and the Basal Ganglia

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Synonyms

Value, actions and reinforcement learning in the basal ganglia

Definition

Sensorimotor learning in the basal ganglia refers to the learning in which neurons in the striatum learn to encode and update the reward values of external stimuli and actions based on the reward prediction error signals from dopamine neurons.

Characteristics

Dopamine-Dependent Plasticity of Cortico-Striatal Synaptic Transmission

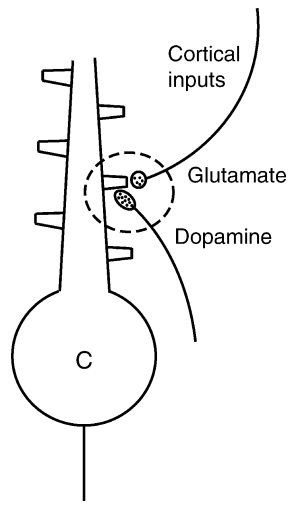
The striatum is a rostro-caudally elongated subcortical structure, and is composed of laterally located putamen and medio-dorsally located caudate nucleus. It is the input stage of the basal ganglia receiving major signals from almost all parts of the cerebral cortical areas and centro-median parafascicular nuclei of the thalamus in a topographically organized manner. These projections use glutamate as a transmitter. In addition, dopamine neurons in the substantia nigra pars compacta, serotonin-containing neurons in the dorsal raphe and noradrenergic neurons in the locus ceruleus project to both the putamen and caudate nucleus. Motor cortical areas in the frontal cortex and post-central somatosensory cortex project to the putamen, while the prefrontal, parietal and temporal cortical areas project to the caudate nucleus.

The axon terminals of cortical pyramidal neurons end and synapse on the spine of dendrite, while those of the thalamus end on the shaft of proximal dendrite of medium-spiny neurons of the striatum. The axons of single cortical neurons make as many as 2,900 (average 879) synapses on the striate neurons [1]. Varicosities of dopamine neurons make synapses on the neck of the dendritic spine (Fig. 1).

For single medium-spiny neurons in the striatum, about 10,000 terminals of pyramidal neurons in the cortex and 1,000 dopamine varicosities are estimated to make synapses on their dendrite [2]. This characteristic arrangement of synapses of cortical and dopaminergic origins makes an ideal framework for modification of cortico-striatal signal transmission by dopamine inputs. Indeed, long-term potentiation of cortico-striatal EPSP occurs in a dopamine D1 receptor-dependent manner [3].

Striatal Neurons Learn to Encode Action-Specific Reward Value

As mentioned above, the striatum is the locus of converging cortical and subcortical signals on actions, external sensory events, motivation or reward value and others in a variety of combinations. This makes the striatal neuron activity so variable. A subset of neurons is selectively activated during limb movement or eye movement, another subset of neurons are activated by external stimuli and appear when the subjects are performing behavioral tasks. Still another subset of

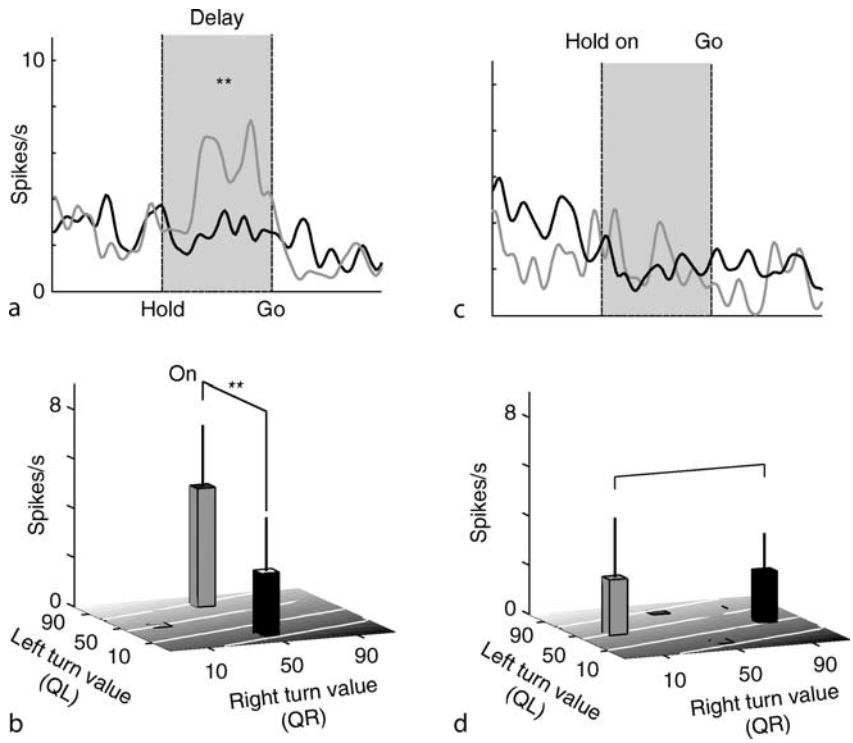


Sensorimotor Learning and the Basal Ganglia. Figure 1 Schema of synaptic arrangement on the dendrite of striate projection neurons. Cortical terminals synapse on the spine, while dopamine varicosities contact with its neck.

neurons is activated when the outcomes of behavioral responses have occurred. While the ▶basal ganglia receive signals of action, sensory events, motivation or reward value in the striatum, their outputs are directed mainly to the cerebral cortex through the cortico-basal ganglia loops [4] and partly to the superior colliculus and brain stem. A key question about the basal ganglia functions is: How are the variety of neural signals represented in the striatum different from those in the cerebral cortex? Limb or eye movement-related neurons are found in both the striatum and cerebral cortex. Similarly, neurons encoding reward value of external events are found in both structures.

Recent studies revealed an important aspect of representation and processing of sensorimotor signals in the striatum. For instance, through T-maze learning of rats, Graybiel and her group found that striatal neurons learn to encode automatized procedures of behavioral acts [5], suggesting involvement of the basal ganglia in habit learning. Caudate nucleus neurons of monkeys respond to visual cues for the directions of saccadic eye movements after which a reward is delivered. The magnitude of the responses is broadly tuned to the contralateral visual field. But if a reward is given only after the saccade to one of eight directions, neuronal responses are strongly biased towards the reward direction [6].

In another study by Samejima et al., monkeys performed a reward-based free choice task of turning a handle to the left or right [7]. They held a handle in the center position for 1 s, and turned the handle in either the left (L) or right (R) direction. The handle-turn was followed by either a large reward or a small reward. The probabilities of a large reward after left- and right-turns were fixed during a block of 30–150 trials, and varied between five types of trial blocks. In the "90–50" block, for example, the probability of a large-reward for the left-turn was 90%, and for the right-turn, 50%. In this case, by taking the small reward as the baseline (r = 0) and the large reward as one hundred (r = 100), the value for the left-turn Q_L was 90 and the value for the right-turn Q_R was 50. There are four asymmetrically rewarded blocks, "90–50," "50–90," "50–10," and "10–50," and one symmetrically rewarded block, "50–50." The neuronal activity related to reward expectation could be dissociated from that related to action selection. Although the monkeys should prefer the left-turn in both the 90–50 and 50–10 blocks, the reward values are different. Conversely, in the 90–50 and 10–50 blocks, although the monkey's choice behavior should be the opposite, the action value for the right-turn Q_R remains at 50. Figure 2 shows a representative neuron in which the delay period



Sensorimotor Learning and the Basal Ganglia. Figure 2 A "left-turn value neuron" Firing rates in 90–50 (grey) are higher than 10–50 (dark) block (a,b), but weak in both 50–10 (grey) and 50–90 (dark) blocks (c,d). Adapted from [7].

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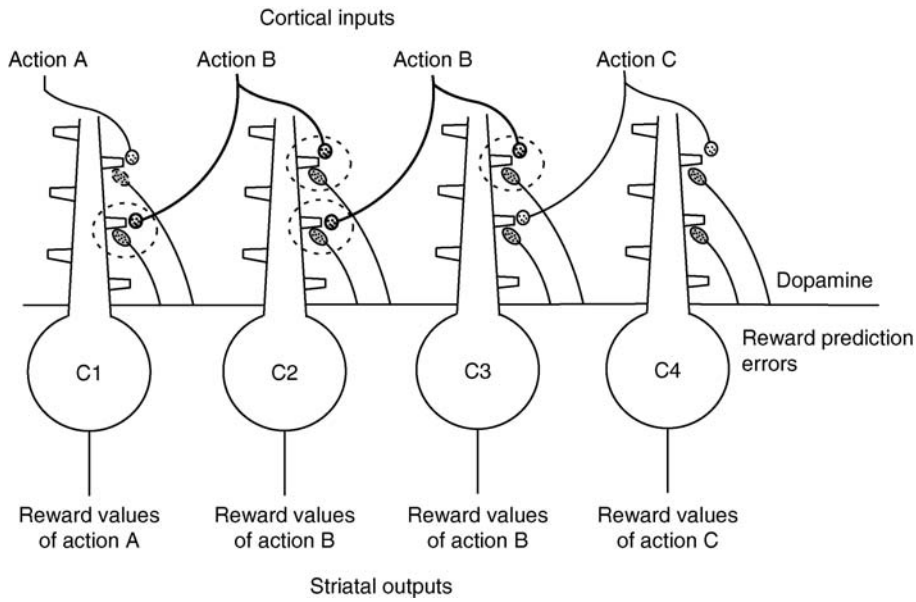

Sensorimotor Learning and the Basal Ganglia. Figure 3 Hypothetical schema of how the striatal neurons encode reward values of actions. The cortical signal of action B is reinforced and updated by dopamine's reinforcement signals.

discharge rate was significantly higher in the 90–50 block (grey) than in the 10–50 block (dark).

This suggests that the neuron is selective to either left-turn action because monkeys turn the handle to the left in most trials of 90–50 block or left-turn value. But, because the neuron is only weakly activated during both 50–10 and 50–90 blocks (Fig. 2c and d), this neuron is regarded as a "left-turn value neuron." There was a similar number of "right-turn value neurons." The observation revealed that action-specific reward values are represented in the activity of the striate neurons rather than in the preparation for particular actions or relative values between the two alternative actions.

Reinforcement Learning in the Basal Ganglia

How are the signals of action-specific reward values represented in the striatum processed for action and cognition, specifically for action selection? An important answer to the question was obtained by examining whether the monkey's action choice could be predicted by action values, which are estimated by previously chosen actions and their outcomes, and updated by reward prediction errors using a standard reinforcement learning model [8]. Samejima et al. [7] showed that the action values thus estimated successfully predicted individual action choices of monkeys. Furthermore, the discharge rates of "left-turn value neurons" and "right-turn value neurons" was correlated with the action values on a trial-by-trial basis [7]. Figure 3 illustrates schematically how the striatal neurons encode and update action-specific reward values based on the action signals from the cerebral cortex and reward prediction error signals from the dopamine neurons.

This suggests that the action values are used for selection among alternative actions, and supports the proposed reinforcement learning model of basal ganglia [9]. On the other hand, it is still to be studied where and how the action value-based selection of action occurs. Does it occur in the striatum or its downstream? Intriguingly, while action value coding neurons are dominant in the striatum, neurons in the internal segment of globus pallidus, output nucleus of the basal ganglia, preferentially encode reward values of chosen actions [10]. This suggests the selection mechanisms are downstream of the striatum. Further research is necessary to answer the key question of how the reward values of behavioral cues and actions are encoded, stored and updated by dopamine signals for pursuing a multi-step action plan towards specific distant goals.

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Sensorimotor Transformation

Definition

The processes in a neuronal network involved in the production of a specific motor output in response to a distinct pattern of sensory inputs.

Sensorineural Hearing Loss

Definition

Hearing loss due to pathology of the inner ear and/or neural pathways.

►Hearing Aids

Sensory Adaptation

Definition

Adaptation to sensory stimuli may involve changes in receptor sensitivity (peripheral adaptation) or inhibition along the sensory pathways (central adaptation).

Sensory cells respond strongly to acute changes in their environment but cease responding when stimuli become constant. A decrease in responsiveness of sensory cells due to continual stimulation.

►Sensory Systems

Sensory Aphasia

Definition

Aphasia resulting from lesion to ►Wernicke's area (posterior part of the temporal lobe adjacent to the occipital and parietal lobes).

Sensory Ataxia

Definition

A►taxia resulting from loss of sensory nerve fibers (►sensory neuropathy), which may be due to a number of diseases. The ensuing loss of ►proprioception (position and movement sense) creates difficulties in standing and walking. Patients stand with feet apart and show the ►Romberg sign with feet together and eyes closed or in the dark. Patients walk with feet widely apart, lifting them more than necessary and flinging the legs forward and outward in abrupt motions. Sensory neuropathy also leads to severe disturbances of voluntary arm and precision movements.

►Romberg's Sign
►Sensory Neuropathies
►Proprioception: Effect of Neurological Disease

Sensory Conflict

Definition

►Central Vestibular Disorders

Sensory Control of Locomotion

►Locomotor Reflexes

S

Sensory Dimension

Definition

The way an individual perceives awareness or intensity of a particular setting, process, characteristic, attitude, or sensation. A full description of a particular item would usually include the sensory dimension of the item, along with its affective, cognitive, and behavioral dimensions.

Sensory-evoked Activity

Action potential electrical discharges recorded in the central nervous system following stimulation of sense organs or (tactile or electrical) stimulation of a sensory or mixed nerve in the periphery.

Sensory Input

Definition

A neural signal which encodes information which has been transduced via a sensory organ or fiber. These neural signals provide afferent information or "input" to neural centers which regulate reflexes, behaviors or homeostatic functions.

►Sensory Systems

Sensory Integration

►Hippocampus: Organization, Maturation, and Operation in Cognition and Pathological Conditions

Sensory Modality

Definition

Is the type of physical phenomena that can be distinguished as a perception associated with the human senses; e.g., vision (light), hearing and touch (mechanical), temperature (thermal), olfaction (chemical).

►Sensory Systems

Sensory Modulation of Central Pattern Generators

►Peripheral Feedback and Rhythm Generation

Sensory Motor Learning/Memory and Cerebellum

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Definition

All animals including human beings obtain information about the external world through sensory organs such as eyes, ears, a nose, a tongue, skin etc., and respond to the stimuli by executing some actions with muscular movements in some cases. The sensory information is processed and integrated in the central nervous system, and the action is coordinated. The cerebellum plays a critical role in the motor control utilizing sensory information. The efficacy or smoothness of action in a particular condition improves with practice. Such improvement is the sensory motor learning. The cerebellum is also implicated in this type of learning, which is classified into the procedural learning (►Procedural memory).

Characteristics

The cerebellum plays roles in the motor control and in the sensory motor learning. Familiar examples of the latter are improvement of skills in sports or riding bicycles with practice. However, the characteristics and mechanisms of sensory motor learning have been studied utilizing simple model tasks such as ►adaptation of vestibulo-ocular reflex or saccadic eye movement, ►prism adaptation, and classical conditioning.

Adaptation of Vestibulo-Ocular Reflex

A head position of animal does not stay still during execution of an action. Thus, the visual scene captured

by an eye would move or drift (retinal slip, image motion on the retina), possibly causing blur of the image. You can experience such blur by watching the replay of video recorded with a camera held by someone's hands that would sometimes make you feel like seasick. However, we can usually get clear vision of the external world even if we are moving, and do not suffer from seasick in daily life. We owe this to two reflex mechanisms that compensate the eye position during the head movement. One is the vestibulo-ocular reflex and the other is the optokinetic response [1]. In the vestibulo-ocular reflex, the inner ears (semicircular canals and otolith organs) sense the head motion and send information to vestibular nuclei, and then to motor neurons controlling extraocular muscles. This reflex pathway enables eyeballs to move in the opposite direction of head motion. In the optokinetic eye movement, the movement of whole visual field is detected and the eyeballs move in the same direction of the visual field movement.

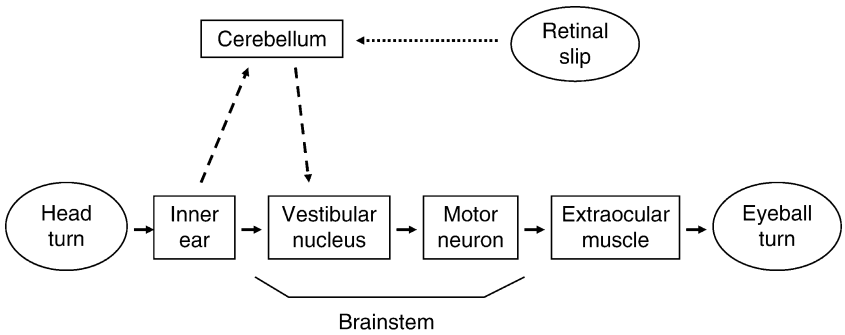
For the best performance of vestibulo-ocular reflex, the eyeball has to turn the same amount as the head turn in the opposite direction without delay. However, this is not an easy job. The sensory input that drives the vestibulo-ocular reflex is not visual signal but the information about the angular acceleration of head turn. Thus, the input sensory system has no way to know how well the retinal slip is suppressed by the reflex. Integration of visual and head rotation information is necessary for the good performance of reflex. The cerebellum adjusts the amplitude and timing of reflex by combining vestibular, visual, and eye movement information. The neuronal circuit controlling the vestibulo-ocular reflex is schematically presented in Fig. 1.

►Purkinje neurons, sole output neurons of the cerebellar cortex, send inhibitory outputs on neurons in the vestibular nuclei. The excitability of vestibular nuclei neurons is controlled by these inputs. Thus, the information transmission through the brainstem reflex pathway is regulated by the cerebellum. A mismatch of the visual and the vestibular inputs alters the vestibulo-ocular reflex so that the retinal slip is reduced. This phenomenon is the adaptation of vestibulo-ocular reflex. The mismatch occurs when a man wear glasses or an extraocular muscle is injured etc. In experiments, the mismatch can be brought about by rotating an animal placed in front of a dotted or striped screen that is moving either in the same or opposite direction to the animal rotation. The activities of Purkinje neurons change gradually when such a mismatch is given to the animal. A cause of the alteration in ►Purkinje neuron activities has been considered the long-term depression, a type of long-lasting modulation of synaptic transmission (synaptic plasticity) occurring in Purkinje neurons. Detailed explanation about the long-term depression is described below. The long-term depression and the resultant alteration of Purkinje neuron activities have been considered to contribute to the adaptive modification of vestibulo-ocular reflex, although implication of additional mechanisms such as alteration in vestibular nuclei neurons has been suggested [2,3].

Optokinetic response also undergoes adaptation in some animal species, in which the amplitude of eye movement is less than that of the external scenery, resulting in a certain retinal slip. Continuous presentation of sinusoidally oscillating scene to an animal gradually increases the amplitude of eye movement so that the retinal slip is reduced. Long-term depression is also implicated in this adaptation.

Eye Blink Conditioning

►Eye blink conditioning is one type of classical conditioning. Application of air puff to an eye or electrical stimulation around an eye makes the eyelid close. This is a simple defensive reflex to prevent injury of an eyeball, and the air puff or electrical stimulation that always induces the response is called an unconditioned stimulus (US), and the response induced



Sensory Motor Learning/Memory and Cerebellum. Figure 1 Neuronal pathways controlling the vestibulo-ocular reflex.

by an unconditioned stimulus is called an unconditioned response (UR). When some sound is presented before application of the air puff repeatedly, the animal learns to close the eye just hearing the sound. This phenomenon is the eye blink conditioning [4], and the sound is called a conditioned stimulus (CS) and the response induced by the conditioned stimulus is called a conditioned response (CR). The eye blink conditioning is similar to Pavlov's conditioned reflex.

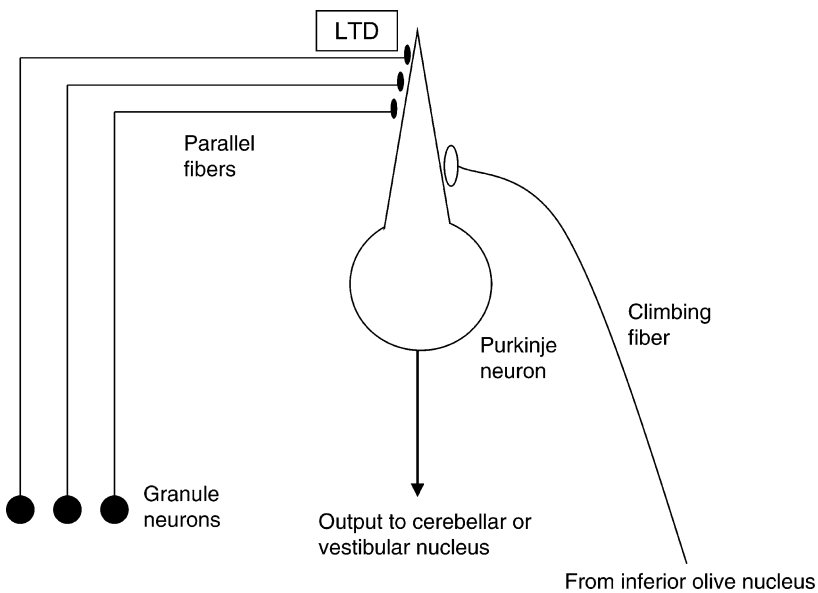
The cerebellum is involved in this eye blink conditioning. The lesion of cerebellum impaired the conditioning. Implication of the long-term depression has been reported. The information about CS is transmitted to a cerebellar nucleus and also to Purkinje neurons through parallel fibers and that about US is transmitted to Purkinje neurons through climbing fibers (Fig. 2).

Mossy fibers and climbing fibers are the major inputs to the cerebellar cortex. A climbing fiber forms large number of excitatory glutamatergic synapses on a Purkinje neuron. On the other hand a mossy fiber forms glutamatergic synapses on granule neurons. More than 100,000 granule neurons form glutamatergic synapses on a Purkinje neuron through parallel fibers (axons of granule neurons). Coupling of CS and US induces the long-term depression at parallel fiber-Purkinje neuron synapses, decreasing Purkinje neuron activities and hence inhibition on neurons in the cerebellar nucleus. Thus, neuronal activities in the cerebellar nucleus are upregulated, facilitating the information flow through the CS pathway including the cerebellar nucleus. Involvement of the central nervous system other than the cerebellum such as the hippocampus in the eye blink conditioning has also been known.

Long-Term Depression

Long-term depression is a type of synaptic plasticity accompanied with the long-lasting decrease in the efficacy of synaptic transmission [5]. In a cerebellar Purkinje neuron, the repetitive coupled activation of parallel fibers and a climbing fiber induces the long-lasting depression at the parallel fiber synapses. It has been proposed that the climbing fiber conveys the information regarding the motor error, and that the long-term depression works to reduce the information flow through the parallel fibers that have been involved in the error production (Fig. 2).

The cellular and molecular mechanism of long-term depression has been studied in vitro preparations such as brain slices and neuronal culture. A climbing fiber forms large numbers of glutamatergic synapses on dendrites of a Purkinje neuron providing exceptionally strong excitatory synaptic drive. Thus, when a climbing fiber is activated, a large increase in the intracellular Ca^{2+} concentration is induced in the postsynaptic Purkinje neuron. In contrast, each parallel fiber forms only one or two glutamatergic synapses on dendritic spines of a Purkinje neuron. The excitatory postsynaptic potential induced by a parallel fiber activation is far smaller than that by a climbing fiber. On the postsynaptic membrane of a Purkinje neuron at parallel fiber synapses, both ionotropic AMPA (α-amino-3-hydroxy-5-methyl-4-isozaxole propionic acid) type glutamate receptor and metabotropic glutamate receptor (mGluR1) are located.



Sensory Motor Learning/Memory and Cerebellum. Figure 2 Synaptic inputs to a cerebellar Purkinje neuron and the long-term depression (LTD).

Glutamate released from a parallel fiber activates both receptors. Activation of AMPA receptors causes the excitatory postsynaptic potential, and that of mGluR1 activates an enzyme called phospholipase C, which produces diacylglycerol and inositoltrisphosphate. The latter contributes to the increase in the cytoplasmic Ca^{2+} concentration through Ca^{2+} release from the intracellular stores, and the former contributes to activation of an enzyme called protein kinase C together with the intracellular Ca^{2+}. Activated protein kinase C phosphorylates the AMPA type glutamate receptor on the postsynaptic membrane. The phosphorylated AMPA receptor is then internalized to the cytoplasm and becomes nonresponsive to extracellular glutamate. This is the current simplified model of induction of long-term depression [5]. Implication of numbers of additional molecules including glutamate receptor δ2 receptor, specifically expressed at parallel fiber-Purkinje neuron synapses, has been reported [6].

Roles of long-term depression in the sensory motor learning have been studied using mutant mice with the impaired long-term depression. These studies have shown the correlation between the long-term depression and the sensory motor learning. However, some sensory motor learning occurs in animals with impaired long-term depression. Thus, the ►cerebellar long-term depression seems not to be the sole mechanism for the sensory motor learning.

Synaptic Plasticity Other than Long-Term Depression

Long-term potentiation, long-lasting increase in the efficacy of synaptic transmission, is also reported to occur at parallel fiber and Purkinje neuron synapses by repeated activation of parallel fibers alone. There are two types in the long-term potentiation. One is accompanied with the increased postsynaptic sensitivity to glutamate, and the other is caused by the enhanced release of glutamate from the presynaptic terminals of parallel fibers. The former long-term potentiation is the counterpart of the long-term depression. Implication of the long-term potentiation in the sensory motor learning has been suggested. The long-term potentiation and the long-term depression seem to play distinct roles in the sensory motor learning [7].

Synaptic plasticity has been reported at other synapses in the cerebellar cortex [8]. The long-term depression occurs also at climbing fiber-Purkinje neuron synapses. The efficacy of inhibitory synaptic transmission on a Purkinje neuron is potentiated for long-term by postsynaptic depolarization. The glutamatergic synapses between mossy fiber and a granule neuron also show long-term potentiation. Further, the synapses between parallel fibers and inhibitory interneurons (stellate or basket cells) also show synaptic plasticity. The respective role of each type of synaptic plasticity is unclear at present. They might contribute to the sensory motor learning in concert with the long-term depression at parallel fiber-Purkinje neuron synapses.

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Sensory Mucous Gland

►Electroreceptor Organs

Sensory Neuropathies

Definition

Diseases of peripheral sensory nerve fibers, either in combination with motor nerve fibers or alone (pure sensory neuropathies). The latter may manifest as (i) pan-sensory (involving all types of sensory fibers), (ii) ►large-fiber sensory neuropathies (with deficits of tactile and vibration sense, ►proprioception, ►areflexia, ►sensory ataxia); (iii) small-fiber sensory neuropathies (numbness, cutaneous hypesthesia to pin-prick and temperature, burning dysesthesias).

►Peripheral Neuropathies
►Sensory Ataxia

Sensory Placodes

Definition

Ectodermal and neurectodermal thickenings at the anterior end of the neural plate giving rise to the major sensory organs of the head e.g., lens of the eye (ectodermal) and olfactory placode (neurectodermal).

►Evolution of the Terminal Nerve

Sensory Plasticity and Perceptual Learning

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Definition

Perceptual learning, a type of sensory plasticity, enhances perceptual performance based on changes in brain physiology and adjusts the cortical representation of the world. *Sensory Plasticity* in general includes both behavioral and physiological changes in perceptual learning, sensori-motor enhancement and long-term adaptation resulting from ►experience.

Characteristics

Improved Perceptual Performance as a Result of Training

Lasting improvement in detecting, discriminating or categorizing sensory stimuli based on preceding experience is usually based on perceptual learning [1–3]. *Perceptual Learning* (PL) improves the representation and analysis of sensory information and reduces ►noise in sensory signals. Perceptual learning and plasticity of behavior are essential for humans to cope with changing environments. Better representation of a stimulus in the brain through learning improves its ►*detection*. Sharper ►*discrimination* from other stimuli – a more elaborate feat – is often task-specific and depends on attention being focused on specific feature(s) of the stimulus, thus restricting the learning to features important for the assigned task. A further aspect of plasticity and learning is the adjustment to the *situation* in general, especially under the usually somewhat artificial conditions of an experiment.

The improvement achieved through PL persists over extended time-spans, thus distinguishing PL from other changes in sensory processing such as short-term adaptation, ►sensitization, ►habituation, attention, and priming. These other processes all produce more transient changes of performance. PL clearly is of the procedural type, produces ►implicit memory traces and cannot be communicated to others, unlike declarative forms of memory such as ►declarative (explicit) memory. Another important characteristic of PL is that it appears to directly modify the neuronal mechanisms processing the task required [4]. Declarative forms of learning, on the other hand, lead to memory traces that are stored at least partly in specialized brain regions such as the ►hippocampus. To detect, discriminate, and extract the most relevant features from the multitude of signals supplied by the sense organs requires extensive PL during especially infancy and childhood. This plasticity of sensory processing continues throughout life even if with decreasing velocity and ease.

Interaction of Different Cortical Levels in Perceptual Learning and the Role of Attention

Sensory plasticity and PL take place on a number of ►cortical levels, including even highly specialized ►early sensory cortices, while, of course, also on higher, more cognitive ones [5]. Hence, an important distinction between different types of PL is whether the improvement achieved through ►training generalizes to other stimuli or tasks, indicating involvement of higher cortical areas, or else is highly stimulus-specific, indicating involvement of early levels.

Psychophysical, imaging and electrophysiological studies all indicate that early sensory cortices are involved in at least some forms of Perceptual Learning while these sensory cortices used to be considered as "hardwired" in adults.

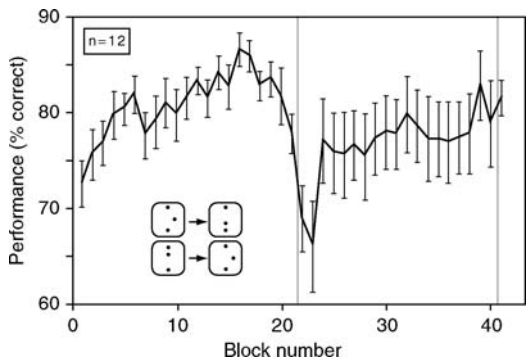
The task required of the subject may be quite different for identical stimuli – the more complex a stimulus is, the higher is the number of different discrimination tasks that can be defined for this stimulus, such as searching for a specific geometrical configuration or color. Therefore, feedback from "higher" to "lower" levels of processing is required for the "early" cortices to be tuned to the task at hand – purely bottom-up information extracted from the stimulus does not suffice to define the task.

The effects of PL are similar to those of attention both behaviorally and regarding enhanced activity of cortical neurons. In both cases, processing of sensory stimuli improves even in "early" cortical areas as demonstrated by ►single-cell recordings in animals. However, while the effects of attention are similar to those of adaptation in that they do not leave any permanent traces, PL *does* leave long lasting traces. The extreme stimulus specificity of some forms of PL sets it further apart from the more general and transitory effects of attention.

Stimulus Specificity in "Early" Perceptual Learning: "Early Selection" in Visual Perception

Training in many ►perceptual tasks enhances performance within about 10–20 min of training to slow down thereafter. But often, the improvement achieved with one stimulus is quite specific for this stimulus and does not transfer to a stimulus rotated by even a few degrees. Improvement is similarly specific for the eye trained (under monocular conditions), for position in the visual field, as well as for motion speed, motion direction, and the exact task trained (Fig. 1).

The enhancement is specific for stimulus orientation for some tasks, for example for vernier discriminations, as outlined above, while not for other perceptual tasks. Learning usually generalizes more on later (cortical) levels than on lower ones since there ►receptive field characteristics are less position specific. Hence, high position specificity indicates changes on early processing levels that select important information as soon as possible [6].



Sensory Plasticity and Perceptual Learning.
Figure 1 Specificity of improvement in Perceptual Learning. One group of observers started with a three dot bisection task, indicating whether the middle one of the dots was closer to the upper or else to the lower end point. The second group started with training a three dot vernier task, indicating whether the middle point was offset to the left or to the right relative to an imaginary line through the end points. Mean performance of both groups improved markedly within an 1-h training session (blocks 1–21). But when the tasks were switched between groups of observers (*left vertical line*), performance dropped even below baseline levels. Hence, improvement through training was highly specific for the task trained, even though the stimulus in both tasks differed by less than a photoreceptor diameter. Retesting the first task at the very end of the second session (*right of right red line*) revealed good performance (from Fahle, M. & Morgan, M.; No transfer of perceptual learning between similar stimuli in the same retinal position. *Current Biology* 6:292–297, 1996).

Generalization of Improvement in Late Visual Perceptual Learning, "Late Selection," and Further Sense Modalities

PL can enhance discrimination between complex classes of stimuli such as different wines, in addition to the improvement in discrimination between simple stimuli. More complex tasks and more noisy stimuli tend to generalize more than simpler ones do, hence enhancement seems to be achieved at a relatively late stage for these forms of PL.

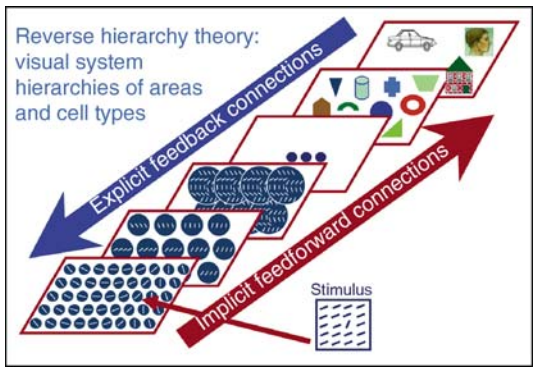
Training *auditory* tasks such as discriminating tone frequencies embetters [►improves] performance and is accompanied by ►reorganization of primary auditory cortex and other brain regions after some forms of PL while not after others. Similarly, training can improve discrimination in the realms of both taste and olfaction, and the representations in motor and somato-sensory cortex often increase in size for those body parts used during motor training, accompanied, for example, by improved two-point tactile resolution [7].

Models of Perceptual Learning

Recent models of PL incorporate both aspects of PL, specificity and ►generalization of learning. These models take into account both internal and external noise, implement recurrent (feedback) connections, and assess the change of internal templates. It turns out that sharper orientation tuning curves may account for the psychophysical results and that training seems to better eliminate external noise, possibly by retuning internal templates.

PL is based on at least two different mechanisms, one fast, the other slower. The first mechanism, as outlined in the Reverse Hierarchy model, starts fast and generalizes improvement at high cortical areas, adding the second mechanism if necessary. This second mechanism involves lower cortical levels leading to slower and more specific enhancement (Fig. 2).

These two mechanisms lead to either an early or a ►late selection of relevant signals in analogy to theories on attention [6]. The slower and more specific mechanism of PL is highly specific for stimulus features – indicating an involvement of "early" stages of cortical information processing. On these early cortical stages, such as the primary visual cortex V1, neurons are specific for the eye and the visual field position stimulated. Therefore, this mechanism apparently involves changes in functional connectivity between neurons already on the level of V1. Such tuning of signal processing on an early level removes irrelevant noise early on. However, the adaptation of processing at peripheral levels modifies the neuronal front end for all possible stimuli and may therefore deteriorate detection for stimuli differing from the recently learned ones by interfering with processing optimized for other tasks. For example,



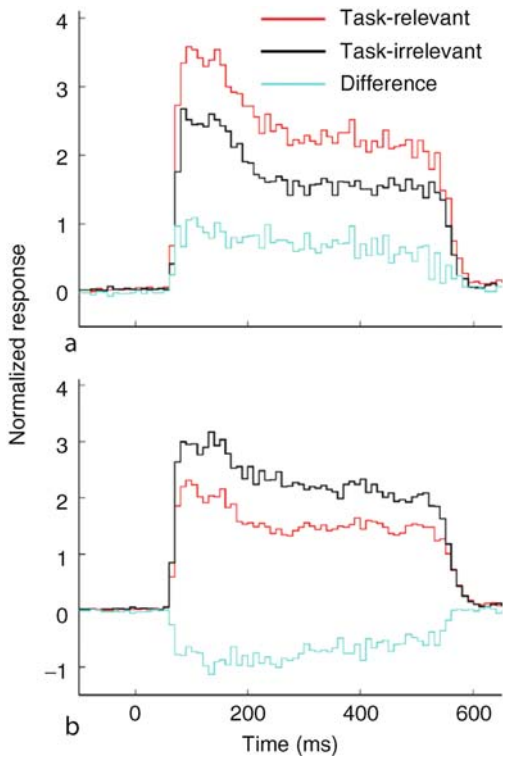
Sensory Plasticity and Perceptual Learning.
Figure 2 The Reverse Hierarchy Model of Ahissar and Hochstein conjectures that Perceptual Learning for easy tasks takes place on a "high" level of cortical information processing, improves performance fast, and generalizes to similar stimuli. If necessary, PL also involves lower levels where it is slower and highly stimulus specific (from Ahissar, M. & Hochstein, S.; The reverse hierarchy theory of visual perceptual learning. *Trends in Cognitive Sciences*, 8:457–464, 2004).

shallow luminance gradients are best detected by large receptive fields, which in turn are unable to detect fine gratings. Training to detect fine gratings would therefore improve their detection by decreasing receptive field size, but deteriorate detection of shallow gradients. Task-dependent switching between different "modes" of early cortical signal processing governed by top-down influence could solve this dilemma. Top-down control would select the most appropriate type of processing for the task at hand from a repertoire of (previously learned) alternatives, for example, by adjusting the neuronal gain of a defined population of neurons, or by modifying the amount of lateral inhibition on an early cortical stage.

The fast mechanism of PL resembles and may be identical with "conventional" forms of learning. It generalizes and is probably implemented in more central sensory cortices, located in the temporal and parietal lobes. Some forms of Perceptual Learning, especially the one generalizing over different stimulus types may take place exclusively on these higher processing levels.

Possible Mechanisms and Electrophysiological Correlates of Sensory Plasticity

To indicate the level of neuronal plasticity is almost impossible on the basis of psychophysical results. But both sum-potential recording and single-cell recording detect plasticity on early stages of sensory cortices in visual, auditory and somato-sensory cortices, indicating some plasticity even in the lateral geniculate nucleus and primary visual cortex of adult animals

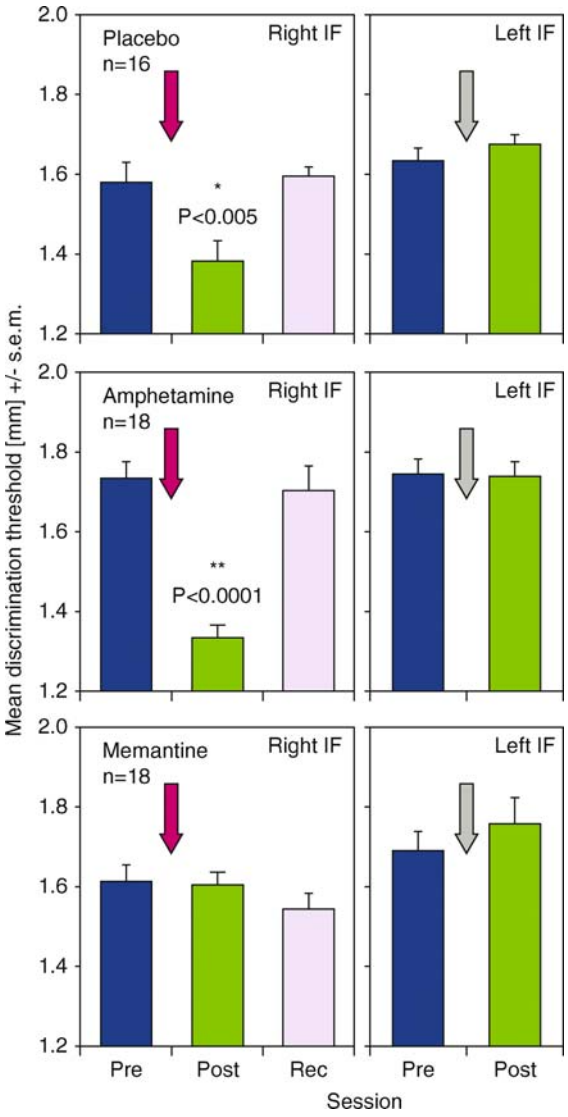


Sensory Plasticity and Perceptual Learning.
Figure 3 The characteristics of receptive fields in the visual cortex of an adult macaque monkey changed significantly as a result of training, though the exact mechanisms are still under debate. In any case, the changes depended on whether or not the stimulus was task relevant with both increase (a) and decrease (b) of responses after training (from Li, W., Piëch, V. & Gilbert, C.D.; Perceptual learning and top-down influences in primary visual cortex. *Nature Neuroscience*, 7:651–657, 2004).

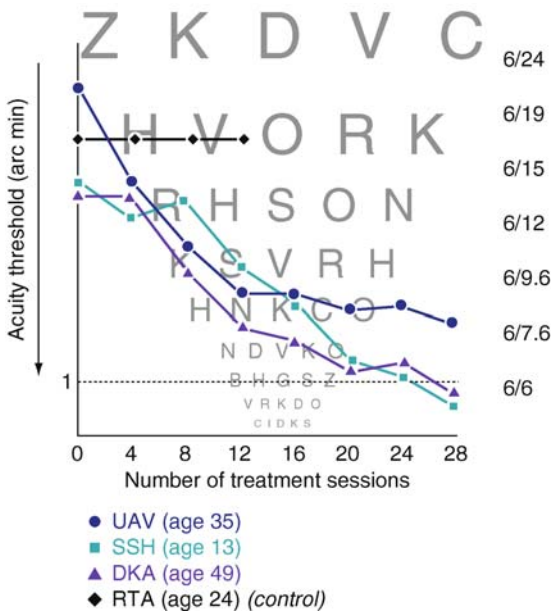
including man (Fig. 3; [8,9]). Plasticity in the somato-sensory system may be especially pronounced [7]. Some of the transmitter substances involved are known (Fig. 4).

Sum potentials in humans change as a result of PL, even at latencies below 100 ms, and most pronounced over the occipital pole. The number of neurons in primary visual cortex representing a given orientation surprisingly decreased in monkeys who trained orientation discrimination for this orientation. This decrease was not associated with any evident changes in permanent receptive field properties, neither in V1 nor in inferior temporal cortex [10].

To sum up, PL changes perception as well as sum potentials and single cell responses and increases activity in the stimulus representation of V1 as demonstrated by fMRI. All these findings point to an involvement of early sensory cortices in Perceptual Learning.



Sensory Plasticity and Perceptual Learning. Figure 4 Pharmacological influences on Perceptual Learning. The amount and speed of Perceptual Learning can be influenced by different pharmacological agents. (a) Memantine, an antagonist of NMDA receptors, abolishes PL (as does GABA receptor blockade), (b) Amphetamine, on the other hand, speeds up the improvement through PL; (c) Under the influence of an placebo, PL is far more pronounced than in (a), but less pronounced than in (b) (from Dinse, H.R., Ragert, P., Pleger, B., Schwenkreis, P. & Tegenthoff, M.; Pharmacological suppression of perceptual learning and associated cortical reorganization. *Science*, 301:91–94, 2003).



Sensory Plasticity and Perceptual Learning. Figure 5 Improvement of amblyopic patients. The classic view is that amblyopia, a functional decrease of visual acuity, due to strabism or optical factors, cannot be cured in adults. However, using a specific type of training, Polat and co-workers (Polat, U., Ma-Naim, T. Belkin, M. & Sagi, D.; Improving vision in adult amblyopes by perceptual learning. *Proc. Nat. Acad. Sci. USA*, 101, 6692–6697, 2004) were able to improve visual acuity in about half of their patients, sometimes dramatically, while those in the control group did not improve.

Conditions for Consolidation of Learning and Visual Rehabilitation of Patients

Consolidation of perceptual improvement achieved through training requires *sleep* or at least restful waking in both visual and auditory learning. In the realm of sensory rehabilitation, patients wearing a ►*cochlear implant* learn to make better use of the signals stemming from the implant, often up to the point of eventually being able to understand speech. Similar approaches are under way for the visual input. Especially amblyopic patients can benefit from PL, since visual training may double contrast sensitivity and significantly increase visual acuity (Fig. 5).

Conclusions and Outlook

Perceptual learning can significantly improve both the detection and discrimination of stimuli after a short training. PL relies on at least two mechanisms, probably represented on different levels of cortical processing. Modifications on early cortical levels require long training and produce stronger improvements, that do not transfer to similar tasks or similar stimuli, such as a slightly rotated stimulus, while the faster mechanism generalizes. No perceptual learning seems to take place without some form of attention. Irrelevant signals including noise must be eliminated as early as possible during processing to achieve optimal performance. Top-down signals may be able to activate modifications

in neuronal processing achieved on early levels in a task-dependent way to prevent interference of learning one task with performance in other tasks. Learning easy perceptual tasks may not modify early sensory cortices, but only higher ones, allowing generalization of improvement to similar tasks. In summary, Perceptual Learning enables humans to sharpen up the detection, discrimination and classification (►Categorization or Classification) of stimuli, to cope with varying sensorimotor requirements and to adjust rather fast to changing environments.

Acknowledgment

This article draws strongly on earlier articles of the same author on the same topic [4,6].

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Sensory Receptor

Definition

Sensory receptors (in physiology) is any structure which, on receiving environmental stimuli, produces an informative nerve impulse. The receptor recognizes a stimulus in the external or internal environment, initiates a transduction process by producing graded potentials (receptor potentials), from which all-or-none action potentials are elicited, that are conducted along afferent fibers originating in the same or adjacent cells.

►Action Potential
►Receptor Potential
►Sensory Systems

Sensory Re-education

Definition

A re-learning process, applied after nerve repair, aiming at a central nervous adaptation to the new pattern of sensory impulses transmitted by misdirected regenerated axons.

►Regeneration: Clinical Aspects

Sensory Responsiveness

►Sleep – Sensory Changes

Sensory Re-weighting

Definition

A mechanism for regulating a sensory integration process by changing the relative contributions made by different sensory systems to a neural representation of a percept or to a neural signal used for motor action.

Sensory Stroke

►Proprioception: Effect of Neurological Disease

Sensory Substitution

Definition

A mechanism whereby information from one sensory modality is replaced by or substituted for information from another sensory modality. This term often refers to prosthetic devices that are meant to convey one form of sensory information through a sensory system that is typically not used for that form of information. An example would be an array of tactile vibrators that represent a visual scene.

Sensory Systems

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Introduction

In order for organisms to survive and reproduce, they need an appropriate habitat. A habitat may be appropriate in terms of chemical constitution, ambient temperature, light conditions, food supply, availability of potential mates, and/or optimal conditions for their offspring. To continuously check for this appropriateness, organisms need information about the environment and the internal state of their body. An essential primary requirement is therefore the capacity to select, acquire and handle suitable information.

Functions of Sensory Systems

Environmental and internal-state signals of importance to the animal (or plant) must be received. This in turn requires specialized ►sensory receptors. The information delivered by receptors must then be processed for particular purposes. Sensory systems usually have multiple functions. On the one hand, they provide signals for regulatory systems. At higher levels, they serve to generate sensations and ►perceptions. Perception requires ►consciousness. In multi-cellular organisms (metazoa), information acquisition, transmission and processing are performed by a more or less complex nervous system. From the viewpoint of the central nervous system (CNS), there are two environments: its own body as an internal environment and the body's external environment.

The general functions of sensory systems can be briefly summarized as follows:

1. Selected representation of aspects of the body's external world in space and time. This in turn requires:
   (a) Selectivity in focusing on world aspects of survival value for the organism.
   (b) Detection, localization, and identification of stimuli from the external and internal environments.
   (c) ►Figure-ground perception discrimination, i.e. isolation, identification and recognition (for perception) of important objects and events (figure) against the background of all existing objects and events (ground).
   (d) Discrimination of invariant and changeable properties of world aspects.
   (e) Memory. Recognition requires current sensory data to be compared with records of past experiences.
2. Selected representation of aspects of the body's internal world in space and time, including:
   (a) Body schema.
3. Provision of inputs for evaluation and decision systems that steer ►behavior.
4. Provision of inputs for fast motor responses, such as escape ►reflexes.

Classification of Senses

Senses can be classified according to several criteria.

Nature of Stimuli

One classification is according to the physico-chemical nature of the stimuli activating peripheral sensory receptors (Table 1). Except in a few cases (e.g. ►vision), the ensuing classes may encompass diverse senses and therefore not be very useful. For example, the "mechanical" category includes hearing (►Auditory neuroscience - Introduction), the ►vestibular system, cutaneous mechano-reception (►Tactile senses-touch) and deep mechano-reception (►Proprioception), sensations arising from visceral receptors etc.

Origin of Specific Stimuli

Senses can be grouped according to the site of origin of the specific stimuli:

1. ►Exteroceptive senses receive stimuli from the world external to the body and comprise ►vision, ►magnetic and electric senses, hearing (audition), ►taste and ►olfaction (►Sensing chemical stimuli).
2. ►Enteroceptive senses receive stimuli arising within the body and comprise proprioception, and various other senses, such as deep thermosensibility and nociception (►Pain).

This division is not unequivocal because some senses bridge the border. For instance, cutaneous mechanoreceptors can be excited by stimuli from both

S

Sensory Systems. Table 1 Sensory modalities, qualities, receptors and adequate stimuli

Modality	Quality	Receptors	Adequate Stimuli
Vision	Brightness	Rods	Electromagnetic radiation
	Green	Cones	
	Red		
	Blue		
Hearing (*audition*)	Tone frequencies	Hair cells	Air pressure fluctuations
Tactile sense	Touch	Meissner	Mechanical deformation
	Pressure	Merkel	
	Vibration	Pacini etc.	
Statokinetic sense	Equilibrium	Hair cells	Absolute head position and acceleration
Proprioception	Body position and motion	Joint and ligamentous receptors	Joint position and motion
		Muscle spindles	Muscle length
		Golgi tendon organs	Muscle force
		Skin mechano-receptors	Joint position/motion
Temperature	Cold	Cold receptors	Electromagnetic radiation 700–900 nm
	Hot (warm)	Warm receptors	
Pain	Fast (first) pain	Nociceptors	Injuries, inflammation etc.
	Slow (second) pain		
Taste (*gustation*)	Sweet	Chemo-receptors	Chemical substances and ions
	Salty		
	Sour		
	Bitter		
	Umami		
Smell (*olfaction*)	Odors	Chemo-receptors	Odorants (pheromones)
Internal mechano-reception	Stomach extension	Extension receptors, pressoreceptors	Extension and pull
	Lung extension		
	Blood pressure		
Internal chemoreception	Osmotic pressure	Chemoreceptors	Osmolarity of body fluids
	CO_2 pressure		pH and pCO_2
	O_2 pressure		pO_2

In some animals: *electric or magnetic senses.*

the exterior and interior world, thus being exteroceptors and proprioceptors. The vestibular system monitors the spatial relation and its changes between the head and external space and thus belongs to both proprioception (with active head movement) and exteroception (with passive head movement). Finally, nociception and temperature senses go under both rubrics of entero- and exteroceptive senses.

Modalities and Qualities (Sub-Modalities)

Using a number of different mechanisms, receptors are specialized to sense specific aspects of external and internal stimuli. These aspects define their ►adequate stimuli, which are those that excite the receptors most easily and at lowest energy levels. Specialization of this sort is the basis of the "law of specific sense energies" propounded by Johannes Müller in 1826 [1]. It states that the quality of a sensation is not due to the stimulus but to the special sensory organ stimulated. Subjective sensory physiology further splits senses into modalities and qualities (or sub-modalities), which in turn are based on specific receptor systems, with some qualification [2]. Modalities refer to large classes of senses and the related receptors, e.g. visual, auditory, olfactory, gustatory and tactile (the five classic senses). Qualities refer to subclasses such as, in the ►visual system, perception of shades of grey from black to white and of different colors, or in the tactile domain, differentiation of pressure, touch and vibration sensations. An overview is given in Table 1.

Proprioception

Proprioception is classically defined as being activated by mechanical stimuli arising from the body's self-generated motor actions [3]. Proprioceptors thus monitor the positions and movements of the body and its parts and include all receptors that carry signals related to these variables, irrespective of whether the signals reach consciousness or contribute to unconscious movement control [4]. Proprioceptors therefore comprise a fairly wide group of different mechano-receptors, from muscle receptors (►muscle spindles, ►Golgi tendon organs, arguably free nerve endings), joint receptors, ligament receptors, to cutaneous mechano-receptors.

Psychophysics

Before the development of objective recording techniques, the study of sensory processes had to rely on observations of subjective phenomena and their relations to the underlying external events (stimuli). A basic question in ►Psychophysics is to what extent attributes of subjective perceptions are linked to properties of stimuli. This approach may diversify into detection, identification, discrimination (from background) and scaling of stimuli.

Sensitivities

An organism should be interested in a great sensitivity to any stimulus that has an important survival value. Sensitivity means a number of things. The detection sensitivity is inversely related to the detection threshold, while the gain sensitivity is related to the steepness of a plot of response vs. stimulus intensity.

Thresholds

Thresholds may be distinguished into absolute threshold and difference threshold, and so are the respective sensitivities.

The *absolute threshold* (S_o) is defined as the minimum stimulus intensity evoking a recognizable response in the receptor cell or perception. However, the peripheral (receptor) threshold and the central (sensation) threshold need not coincide because the latter is influenced by processes such as context, attention etc. (see below). Many receptor systems are exquisitely sensitive to their adequate stimulus. For example, a ►photoreceptor of the visual system can be excited by a single photon; the inner ear of some vertebrates reacts to very weak sounds barely above the mechanical noise level; and the bacterium Escherichia coli reacts to a few molecules of a chemical agent of interest, such as the amino acid aspartate [5]. Mechanical systems are often much less sensitive.

The *relative threshold* is defined as the minimum *just-noticeable difference* (ΔS) in a stimulus variable. For intensity, this difference, ΔS, is taken relative to the starting intensity, S. For example, $\Delta S/S$ is about 1–2% for vision, 3% for pressure and between 10 and 20% for other senses. Relative thresholds can also be defined and measured for other stimulus dimensions like quality, time and space. For instance, in vision, relative thresholds exist for brightness (intensity) and color (frequency resolution). In hearing, relative thresholds determine the frequency resolution of different sounds; and differences in the times of arrival in both ears are important for the location of a sound source (►Interaural time difference (ITD)). Finally, the spatial resolution is important for stimulus localization and distinction (below).

Psychophysical Functions

Of prominent interest in supra-threshold psychophysics is the relationship between the stimulus intensity, which can be measured objectively, and the subjective intensity of sensation, which needs to be measured in some indirect way using scales. This relationship has been studied using various methods, leading to different quantitative descriptions (►Psychophysics).

Spatial Discrimination

Of major importance for organisms is the localization of stimuli (topognosis). The spatial localization and discrimination capacities vary widely between different senses, being very good in vision and audition, modest to good in cutaneous mechano-sensation, (►Tactile senses-touch) and almost nil in taste and ►smell. In vision, the relative threshold in the fovea centralis is ca. 1′ under favorable conditions, but in touch, the relative threshold (as determined by ►two-point discrimination) is much worse and varies considerably across the body surface, being greatest at the fingertips and on the lips (1–4 mm).

Information, Signals and Carriers

Information is an abstract entity that needs to be encoded in a signal to be transmitted. Signals in turn are generated by some material substrate or carrier, which uses some mechanism to produce the signal. In the nervous system, there are essentially only two broad classes of signals: membrane potential changes (►Membrane potential-basics) and concentrations of chemical substances (although at many chemical ►synapses, the concentrations of released ►neurotransmitters may be immaterial because they are so high as to saturate the available postsynaptic receptors). Membrane potential changes occur in two forms: continuous, ►graded potentials (depolarizations or hyperpolarizations), and ►action potentials (►spikes). These signals are essentially produced by and at membranes as carriers, and the mechanisms used are manifold. The existence of two forms of signal suggests that they need to be transformed into each other (see below).

Principles of Receptor Systems

The limited set of signal types used by the nervous system contrasts with the abundance of physiologically important world aspects. This requires that the receptor cells convert these diverse forms into one common primary nervous language. For this purpose, sensory receptors have evolved specialized ►sensory transduction and accessory structures.

Receptor Cells

Sensory receptor cells may be of neural or epithelial origin. Due to their limited expansion, each receptor can sample stimuli from only a limited body region called ►receptive field (RF). Sensory receptors may produce the first-order sensory axon as part of the cell or make synaptic contact with another neuron. Primary sensory axons may travel considerable distances (more than a meter) to reach their first postsynaptic neurons at the next processing stage (e.g. in the spinal cord).

Stimulus Transformation

Conversion of a stimulus into a form suitable for excitation of the receptor membrane is called sensory transformation. Important factors in this process are:

1. Location of receptors. For example, different types of ►cutaneous mechano-receptors, (►Cutaneous mechanoreceptors, anatomical characteristics) giving rise to tactile sensation lie in different regions and strata of the skin; and it is the different spatial relation and mechanical coupling to skeletal muscle fibers that makes sensory endings of ►muscle spindles and ►Golgi tendon organs respond to different mechanical variables of muscle performance (►Proprioception: Role of muscle receptors).
2. "Auxiliary" or "accessory" structures. For instance, cutaneous mechano-receptors display specific sensitivity to particular temporal aspects of mechanical stimuli because of the filtering properties of the special anatomical structures associated with their sensory endings; in the auditory system, the complete mechanical apparatus from the tympanic membrane to the ►basilar membrane transforms and filters the frequency content of the mechanical stimulus before reaching the ►hair cells in the inner ear; and in the ►visual system, light refraction and focus are performed by accessory structures (cornea, lens, etc.).

Sensory Transduction

The transformed stimulus then strikes the receptor cell. By the process of transduction, the transformed stimulus causes the opening or closing of ►ion channels in a local membrane region and produces a ►receptor current, which in turn gives rise to a ►receptor potential. In most receptors, the receptor potential is in depolarizing direction, while in photoreceptors it is hyperpolarizing. The ions involved in the production of receptor potentials depend on the specific receptors. The receptor potential encodes various stimulus properties in a continuous amplitude-modulated way.

Encoder

Since receptor potentials usually are graded local events in neurons (graded potentials) and thus undergo the typical electrotonic decrement in amplitude and slowing of their temporal transients when spreading electrotonically (►Electrotonic spread), action potentials are needed to carry information over long distances. Thus, there must be a neuronal site, where the receptor potential is translated (encoded) into a train of action potentials. This site may be in the receptor cell itself or in a following nerve cell, depending on the organization of a particular sensory system.

In so-called primary receptor systems, the receptor cell itself has an axon to propagate action potentials to central nervous structures. The receptor cell proper thus contains the ►encoder. In this case, ►receptor current and potential are also called ►generator current and ►generator potential because they generate action potentials.

In so-called secondary sensory systems or tertiary sensory systems, such as the ►inner ear or ►retina, the receptor potential of the primary receptor cell is, via intermediate steps involving synapses, converted into membrane potential changes in secondary or tertiary cells, which then encode these changes into action potential sequences.

Coding of Modality and Quality

Many sensory receptors are most sensitive to selected stimulus energies (receptor specificity). Their excitation thus defines the stimulus modality or quality in a ►labeled-line code [6]. However, there are many ►polymodal receptors, many of which are associated with small-diameter axons. In particular, ►chemoreceptors for ►taste and ►smell often respond to several chemical agents, any one of which cannot, therefore, be coded in the discharge of individual receptor types, but only in the activity patterns of populations of receptor afferents (►across-neuron pattern code [6]). This may also apply to other modalities. For example, in ►vision, any particular wavelength is sensed by more than one retinal cone ►receptor type (►Photoreceptors; ►Retinal color vision in primates; ►Color processing) and in cutaneous mechano-sensation, natural stimuli usually excite more than one type of mechano-receptor (although the excitation of individual mechano-receptors may lead to defined sensations) (►Processing of tactile stimuli).

Coding of Stimulus Intensity

The quantitative relationships between the intensity of a stimulus and the discharge rate of an afferent sensory nerve fiber may take different forms in different sensory systems. In many mechano-sensory systems, it is close to linear, while in the visual and auditory systems it can be approximated by logarithmic or power-law functions with exponents <1. This diversity is related to the range of stimulus intensities encountered in these systems. As a gross rule, linear relationships prevail where stimulus range is relatively limited, and nonlinear mappings occur in systems where stimulus intensity can vary over many orders of magnitude, such as in the visual and auditory systems.

Another factor important for intensity coding is a spatial characteristic, especially in higher metazoa: recruitment. As the intensity of a stimulus increases, increasingly more sensory receptors and axons are excited and contribute to the flow of information in parallel channels. This is a ►population code.

Coding of Stimulus Time Course

The filtering characteristics of sensory receptors vary. Based on their temporal response profile to stimuli, receptors are traditionally classified grossly into rapidly adapting or slowly adapting. Rapidly adapting receptors, such as cutaneous hair-follicle endings (►Cutaneous mechanoreceptors, functional behavior), which produce only one or little more action potentials to sudden and then maintained deflection of a skin hair, are also called phasic types. Slowly adapting receptors, such as the ►muscle spindle, are also referred to as tonic types. Usually, however, most of them show an initial firing-rate overshoot in response to a step increase in stimulus intensity. They only differ in the relative amplitude of overshoot and the rate of firing decay (adaptation) from the overshoot. Thus, even tonic receptors often display a marked initial overshoot, which is an expression of sensitivity to change in the adequate stimulus. Adaptation may occur in all the processes important for sensory reception: transformation, transduction and encoding. An example for the filtering effects of the accessory apparatus is the ►Pacinian corpuscle, (►Vibration sense) in which the onion-like sheath surrounding the sensory nerve ending filters out maintained stimulus components and makes the receptor a ►high-pass filter. The next site of adaptation is the transducer. That is, even though a stimulus may be maintained, the receptor potential adapts. Finally, the encoder translating the receptor or generator potential into a train of action potentials may also adapt. Spike-frequency adaptation also occurs in central neurons, such as ►motoneurons, in response to supra-threshold, step-like, maintained depolarization and is the result of several underlying processes. One is the inactivation of transient voltage-gated Na^+ channels (►Action potential), this process being specifically referred to as accommodation [7].

Principles of Central Processing

In general, processing of sensory signals occurs through a succession of hierarchically organized stages from the periphery to the cerebral cortex, with many descending feedback and cross-connections. A few general principles are as follows.

Modularity

One of the leading concepts in sensory physiology is the existence of parallel processing in various subsystems, here of signal flow from the periphery to the cerebral cortex [2]. Parallel processing is evident in various forms. First, individual receptor cells and their receptive fields need to be small for adequate spatial resolution and cannot therefore cover the whole area to be monitored, which instead requires a multitude of receptors. In several sensory systems (e.g. cutaneous senses, retina), receptor cells are arranged in two-dimensional sensory surfaces, which are tesselated by the receptor cells. The spatial order of this tessellation is maintained up to the cerebral cortex (topography), albeit in distorted form. Second, in some cases, the different modalities and submodalities are processed in functionally specialized systems, as, for example, in vision (►Visual Processing Stream in Primates; ►Extrastriate visual Cortex). However, at some stage, the pieces of information transmitted through, and processed within, spatial and functional channels must be integrated into unified representations (see below).

Topography

In several sensory systems, the pattern of neighborhood relationships among receptor cells is preserved throughout their central projections to higher stages, thus giving rise to topographic projections and topographic maps. Thus, the retina is mapped retinotopically onto several visual cortex areas (►Vision); the cochlea is mapped cochleotopically or tonotopically onto the auditory cortex; and the skin surface is mapped somatotopically onto somatosensory cortex areas (►Somatotopic organization; ►Primary somatosensory Cortex (s1); ►Somato-sensory Cortex, plasticity). Similar maps exist in subcortical structures such as ►thalamus, ►colliculus superior and cerebellum.

Functions of Maps

In considering the functional role of orderly maps, one has to take into account that there are different kinds of maps, which most likely have different functions [8]. Topographic maps allow for spatially close stimuli impinging on the receptor surface to be processed by

computations in local networks of neurons or modules that need not be connected via metabolically costly and space-consuming long-range connections. Also, local continuity on the map might serve as a metric for similarity in the space of the represented variables. For example, in the cochleotopic map of the auditory system, neighboring frequencies are represented such that they can interact over fixed distances [8]. Furthermore, cross-correlated activity in adjacent cell groups may serve to detect combinations and associations of the variables represented by any single group. Since most cortical connections are of short range, this mechanism would most readily work between adjacent cell groups. It may be assisted by the fact that gross topographic maps are often split into interdigitated reiterated slices representing different variables (features) and leading to multiple mappings within each small representational area. This pattern appears to make good sense in that a multi-dimensional variable or feature space (as in vision) is represented on a virtually two-dimensional surface. These additional variables (e.g. modalities or sub-modalities) can thus be labeled with a common spatial sign before being assembled into more complex higher-level entities.

Integration of Senses

Events or objects in external space manifest themselves by emanating different kinds of energy, which are picked up by different senses, e.g. vision, audition, somato-sensation, smell. Despite this analysis in parallel sensory systems and sub-systems, the nervous system must ultimately come up with a unified ►percept of the event or object, which requires that the different aspects and features supplied by the sensory systems be integrated (►Multimodal integration). This integration must even be accomplished within individual sensory systems that often analyze objects according to different sub-modalities in different brain areas (e.g. in vision: form, color, depth and motion in space etc.). But integration must also be achieved intermodally. How and at what neural stage this integration is performed is referred to as the ►binding problem (e.g. [9]).

Psychophysical, neurophysiological and brain-imaging studies have provided increasing evidence of vigorous interactions between sensory modalities. For example, vision and audition heavily interact, as already evidenced by the "►ventriloquist effect," but there are many other examples of cross-modal influences. Many of these interactions appear to take place at cerebro-cortical level, but at stages before the elaboration of conscious percepts [10].

Multimodal Integration

There have been several hypotheses as to how the nervous system might handle the binding problem. One hypothesis is based on the convergence of pathways from different receptor systems onto multimodal neurons [11–13]. Such multimodal convergence occurs throughout the neuraxis. Already in the spinal cord, different afferent nerve fibers carrying sensory information from different types of sensory receptors converge on central neurons [14,15]). The best investigated structure for multimodal convergence is the ►superior colliculus of the midbrain, which integrates sensory signals from vision, hearing, somato-sensation and pain for attentive and orientation behaviors [11–13]. Multisensory convergence also takes place at cerebro-cortical levels. For example, areas in the posterior parietal cortex contribute to the multisensory construction of spatial frames of reference (see Sect. 8.1) for planning eye, arm and hand movements [16,17]. And the human lateral occipital complex contains a subregion, which is activated by objects when either seen or touched. This convergence of visual and somatosensory signals appears to enable the precise recovery of object shape [18].

Another hypothesis posits that separate cell groups representing different object features are temporarily linked by dynamic connections that entail, and are maintained by, synchronization between their discharges. If synchronization is understood in a loose way, it is easily seen that an object will elicit nearly simultaneous activity in different regions of the brain, all of which may be concerned with one or the other aspect of it. But it has been hypothesized that synchronization on a millisecond time base may couple many neurons into assemblies representing objects [9]. On a gross scale, these synchronizations often appear in the form of oscillations in the high-frequency γ-range (20–80 Hz), which may be widespread over the cerebro-cortical surface. In the locust olfactory system, higher-order cells appear to be able to read out input synchronization and use it to fine-tune their sensory properties [19].

An exaggerated form of multimodal integration may be ►synesthesia, which is a condition in which otherwise normal persons experience sensations in a non-stimulated sensory modality by a stimulus applied to another sensory modality or ►sub-modality (also quality).

Memory

In order for organisms to properly appreciate objects and events, they should compare them with previous experiences, that is, stored information about themselves and the environments. This "knowledge" (not necessarily conscious, of course) is diverse, ranging from genetic information via internalized standards (e.g. sustainable substance concentrations) to fairly intricate internal representations or ►internal models (►hearing and memory).

Representation of Space

A basic requirement for perception, orientation, movement and object manipulation is the representation of space and spatial relationships between objects, including the own body. Although theoretically this representation need not be based on frames of reference and coordinate systems as used in physics and engineering, there is much experimental evidence for the existence of such frames [20].

Frames of Reference

Perceptual determination of an object's location, orientation and three-dimensional shape could make use of clues from several senses, e.g. vision, audition, proprioception and touch, not all of which may be available all the time. The sense receptors involved have different orientations to internal (body) and external space. For example, when an invisible object is localized by the position of the fingers touching it, finger position relative to the body can be determined making use of proprioception, which heavily involves muscle spindles. Since muscle spindles measure muscle lengths, their signals vary along dimensions of an *intrinsic frame of reference*. By contrast, when vision is primarily used for object localization, the object is projected onto the eye-fixed retinas, in an *extrinsic eye-centered* coordinate system. Already at this stage, three points are clear. (i) There is a difference between proprioception and vision in that the former can be used only in *peripersonal space*, whereas the latter covers far space as well, which imposes functionally differentiated roles on different senses. (ii) The spatial representations based on data from different senses operating with different reference frames must be brought in register with each other, involving *coordinate transformations* and *calibrations*. (iii) As a corollary, this process requires multimodal integration (see above).

The concepts of reference frames and coordinate transformations are extended when skilled movements guided by sensory feedback and thus involving sensorimotor transformations are considered. For example, consider a goal-directed movement such as pointing to a visible target. This task involves localization of the target and of initial hand position and collapsing hand with target position. As outlined above, the target is first projected onto the eye-fixed retinas, in an *extrinsic eye-centered* coordinate system. Since the eyes can move within the head, the eye-centered representation must be transformed into a head-centered representation, and, if the head is movable on the trunk, the head-centered representation must be transformed into a body-centered representation. When hearing is used for object localization, a head-centered auditory representation is the first step. Finally, the position of the arm/hand must be represented. The hand position can be given in terms of an intrinsic, rectangular Cartesian coordinate system, where the x-axis is in a parafrontal and the y-axis in a parasagittal plane through the shoulder. Alternatively, the hand position can be described in terms of joint angles, thus establishing an intrinsic system based on body geometry. Both systems are used by the nervous system, with their relative weight often depending on conditions. Note that motor actions are ultimately expressed in the latter system, that is, as changes in joint angles. The organization of goal-directed movements must therefore include transformations of all needed sensory signals in different reference frames into the intrinsic frame of joint angles, which involves a cascade of processes. All these systems are egocentric coordinate systems related to the organism. There is evidence that monkeys and humans are able to build ►allocentric (world-based, e.g. object-centered) ►reference frame, for example in the ►supplementary eye field. As mentioned and emphasized again, object locations are often determined from contributions of several senses (vision, hearing, vestibular, tactile, proprioceptive systems), whose different representations must be unified into one multimodal representation, requiring that the different coordinate systems be aligned [16,20–22].

Body Schema

In order to perceive and act, the nervous system must be able to relate the positions of the body and its parts to each other and to a representation of the external world. This complex representation is called the ►body schema. Humans normally are consciously aware of their body configuration, but often do not pay much attention to it. There are many pathological conditions, however, in which the existence of a body schema becomes strikingly apparent:

1. Phantom limb. When a limb is amputated or otherwise lost, the patient often feels the missing limb as if still existing. The configuration can change over time, however.
2. Hemispatial neglect arises in some forms of brain damage and may entail that the patients neglect entire parts of the external world or do not accept parts of their own body and associated extracorporeal objects (such as rings etc.) as belonging to them.
3. Paranoid ►schizophrenia may lead the patients to over- or underestimate the size or their limbs.

The body schema incorporates a representation of verticality based on signals from visual, vestibular, proprioceptive and several gravity receptors in the trunk [23], as well as a representation of the shape of the body and its dynamic changes. The sensation of shape depends on sensory signals carried by group Ia afferent fibers from muscle spindles [24] and conveying the positions of body parts relative to each other [25]. The sensory origin of the dynamic

movement information is not quite clear yet. How the body schema is generated centrally is largely unknown.

Modulation of Sensory Processing

Potentially, the many sensory systems could deliver immense amounts of information, which, if processed unsifted, would swamp the processing capacities of the nervous system. Moreover, much of the sensory information impinging on the nervous system is not immediately relevant behaviorally. Thus, extensive processing of sensory signals can, and needs, only be done on selected aspects.

The consequence is that, as best investigated in ►vision, the many objects in a visual scene compete for neural representation ([26] ►Visual attention). Resolution of this competition requires mechanisms ensuring

1. Selection of relevant pieces of information, involving
   (a) Suppression of unneeded information
   (b) Facilitation of needed information
2. Localization of the relevant information and directional processes toward this locus
3. Eye movements toward selected objects (if needed) to focus and observe them at high spatial resolution

The competition can be resolved by means of various processes steering ►attention [26]:

1. Bottom-up modulation by stimulus-driven processes
2. Top-down modulation, involving directed selective attention

Descending modulation of sensory processing can occur all the way from the cerebral cortex to the peripheral receptors, in the latter case by efferent control of receptor sensitivity (e.g. of auditory and vestibular ►hair cells, ►muscle spindles).

Bottom-Up Mechanisms: Salience

Stimulus-driven processes are based on the salience and "pop-out" of stimuli. Bottom-up means that attention is captured more easily by stimuli that are stronger, more extensive and/or move faster than others. Salient stimuli are easily detected among a number of distractors.

Top-Down Mechanisms

Top-down refers to attention-shifting processes controlled by the brain.

Selective Attention

Generally speaking, attention is the mental capability to select stimuli, responses, memories or thoughts, which are behaviorally relevant, from among those that are not [27]. Selection is achieved, at any time, by funneling the information flow through a small window of attention that may be shifted appropriately to interesting things currently relevant to behavior. If relevant information is to be selected from non-important one, neuronal activities must be facilitated and/or suppressed appropriately. This implies that neuronal activities must be susceptible to attention. Directing attention like a searchlight again requires the multimodal integration of senses to construct a common spatial frame [17].

Enhancement of Neuronal Response and Sensitivity

Neuronal responses and sensitivities to a stimulus are enhanced when attention is directed to the receptive field as compared to attention directed outside the receptive field. In vision, such attentional effects have been demonstrated in various visual areas (►Visual attention). Compatible results have been obtained in humans using functional brain imaging and event-related potentials. Response enhancement also occurs when attention is directed to a specific stimulus attribute, such as luminance, orientation, shape, color, and direction or speed of motion [26].

Sources of Attentional Top-Down Influences

The top-down attentional modulations probably originate in a distributed network of higher-order areas in parietal and frontal cortex. For spatially directed attention, these areas include the superior parietal lobule (SPL), frontal eye field (FEF), supplementary (frontal) eye field (SEF) and perhaps inferior parietal lobule (IPL), middle frontal gyrus (MPF) and anterior cingulate cortex [26].

Plasticity of Sensory Systems

The nervous system must be able to adapt to changing circumstances, at time scales from seconds to years. In ontogeny, this involves the dynamic establishment and maintenance of appropriate connections, including topographic representations of sensory surfaces and the peripheral motor apparatus [28]. However, such representations in sensory and motor cortices (and related subcortical structures) are alterable throughout life, in response to environmental and internal changes, e.g. frequent types of stimulation and lesions [29–35]. For example, consequent to loss of a digit, the somatotopic maps along the mechano-sensitive route to the cortex can be reorganized at all the intermediate processing levels, e.g. spinal cord, ►dorsal column nuclei, thalamus and cerebral cortex [35] (►Somatosensory Cortex, plasticity).

Mechanisms of Map Plasticity

A number of different processes and mechanisms contribute to the plasticity of topographic maps, from the influence of inhibitory interneurons to structural changes of axons and dendrites to synaptic plasticity. Structural changes, such as axon sprouting, synapse creation, retraction or elimination, occur in the initial

build-up of appropriate connections and have also been implicated in long-range reorganizations. Changes in dendritic arborization following prolonged exposure to complex environments or to specific motor tasks may be involved as well. Some mechanisms commonly shared with long-term synaptic plasticity may be at play here as well.

Information Transfer and Neural Codes

Each stage of neural processing converts the input into an output, and each of these conversion processes distorts the signals to some extent. There are several reasons, among which three pop out:

1. Dynamic range. A neuron's response range is limited.
2. ►Bandwidth. Each neural channel is bandwidth-limited, limiting its speed of response and temporal resolution.
3. ►Noise. Each channel is corrupted by noise.

Statistical Nature of Information Transfer

Noise implies that the coding and transfer of information are not completely reliable. Neuronal input-output relations are therefore of probabilistic nature. For instance, peripheral sensory systems encode stimuli into sequences of action potentials. Noise or uncontrolled variables in the encoding process entail that any particular stimulus may evoke several different sequences of action potentials and, conversely, any particular action potential sequence may be related to different stimuli. The same applies to synaptic inputs to neurons. Synapses may be fairly unreliable because transmitter release is a stochastic process with occasional failures.

Neural Encoding

Noise, and dynamic–range and bandwidth limitations, co-determine the efficiency of any code used to encode and transmit information. Inefficiency would be expensive because it would imply more storage space, more expenditure of transmission energy, longer transmission times or larger bandwidths or dynamic ranges to store or transmit the same information [36]. The ►efficient coding hypothesis posits that sensory receptors and neurons have adapted so as to minimize the costs and get the job "done just right-enough" [37].

How efficiently do sensory systems code sensory signals into action potential trains?

Sources of Inefficiency

One problem to be dealt with by sensory systems is natural stimulus statistics, i.e. the non-random statistical properties of environmental stimuli impinging onto sensory surfaces [38]. There are two main sources of redundancy:

1. Unequal probabilities of stimulus elements
2. Correlations between stimulus elements:
   (a) Spatial correlations between parallel stimulus elements
   (b) Temporal correlations between sequential stimulus elements

Unequal Probabilities of Stimulus Elements

Consider primate vision. The image is cast on the retina and sampled by photoreceptors (and can thus be regarded as a two-dimensional array of picture elements: pixels). Natural images contain an abundance of statistical regularities that may in fact be important for survival [39]. For example, in indoor, outdoor and natural environments, the orientations of contour segments defining objects occur at different frequencies, with vertical and horizontal orientations occurring more frequently than oblique ones [40,41].

Spatial Correlations between Parallel Stimulus Elements

Stimulus attributes at different pixels are correlated with each other [42] (see also [41]. This implies that "knowledge" of some section of an image can be used to predict other sections. In line with the above results, different contour segments of natural objects show orderly patterns, explaining the existence of long-range correlations in the distribution of oriented line segments over the visual field [43].

Temporal Correlations between Sequential Signal Elements

The time courses of natural signals differ from white noise, in which successive values vary randomly. Stimuli vary smoothly and continuously in time, making any value at any time instant dependent on the previous history. This also applies for neural signals and is readily apparent in receptor and synaptic potentials, but often holds true also for spike trains, where the probability of a spike depends on the occurrence of previous spikes.

Code Optimization

Because of its limited resources, the nervous system should try and reduce any coding inefficiency. Whether it does so, and if so what mechanisms it uses, is only partially known and may depend on the specifics of particular channels (see, e.g. [39]). There may be channels with limited capacities, in which coding efficiency may be pressing (for example, the optic nerve in mammals). By contrast, at other places (e.g. the cortical visual areas), redundancy might be of advantage; after all, the regularities in the environment allow the nervous system to make predictions [39].

An example for how to construct an optimal code is presented by the fly compound eye with possible extensions to the mammalian visual system [44]. Pictorial information is derived from the two-dimensional

spatial array of light intensities and their changes in time. The intensities in ambient daylight may vary over several orders of magnitude. If this range were transduced linearly into photoreceptor potentials, the gain would be uniformly low. Moreover, of prime importance in an image are changes, spatial contrasts and temporal variations, which delineate objects from others. Thus, some other form of coding is required. ►Contrast is a measure of relative intensity at some point in relation to the average (background) intensity level, I, in its surroundings, usually expressed as $\Delta I/I$.

The background intensity I can be estimated as a weighted average of the signals from surrounding photoreceptors. Such weighting functions have been computed for pictures of different statistical properties and intensities and different ►signal-to-noise ratios, and compared with measured data. To remove temporal correlations requires a biphasic response to an instantaneous flash (►impulse response). Thus, the weighting functions necessary for this computation are functions of space and time, over which the local means should be determined. This coding scheme has some essential features:

1. ►Center-surround antagonism in the receptive field (RF). Here the center is excitatory and the surround inhibitory. This receptive field organization is often found in sensory systems.
2. Reduction of redundancy resulting from spatio-temporal correlations. These correlations can be captured by properly designed weighting functions, and subtraction of the predictive signal thus removes or at least reduces the correlation-based redundancy from the center signal.

In summary, center-surround antagonism in receptive fields is capable of enhancing spatial contrasts, and this in turn reduces spatial redundancy that would otherwise be present in the signals of parallel neuronal elements due to spatial correlations in the sensory signals. Similar principles apply in the temporal domain, where properly chosen impulse functions may reduce temporal redundancy.

Acknowledgment

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I am grateful for encouragement and suggestions for improvement to Marc D. Binder and Douglas G. Stuart."

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Sensory Transduction

Definition

Sensory transduction denotes the process by which, in a sensory receptor cell, a physico-chemical stimulus is converted, by the opening or closing of ion channels in a local membrane region, into a receptor current, which in turn gives rise to a receptor potential.

►Receptor Potential
►Sensory Systems

Septal Complex

►Evolution of Septal Nuclei

Septal Nuclei

Synonyms

►Nuclei septales

Definition

The nuclei located in the septum verum (lateral septal nuclei, medial septal nuclei, nucleus of diagonal band) are involved in complex function circuits between hypothalamus and hippocampus. Lesions and stimulation show that the nuclei are involved in autonomic behavioral processes such as eating, drinking, micturition, defecation, sexual, reproduction and aggression behavior.

►Telencephalon

Septal Organ

Definition

"Organ of Masera," bilaterally, isolated small patch of olfactory epithelium in several mammalian species at the nasal septal wall with axonal projections of specific

glomeruli in the olfactory bulb. Discovered 1921 by Broman, function yet unknown.

►Chemical Senses
►Olfactory Perception

Septal Region

Definition

The septal region (area septalis) lies medial and dorsal to the nucleus accumbens, and terminates dorsally in the septum pellucidum. The septal regions contains the septal nuclei and the diagonal band of Broca.

►Evolution of Septal Nuclei

Septum, Lateral

Definition

Part of the septal complex, comprising mostly GABAergic medium sized, spiny neurons, that receives massive inputs from the hippocampus and projects strongly to the preoptic region and medial septumdiagonal band complex, which is rich in cortically projecting cholinergic and GABAergic neurons.

Septum Medullae

►Floor Plate

Septum Pellucidum

Definition

The septum pellucidum is part of the medial border of the cerebral hemisphere and third ventricle. It consists of a thin layer of glial tissue almost void of neurons. The septum pellucidum spans between corpus callosum, fornix, and septal region. The septa pellucida of both hemispheres are partially adherent but may contain the cavum septi pellucidi, a cavity filled with fluid.

Sequence Learning

Definition

Sequence learning is of behavioral procedures or "how to," which is similar to skill learning. But it is learning of a series of multiple discrete movements towards a goal, like learning to play a musical instrument or learning to play tennis. It can reflect acquisition of processes of simple stimulus-response association or more extensive, sequential patterns of discrete movements.

In this learning, cortical motor areas, prefrontal cortex and subcortical areas especially the basal ganglia play major roles. Basal ganglia with dopamine system and prefrontal cortex are responsible for acquisition of a series of movements or actions towards a goal, favorable condition.

►Sensorimotor Learning and the Basal Ganglia

Sequence of Pulse Intervals (SPI)

Definition

A measure of the temporal patterning of electric organ discharge (EOD) production. Refers to the intervals between adjacent EODs over time.

►Reafferent Control in Electric Communication

Serial Analysis of Gene Expression

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Synonyms

SAGE; LongSAGE; SuperSAGE

Definition

Serial Analysis of Gene Expression (SAGE) is a sequence-based approach that allows for global analysis of ►mRNA transcripts, without the requirement of

a priori knowledge of an organism's ►transcriptome. SAGE produces a large library of short sequence tags that originate from mRNA extracted from a tissue or purified cell sample [1]. The frequency of each tag directly reflects transcript abundance while the sequence is sufficient to identify known transcripts in database searches. SAGE can be utilized to discover previously uncharacterized transcripts, unlike some types of ►microarray analysis, but currently costs several fold more than microarrays to implement.

Characteristics

Overview

Diverse interactions of many neuronal and glial cell types allows for intricate wiring and organization of the nervous system, making it one of the most complex tissues in animals. Although each cell in the nervous system contains an identical copy of the organism's genome, distinct gene expression profiles allows for variegated cellular and functional diversity. In the past, global differences in gene expression profiles have been examined by Northern Blotting, subtractive hybridization, comparative ►expressed sequence tag (EST) analysis and differential gene display [2]. However, these methods are capable of analyzing only a limited number of highly expressed transcript species and do not provide quantitative data on expression levels. Therefore, an approach to quantitatively and qualitatively examine the expression of large numbers of genes expressed at both low and high levels was needed to yield more detailed information on transcript expression profiles. SAGE, originally developed by Velculescu et al. (1995) [1], fulfilled this requirement and was readily adopted by investigators in many fields of biology in subsequent years. While genomics has been extremely successful in cataloguing protein coding gene sequences, it has provided less information on how these genes work in concert to maintain homeostasis by responding to environmental and internal cues, SAGE, therefore, offers an opportunity to increase our understanding of how large numbers of genes operate in a global manner.

Purpose

SAGE data is utilized to determine the qualitative and quantitative expression distribution of thousands of transcripts simultaneously from a single RNA sample through the generation and sequencing of oligonucleotide tags derived from RNA transcripts [1]. These data can be used to describe the gene expression profile of a single cell or tissue type, or be used to compare different gene expression profiles of two or more samples [3–6]. SAGE tags without a match to known transcripts can also act as a starting point for the investigation of previously unknown genes. Further, SAGE libraries are digital and are thus easily stored in publicly accessible databases for future comparison and analysis.

Principles

Firstly, sufficient information is contained in a short nucleotide sequence, termed a "tag," to accurately identify the transcript [1]. Standard SAGE tags are 10 nucleotides long, while the currently more favored LongSAGE tags are 17 nucleotides long [7]. (Note: these SAGE tags are actually 14 or 21 nucleotides long, respectively, but all tags contain a common nucleotide restriction enzyme recognition site at the 5′ end meaning that only 10 or 17 nucleotides are unique to each tag.) Thus, 4^{10} or 4^{17} (1.04×10^6 or 1.72×10^{10}) unique permutations can be represented using this short sequence. For comparison, the human genome contains a total of $\sim 3 \times 10^9$ nucleotides, not all of which are transcribed. Secondly, from 25 to 50 concatermerized tags can be cloned into a single vector, allowing for serial analysis of multiple tags in a single sequencing run. Thirdly, each unique SAGE tag provides information on the genes contributing transcripts to the RNA population, as well as the frequency of occurrence when compared to the total populations of transcripts in the SAGE library.

Method

Biochemistry

A standardized protocol for SAGE based on the original method developed by Velculescu et al. (1995) [1] is available to researchers and can be accessed at http://www.sagenet.org. LongSAGE [7] and SuperSAGE [8] are performed in a similar manner but utilize different tagging enzymes to generate longer tag lengths. Briefly, RNA is separated from proteins and cellular debris. One strand of cDNA is produced from mRNA by using reverse transcriptase and 5′-biotinylated oligo(dT) primers. Double stranded ►cDNA is then produced by digesting the original mRNA template with ►RNAse H followed by DNA synthesis with DNA polymerase and DNA ligase. A type II ►restriction endonuclease, *Nla*III, called the anchoring enzyme (AE) in this context, cleaves the resulting double stranded cDNA. The product of the anchoring enzyme step is washed over ►streptavidin coated magnetic beads, capturing the biotinylated double-stranded cDNA fragments while the remaining cDNA is washed away. The anchored tags are then divided into two pools. Different linker sequences are ligated to each pool of anchored tags. The linkers contain a recognition motif for a type IIs restriction endonuclease, such as BsmFI, which cleaves DNA at a set distance from the recognition site. Blunt ends are generated by use of ►Klenow fragment. Mixing of the two populations of tags is followed by the ligation of these tags with DNA ligase to form ditags. PCR

amplification of the ditags is performed followed by purification of the PCR products by gel electrophoresis and extraction. The linker portions of the ditags are released with digestion by the anchoring enzyme (*Nla*III). The ditags are concatenated with DNA ligase and inserted into a ►plasmid vector for sequencing.

Sequence Analysis and Tag Identification

High throughput sequencing methods produce digital datafiles of the concatamers. The beginning and end of each tag in the concatamer are identified by searching for the restriction site of the anchoring enzyme contained in each tag (CATG in the case of *Nla*III.) The sequence of each tag is then logged in a data file for further analysis. A conventional SAGE library will contain 50,000 to 100,000 total tags [3,4,6].

Virtual tag libraries have been generated *in silico* from cDNA sequences archived in the GenBank databases. These cDNA sequences are both cDNAs of described genes and ESTs. Software programs are used to compare the experimentally generated SAGE library with the *in silico* library. When an experimentally generated SAGE tag matches a virtual tag, the identity of the transcript or the gene from which the virtual tag was extracted is assigned to the experimentally generated SAGE tag.

Data Analysis and Presentation

A common pattern of SAGE data presentation has evolved. The fraction of total tags is often plotted against the frequency with which the tags appear in the population. This relationship often assumes a power law distribution in which a small number of the tags found in the library is present at a very high frequency, while many different types of low copy number tags make up the bulk of the tag population. Tag frequency, sequence, and identity are presented in tables. Tags are often grouped into functional classes based upon Unigene Gene Ontology nomenclature. When two or more samples are compared, tags are presented in tables with the greatest differences between samples listed in descending order. Difference in gene expression level is evaluated based on the result from a statistical test rather than simple fold-difference in tag count between the groups being compared. These methods include a Poisson approximation developed by Audic and Claverie [4], Bayesian method, Monte Carlo Simulation or Fisher's Exact test [6]. Each technique has its own strengths and weaknesses; however, in each case a probability value (p-value) is generated that represents the probability of obtaining a result as extreme as the given case, assuming the case was generated by probability alone. When the p-value is less than an a *priori* chosen significance level (α), usually $\alpha = 0.05$ or 0.01, the null-hypothesis of no difference between gene expression levels is rejected.

Advantages and Disadvantages

Advantages

Techniques such as reverse real-time quantitative PCR (►RT-qPCR) and northern blotting are useful for studying the expression levels of one or a limited number of known genes [6]. Larger scale screening methods such as cDNA subtraction utilize hybridization to uncover differential expression of unknown genes on a small to medium scale, but provide little information on transcript abundance [2]. Conventional microarray analysis is usually used to study known transcript expression. However, recently developed tiling microarrays employ probes representing large stretches of a genome and can detect previously uncharacterized transcripts [9]. In contrast, SAGE provides exact counts of transcript frequency and identity within a library. SAGE can be considered an open experimental format where prior knowledge of the subject's genome is not required, and previously uncharacterized transcripts can be identified. Nevertheless, the true power and utility of SAGE is only fully actualized when a well annotated genome is available to match tags to known genes. Further, the number of SAGE tags collected in an experiment can easily be increased so that even very rare transcripts can be identified with a high probability that these rare transcripts will be previously uncharacterized.

Disadvantages

Tag sequence specificity has been cited as a weakness in SAGE. Transcripts from two or more different genes can share the same tag sequence [7,8]. This weakness has been addressed by the development of LongSAGE [7] and SuperSAGE [8] approaches that expand SAGE tags from 10 to 17 or 26 nucleotide long tags, respectively, greatly increasing tag specificity.

In many studies, from 30 to 50% of SAGE tags do not map to known transcripts or genes [4,6]. Many of these unmapped tags appear as ►singletons. These unmapped transcripts could originate from introduction of base changes or sequencing errors since multiple steps are involved in SAGE tag collection and single pass sequencing can contain base errors. However, recent work utilizing tiling microarrays has shown that much of the genome may actually be transcribed at low levels suggesting that these unmapped tags may indeed represent unknown low abundance transcripts [9]. In many studies, singleton transcripts are excluded from further data analysis. Obviously, this approach, while simplifying interpretation of the data, detracts from the experimental power of SAGE to discover uncharacterized low copy number transcripts.

Uses of SAGE in Neuroscience

The use of SAGE in neuroscience spans the genetic and neural complexity of organisms from the nematode *C. elegans* to mouse and human. The following

summaries of studies utilizing SAGE libraries have been chosen to highlight the diverse applicability of SAGE in neuroscience, but in no way acts as a comprehensive catalogue of the research done to date.

A. *Effects of signaling molecules on the central nervous system*

Datson et al. (2001) [3] utilized SAGE to identify corticosterone responsive genes in the ►hippocampus of the rat. Stress causes an increase in the release of corticosterone in rats by increasing the activity of the hypothalamic-pituitary-adrenal axis. Response to glucocorticoids occurs via binding of corticosterone to intracellular mineralocorticoid (MR) and glucocorticoid receptors (GR) which in turn activate or repress target genes. MRs are approximately 10 times more responsive to corticosterone than GRs. Exposing adrenalectomized animals to low or high corticosterone levels resulted in differential gene expression. Furthermore, comparison of MR- and GR-dependent expression profiles revealed that the majority of the corticosterone-responsive genes were regulated either by activated MR or by activated GR, while only a few genes were responsive to both. These differentially expressed genes were grouped into classes such as: energy expenditure and cellular metabolism; protein synthesis and turnover; signal transduction and neuronal connectivity; and neurotransmission. Although some genes were already known to be corticosterone responsive, such as GAP-43 and metallothionein-I, many were novel. Differential expression of six randomly chosen, previously identified genes was examined by *in situ* hybridization and found to correlate strongly with the SAGE data.

B. *Development and differentiation of neuronal types*

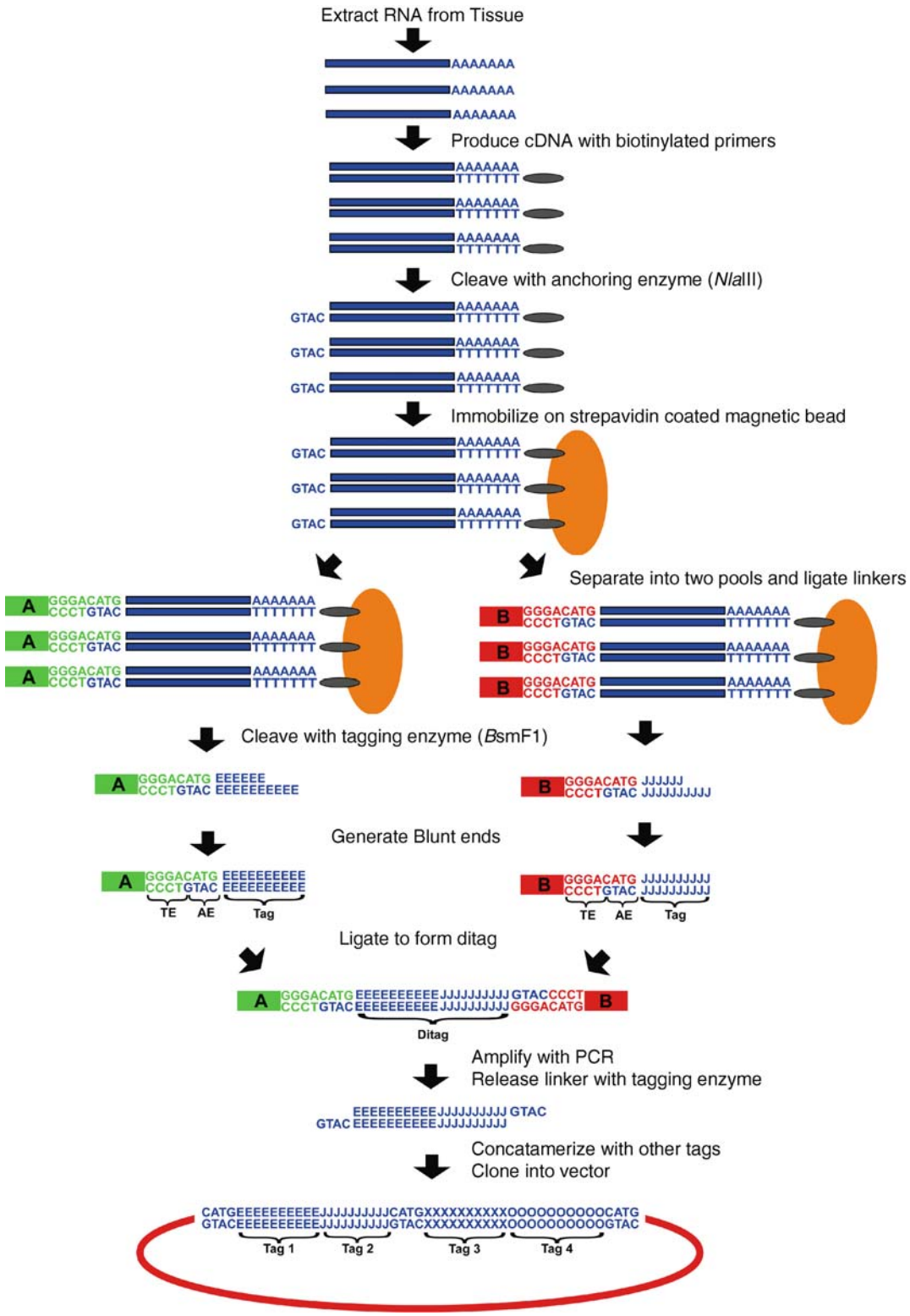
Etchberger et al. (2007) [4] utilized SAGE to compare the expression profile of gustatory neurons (ASE neurons) with thermosensory neurons (AFD neurons) of *C. elegans* and were able to identify >1,302 differentially expressed genes. These genes included transcription factors, ion channels, neurotransmitters, and receptors, as well as seven-transmembrane receptor-type putative gustatory receptor genes. Examination of the *cis*-regulatory sequences, through consecutive deletions of the promoter region of multiple differentially expressed genes, followed by sequence alignment and site-directed mutagenesis revealed a previously uncharacterized "ASE motif" required for the expression of many ASE-expressed genes. The ASE motif was identified as a binding site for the C2H2 zinc finger transcription factor CHE-1, which is essential for proper differentiation of the ASE cell type. This study highlights the usefulness of SAGE when combined with other more conventional approaches to interrogating the genome.

C. *Molecular profile of pathophysiological processes*

Focal Brain Ischemia Reperfusion injury (stroke) has been characterized as having acute and delayed phases. During the acute phase, hypoxia and energy failure cause cell necrosis, while delayed events, involving altered gene expression after blood flow has been re-established, are involved in subsequent inflammation and apoptosis. Trendelenburg et al. (2002) [6] utilized SAGE to identify candidate up-regulated and down-regulated genes involved in the delayed response. Metallothionein-II (MT-II) was the transcript most significantly increased 14 h after ischemia as compared to controls. However, the expression of the closely related gene Metallothionein-I (MT-I) could not be analysed using SAGE as it did not contain a NlaIII anchoring restriction site. Northern Blotting and semi-quantitative Western Blotting was utilized to confirm MT-II up-regulation. Immunohistochemistry revealed that both MT-I and MT-II were expressed in reactive astrocytes around the infarct core. MT-I and MT-II deficient knock-out mice were shown to have an infarct volume three times that of wild-type animals. This study demonstrates how SAGE data can be linked to functional relevance. Taken together, these findings suggest a protective role of metallothioneins in a model of stroke.

D. *Comparative Gene Profiles of Developing Brain Regions*

The two cerebral hemispheres of the human brain are specialized for distinct cognitive and behavioral functions. For example, language function is predominantly localized to a distributed network in the left cortex surrounding the lateral sulcus, called the perisylvian cortex, in ~97% of right-handers and ~60% of left-handers. Sun et al. (2005) generated SAGE libraries from the left and right perisylvian regions of human fetal brains at 12, 14 and 19 weeks of development. In all, 49 differentially expressed genes were found between the left and right regions in the 12 week old brain and 68 in the 14 week old brain. Factors known to play a role in cortical development, such as ID2, NEUROD6 and Lim Domain Only 4 (LMO4) were found to be asymmetrically expressed. LMO4 was further investigated with RT-qPCR and shown to be expressed at a higher level in the right cortex compared to the left at 12 weeks and 14 weeks, but not 19 weeks. *In situ* hybridization performed on brains at several different stages from 12 to 19 weeks of development also demonstrated that LMO4 expression is found to a greater extent over the right perisylvian cortex than the left, with diminishing asymmetry over the same period of development. LMO4 expression was also profiled in embryonic mice and exhibited a similar temporal pattern of lateral asymmetry but was not consistently lateralized to the right or left side. This may



Serial Analysis of Gene Expression. Figure 1 Schematic of SAGE Library Construction. Double stranded cDNA is produced from polyadenylated RNA transcripts. The anchoring enzyme defines the 5′ end of the tag. After ligation to linkers, the tagging enzyme defines the 3′ end of the tag. The anchoring enzyme is used to free the tags of the linkers before they are blunt-ended and ligated together to form ditags. The ditags are then concatenated and inserted into a plasmid for sequencing.

relate to motor asymmetries which are observed in individual mice, like paw preference, but are not biased on a population level as they are in humans where 90% of the human population has naturally greater dexterity with their right hand. The left-right differences in LMO4 expression in humans could potentially represent either a differing topographic mapping in the two hemispheres or alternatively a difference in the rate of cortical development, with the right hemisphere's development occurring more rapidly than the left.

Future of SAGE

Currently, the sensitivity of SAGE to detect low copy number tags, many of which may represent real transcripts, is limited by cost-efficiency due to the current expense of DNA sequencing on conventional systems. New sequencing technologies are becoming available that should allow sequencing of millions of base pairs for a few hundred to a few thousand dollars with much higher throughput [10]. Furthermore, massively parallel sequencing-by-synthesis approaches like the Solexa 1G system or the 454 system that allow simultaneous sequencing of thousands of short nucleotide sequences at once should theoretically negate the need for cloning or concatamerization; instead, allowing a modified form of ditags to be directly sequenced [10]. Therefore, SAGE, or variations thereof, has the potential to play an increasing role in transcriptome and genome studies for the foreseeable future.

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Serial Learning

Definition

Serial learning is learning to make a series of responses in exact order. In other words, it is a procedure of learning where the learner is exposed to stimuli to be remembered and later recalls those stimuli in the same order in which they initially appeared. Memory for words is a representative type of serial learning.

Series Arrangement

Definition

A combination of two rheological elements, such that the force is common to both and the elongations are to be added to obtain the elongation of the combined element.

►Mechanics

Series Elasticity

►Tendon

Serotonin Actions on Suprachiasmatic Nucleus

Definition

One of the major transmitters in the nervous system. Serotonergic neurons from the raphe region densely innervate the suprachiasmatic nucleus (SCN). Raphe

neurons typically generate action potentials and release 5HT during the phases of the daily cycle in which the animals are awake. A diverse array of 5HT receptors have been reported in the SCN including the 5HT1A, 5HT1B, 5HT2A, 5HT2C, 5HT5A and 5HT7 receptor types. These G-protein linked receptors are coupled to adenylyl cyclase or phospholipase C. Activation of these signaling pathways could produce a variety of cellular effects in SCN neurons. The modulations of potassium and calcium channels most commonly mediate the ionic actions of 5HT in other brain regions although the specific ionic mechanisms that underlie 5HT's actions in the SCN are unknown.

Functionally, 5HT receptor agonists cause phase shifts of the SCN circadian oscillator when administered at times in the circadian cycle during which light does not cause phase shifts both in vitro and in vivo.

Evidence suggests that this pathway may mediate nonphotic activity induced phase shifts of the circadian system. In addition, a variety of evidence suggests that 5HT can also modulate photic input to the SCN. Neurotoxic destruction of the serotonergic input to the SCN alters the relationship between the light-dark cycle and locomotor activity and increases in 5HT levels alter the effects of light on the circadian system. Administration of 5HT can inhibit optic nerve induced field potentials in the SCN brain slice preparation, light-induced Fos expression and phase shifts of the circadian rhythm of wheel-running activity. Interestingly, 5HT receptor antagonists have been reported to enhance light-induced increases in the firing rates of SCN neurons and light-induced phase shifts. These results raise the possibility that 5HT may be involved in a tonic inhibition of the light-input pathway to the SCN. These studies are all consistent with the hypothesis that the serotonergic innervation of the SCN serves to modulate light input as well as mediate non-photic activityinduced phase shifts of the circadian system.

►Circadian Rhythm
►Slice Preparation
►Suprachiasmatic Nucleus

Serotonin (5-hydroxytryptamine; 5-HT)

Definition

Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from L-tryptophan and can be converted to melatonin. It is a monoaminergic neurochemical that is common to the nervous and immune systems. Neurons containing serotonin are located near the midline or raphé regions of the brainstem. Serotonergic fibers project widely throughout the central nervous system (CNS) and exert complex neuromodulatory effects mediated through 15 receptor subtypes. 5-HT contributes to functions such as endocrine and circadian rhythms, sleep, body temperature regulation, appetite, food intake, sexual and reproductive activity, aggression, motor functions, cognition, mood, anxiety, learning and memory. Outside the central nervous system, 5-HT is present in immune cells such as platelets, lymphocytes, monocytes and macrophages.

►Circadian Rhythm
►Melatonin
►Raphé Nuclei

Servo Control

Definition

The operation of a proportional feedback controller whereby the feedback loop serves to minimize the error between the desired and actual values of the controlled variable.

►Feedback Control of Movement

Servomotor

Definition

A motor that automatically controls the action of a mechanical device in a feedback system consisting of a sensing element and an amplifier.

Set-point

Definition

In the body, certain variables must be kept within a narrow limit for survival. This desired or reference point is called set point.

►Homeostasis

Set-point in Temperature Regulation

Definition

The value of a regulated variable that is stabilized by the processes of regulation. In temperature regulation, this variable is the core temperature (T_c). In fever, its value shifts due to pyrogen-induced changes in the characteristics of the thermal controller such that the properties of the various feedback, feedforward and open-loop components that together contribute to thermal balance cause this balance to occur at a higher than "normal" T_c.

►Endotoxic Fever

Seven Transmembrane Receptors

►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages

Severe Myoclonic Epilepsy of Infancy (SMEI)

Definition

SMEI is a rare form of childhood epilepsy. The symptoms of this disorder begin with tonic/clonic seizure during the first 6 months of life and accompanied by elevated body temperatures. As time progresses, increasingly worse symptoms develop, such as myoclonic seizures, ataxia and photosensitive seizures. In 70% of children with SMEI bear a missense, frameshift and nonsense mutations in the SCN1A sodium channel gene that results in nonfunctional and truncated proteins.

►Epilepsy

Sex

Definition

Biological construct used to divide members of a species into reproductively distinct and often complementary groups. A term used to classify organisms as male or female according to genetic composition and consequent anatomic structures and functions. The term sex can be used in reference to human or non-human animals.

►Gender/Sex Differences in Pain

Sex Differences in Pain

►Gender/Sex Differences in Pain

Sexual Behavior

Definition

Behavior that is directed towards a sexual partner, includes courtship and copulation.

Sex Lethal

Definition

A name of a gene in Drosophila that undergoes sexspecific splicing to form an active Sex lethal protein in females, and non-active Sex lethal protein in males. The active form of Sex lethal initiates the female-specific development.

Sexual Neurophysiology

►Neurophysiology of Sexual Spinal Reflexes

Sexual Reflexes

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Definition

Sexual reflexes in males and females comprise of complex integrated systems that are influenced by hormonal levels and sensory signals that are regulated by the central and peripheral nervous systems. Genital reflexes in males and females, such as genital arousal, erection and climax arise from spinal cord reflex mechanisms that are modulated by brain inputs. Other pathways, such as sexual desire and arousal may be regulated by higher central nervous system mechanisms, yet to be determined.

The structural components and mechanisms that lead to Sexual Reflexes, in particular genital reflexes, are outlined in this essay.

Characteristics

Higher Level Structures

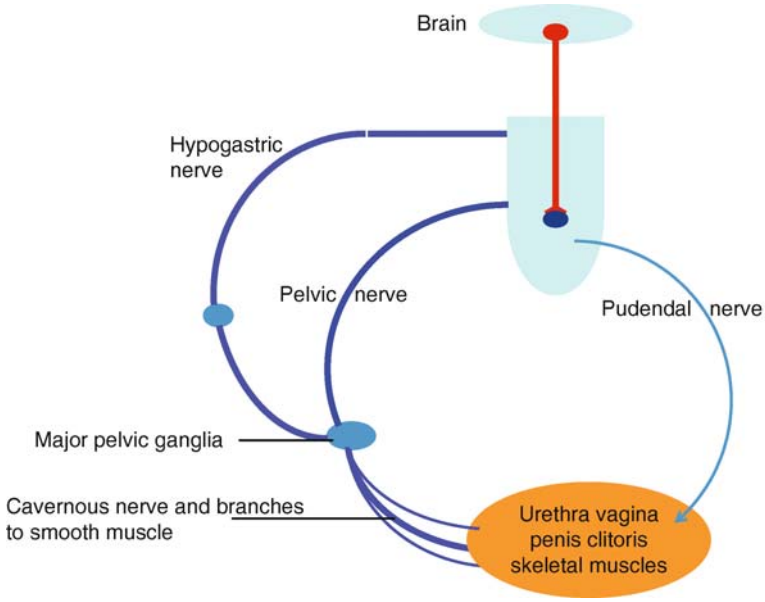
Major Components: Peripheral Nerves, Spinal Cord and Brain (see Fig. 1)

Sexual reflexes such as clitoral and vaginal ►vasocongestion, erection, ejaculation and sexual climax are organized at the spinal level. This conclusion is based on experimental studies in animals with transected spinal cords and in human patients with spinal cord injury. Sensory stimulation from peripheral nerves increases activity in the spinal cord, which results in increased sexual motor output. For the most part the organization of the neural structures mediating sexual reflexes are similar in males and females.

Sexual responses require the complex coordination of sympathetic, parasympathetic and somatic efferents that are distributed over several spinal segments. These efferents must be coordinated by an interneuronal system that traverses multiple spinal segments. These spinal circuits are regulated by peripheral sensory inputs and descending inputs from the brain. The major supraspinal input is inhibitory and neurons in the caudal ventral hindbrain, in a region known as the nucleus paragigantocellularis, mediate the inhibition in both males and females. Forebrain sites can also facilitate activity of the spinal circuits.

The medial preoptic area is essential for male copulatory behavior (erections and ejaculation) in every species tested [1], and stimulation of this site evokes sexual reflexes in male rats [2]. In females, the brain sites facilitating sexual reflexes are less clear. The medial preoptic region in rats inhibits the display of ►lordosis, but may facilitate genital reflexes. The ventromedial nucleus of the hypothalamus is critical for the expression of lordosis [3], but lordosis is not seen in all species.

Other forebrain regions involved in sexual function have largely been identified on the basis of visualization



Sexual Reflexes. Figure 1 Diagrammatic representation of the major components involved in sexual reflexes. Peripheral sympathetic (hypogastric), parasympathetic (pelvic) and somatic (pudendal) nerves regulate sexual reflexes. The spinal cord inputs (afferents) and outputs (efferents) are located on the lumbar and sacral cord. The brain modulates the activity of the spinal circuits, mainly be descending inhibition.

of activated neurons in association with particular events, for example, ejaculation or vaginocervical stimulation. The medial amygdala, bed nucleus of the stria terminalis, medial preoptic area, paraventricular nucleus, ventromedial hypothalamus, lateral hypothalamus and central gray are most consistently activated in response to sexual reflexes [4]. These areas may be part of the sensory, motivational or reward circuits that are associated with sexual satisfaction, in addition to regions processing sexual reflexes. Imaging studies in humans have identified areas in the cortex (inferior frontal cortex and insular cortex), midbrain and cerebellum that are activated with visually-evoked sexual stimulation or climax [5].

Lower Level Components

Peripheral Nerves and Spinal Circuits

The peripheral innervation of the pelvic organs involved in sexual reflexes comprise of the autonomic (pelvic and hypogastric) and somatic (pudendal) nerves. Spinal afferents and efferents that regulate sexual function are located in the lower thoracic lumbar region (T11-L2 in humans, sympathetic) and sacral cord (parasympathetic and somatic). Sensory information from the genital areas travel in the afferent fibers of the pudendal nerve, which enter the spinal cord through the superficial dorsal horn and project to the dorsal gray commissure, which is located in the medial cord, where they terminate. The afferent neurons then synapse on spinal interneurons, which eventually send signals to the efferent spinal neurons that control the pelvic organs. The sensory information is also sent to other spinal segments and to the brain. The sensory afferents of the pelvic (parasympathetic) and hypogastric (sympathetic) nerves may also contribute to sexual reflexes; these fibers enter the dorsal horn and terminate in the lateral and medial gray matter. The efferent fibers of the pudendal nerve provide innervation of the pelvic floor, anal and urethral sphincters. The pudendal motor neurons are located in the ventral horn of the spinal cord (Onuf's nucleus). The efferent sympathetic and parasympathetic fibers relay through the major pelvic ganglion and the hypogastric plexus to form the ►postganglionic nerves (cavernous nerve, dorsal nerve of the penis and clitoris).

Ascending and Descending Spinal Pathways

The ►spinothalamic and ►spinoreticular pathways relay sensory information to the brain. These pathways travel in the dorsal region of the spinal cord and terminate in the thalamus. Most of the spinoreticular fibers travel in the lateral columns that terminate in the brainstem reticular formation. Descending information from the brain also passes through the dorsal spinal cord. The majority of these pathways cross over to the opposite side.

Brain Sites

The nucleus paragigantocellularis projects directly to efferent neurons of the hypogastric, pelvic and pudendal nerves as well as interneurons in the spinal cord [2]. Lesions of this nucleus allow climactic-like responses to be evoked by peripheral stimulation [2]. Higher brain regions involved in sexual function, for example the medial preoptic area, paraventricular nucleus of the hypothalamus, ventromedial nucleus of the hypothalamus and amygdala, either project directly or indirectly to the nucleus paragigantocellularis and/or to the spinal cord. However, research from a number of laboratories has shown that the central gray is an important relay center for ascending and descending sexually relevant stimuli. Reciprocal connections between most of the brain regions involved in sexual reflexes have been identified.

Structural Regulation

Spinal sexual reflexes are regulated by the amount of peripheral sensory stimulation received and by inhibition from brainstem regions. These spinal reflexes can function independently from inputs from the brain (as in the case of complete spinal cord injury). However, higher brain regions can evoke sexual reflexes, for example during nocturnal erections and ►psychogenic elicitation of climax.

The spinal and brainstem sites are relatively insensitive to the effects of gonadal steroid hormones (estrogen, progesterone, and testosterone). However, these hormones can modulate sexual reflexes in part by affecting the higher brain control of reflexive mechanisms, as well as altering the sensory threshold of the peripheral nerves.

Higher Level Processes

Figure 2 summarizes the major processes.

The pelvic and hypogastric nerves mediate sensory information from the internal pelvic organs. Sensations to light touch, chemical stimuli and noxious stimuli of the vagina, cervix, penis and uterus are mediated via the pelvic nerve. Therefore, the pelvic nerve relays sensory information from genital manipulations during sexual behavior. The pelvic nerve is also crucial for the induction of pregnancy or pseudocyesis induced by mating or cervical stimulation. The hypogastric afferents that innervate the uterus, cervix and ovaries may be important in the transmission of noxious stimuli from the uterus. Both the pelvic and the hypogastric nerves are sensitive to circulating gonadal steroid hormones. These preganglionic nerves and their postganglionic nerves also control the contractile and blood flow changes that occur in the genital organs during sexual responses and regulate the secretion of seminal fluids into the urethra. The pudendal nerve mediates sensory

stimuli from the external genitals, the pelvic floor musculature, and surrounding areas including the perineum, clitoris, penis and urethra. The sensory signals that relay through the pudendal nerve are essential for lordosis and ▶urethrogenital reflexes.

Many brain sites receive genital sensory information, indicating that the descending control of spinal sexual function is itself strongly influenced by peripheral stimuli. For example, the nucleus paragigantocellularis, the paraventricular nucleus, the central gray and medial amygdala have all been shown to contain neurons whose activity is modulated by pelvic sensory input. These nuclei are involved in the modulation of spinal sexual reflexes and their activity is, in turn, modulated by genital sensory input.

Higher brain sites (midbrain, hypothalamus and amygdala) also receive cognitive sensory information and have estrogen and androgen receptors on the neurons. These structures are likely sites by which hormones regulate sexual behavior and motivation. However, lack of reward or increased inhibition of the CNS circuits may lead to disruption of the sex cycle and can terminate the occurrence of sexual reflexes.

Lower Level Processes

Peripheral Mechanisms

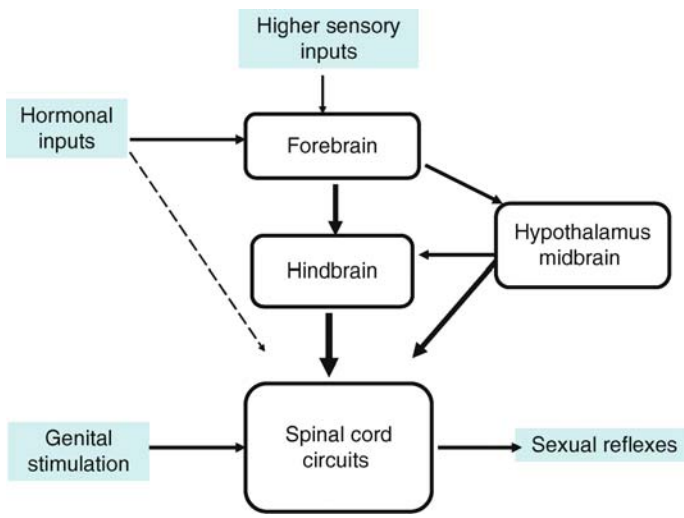
Noradrenaline and neuropeptide Y released by sympathetic nerves results in smooth muscle contractions of the penis and clitoris. Acetylcholine, vasoactive intestinal polypeptide and nitric oxide are released by the parasympathetic nerves. Acetylcholine release results in contraction of the smooth muscle and stimulates release of endothelial nitric oxide. Vasoactive intestinal polypeptide and nitric oxide act to relax smooth muscles, which results in increased blood flow causing erection and vaginal and clitoral engorgement. Acetylcholine released from somatic nerves causes contractions of skeletal muscles.

Spinal Mechanisms

Multiple neurotransmitters and their receptors are present in the spinal cord and may mediate the inhibition and/or facilitation of sexual reflexes. These include, but are not restricted to, adrenaline, dopamine, serotonin, oxytocin, substance P, melanocortin, nitric oxide, enkephalin, galanin, glutamate, and GABA.

A number of studies have shown that the descending inhibition of spinal sexual reflexes is mediated in part by serotonin [2]. Multiple serotonin receptors are present in the spinal cord, and serotonin receptor 1A and 1B are presently prime candidates for mediation of this inhibition. Peripherally evoked sexual reflexes are also altered by these classes of drugs; dopaminergic, adrenergic, peptides, steroids, hormones and cholinergic compounds. More information is needed as to the mechanisms of these drug effects.

Recent evidence from studies in male rats has demonstrated a group of galanin containing cells in the lumbar cord is essential for ejaculation, and may be part of a spinal ejaculatory generator in males [6]. These cells are also present in female rats but their function has not yet been determined.



Sexual Reflexes. Figure 2 Diagrammatic representation of the higher level processes regulating sexual reflexes. Genital sensory information enters the spinal cord; interneurons then relay messages through the spinal cord through multiple segments. These signals may also be sent to the brain. The efferent output then coordinates the appropriate sexual motor output, for example orgasm. Sensory and hormonal inputs also regulate the forebrain to activate sexual responses. Pathways relay through multiple sites including the hypothalamus and the nucleus paragigantocellularis in the hindbrain. The brain messages may also act on spinal cord circuits, either to inhibit or evoke sexual responses.

Brain Mechanisms

Due to the complexity of neuronal connections in the brain and the multiple brain regions involved in sexual reflexes the brain mechanisms mediating sexual reflexes is still under study. However, a number of regulating mechanisms are known. Serotonin neurons in the nucleus paragigantocellularis are involved in the tonic inhibition of sexual reflexes [2]. Dopamine mechanisms in the forebrain appear to mediate the facilitation of sexual reflexes [7]. In addition, serotonin also acts in the forebrain and may alter dopamine release to decrease or increase sexual reflexes. During sexual arousal and orgasm, oxytocin from the paraventricular nucleus is secreted from the posterior pituitary into the blood stream in males and females [8–9].

Process Regulation

Cognitive emotional desire may lead to arousal, which in turn may cause erection or genital vasocongestion (arousal), which may in turn lead to orgasm which terminates the sex cycle for some refractory period. Alternatively, genital stimulation may activate spinal pathways that lead to arousal and orgasm.

The spinal systems generating sexual responses can be excited or inhibited by peripheral sensory stimuli. A major afferent pathway travels in the pudendal nerve and is responsible for transmitting sexual stimuli from the external genitals and perineum. Visceral afferents in the pelvic and hypogastric nerve have been shown to transmit pain signals from the internal genitals and are probably inhibitory to sexual responses.

The spinal sexual reflex mechanisms are under descending excitatory and inhibitory control from the brainstem and hypothalamus. A major inhibitory site in the medulla has been shown to suppress sexual reflexes through serotonergic mechanisms. Hypothalamic stimulation can elicit sexual responses.

Many of the supraspinal sites influencing spinal sexual reflexes are interconnected and also receive genital sensory information.

Sensory and efferent information related to genital responses may also be relayed through the vagal nerve in addition to the spinal cord. The vagal pathway remains functional after spinal cord transection and may account for the menstrual cramping, analgesia, and orgasm reported in women with complete spinal cord transections [10]. However, further animal studies and verification of this hypothesis in clinical studies is required.

Function

Sexual reflexes facilitate reproductive processes, male sperm transportation and induction of pregnancy. In addition sexual behavior is often rewarding.

A number of autonomic responses accompany sexual reflexes. Heart rate, blood pressure and respiration increase. In addition, swelling or vasodilatation of the nipples, flushing, and sweating may occur. Reduced pelvic pain may also occur during sexual responses. Contractions of the anal sphincter, vagina, pelvic floor muscles and perineal muscles accompany climax. Prolactin, catecholamine and oxytocin are also released into the circulation with orgasm.

Pathology

Erectile dysfunction in males may arise from inadequate vasodilatation, nerve degeneration, structural abnormalities such as Peyronie's disease, psychological disorders or as side effects of treatment for other disorders such as hypertension and depression. Premature ejaculation may arise due to hormonal imbalance in the CNS or hypersensitivity of the peripheral nerves. ►Anorgasm in males and females may occur if there has been peripheral nerve damage, lower spinal cord injury, or may be a result of psychological disorders including stress or as a result of treatment therapies for depression. Neurological disease that can cause sexual dysfunction include stroke, tumors, Parkinson's disease, dementia, epilepsy and diabetes, in addition to peripheral or central hormonal changes, like those present after giving birth and during and after menopause, or low testosterone levels. Dysparunia and vaginismus are common painful disorders in females that may be due to structural changes or psychological problems. Surgeries such as hysterectomy or removal of the prostate may result in nerve injury that leads to decreased sexual function.

Therapy

The most common treatment for erectile dysfunction is PDE5 inhibitors e.g., sildenafil, vardenafil and tadalafil, which act on penile corpus cavernosal smooth muscle to aid relaxation by inhibiting the action of PDE5, which is an enzyme that degrades cGMP. The increased levels of cGMP lead to alterations in calcium concentrations that aid relaxation of the tissue; without penile stimulation the PDE5 inhibitors are not effective. Similar mechanisms are found in the clitoris. In addition, topical vasodilator substances, for example alprostadil or papavarine, may be used to increase blood flow to the genital organs and thus facilitate arousal-like responses. Vibratory and vacuum stimulatory devises can be used to facilitate genital arousal by increasing sensory inputs.

Structural abnormalities may be normalized with surgery or implants, but care is needed to avoid nerve damage.

A few drugs have gained some success in treating CNS disorders (yohimbine, apomorphine, bromocryptine, androgens). However, side effects do occur and the completeness of treatment is still unclear. Usually, psychotherapy and sex therapy is recommended prior to, or concomitant with, any drug therapy [11].

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Shaker-Channels

Definition

Shaker-channels, eag (ether-á-go-go)-channels, slo (slow-poke)-channels were cloned from behavioral Drosophila melanogaster mutants. The channels were named according to the Drosophila mutant phenotype, Shaker, ether-go-go, slow-poke. Subsequently, eagcDNA was used to clone related voltage-gated potassium channel subunits erg (eag-related) and elk (eaglike). The human erg ortholog (HERG) mediates cardiac IKS.

Shannon Theory

►Information Theory

Shape Processing

Definition

Shape refers to a distinctive combination of boundary and surface properties of a visual form. Shape processing refers to the brain's ability to combine many types of locally ambiguous visual signals, such as edges, texture, shading, depth, and color, to generate an emergent representation of an object's shape.

►Form Perception
►Visual Object Representation

Sharpening

►Contrast Enhancement

Shear Strain

Definition

The components of strain associated with shear – e.g. one layer of tissue attempting to "slide" over another.

Shear Stress

Definition

The components of stress generated by the material shear strain.

►Shear Strain

Shearing

Definition

In any layer of tissue, a number of theoretical parallel planes can be distinguished. Shear is deformation of such a tissue layer in such a way that the parallel planes remain parallel but are shifted relative to each other along their original direction. If, for example, a square shape is sheared it turns into a parallelogram. Note that the legs of the parallelogram have changed length due to shearing.

►Intramuscular Myofascial Force Transmission

Sherrington's Law of Reciprocal Innervation

Definition

The contraction of a muscle is accompanied by simultaneous and proportional relaxation of its antagonist; also attributed to Descartes.

►Burst Cells – Medium Lead – Horizontal
►Omnipause Neurons

Shift Work

Definition

Working outside the traditional 08:00 (8 A.M.) to 17:00 (5 P.M.) day shift. It is common to distinguish early morning shifts starting before 08:00 (8 A.M.), afternoon and evening shifts starting after 12:00 (noon), and night shifts typically starting at 23:00 h (11 P.M.). Working night shifts or morning shifts usually leads to sleep restriction, as one is forced to sleep during the day or early evening despite a high Alertness Level due to elevated wake drive in the circadian cycle. Working afternoon or evening shifts typically yields the most sleep of any of the possible shift work regimens including the normal day shift.

►Alertness Level
►Internal Desynchrony

Short Lead Burst Neurons, SLBNs

►Burst Cells – Medium Lead – Horizontal

Short-Term Memory

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Definition

This is one of the three storage systems of memory, i.e., sensory store, short-term memory and long-term memory. Short-term memory (►short term memory syndrome) is a system for temporarily storing and managing information necessary to conduct learning and cognitive tasks. It acts as a scratch-pad for temporary recall of information under process and is involved in the selection, initiation, and termination of the information processing functions such as encoding, storing, and retrieval. Short-term memory is sometimes referred to as primary memory or active memory (►active learning/memory) and relationship to ►working memory is often discussed in psychology and neuroscience.

Characteristics

Rapid Decay

Short-term memory decays rapidly. It retains information for a limited length of time only, no more than about 30 s, if no rehearsal of the information is carried out. Memory that exceeds short-term memory duration limits is known as long-term memory. In order to overcome the limitation of short-term memory, and retain information for longer periods, the information must be periodically rehearsed. During the rehearsal, the information re-enters the short-term store and be retained for a further period. The process of consolidation, i.e., transferring short-term memory to long term memory, is enhanced by the relationship of an item of short-term memory to an item in long-term memory.

Limited Capacity

Short-term memory has a limited amount of capacity. Human short-term memory has a forward memory span of approximately seven items plus or minus two [1], called "magical number seven". Recent psychological researches have shown that this magical number seven is roughly accurate for college students recalling lists of

digits. Such length of recalled digits is sometime called "►digit span." Digit span is based on capacity of short-term memory, but the order of digits is required to be recalled. To test the auditory digit span, for instance, numbers are said slowly, then a person repeat it back. The average correctly recalled numbers are seven, the magical number seven.

However short-term memory span varies widely with populations tested and with material. For example, the ability to recall words in order depends on a number of characteristics of these words: Fewer words can be recalled when the words have longer spoken duration; this is known as the "word-length effect" [2]. Fewer words can be recalled when their speech sounds are similar to each other, this is called the "phonological similarity effect" [3]. More words can be recalled when the words are highly familiar and/or occur frequently in the language; recall performance is also better when all of the words in a list are taken from a single semantic category (such as sports) than when the words are taken from different categories.

Chunking

Though the magical number seven, retaining about 7 ± 2 different items in short-term memory is generally supported by experimental evidence, chunking of information can lead to an increase in the short term memory capacity and greatly increase amount of recalled items. Through putting each unit into a meaningful word or phrase, a person's recall ability can improve through practice [4]. For example, in recalling a phone number, the person usually chunks the digits into three groups: first, the area code, then a three digit chunk and lastly a four digit chunk. This method of remembering phone numbers is far more effective than attempting to remember a string of ten digits.

Separation From Long-Term Memory (Psychology)

An example of experimental psychology studies showed that some manipulations (e.g., a distracter task, such as repeatedly subtracting a single-digit number from a larger number following learning) impair memory for the 3–5 most recently learned words of a list (presumably still held in short-term memory), while leaving recall for words from earlier in the list (presumably stored in long-term memory) unaffected; other manipulations (e.g., semantic similarity of the words) affect only memory for earlier list words, but do not affect memory for the last few words in a list [5]. These results suggest that different factors affect short term recall (disruption of rehearsal) and long-term recall (semantic similarity). Together, these findings indicate that long-term memory and short-term memory can vary independently of each other. This is regarded as "double dissociation" and constitutes evidence for separate systems underlying short-term and long-term memory.

Separation From Long-Term Memory (Neuropsychology)

One form of evidence in favor of the separate existence of short-term memory from long-term memory comes from anterograde amnesia, the inability to learn new facts and episodes. Patients with this form of amnesia, typically caused by damage to the medial part of temporal lobe, especially to the hippocampus have intact ability to retain small amounts of information over short time scales (up to 30 s) but are dramatically impaired in their ability to form long-term memories (a famous example is patient H.M.) [6]. This is interpreted as showing that the short-term memory is spared from amnesia.

Related Brain Structures

Short-term memory is, as like the most types of memory, appear to be stored in the cerebral cortex. Different sensory areas of the cerebral cortex receive sensory information from eyes, ears, and other body parts and hold the information for a fraction of a few seconds in the sensory stores. Then only the attended information are encoded into short-term memory and not attended information will be lost. The short-term memory then is stored in the sensory areas of cortex and some of them are further transferred to the hippocampus and encoded into the long-term memory [6]. However, some neuroscience researchers suggest that short-term memory is further converged to the prefrontal cortex and then serve the information to working memory, speculated to be involved in the prefrontal cortex [7].

Synaptic Mechanisms

Short-term memory is plastic and dynamic in nature and is still a matter of subject of various arguments not only about the related brain structures but also about underlying neural and synaptic mechanisms. It often describes synaptic events and refers particularly to the temporal sequence of events leading to stable and structural changes in synaptic efficacy [6]. Short-term memory may be formed by brief changes in synaptic transmissions. In the dynamic theory, it may arise out of a reverberating feedback circuit of neurons, where a memory is held electrically within a loop [8]. Thus, no physical changes are made, and synaptic connections are not modified. On the other hand, long-term memory, may be encoded by plastic changes of structures in existing synapses.

Relationship to Working Memory

The relationship between short-term memory and working memory differently described by many theorists, but it is generally acknowledged that the two concepts are distinct. Working memory is a workspace or memory buffer in which information is maintained and

manipulated while it is being processed. It is a theoretical framework that refers to structures and processes used for temporarily storing and manipulating information. As such, working memory might also just as well be referred to as attention and processing. Short-term memory generally refers to just short-term storage of information. In other words, short-term memory may be passive memory and ►working memory is active memory. Thus while there are short-term memory components to working memory models, the concept of short-term memory is distinct from these more hypothetical concepts. Within one influential model of working memory [9] there are two short-term storage mechanisms: the phonological loop and the visuo-spatial sketchpad.

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Sicca Syndrome

Definition

Sicca symptoms include dry eyes and mouth, difficulty to swallow, caries and reduced sense of taste and smell. The term sicca syndrome is used as a synonym for Sjögren's Syndrome.

►Central Nervous System Disease in Primary Sjögren's Syndrome
►Sjögren's Syndrome

SIDS

Definition

►Sudden Infant Death Syndrome.

Sigma-1 Receptor Ligands

Definition

Sigma receptors are widely distributed in the mammalian brain, and two subtypes exist, sigma-1 and sigma-2 receptors. Sigma-1 receptors have been cloned, and their distribution and physiological functions characterized. Thus, sigma-1 receptors are proposed to be involved in learning and memory as well as in certain neuropsychiatric disorders. Sigma-1 receptor ligands have been suggested to represent a new class of therapeutic agents for neuropsychiatric disorders.

►Memory Improvement

Sign Stimuli

Definition

Highly specific stimulus that symbolizes an object or event of biological importance (see also Key Stimulus).

Signal Conversion

►Transduction

Signal Detection Theory

Definition

Signal detection theory (SDT) is a model of information processing that has been applied to the psychophysics of stimulus detection and discrimination.

►Psychophysics
►Pain Psychophysics

Signal Peptide

Definition

Signal peptide is a short peptide attached to the amino terminus of secreted or transmembrane proteins, which is bound by a signal recognition particle as soon as the protein leaves the ribosome, and results in targeting of the protein to the endoplasmic reticulum.

Signal-to-Noise Ratio (SNR)

Definition

Physiological measurements record changes of light or electricity or other physical parameters. However, measurements always have a component of noise, be it from the technical apparatus, from the physical properties of the processes involved (e.g. the statistical nature of light), or from biological sources (e.g. the statistical nature of neuronal signaling). The signal-to-noise is the ratio between the power of the signal of interest and the noise accompanying it. The SNR is usually expressed in logarithms of this ratio, a unit known as Bell, or in units of one-tenth of a Bell, the decibel or dB.

►Signals and Systems

Signal Transducers and Activator of Transcription 3 (STAT3)

Definition

STATs belong to a transcription factor family activated by Janus Kinase (JAK). STATs have SH2 domains which bind phosphotyrosine residues on cytokine receptors and are themselves tyrosine-phosphorylated by JAKs. Following phosphorylation, STATs dissociate from the receptors and regulate gene expression.

Signal Transduction

Definition

Signal transduction includes an ensemble of mechanisms by which uni- and multi-cellular organisms recognize sensory messages (photons, odorants, pheromones) or inter-cellular messages (hormones, neurotransmitters) and transduce them into biochemical and biophysical modifications in order to modify the cellular response: depolarisation, differentiation, movement, division, etc.

►New Developments in G Protein-Coupled Receptor Theory

Signal Transduction Cascade

Definition

Signal transduction cascade is the pathway of sequentially activated or inhibited signaling molecules that leads from the activation of a receptor at the plasma membrane to a downstream effect within the cell.

Signaling

►BMP Signaling and Synaptic Development

Signaling Protein

Definition

Secreted protein that have an effect on the fate of adjacent tissue in a concentration-dependent manner. Signaling proteins are often (but not only) produced in organizer centers are called “morphogens.” Examples of signaling proteins are bone morphogenetic proteins (BMPs), Wnts, Sonic hedgehog (Shh) or fibroblastic growth factors (FGFs).

►Evolution and Embryological Development of the Forebrain

Signals and Systems

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Definition

Description of the Theory

Introduction

Biological systems are frequently analyzed using engineering tools. This can be done in several ways, two of which are through the investigation of the signals produced by the system and by modeling the system and its environment to predict their behavior under different conditions. These are closely related approaches, and many of the tools developed for one are applicable to the other. This essay gives a broad overview of these tools, known collectively as the field of signals and systems.

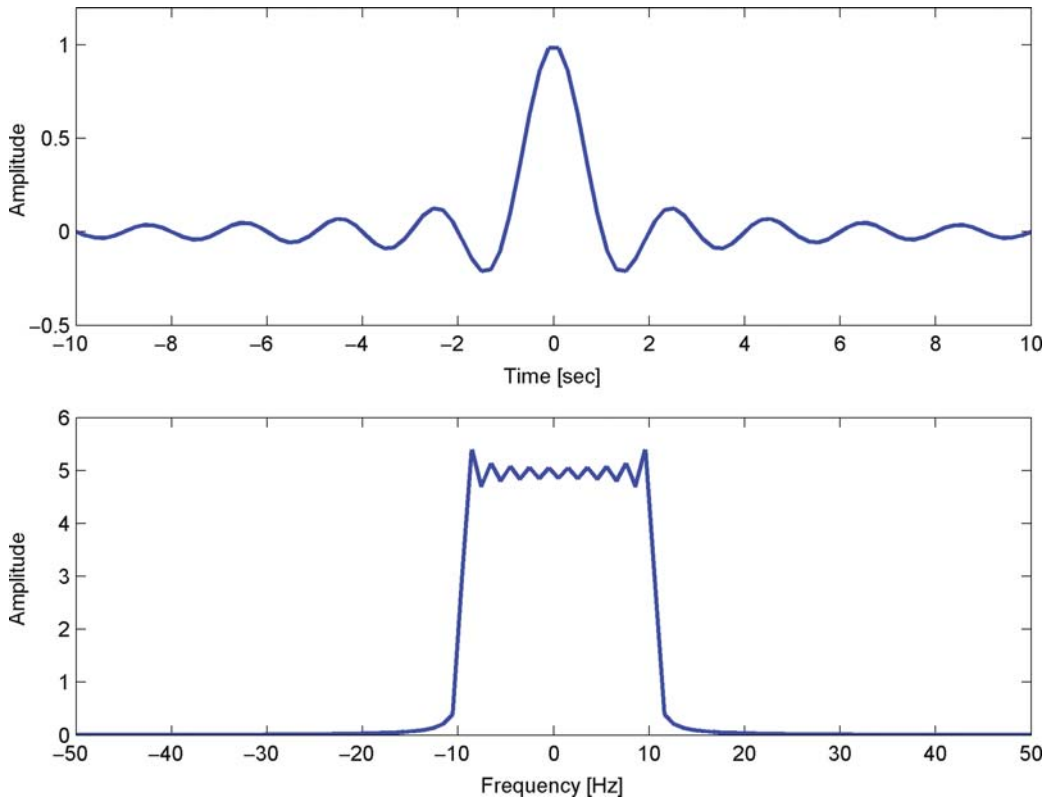
Signals

The human body generates a multitude of signals, many of which can be used to track its activity. However, meaningful information can usually be gained only after these signals are recorded and processed. In this section, various methods of processing are described.

An important aspect of signal processing is the notion of the ▶time domain and the ▶frequency domain of signals. The time domain of the signals is a description of their progression through time. The frequency domain is a description of the signal as a sum of (a possibly infinite number of) sine waves at different frequencies and phases (the actual description is simply the phase and amplitude of each sine). This description, also known as the spectrum, is extremely useful in many applications, for example, ▶filtering. One should note that processing in one of these dimensions directly affects the other.

The frequency content of a continuous signal can be computed using the ▶Fourier Transform [1]. The output of this transform is the amplitude and phase of the sines at each frequency in the spectrum, which, if summed, will exactly match the signal in the time domain. Fig. 1 shows an example of a signal (the function sin(x)/x in the time domain and its amplitude in the frequency domain).

The frequency-domain representation can be transformed back to the time domain using the Inverse Fourier Transform. Essentially, the Fourier transform is computed



Signals and Systems. Figure 1 A signal in the time domain and in the frequency domain. The top figure shows the progression of the signal sin(x)/x through time. The bottom figure shows the amplitude of the frequency-domain representation of the same signal.

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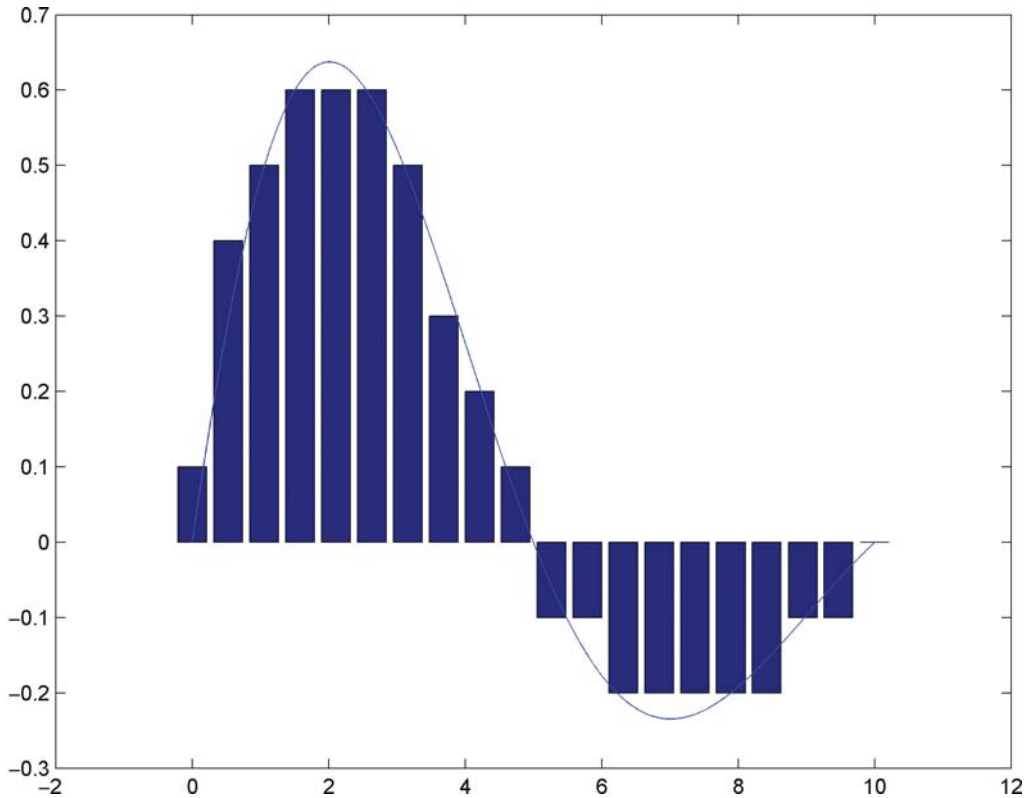
by finding the projection of the signal on sine functions (the kernel functions for this transform) at each frequency. There are special variants of this transform to deal with periodic signals and with discrete signals. If the signal is discrete, the relevant transform is the ►Discrete Fourier Transform (DFT). The efficient algorithm for computing the Discrete Fourier Transform is known as the ►Fast Fourier Transform (FFT).

Nowadays, most processing of signals is done digitally. Many of the methods we describe in this section can be performed on analog signals, but for the sake of clarity, they will be described in the digital domain.

The first stage in digital processing of a signal (after the appropriate sensor has acquired the signal) is to sample it. ►Sampling is the process of taking a continuous signal (i.e. one that has a value for each point in time) and recording its value in discrete points. The sampling rate needed in order to be able to reconstruct the signal back to its original (analog) form, without loss of information, should be at least twice as fast as the highest frequency component in the signal, as stated in ►Nyquist's sampling theorem [2]. Since most analog signals are not strictly band-limited, that is, they cannot be said to have frequency components with a certain highest limit, most signals need to be filtered before sampling to comply with Nyquist's theorem. This is done using analog filters known as ►anti-aliasing filters, which allow only those components that have a frequency lower than a certain threshold to pass into the sampler.

After sampling, the signal is quantized and each sample given a discrete value. This discrete value depends on the range of the sampling device (e.g. in a 12 bit sampling device, the signal is given the closest of $2^{12} = 4096$ values). A sampled, quantized, signal can then be stored on a computer or processed as needed. Fig. 2 shows a continuous signal and its sampled, quantized, representation.

There are a number of categories, by which signal processing systems are classified, among which the most important are linearity, time invariance, finite or infinite response, and causality. ►Linear systems are those that if two signals are passed through them, each multiplied by a constant, and summed, would give the same output if the signals were summed and only then passed through the system. An example of a linear system is an amplifier, which changes the gain of a



Signals and Systems. Figure 2 A continuous and a sampled signal. This figure demonstrates the process of sampling and of quantization. The line is a continuous signal (i.e. one that has a value at each point in time). The bars show the same signal after it has been sampled and quantized. Sampling causes each time span to be represented by a single (usually average) value, while quantization rounds this value to the nearest value acceptable by the digital system.

signal by a constant factor. A time invariant system is one whose output behaves in a similar matter (albeit delayed) when the same signal is entered twice, with a delay between inputs.

Any digital computer can represent numbers up to a finite value. In finite response systems, it is guaranteed that any finite input will result in a finite output. An example of an infinite system is one that returns the reciprocal value of the inputs. Such a system, when presented with a zero input, will return an infinite value, which in practice means that the output will be distorted. Finally, it is usually desirable for a system to use data from the past and present, not from the future. Such systems are known as causal systems. Note that non-causal systems can still be implemented if a delay in the output is possible.

One of the basic operations, which can be performed on either an analog or a digital signal, is filtering. Filtering reshapes the signal, usually to give required frequency content. A (causal) digital filter operates on a signal by multiplying the filter coefficients by the inputs (current and previous), and possibly some of the previous outputs, and summing them. The most common filter types are the low-pass filter (►low-pass filtering), which passes only those frequency components at the low range of the spectrum; the high-pass filter (►High-pass filtering), which does the same for the high end of the spectrum; the ►band-pass filter; and the notch filter, which removes a slim band of the spectrum, for example, the range occupied by the mains current. Fig. 3 shows an example of how filtering reshapes a signal. The left part of the Fig. 3 shows a signal comprised of the sum of two sines at different frequencies (as is evident from its spectrum in the lower left Fig. 3). This signal is passed through a low-pass filter, which removes the sine at the higher frequency so that the remaining signal is an almost pure sine.

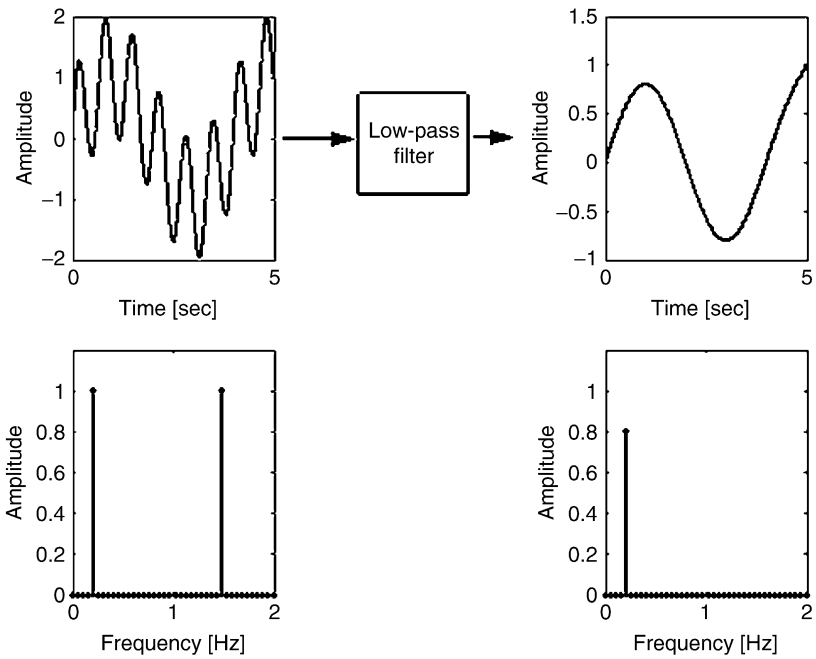
Filters are categorized by the following parameters:

Their ►frequency response determines how the amplitude and phase at each frequency is modified by the filter. The ►bandwidth of a filter is the width of the effective frequency range passed by the filter.

The filter length describes the number of coefficients of the filter. A longer filter makes it possible to design filters with a sharper frequency response, at the cost of higher delays and poorer localization in the time domain due to the filter length.

The ►impulse response of the filter, explained below.

The impulse, known in the continuous domain as the ►Dirac delta, is a signal whose integral is unity, and its width approaches zero (which implies that its height approaches infinity). In the digital domain, it is a signal that is zero everywhere except for a single sample with a value of unity. The impulse is useful for typifying the



Signals and Systems. Figure 3 Filtering a signal. This figure shows the effect of filtering on a signal. The leftmost figures show a signal comprised of the sum of two sines at different frequencies. The top left figure shows the signal in the time domain, while the bottom left figure shows the same signal in the frequency domain. The rightmost figures show the signal after it has passed through a low-pass filter, which removes one of the sine functions (the one of higher frequency). A by-product of this filter is a reduction in the amplitude of the remaining sine function.

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time-domain behavior of a filter. Furthermore, filters are commonly classified as either having a finite or infinite impulse response. The former, when presented with an impulse as an input, will generate non-zero output for a finite time period, while the latter may continue to have a non-zero value indefinitely.

Although they are sometimes approximated as such, biological systems are never completely deterministic. The current state of the system, its environment, etc. affects processes. Thus, it is frequently useful to model the system and its signals as stochastic, or at least one to which random noise is added. Such signals require statistical tools for processing.

Arguably, the simplest parameters to estimate are the average and standard deviation of a signal, or its variance. In the case of several signals, we can instead measure the ►cross-covariance between these signals, and its normalized version, the cross-correlation (or simply the ►correlation). These latter parameters are used for measuring the linear dependency between signals. Higher-order correlations (or moments) can be useful in typifying systems, but these are rarely used in the processing of biological signals, except for cases where the object of the analysis is to discover ►oscillator coupling between signals (For example, [3]).

The correlation [1] can be computed at various time differences between signals (or between a signal and itself), yielding the cross-correlation function (or, similarly, the auto-correlation function). This yields information about the linear dependency between signals, assuming some delay between them.

The spectrum of a stochastic signal is computed by transforming the cross-correlation function instead of performing the Fourier transform on the signal itself. Such ►cross-spectrum (or, in the case of auto-correlation, the ►autospectrum) is useful, for example, in detecting frequencies where signals correlate. Similar functions are achieved by the ►coherence function, which is the cross-spectrum normalized by the square root of both auto-spectra.

Note that when the spectrum of a signal is estimated from a finite sample of data, the resulting auto-spectrum is only one of an infinite number of possible estimations of the spectrum, since the data itself is stochastic. There are two parameters of interest when assessing how close this estimation (like all other estimations based on stochastic data) is to the real spectrum. These are the ►bias and the ►variance of the estimate. The bias refers to how far the estimation would be from the real value, if an infinite number of signals were used to generate spectra estimations, and these would in turn be averaged. The variance is the variance of a finite number of spectra. In practice, one can usually minimize either the variance or the bias, but not both.

►Noise is a signal that accompanies the signal of interest, but does not convey useful information. If, for example, we were interested in a specific component of the ►electroencephalogram (EEG), any other parts of the recorded signal, including other components of the EEG, would be considered noise. In most cases, it is assumed that the noise is added to the signal. The relation between the power of the signal of interest and that of the noise is measured by the ►Signal-to-Noise ratio (►SNR), expressed in decibels, that is: SNR = 10 log (Signal power/Noise power).

The spectrum of the noise is also of interest. If the noise has a flat spectrum, which implies that it is completely uncorrelated in time, it is known as ►white noise. Similarly, a noise that has a non-flat spectrum is known as ►colored noise. If the noise is distinctly different from the signal in some way, it might be easily separated from the signal (for example, if its frequency range is different from that of the signal, it can be removed using an appropriate filter). Unfortunately, there are many cases where such separation does not exist. In such cases, more sophisticated processing methods are needed, for example, [4–7].

Fourier transform is limited by the fact that it implicitly assumes that the signal is infinite in time. Thus, when a limited number of samples are available, the estimation of the frequency components at low frequencies is problematic. Furthermore, the Fourier transform is limited in that one can either observe the time domain or the frequency domain, but not both. This limitation is slightly reduced by the Short Time Fourier Transform, essentially a division of the signal into short time sequences. In recent years, however, several methods, which enable simultaneous investigation of both the time and the frequency domain, have emerged. Essentially, instead of using a sine for a kernel function, as in the Fourier transform, a different function with a limited time span is used. Many families of such functions (known as wavelets) are known. Probably the most widely used are the Gabor, Daubechies, Mexican Hat, and Haar wavelets. The output of the wavelet transform for a one-dimensional signal is a two-dimensional representation of the time-frequency plane. Thus, local changes in both time and frequency can be observed.

Systems

Modeling a complicated system is an extremely useful method for gaining understanding into its behavior, and for predicting its performance under various conditions. Modeling a system through the tools of system analysis is performed by identifying the inputs and outputs of the system, and representing its internal workings as a set of equations. A system can have single or multiple inputs, as well as single or several outputs.

Modeling biological systems has proved advantageous for diverse applications. Among them (to name only a few) are pacemaker design, ►seizure prediction based on EEG [8], as well as theoretic studies on ►movement planning [9].

Categories, similar to those used for typifying signal processing systems (outlined in the previous section), are used for classifying modeled systems. These include their linearity, stability, sensitivity to initial conditions, and time-invariance.

The set of equations used for modeling a system is frequently approximated as a linear set, so that the sum of outputs of two signals is equal to the output of the sums. This approximation is useful because there are many more tools for analysis of linear systems than for analysis of non-linear systems. Even when a system is known to be nonlinear, methods exist for ►linearization around a given area of its operational envelope. For example, time delay, which is a non-linear operator, can be approximated in the frequency plane using the Pade approximation.

An important parameter for systems is their stability. A stable system will have a finite output for every finite input value. Determining if a system is stable or not, based on its equations, has been an object of much research. Popular tools for ascertaining system stability examine the system equations in the frequency plane (importantly, both phase and amplitude), using diagrams known as Bode diagrams and Nichols charts. The result of this analysis is both the knowledge whether system is stable or not, as well as how far the system is from instability, as measured by the Phase Margin (PM) and Gain Margin (GM).

The full description from input to output of a system is known as the ►transfer function. Usually, the transfer function of linear systems is defined in the frequency plane or as a system of ►differential equations. When the frequency-plane description is used, instead of using the Fourier Transform for converting the system equations into the frequency plane, system engineers traditionally use the Laplace Transform for continuous systems and the Z-Transform for sampled systems. Both these transforms are identical to the Fourier Transform and the Discrete Fourier Transform, except for a change of variables. The roots of the transfer function polynomial (of linear systems) are useful for determining system stability. The roots of the nominator are known as ►zeros, while those of the denominator as ►poles. The Root-Locus method can be used for determining if the system is stable, and if so, under which conditions.

As noted above, a system can be modeled as a list of differential equations, where some of the equations describe the dependency between the internal variables of the system and previous inputs, while other equations describe the relation between internal and output variables. This description is known as the ►statespace description of a system. The states, in this description, are a particular combination of the internal variables.

An underlining assumption when analyzing a system in the frequency plane is that they are working in their steady-state mode, that is, any changes in behavior resulting from initial conditions have disappeared for all practical purposes. However, the sensitivity of a system to its initial conditions can be highly important. Some systems exhibit chaotic behavior, defined as an extreme sensitivity to initial conditions. A chaotic system will reach vastly different steady states for slightly different initial conditions. In such systems, the behavior in state-space is one where, for some initial conditions, the system does not reach a final single state, but rather it hovers around a point (or several points) known as attractors.

It is possible to distinguish between random systems and systems that are chaotic (and thus contain a structure) by measuring their ►correlation dimension. This is a measure of the size of the attractors in the system. Note that this size can be a ►fractal, a term coined by Benoit Mandelbrot in 1975 [10] to describe objects built using recursion. Thus, while the dimension of a line is one, and of a rectangle two, fractal shapes have a non-integer dimension.

It is sometimes useful to model a system or a subsystem using only its statistical properties. This is useful, for example, in order to generate some stochastic behavior with parameters that are similar to those of a chosen system. Systems that can be modeled in this way, by generating white noise (the driving noise) and passing this noise through a differential equation that depends on previous outputs and the current value of the noise, are known as Auto-regressive (►Auto-regressive model) (AR) systems. Systems that can be modeled through a differential equation that operates on previous values of the noise are known as Moving-Average (►Moving-Average Model) (MA) systems, while those where the differential equation operates on both previous values of the noise and those of previous outputs are known as Auto-regressive Moving Average (►Auto-regressive Moving Average Model) (ARMA) systems. There are several methods for finding the coefficients of the differential equations given data recorded at the output of the system to be modeled. However, finding the coefficients of AR systems involves solving linear equations, while the coefficients of MA and ARMA systems are solved using non-linear equations. There is a useful extension to AR systems whereby, in addition to the driving noise, there is a deterministic input; these systems are known as Autoregressive with Extrageneous input (ARX) systems. One of the most popular applications of AR models is for compression of ►speech. The speech is cut into segments, each a few hundred milliseconds long. Each segment is modeled using its AR coefficients. Instead of transmitting the samples of the speech, only the AR coefficients are transmitted, and at the receiving end, the speech is regenerated using these coefficients and white noise.

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Silent Nociceptor

Definition

A group of nociceptive C fibers in human cutaneous nerves which are unresponsive to mechanical stimulation in intact skin. The term is misleading, since these nociceptive afferents respond to noxious heating and to chemical agents, e.g., capsaicin. A synonym "sleeping nociceptor" is derived from the observation that these units become sensitized ("awakened") to mechanical stimulation in the course of inflammatory processes.

►Nociceptors and Characteristics

Silent Period (SP)

Definition

The period of electrical silence in the electromyographic recording during voluntary activation of muscle(s), evoked by stimulation of the nervous system.

►Transcranial Magnetic Stimulation

Silent Synapse

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Definition

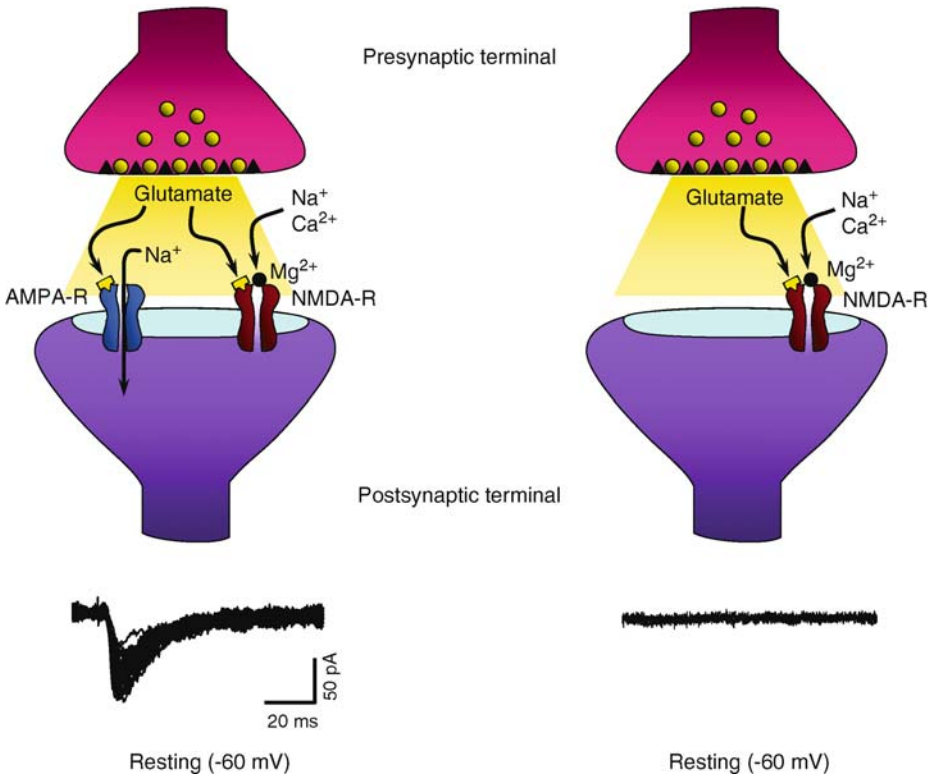
The vast majority of excitatory neurotransmission in the brain is mediated by ►glutamate and its ►ionotropic receptors, AMPA- and ►NMDA-type glutamate receptors. In neuroscience, a silent synapse is an excitatory glutamatergic synapse whose postsynaptic membrane contains only NMDA-type glutamate receptors (►NMDA-Rs) and no AMPA-type glutamate receptors (►AMPA-Rs) (Fig. 1).

An action potential that invades the presynaptic terminal causes calcium entry into the terminal and fusion of neurotransmitter-filled synaptic vesicles releasing glutamate into the synaptic cleft. Presynaptically released glutamate binds to glutamate receptors present at the postsynaptic membrane briefly activating the conductance associated with them. Activation of AMPA-Rs leads to a fast inward current that depolarize the postsynaptic membrane. Activation of NMDA-Rs, however, does not cause an inward current because at the normal neuronal resting potential – around −60 mV – the receptor's channel is blocked by physiological concentration of extracellular magnesium [1]. Thus, in normal synapses containing both, AMPA-Rs and NMDA-Rs, the inward current observed in response to glutamate release is mediated by the AMPA-R (Fig. 1, left). Some synapses, however, contain only NMDA-type receptors. The blockade of the NMDA-R channel by magnesium renders these synapses inactive or "silent" to the release of presynaptic glutamate (Fig. 1, right). It is important to note that if activation of a silent synapse occurs when the postsynaptic membrane is depolarized, the magnesium blockade is relieved and the NMDA-R will conduct current.

Characteristics

Description of the Structure

Excitatory glutamatergic synapses in the central nervous system (CNS) consist of a presynaptic button with glutamate-filled vesicles and a postsynaptic



Silent Synapse. Figure 1 The Glutamatergic Synapse. Left, synapse containing postsynaptic AMPA-Rs and NMDA-Rs at resting potential. Glutamate released from the presynaptic terminal binds to both receptors; however, the recorded excitatory post-synaptic current (EPSC) is due only to the activation of AMPA-Rs (lower traces). NMDA-Rs are blocked by physiological concentration of extracellular Mg^{2+}. Right, silent synapse containing only NMDA-Rs at resting potential. Presynaptically released glutamate fails to activate NMDA-R responses due to the blockade by Mg^{2+}; therefore no EPSC is recorded postsynaptically (lower traces).

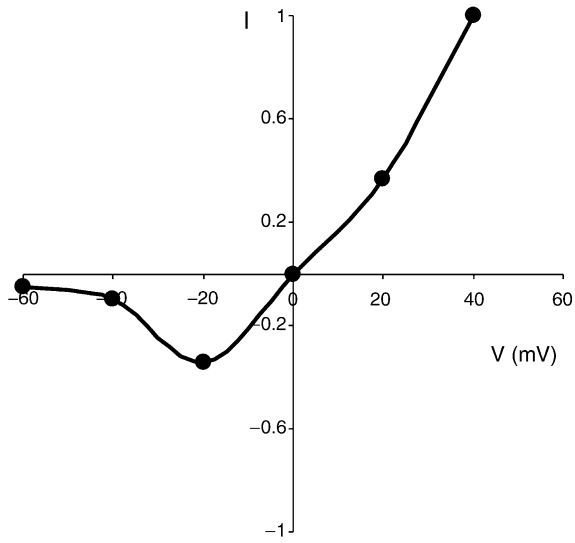
structure containing glutamate receptors. Two types of glutamate receptors can be present at the postsynaptic membrane: (i) metabotropic receptors, associated to signal transduction mechanisms and second messenger cascades, and (ii) ionotropic receptors, directly coupled to ionic conductances. Glutamatergic ionotropic receptors can be further divided into non-NMDA receptors and NMDA receptors (NMDA-Rs) based on their affinity for the agonist NMDA. The most abundant and better understood non-NMDA receptors are the AMPA receptors (AMPA-Rs) [2].

At excitatory chemical synapses, synaptic transmission is mediated by activation of AMPA-Rs and NMDA-Rs. Activation of AMPA- or NMDA-receptors by presynaptically released glutamate results in the opening of an ionic channel which is non-selective to cations. This allows the flow of Na^+ and K^+ ions depending on the electrochemical gradient across the postsynaptic membrane. A significant fraction of the current flowing through NMDA-Rs is also carried by Ca^{2+}. Calcium entry through postsynaptic NMDA-Rs is thought to play a critical role in synaptic plasticity, a cellular mechanism for learning and memory, as well as in some neuropathologies. Certain AMPA-Rs are also permeable to Ca^{2+}.

The conductance associated with the NMDA-R has slow rising and decay kinetics and – as mentioned – can be blocked by physiological concentrations of extracellular Mg^{2+}. This blockade is strongly voltage-dependent and can be removed when the postsynaptic membrane is depolarized to around −40 mV (Fig. 2).

Thus, partial depolarization of the postsynaptic membrane relieves the magnesium block and allows the flow of ions through the channel when activated by glutamate. It is this property that allows the NMDA-receptor to be a coincidence detector of pre- and post-synaptic activity required in Hebbian models of plasticity [3].

In the hippocampus and other brain regions, the ratio of AMPA-R to NMDA-R mediated transmission is initially low and increases over development. Furthermore, many synaptic events, particularly early in development, are mediated by the activation of only NMDA-receptors. Such responses are proposed to



Silent Synapse. Figure 2 Voltage dependency of Mg^{2+} blockade of the NMDA-R. Relationship of membrane voltage (V) and normalized current (I) flowing through the NMDA-R when activated by glutamate. The receptor is expressed in heterologous cells and glutamate is puffed onto the surface of a voltage-clamped cell in the presence of physiological concentration of Mg^{2+}. Notice that at –60 mV there is practically no current.

occur at structures termed postsynaptically silent synapses, because transmission can only be detected if the postsynaptic membrane potential is raised above the resting level [4]. The prevalence of pure NMDA-R responses measured electrophysiologically decreases during development.

The presence of functionally silent synapses, that lack responses when presynaptic fibers are stimulated at resting potentials, can be explained by other mechanisms. Some scenarios consider the presence of both AMPA-Rs and NMDA-Rs at synapses, and they propose that early in development only low concentrations of glutamate reach synapses. NMDA-Rs exhibit higher affinity for glutamate than AMPA-Rs; therefore, low concentrations could activate primarily NMDA-Rs and not AMPA-Rs. Low concentration of glutamate could be achieved by a presynaptic vesicle that does not release all its content at once [5]. This could cause that glutamate concentration in the synaptic cleft increases slowly, activating only high affinity NMDA-Rs but not low affinity AMPA-Rs. A similar situation will occur if low concentrations of glutamate "spill over" from neighboring synapses [6]. Also, a synapse with a very low presynaptic probability of release will be rarely activated when its input is stimulated appearing to be silent [7]. These hypotheses are controversial and matter of discussion [8].

The existence of synapses lacking AMPA-Rs has been tested directly by immunogold labeling studies, which have shown that the fraction of synapses containing NMDA-R but not AMPA-R immunoreactivity decreased from 84% at postnatal day 2 to 50% at 5 weeks with little changes in NMDA-R immunoreactivity [9].

Thus, silent synapses containing only NMDA-Rs are especially prevalent in development and have been found in many brain regions, including the hippocampus, cerebral cortex, and spinal cord. The molecular properties of NMDA-Rs explain why at resting potential there are no responses when presynaptic fibers are activated. The existence of such synapses has been corroborated with functional and anatomical studies.

Regulation

Silent synapses stop being silent once they acquire AMPA-Rs and an inward current is produced postsynaptically in response to glutamate released from the presynaptic terminal. Conversion of silent synapses to functional synapses is a developmentally regulated process that requires synaptic activity or sensory experience. Also, silent synapses can acquire AMPA-Rs when cells are stimulated by protocols inducing long-term potentiation (LTP), a synaptic plasticity phenomenon thought to be the cellular correlate of learning and memory. In both cases, incorporation of AMPA-Rs into synapses is a tightly regulated process and requires synaptic activity and Ca^{2+} influx into the postsynaptic cell. AMPA-Rs with different subunit composition have different activity requirement to be incorporated into synapses. Trafficking of AMPA-Rs in and out of synapses involves the coordination of several kinases and phosphatases, as well as the interaction with several scaffolding proteins. Since the discovery of silent synapses, regulation of AMPA-R trafficking has been intensively studied and is currently a very dynamic field in neuroscience [10].

Over the past few years, a number of studies have tested the notion that silent synapses lack AMPA-Rs and that AMPA-Rs can be rapidly delivered to synapses during the induction of LTP. This model suggests that there must be a pool of non-synaptic AMPA-Rs near synapses available for delivery. Several studies have found ample amounts of non-synaptic AMPA-Rs on both surfaces and intracellular regions of dendrites that are delivered to synapses in response to LTP inducing protocols [10].

It is thought that rapid delivery of AMPA-Rs from non-synaptic sites to the synapse occurs via a mechanism analogous to the exocytosis of presynaptic vesicles during transmitter release. This rapid delivery of AMPA-Rs is thought to underlie the increase in synaptic transmission after LTP induction. Early studies in hippocampal slices showed that loading postsynaptic cells with toxins that specifically perturb membrane fusion could block LTP. Also, in dissociated

cultured neurons a form of dendritic exocytosis that was mediated by activation of CaMKII, a key enzyme in LTP induction, has been identified.

Function

Several lines of evidence indicate that NMDA-receptors are present in synapses before AMPA-receptors and that during development AMPA-receptors are progressively added. Silent synapses are not a separate class of excitatory synapses that lack AMPA receptors, but rather an early stage in the ongoing maturation of the glutamatergic synapse. The fact that silent synapses generate no postsynaptic electrical signal when the postsynaptic cell is at its normal resting membrane potential, but can transmit robust postsynaptic electrical responses once the postsynaptic cell is depolarized, suggest an interesting and simple mechanism to modify neural circuitry. Activation of NMDA-Rs when the postsynaptic cell is depolarized will allow Ca^{2+} entry and the triggering of several calcium-dependent processes including the addition of AMPA-Rs to that specific synapse and activation of signaling pathways necessary for synapse stabilization, dendrite growth, and cell survival.

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Silver Impregnation

Definition

Nerve tissue has an affinity for silver (argyrophilia) and is easily impregnated by dilute silver solutions. Reducing the silver enables it to be deposited within the neuron's processes thus outlining the neuron (see below).

Silver Staining

Definition

Silver staining of nerve tissue is made possible by a variety of so-called reduced silver methods. The neurons appear as golden or dark brown against a yellow background.

Simple Cell

Definition

Simple cells are one of two main physiological types of cells in the primary visual cortex. They have receptive fields built of elongated, adjacent On and Off subregions that have a mutually suppressive influence.

The basis of this antagonism is a push-pull relationship between stimuli of opposite contrast in each subregion; e.g. where bright stimuli excite, dark stimuli inhibit. As a result of the geometry of the receptive field and the antagonism between neighboring subregions, simple cells are sensitive to stimulus orientation – they are good edge detectors. Cells with simple receptive fields were first discovered in the cat, where they are found only at the first, or thalamocortical, stage of processing.

►Form Perception
►Geniculo-striate Pathway
►Striate Cortex Functions
►Visual Cortical and Subcortical Receptive Fields

Simple Lobule

Synonyms
►Lobulus simplex

Definition
The simple lobule belongs to the posterior lobe and is part of the cerebellar hemispheres. Apart from the areas in proximity to the vermis (intermediate part), the hemispheres belong to the phylogenetically young neocerebellum and receive their afferents via the mossy fibers of the pontocerebellar tract from the pontine nuclei. All hemisphere segments are hence also assigned to the pontocerebellum.

►Cerebellum

Simple Receptive Fields

►Visual Cortical and Subcortical Receptive Fields

Simple Sound

Definition
A sound with one frequency component, or a sinusoidal sound, or a pure-tone sound.

►Acoustics

Simulated Annealing

Definition
A type of supervised learning algorithm based on ideas from statistical physics. It can be used in networks with arbitrary architectures.

►Neural Networks

Simulated Microgravity

Definition
Simulated microgravity encompasses ground-based conditions simulating changes in the internal environment of the living body such as changes in fluid distribution in space. For example, methods to induce headward fluid shift as seen in microgravity in space using head-out water immersion, lower body positive pressure, head-down bed rest, etc.

►Autonomic Function in Space

Single-cell Recording

Definition
Recording of the electrical activity of single neurons in the nervous system by means of electrodes introduced into the nervous tissue.

►Extracellular Recording

Single-channel Activity

Definition
Activity of a single ion channel viewed through the ion current passing through an open channel. Single-channel activity is measured in voltage-clamp conditions using the patch-clamp technique in cell-attached, outside-out and inside-out configuration. Single Ca^{2+} channels give rise to membrane currents in the order of picoamperes (pA) in high Ba^{2+} solutions.

►Calcium Channels – an Overview
►Inracellular Recording

Single-fiber Action Potential

Definition
Extracellular potential detected due to the propagation of the transmembrane action potential along a muscle fiber when stimulated.

►Electromyography

Single-joint Movement

Definition
Movement that involves rotations in a single joint.

►Motor Control Models

Single-Photon Emission Computed Tomography (SPECT)

Definition
Is a tomographic imaging technique based on the emission of gamma rays by a tracer that is absorbed by tissue (e.g., brain tissue) proportional to blood flow. The technique permits measurements of perfusion, which is coupled to metabolism.

Singleton

Definition
A set with exactly one element. A term used in SAGE studies to describe unique sequence tags appearing only once in a library.

►Serial Analysis of Gene Expression

Single-unit Recording

Definition
Recording from an individual nerve, glia or muscle cell (unit).

►Extracellular Recording

Sinus Hair

Definition
The sinus hair is a highly specialized hair follicle characterized by a well-developed venous sinus associated with the hair follicle, and is usually located in the facial skin of mammals except humans. Vibrissae are examples of sinus hairs arranged in rows on the upper lips of cats, dogs, and rats. The sinus hair contains different kinds of sensory receptors including Merkel cell-neurite complexes, various kinds of palisade endings, and lamellated corpuscles.

►Merkel Cell-Neurite Complex Regeneration

siRNA

Definition
A small (or short) interfering RNA is a 20–25 nucleotide long double stranded RNA that shows complete complementary to the sequence of a mRNA and interferes with its expression by targeting it to the RNA interference pathway.

Sister Groups/Sister Taxa

Definition
In cladistic classification, any two taxa are sister groups if they are descended from the same node in a dichotomous branching tree

►The Phylogeny and Evolution of Amniotes

Situational Factors in Pain

Definition
Situational factors are contextual and psychological factors that can vary with the circumstances in which an individual experiences pain. These include: cognitive factors such as understanding of the pain problem, knowledge of effective therapies, and expectations for recovery; behavioral factors such as the specific distress behaviors during pain and the wider behaviors in response to a recurrent or chronic pain; and emotional factors such as fear, frustration, anxiety or depression.

►Pain in Children

Sjögren's Syndrome

Definition

Sjögren's syndrome is named after the Swedish ophthalmologist Henrik Sjögren who first described it in 1933. It is a chronic autoimmune disorder in which immune cells cause damage to salivary and lacrimal glands giving dry mouth and dry eyes. Sjogren's syndrome occurs in a primary and a secondary form. The secondary form is associated with rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus ("lupus"), and polymyositis.

►Central Nervous System Disease in Primary Sjögren's Syndrome
►Rheumatoid Arthritis (RA)
►Salivary Secretion Control
►Systemic Lupus Erythematosus (SLE)

SK Channels

Definition

Small-conductance Ca^{2+}-activated K^+ channels present in autonomic neurons and sometimes involved in after-hyperpolarization.

►Neuronal Potassium Channels
►Action Potential

Skeletal Muscle Architecture

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Definition

Muscle architecture is the structural design of a skeletal muscle in terms of the arrangement of the muscle fibers, muscle units, and connective tissue elements within and around which they are embedded. These design features define the axis of force and displacement generation of a muscle-tendon complex.

Characteristics

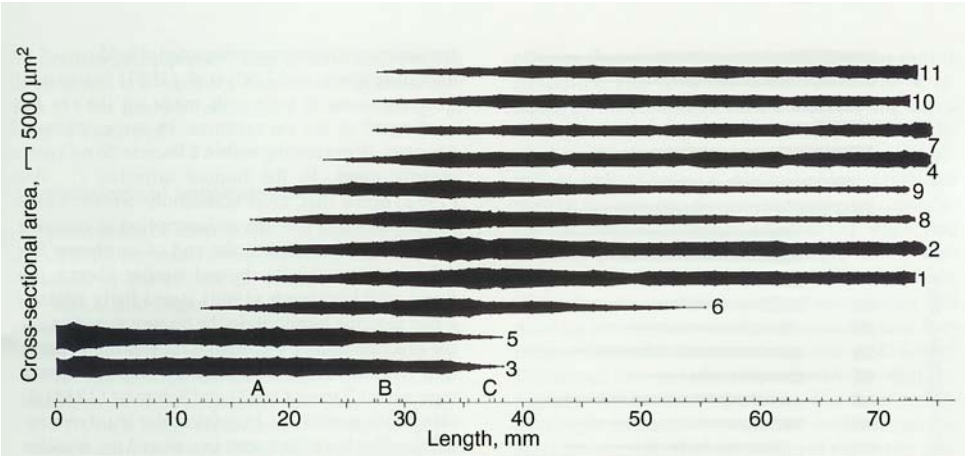
Muscle Fiber Architecture

Single skeletal muscle fibers are elongated, multinucleated cells that have variable lengths and shapes. A fiber is comprised of a number of myofibrils arranged in parallel and comprised of sarcomeres arranged in-series. A ►sarcomere, in turn, is comprised of myofilaments, i.e. namely myosin and actin, and is the functional unit of muscle contraction. The basal lamina defines the anatomical boundary of a single fiber. A majority of muscle fibers have a single point of innervation identified as the ►neuromuscular junction or motor endplate. Myonuclei are distributed along the length of the fiber, with a higher density usually observed at specialized regions, i.e. the neuromuscular junction and the ►myotendinous junction. The anatomical length of an individual muscle fiber is highly variable, e.g. the range in humans is from a few mm to several cm. In many cases, short muscle fibers are arranged in-series and activated simultaneously such that the functional length of the muscle fiber is enhanced significantly. The shape of an individual fiber is also highly variable (Fig. 1).

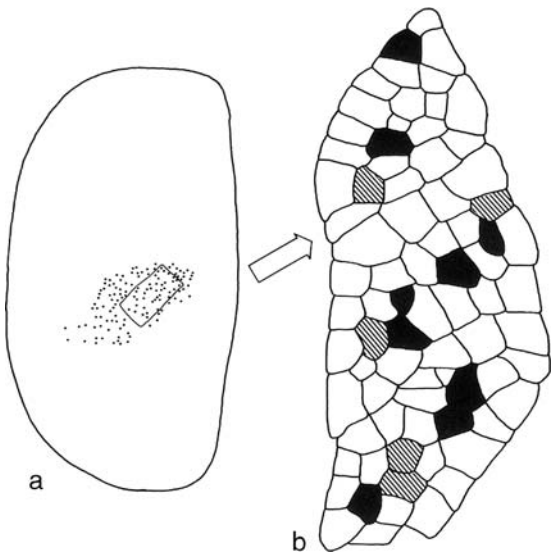
The cross-sectional area of a fiber can be relatively homogeneous throughout its length, or the fiber can taper (show a decrease in fiber area) at one or both ends. The amount of tapering can vary from a partial tapering to a full taper where the cross-sectional area becomes a filamentous strand. The termination of a muscle fiber usually involves some connective tissue interface, i.e. at a tendon, aponeurosis, the end of another muscle fiber, or intrafascicularly. The muscle fiber: connective tissue interface of a non-tapering fiber is usually a blunt ending, i.e. an abrupt termination with complex infoldings between the ►sarcolemma and connective tissue elements. The termination of tapering fibers is much more complex and variable, ranging from blunt-like endings between the sarcolemmal membranes of two fibers arranged in-series to interdigitating myomyonal junctions between the tapering ends of two adjacent fibers.

Motor Unit and Muscle Unit Architecture

A single ►motor unit is defined as an α-motoneuron and all of the muscle fibers that it innervates. Using repetitive stimulation of a single motor axon or an individual motoneuron, the fibers belonging to a motor unit can be depleted of their glycogen and then identified on histological sections stained for glycogen content. All muscle fibers within a motor unit are, in general, of the same phenotype, i.e. have similar, although not identical, mechanical and metabolic properties. The architectural properties of the constituent fibers vary within a motor unit, although it appears that slow motor units have a higher percentage of non-tapering fibers than fast motor units. The spatial distribution of the fibers in any cross section of a muscle is nonrandom and



Skeletal Muscle Architecture. Figure 1 Cross-sectional area of eleven fibers reconstructed from serial sections of a glycogen-depleted fast motor unit in the cat tibialis anterior muscle. All fibers are from one well-defined ►fascicle. The proximal end of the muscle is at 0 mm. Note the various shapes of the fibers to include full and partial tapering, and blunt and tapered fiber terminations. (Taken from [1], Fig. 5).



Skeletal Muscle Architecture. Figure 2 (a) Distribution of glycogen-depleted muscle fibers (*black dots*) belonging to a single motor unit within a single cross section of a cat tibialis anterior muscle. The outlined region in the motor unit area was selected for analysis. (b) Schematic representation of a single fascicle from the area outlined in (a). All fibers in the fascicle were classified as being depleted of glycogen (motor unit fibers) or not depleted of glycogen (non-motor unit fibers) and as slow or fast based on myofibrillar ATPase staining. Muscle fibers are identified as fast, depleted motor unit fibers (*striped*), slow non-depleted fibers (*black*), or fast non-depleted fibers (*white*). (Taken from [2], Fig. 1).

Skeletal Muscle Architecture. Figure 3 The territory of a fast fatigable motor unit (*white area*) along the proximodistal (*right to left*) axis of a cat tibialis anterior muscle is shown. Segments of the outline of the muscle are deleted to allow visualization of the motor unit territory. Note that the territory tapers and shifts from one surface to the other along the length of the muscle. (Taken from [3], Fig. 1).

is thought to reflect the axonal growth processes occurring during innervation at a developmental stage **(**Fig. 2**)**. In most muscles, the muscle fibers of a single motor unit occupy only a portion of the cross section along the length of the muscle and the extent of this motor unit territory varies considerable. The 3-D shape of the motor unit territory reflects the distribution and length of the fibers comprising the motor unit **(**Fig. 3).

S

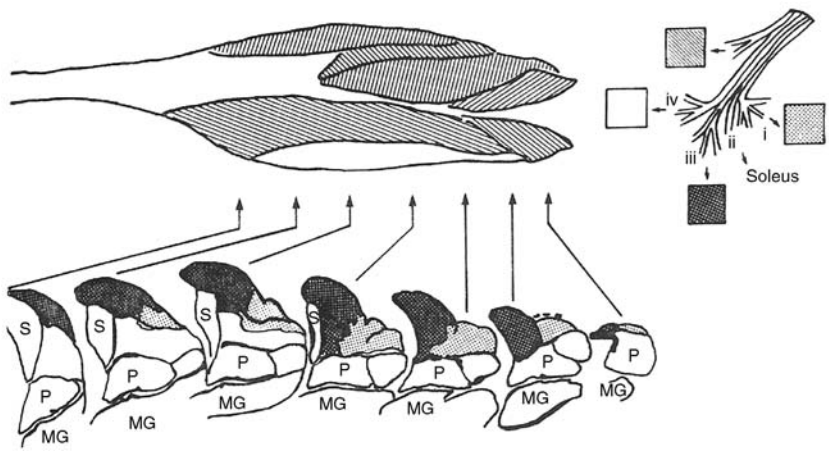
Connective Tissue Framework

There is a highly specialized connective tissue framework that is distributed throughout a skeletal muscle [7]. As stated above, individual muscle fibers are enveloped by a basal lamina containing primarily type IV collagen, fibronectin, enactin, and laminin. The remainder of the extracellular matrix has been divided into three levels of organization based on its relation to the muscle fibers. The ►endomysium is a collagenous sheath that is contiguous with the basal lamina of the muscle cells. The ►perimysium is the thickened endomysium that circumscribes fascicles of muscle fibers. The ►epimysium surrounds the outer surface of the muscle. These levels of organization are distinguishable primarily by their morphology rather than differences in their composition. All three are composed primarily of types I and III collagen. The endomysium and perimysium are usually referred to collectively as the intramuscular connective tissue. A dramatic illustration of the 3-D structure of the intramuscular connective tissue can be found in ►Figure xx in Huijing et al. (Chapter xx in this book). If the reader imagines this honeycomb of connective tissue extending to each end of the muscle, it is possible to conceive the muscle as a continuous tendon with muscle fibers embedded within.

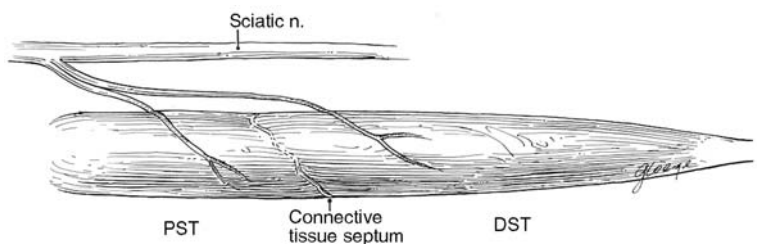
Muscle Compartmentalization

A large number of mammalian skeletal muscles are compartmentalized, i.e. subdivided into anatomical sub-compartments each having a separate primary nerve branch and showing some sensory partitioning (Figs. 4 and 5).

The arrangement of the compartments within a muscle can be in series, in tandem, in parallel, etc. Many muscles and muscle compartments can also be subdivided by their fiber type composition. For example, many



Skeletal Muscle Architecture. Figure 4 Compartmentalization of the cat lateral gastrocnemius muscle is illustrated. Muscular subvolumes (compartments) supplied by primary nerve branches are identified. Shown are a compilation of serial sections from several glycogen-depletion experiments that describe the regions innervated by primary muscle nerve branches. Proximal end of the muscle is on the right side. (Taken from [5], Fig. 6).



Skeletal Muscle Architecture. Figure 5 Schematic drawing of the cat semitendinosus (ST) muscle. A dense connective tissue band divides the ST into a proximal (PST) and distal (DST) end. The muscle fibers of each end are arranged in parallel (angle of pinnation = ~0°) and are connected in series at the connective tissue band, with distal fibers being approximately twice as long as the proximal fibers. Each muscle compartment is innervated by a separate branch from the sciatic nerve. (Taken from [6], Fig. 1).

muscles and muscle compartments show a much higher percentage of slow fibers in the regions that are closer to the center of the limb or trunk, i.e. close to the bony elements, than regions that are more superficial, i.e. away from the bony elements. This type of compartmentalization is much less evident in the muscles of humans compared to most other animals. Compartmentalization has some functional implications [7]. For example, in many instances, the individual compartments can be recruited independently of each other during specific motor tasks. Similarly, a region of a muscle comprised of a relatively high proportion of slow fibers is normally recruited at lower force levels than a region having a lower proportion of slow fibers.

Structure-Function Relationships

The arrangement of the fibers/fascicles within a muscle influences its mechanical properties. A muscle that has relatively long fibers or fascicles, i.e. a large number of sarcomeres in series, is optimally designed for producing long excursions and thus for speed of contraction. In contrast, a muscle with relatively short fibers or fascicles, i.e. a large number of fibers or fascicles in parallel, is optimally designed for force production. The muscle fibers/fascicles within a muscle can be arranged in parallel to or displaced from (pinnated) the axis of force- or displacement-generation. In pinnated muscles, the muscle fibers can be arranged in a unipinnate or multipinnate arrangement depending on the intramuscular connective tissue framework. The significance of the pinnation angle of the muscle fibers is that the transfer of force or displacement is theoretically compromised along the axis of the force- or displacement-generating axis, i.e. decreased by the cosine of the angle of pinnation. An advantage of fiber pinnation is the increase in the number of fibers that can be arranged in parallel, and thus an increase in force potential. The angle of pinnation in a rested state has been reported to be relatively small across most muscles. Although there are minimal data on sarcomere function in vivo, the fiber angle in some muscles appear to increase dramatically during dynamic contractions, i.e. the fibers are free to rotate during a contraction. This has been elegantly demonstrated in humans using ultrasound techniques. The ability of force to be transmitted laterally via interconnections among the individual fibers arranged in parallel and eventually to the site of insertion ensures the effectiveness of force transmission, even when there is a large angle of pinnation (▶see Chapter xxx by Huijing in this book). A final point here is that, many of the relatively large muscles in humans have multiple compartments and complex tendons of insertion and origin, and we do not understand at all how these compartments interact to generate a given force and displacement.

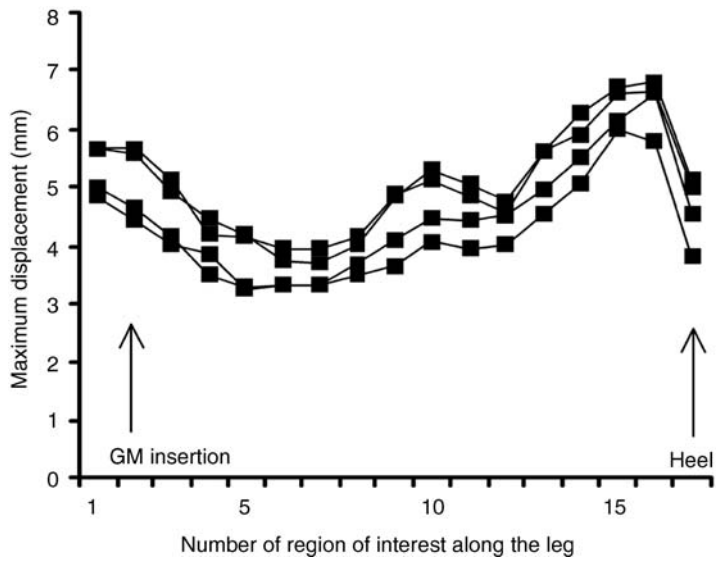
Plasticity of Muscle Architecture

The architectural properties of a muscle are highly plastic. Muscle and fiber size will increase (hypertrophy, e.g. with resistance training) or decrease (atrophy, e.g. with aging) with changes in the activation/loading conditions. Chronic stretching of a muscle fiber results in the addition of sarcomeres and thus a lengthening of the muscle fiber, whereas chronic shortening has the opposite effect. Hypertrophy of a muscle increases, whereas atrophy decreases, the angle of pinnation of the muscle fibers/fascicles. These considerations may become highly relevant under certain circumstances.

Functional Implications

It is interesting to note that almost all of the variables measured to characterize muscle architecture are based on the muscle fibers themselves, i.e. the number of sarcomeres arranged in series and in parallel and the angular arrangement of these fibers with respect to the direction of pull of the muscle. There is no inclusion of any of the passive tissues of the musculo-tendinous complex in these measurements. In most experiments any potential contribution of the interfiber matrix, the connective tissue that forms fascicles, aponeuroses and tendons are omitted from the formula to calculate the force and velocity of shortening potential of a muscle. Furthermore, most experiments are specifically designed to eliminate elastic properties. This omission is practically universal, in spite of the fact that it is clear that one cannot predict these measures of function based on muscle fiber architecture and sarcomere dynamics derived from isolated single muscle fibers, in large animals as it can in the smaller animals such as the mouse, rat and guinea pig. The formula classically used to calculate physiological cross-sectional area of a muscle provides highly variable estimates of maximum force and velocity of shortening in human muscles. This limitation suggests that there are some novel fundamental design strategies that have been used in the evolution of larger animals. For example, the difference in body and muscle volumes in the human and the cat may differ 50-fold, whereas the lengths of the fibers in homologous muscles are approximately the same in many cases.

For the physiological cross-sectional area of a muscle to represent its maximum force potential, it must be assumed that the force generated by a single fiber is independent of its length, which in turn implies that all forces among the sarcomeres are transmitted in series and entirely to the end of the muscle fiber to the myotendinous junction, which then transmits the forces to the aponeurosis and/or tendon. It is quite clear now that this is not the case. Muscle forces are transmitted from sarcomeres along the entire length of muscle fibers laterally to the interfiber matrix, and the matrix in turn transmits these forces to connective tissues that form



Skeletal Muscle Architecture. Figure 6 Example of the maximum displacement at various regions of interest along the aponeurosis-tendon of the gastrocnemius muscle (GM) for one subject during four trials (contractions) in one session. Displacement was calculated using cine phase-contrast magnetic resonance images. Note the nonuniformity in the strain along the aponeurosis-tendon complex. (Taken from [9], Fig. 4).

fascicles, aponeuroses and eventually a tendon. In effect, in large muscles this lateral transmission of forces from sarcomeres along the length of fibers will require much more detailed and sophisticated models of force transmission than is represented by the simpler, traditional models which assume transmission of forces only from sarcomere to sarcomere along the length of the fibers and eventually only to the myotendinous junction. Other sections in this series have addressed some of these issues, demonstrating the potential importance of mechanical interactions from muscle to muscle via the connective tissue sheets that surround them, as well as the interactions of the connective tissues within the muscle, including the interfiber connective tissue matrix (►see Chapter xxx by Huijing in this book).

Obviously, the ability to monitor sarcomere dynamics, muscle fiber shortening and orientation and strains among and within the different levels of organization of the connective tissues that encase the muscle fibers to form a muscle is a technological challenge, even for small muscles in small animals. Some progress has been made in attempting to monitor in vivo sarcomere dynamics in a fish during swimming, in human muscles during normal voluntary isometric activation of selected muscle groups as well as during dynamic jumping movements using ultrasound and magnetic resonance imaging [8]. The initial examinations of the intramuscular dynamics during isometric contractions of the triceps surae in humans demonstrate a remarkable complexity and spatial heterogeneity in the strain of events that occur throughout the triceps surae and particularly the soleus muscle. It is also evident that the strain that occurs within the aponeurosis of the Achilles tendon varies along its length during an isometric contraction **(**Fig. 6**)**. These studies represent only a beginning of the efforts that are likely to reveal important new basic concepts in muscle design, which will enable us to more accurately predict the physiological potential of a given muscle-tendon complex. This information could also be important in efforts to design artificial muscles that can be used to assist or replace dysfunctional muscles.

Therapeutic Interventions

The consideration of muscle architecture has become prominent in the area of tendon transfers in patients with a variety of musculoskeletal diseases [10]. In instances where a muscle or muscle group has become dysfunctional, it is a common procedure to transfer the tendon of a nearby muscle to compensate for the loss of specific movements. Lieber and colleagues have clearly shown that a crucial consideration in these procedures is the operating range of the musculoskeletal unit to be transferred, i.e. the architectural features of the unit should closely match the kinematics of the desired movements.

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Skew Deviation

►Vestibular Tests Ocular Tilt Reaction

Skill

►Coordination

Skill Learning

Definition

Skill learning is learning of behavioral procedures or "how to." Examples of skill learning are learning to ride a bike, learning to touch type, learning to play a musical instrument or learning to swim. This learning proceeds implicitly and unconsciously by using feedback information. Skill learning can reflect acquisition of an "internal model" of an external object to control. For instance, in the cerebellum, movement trajectories of limb or eye directed to an object are computed by an "inverse model" which transforms from desired trajectory input to motor command output to skeletal muscles.

►Internal Models
►Sensorimotor Learning and the Basal Ganglia

Skin Photoreceptor

Definition

Photoreceptors in the skin (or dermal photoreceptors) in non-mammalian vertebrates that regulate some non-image forming photoresponses. An opsin-like molecule in photosensitive pigment cells known as melanophores of Xenopus laevis was named melanopsin. The photoreceptor(s) in the skin of fish exhibits several properties of the opsin family of photopigments, but is not yet identified.

►Photopigments

Slave Oscillators

►Internal Desynchrony

Sleep

Definition

Sleep is a state of rest in animals that is characterized by behavioral quiescence and decreased responsiveness to environmental stimuli. The timing of sleep is controlled by an animal's internal biological clock and sleep occurs mostly during the night (diurnal species) or during the day (nocturnal species). Other aspects of sleep behavior (e.g., daily sleep amounts, specific sleep

postures, preference to sleep in a protected environment such as a nest) vary considerably across species.

Common to all species is the expression of rebound increases in sleep amount when animals are deprived of sleep during all or part of their normal rest period.

►Sleep Generating Mechanisms

Sleep – Developmental Changes

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Definition

Sleep undergoes characteristic changes across the developmental progression from birth to early adulthood, including total sleep time, the proportion and timing of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, and electrophysiological features of sleep. These features may serve as markers of nervous system development, and sleep itself may be critical for normal development.

Characteristics

Introduction

Sleep is a complex, highly organized state associated with reversible changes in consciousness, neuronal network firing properties, cerebral blood flow, gene expression profiles, brain chemistry, and autonomic nervous system activity. The precise functions of sleep remain poorly understood, but it is likely that a prominent function of sleep is to promote neuronal repair and reorganization in the brain [1]. Therefore, "sleep is of the brain, by the brain, and for the brain" [2]. With this framework in mind, it is not surprising that the most rapid changes in the organization and physiology of sleep occur during development.

Total Sleep Time

In the neonatal period (first 28 days of life) in humans, total sleep time tends to occupy 16 or more hours per day, declining to roughly 13 h at 6 months, 10 h at 2 years, and 9 h by age five. Shortly after birth, a large proportion of sleep occurs during the daytime, and with age sleep gradually becomes primarily a nocturnal phenomenon. This is likely due to maturation of the ►circadian pacemaker and the endogenous rhythm of ►rest-activity cycles [3].

Sleep States: Rapid and Non-Rapid Eye Movement Sleep

Sleep is not a homogenous state and is generally divided between ►rapid eye movement (REM) sleep and stages of ►non-rapid eye movement (NREM) sleep. Sleep stages are defined by the patterns of electrical activity recorded over various scalp locations, changes in muscle tone or body movements, eye movements, and in infants the regularity of the respiratory pattern. Visual scoring has been used to characterize behavioral states in neonates into active and quiet sleep. Active sleep is characterized by: closed eyes, rapid eye movements, irregular respirations, and body twitches, and this is likely the precursor to REM sleep. Quiet sleep is characterized by: closed eyes, minimal eye and body movements, and regular respirations. This is likely the precursor to NREM sleep. In neonates, a substantial proportion of sleep may not be easily recognized as active or quiet sleep, and the term indeterminate sleep may be used.

During the first few months of life NREM sleep becomes divided into stages of lighter sleep, stage 1 and stage 2 sleep, as well as deeper stage 3 and stage 4 sleep (now generally combined as ►slow wave sleep). The depth of NREM sleep relates to the ease at which an environmental stimulus can cause an arousal from sleep to wakefulness. Sleep architecture, or the orderly progression of sleep stages across the night, changes significantly during development.

During early infancy, the oscillations between REM and NREM occur at roughly 60 min cycles, lengthening to about 90 min in the adult. Newborns and infants in the first month of life make the transition from wakefulness to sleep through REM or with only a few minutes of intervening NREM sleep prior to the first REM period [4]. After about 2–3 months of age, sleep is generally entered through NREM sleep through adulthood except under abnormal conditions such as: narcolepsy, the withdrawal of REM suppressing medications, or significant prior sleep restriction. The proportion of REM sleep is roughly 50% of sleep in the newborn, gradually declining to roughly 15–20% by the end of puberty [5]. The proportion of slow wave activity during NREM sleep declines sharply during adolescence.

Electrophysiological Changes during Development

The electrophysiological patterns recorded by the electroencephalogram (EEG) undergo characteristic changes across gestational age, which is the time elapsed since the first day of the mother's last normal menstrual cycle. EEG patterns have been characterized in normal premature infants as early as 25–27 weeks

gestational age [6]. The EEG is initially discontinuous, with relatively long periods of electrical silence for periods of 30 s or more mixed with bursts of relatively high voltage activity lasting up to 20 s. It was previously felt that before 32 weeks, distinguishing ►waking and ►sleep states by EEG was not possible, but EEG differentiation may be possible as early as 28 weeks [6]. By 31–32 weeks, active sleep, quiet sleep, and wakefulness reliably show differential activity patterns. The EEG becomes more continuous, with general continuity in active sleep and wakefulness. During quiet sleep, the *trace alternant* pattern emerges with bursts of large slow frequency waves and relatively short periods of EEG quiescence. This generally disappears by 47 weeks development at which time the EEG becomes continuous in all behavioral states. ►Sleep spindles, which are short, high frequency bursts generally in the 12–14 cycles per second frequency range, begin to develop by 2–3 months post term. Sleep spindles are the hallmark of stage 2 NREM sleep. Spindles are initially asymmetric, but they become synchronous over both hemispheres during infancy. Generally by 3 months of age, the proportion of slow waves increases and starts to become similar to adult slow wave sleep [7]. Generally by 4 months of age, spindles and slow wave activity are present to a degree that allows confident segmentation of NREM sleep into its component stages. ►K complexes, another feature of Stage 2 NREM sleep, are present generally by 6 months of age. These are waves with a characteristic biphasic shape (negative then positive polarity). The posterior dominant rhythm of relaxed wakefulness gradually increases in frequency from 3 to 4 cycles per second at 3 months, 5–6 cycles per second at 6 months, 7–8 cycles per second by age three, and 8–10 cycles per second by age 15 [4]. Attenuation of the posterior dominant rhythm aids in the recognition of the transition from wake to sleep. Detailed descriptions of the electrophysiological changes of sleep across development have been documented elsewhere [4,7]. The key concept is that changes in the electrophysiological features of sleep are intimately coupled to gestational age and the level of maturation of the nervous system.

Sleep and Developmental Milestones

The electrophysiological changes that occur during maturation reflect changes in network firing properties and patterns of depolarization and hyperpolarization of cortical neurons. The precise changes in the nervous system associated with the developmental progression of the sleep EEG are poorly understood. It has long been speculated that increasing myelination of the brain during development is a key factor in the timing and characteristics changes of the sleep EEG. Other mechanisms are possible as well. For example, in developing neurons there may be a shift in the post-synaptic receptor profiles and responsiveness to various neurotransmitters [5]. The changes in sleep behavior and physiology across development may be considered milestones of brain maturation, similar to other milestones such as the disappearance of various reflexes, development of fine motor skills, or language development. As such, features of the sleep EEG may be associated with the brain's capacity for information processing. For example, the precise electrophysiological characteristics of sleep spindles may be markers of general cognitive ability [8].

Sleep may Influence the Development Process

Sleep may not only serve as a useful marker of the developmental state of the brain, but sleep may be a critical process to promote normal nervous system development. There is a growing body of literature for the role of sleep in the off-line processing of memories during a period of consolidation. This is an example of the role of sleep in plasticity, or the experience dependent changes that occur at the synaptic level. Changes in synaptic connections may increase or decrease the probability of activating particular neural networks, shaping the information processing capabilities of the brain.

The proportion of REM sleep is highest in the neonatal period, the phase of the life cycle associated with the most rapid re-organization of the brain. REM sleep deprivation experiments in animals have been used to determine the influence of this sleep stage on neural network connectivity. A particularly influential model for understanding development of neural connectivity has been monocular visual deprivation in developing animals. When one eye is deprived of visual input during a critical period of development, the brain undergoes reorganization so that cortical structures involved in visual processing become more heavily connected to the open eye. REM sleep deprivation during this critical period shifts the balance further, enhancing connections to the open eye at the expense of the visually deprived eye [9]. This has been interpreted to signify that normal REM sleep provides an opportunity for the deprived eye to compete for cortical connectivity despite the lack of external visual input. REM sleep is a state of high neuronal firing rates and brain metabolism that is similar to waking levels, and there is particular activation of visual processing areas such as occurs during ►dreams. Endogenous neuronal activity of visual pathways during REM sleep may enhance connectivity, so that maturation of the visual system may occur during sleep when there is no visual sensory input through closed eyes. Promoting use dependent plasticity in the visual system

during REM sleep is one example of how sleep processes can interact with the brain to promote normal connectivity. Slow wave sleep may also provide an opportunity for the brain to strengthen specific networks, for example, during the neuronal re-play of recently acquired memory traces during slow wave sleep.

Clinical Implications

The sleeping brain reflects a highly organized pattern of neural activity, involving both cortical and subcortical structures. Changes in sleep behavior and physiology are intimately coupled with nervous system development. As an extension of the neurological examination, improved methodology to capture the physiological processes of sleep may provide sensitive markers of brain maturation. Therefore, sleep analysis may become a valuable tool for predicting neurological prognosis. Sleep is not only a window to the organization of the brain, but sleep may also be critical for its development. Cognitive and emotional difficulties later in life may result from abnormal sleep quantity or quality during development. For example, early REM deprivation may lead to mood disorders such as depression [10]. Sleep is important for the consolidation of memories and may have other benefits on cognitive function. Public health education to foster optimal sleep habits for children and effective screening tools for childhood sleep disorders may improve school performance, social functioning, and overall wellbeing.

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Sleep – Endocrine Changes

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Definition

The inter-relationships of hormone concentrations, sleep and circadian rhythms. The frequency and/or amplitude of pulsatile hormone release may be affected by sleep, specific sleep stages and/or circadian rhythms. In turn, hormone concentrations may affect sleep and the circadian timing system.

Characteristics

Introduction

A hormone is a chemical messenger that carries its signal via the blood. Many hormones are rhythmically released. Their periodicity can be ►ultradian (i.e., with a period shorter than 24 h, e.g., ~90 min pulses of thyrotropin [TSH]), circadian (i.e., with a period close to 24 h, e.g., melatonin), or infradian (i.e., with a period longer than 24 h, e.g. sexual hormones such as Luteinizing Hormone or Follicule Stimulating Hormone) or combinations of these periodicities; one example is circadian variation in ultradian pulse frequency or amplitude.

Daily oscillations of endocrine activity are driven by mechanisms that can be endogenous (internal), exogenous (environmental), or by a combination. In addition to the conventionally considered biochemical regulatory mechanisms for each hormone's synthesis, release and clearance, other influences include the endogenous circadian biological clock, located in the ►suprachiasmatic nuclei (►SCN) of the ►hypothalamus, and endogenous sleep/wake-related processes) [1]. Environmental factors that are known to affect hormone release are: posture changes, physical activity, food intake, temperature, and light. In individuals living in real life conditions, endogenous and exogenous factors are usually confounded. For example, sleeping usually occurs a specific circadian phases and is not only a change in conscious state, but also is usually accompanied by a change in posture, feeding/fasting, light levels and social contacts, all of which may individually affect hormones. Only controlled laboratory studies allow for separation of those factors, and permit to infer controlling mechanisms of hormonal release.

The most thoroughly studied hormone-sleep interactions are those of the pituitary hormones. Early studies have described three categories of sleep-hormone

interactions: (i) hormones weakly influenced by sleep, such as adrenocorticotropic hormone (ACTH), cortisol and ►melatonin, (ii) hormones strongly influenced by sleep as a whole, such as prolactin (PRL) and TSH; (iii) hormones influenced by a particular stage of sleep, such as growth hormone (GH) [2]. More recently, a variety of protocols have been used to investigate the relationships between hormones and sleep and circadian systems, including: complete and partial sleep deprivation, acute or chronic shifts of the sleep time, administration of pharmacological agents which disturb either sleep or hormone secretion, and the use of pathologies in which either endocrine or sleep disturbances are observed [1,3,4]. Using frequent blood sampling rates, sensitive hormonal assays, and controlled protocols, those studies have found that, most hormones are influenced, with different respective contributions, both by circadian and sleep-related processes.

Specific Relationships between Sleep and Hormones

Prolactin (PRL)

Under baseline conditions, 24-h profiles of PRL show low levels during daytime and high levels during sleep. Studies using experimental strategies such as shifts of the sleep episode have shown a close association between sleep and the increase in PRL release. Figure 1a illustrates the effect of an 8-h shift in the sleep period on the 24-h PRL profiles in a group of young subjects. In order to differentiate circadian influences from sleep-related effects, day-active subjects were studied once under a normal 24-h ►sleep-wake cycle (sleep from 2300 or 23 to 0700 or 7 h), and once under a 24-h cycle where sleep was delayed by 8-h (sleep from 0700 or 7 to 1500 or 15 h). In both conditions, PRL is high during sleep time and low during waketime, showing the strong influence of sleep on PRL release. It is important to note that, a systematic PRL pulse was found in all subjects during the night of ►sleep deprivation, at the time of habitual sleep. This pulse, also observed in ►jet lag studies, is thought to reflect an influence of the circadian timing system on PRL release, independent of sleep [4].

The search for an association between the internal sleep structure and the episodic PRL pulses has led to conflicting reports. A relationship between the alternation of ►REM and ►NREM sleep episodes and the occurrence of nadirs and peaks, respectively, in plasma PRL levels has been described in some studies, but not in others. Using spectral analysis of the sleep EEG, however, a clear temporal link between PRL release and the ►electroencephalographic activity (►EEG) during sleep has been described. PRL secretory rates have been found to be positively correlated with delta wave activity (also called ►slow wave activity, ►SWA, 0.5–3.5 Hz), an indicator of sleep depth, and negatively correlated with alpha (8–12.5 Hz) and beta frequency bands (13–35 Hz), indicators of relaxed wakefulness, and active wakefulness respectively (Fig. 1b) [3].

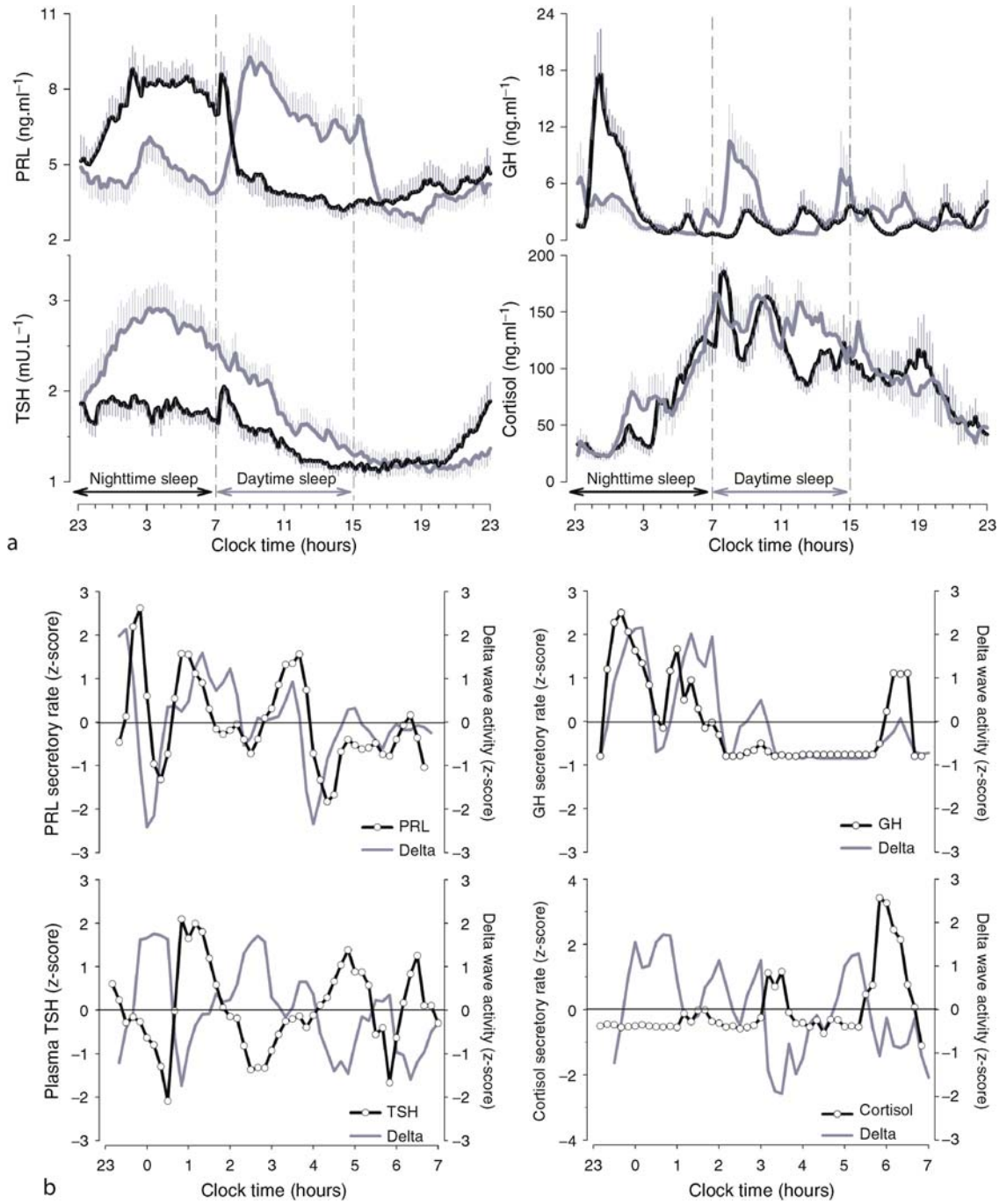
Growth Hormone (GH)

The 24-h profile of GH is characterized by a sleep-dependent rhythm, with a large secretory episode occurring just after sleep onset, temporally related to the first episode of ►slow-wave sleep (SWS). Other pulses may occur later during sleep and during wakefulness, especially in women. Figure 1a illustrates the mean GH profiles during a normal 24-h period, and during a 24-h period where sleep was delay shifted by 8-h. In both conditions, a large GH pulse is measured just after sleep onset. This hormone is therefore clearly controlled by sleep mechanisms. A weak circadian influence on GH release has been proposed, as GH pulses are usually observed during sleep deprivation at the habitual sleep time [4].

Despite the large number of studies, the underlying mechanisms coupling GH and SWS have not yet been clearly identified. Some authors have concluded that the temporal association observed between GH pulses and the first episode of SWS may be fortuitous. In more recent studies, however, a close temporal relationship has been found between SWS and GH secretory rates. In addition, a significant correlation has been described between the amount of GH secreted during SWS and the duration of the associated SWS episodes, under normal conditions, as well as after pharmacological enhancement of SWS with gamma-hydroxybutyrate [4]. This result has been confirmed by another study describing a quantitative relationship between the amount of GH secreted and the concomitant amount of delta wave activity (Fig. 1b). Interestingly, when sleep is enriched in SWS by ritanserin (a 5-HT2 receptor antagonist), an equivalent increase in delta wave activity and GH secretion is found [5]. Taken together, these results suggest that the regulatory mechanisms involved in the control of delta wave activity and GH secretion share common pathways. In rodents, growth hormone releasing hormone (GHRH) neurons could be the common link between GH release by the pituitary and SWS generation.

Thyrotropin (TSH)

TSH exhibits a 24-h rhythm generated by amplitude and frequency modulation of secretory pulses. TSH has low daytime values which begin to increase in the late afternoon, reaching maximum levels around the time of sleep onset. Subsequently, a slow decline, generally attributed to an inhibitory influence of sleep, occurs during the night. Figure 1a illustrates 24-h profiles of TSH both during a normal 24-h period and a sleep shift. During sleep deprivation, TSH levels continue to rise, peaking later in the night. It is generally admitted that sleep exerts an inhibitory influence on TSH secretion,



Sleep – Endocrine Changes. Figure 1 (a) 24-h profiles of PRL, GH, TSH and cortisol in a group of eight healthy young subjects, measured once under a normal 24-h sleep-wake cycle (sleep from 23 to 7 h, dark line), and once under a 24-h cycle after a delay shift of the sleep episode by 8-h (sleep from 7 to 15 h, gray line). (b) Nocturnal hormonal profiles of PRL, GH, TSH, and cortisol (dark line with open circles) and concomitant with delta wave activity, as a marker of sleep depth (gray line). Adapted from [3].

and that sleep deprivation removes that inhibition. It is considered that the 24-h TSH profile results from an interaction between the endogenous circadian timing system and a sleep-related inhibitory effect. When the depth of sleep at the habitual time is enhanced by prior sleep deprivation, the nocturnal TSH rise is markedly reduced, suggesting that SWS is probably the primary determinant of the sleep-associated fall [3,4].

A temporal association has been described between the internal sleep structure and TSH pulses, such that

SWS is associated with declining plasma TSH levels, and awakenings with rising levels. These relationships have been confirmed using spectral (frequency) analysis of the sleep EEG, which demonstrated that the nocturnal TSH profile was negatively correlated with the delta wave activity. Figure 1b shows that increases in TSH levels are linked to decreases in delta wave activity, and conversely, that decreases in TSH levels are associated with increases in delta wave activity. The nocturnal TSH profile closely reflects variations of sleep EEG activity. Whether EEG activity has a modulatory role on TSH levels, or inversely, whether TSH variations could influence sleep structure, remains to be clarified. However, the fact that sleep deprivation is associated with an increase in TSH release favors the hypothesis that it is SWS that inhibits TSH secretion [3].

ACTH/Cortisol

The 24-h cortisol rhythm is generally considered to be mainly under endogenous circadian control, and therefore to be relatively independent of sleep. Indeed, it is only slightly affected by short-term manipulations of sleep such as sleep reversal, selective and total sleep deprivation, and abrupt shift in the sleep period (Fig. 1a). However, temporal relationships between cortisol and sleep have been found, and sleep has been proposed to exert an inhibitory effect on cortisol release [6], particularly in the first few hours of the night. This finding has been challenged by other studies, which concluded that sleep does not inhibit cortisol since ►diurnal sleep does not suppress cortisol release [3].

Despite these discrepancies, temporal relationships between cortisol pulses and the internal sleep structure have been described. Awakenings or light sleep periods are associated with increasing plasma cortisol levels, whereas SWS is associated with low or decreasing cortisol levels. Using spectral analysis of the sleep-EEG and deconvolution procedures for estimation of cortisol secretory rates, an inverse relationship between cortisol secretory pulses and oscillations in delta wave activity during nocturnal sleep as well as during diurnal sleep was described. Increases in cortisol secretory rates were associated with decreases in delta wave activity, and conversely, peaks in delta wave activity occurred only during low cortisol secretion (Fig. 1b). It is possible that both sleep is inhibited by cortisol release and cortisol release is inhibited by sleep (SWS in particular). Cross-correlation analyses between delta wave activity and cortisol secretory rates revealed that cortisol oscillations precede the changes in EEG activity by about 10 min, suggesting that cortisol secretion or its secretory processes may modulate the EEG activity, rather than the inverse [3]. At the same time, this finding does not exclude that SWS exerts an inhibitory influences on cortisol release through delayed effects. Until new data is available, in particular from studies in which sleep and circadian influences can be separated (such as in ►forced desynchrony protocols), the safest statement that can be made at this point, is that reciprocal negative interactions exist between SWS and cortisol secretion.

Other Hormones and Neuropeptides

Sleep is a strong modulator of glucose and insulin secretion, since high glucose and high insulin levels are seen during sleep, irrespective of sleep timing. Endogenous circadian rhythms of glucose and insulin secretion have been reported, but they are rather of low amplitude. The 24-h rhythm of satiety-sensing hormone leptin has a nocturnal increase that is under both circadian control (persisting during sleep deprivation) and sleep control (sleep deprivation dampens its amplitude) [4]. The appetite stimulant hormone ghrelin also shows a sleep-associated increase at night [4]. Recent studies have investigated the rhythmicity of ►orexin/hypocretin, a brain neuropeptide involved in sleep maintenance. Orexin levels increase during the day and decrease at night, under the dual control sleep/wake and circadian processes. Indeed, lesions of the SCN abolish the circadian rhythmicity of orexin, and sleep deprivation lead to subsequent increases in orexin levels [7]).

Sleep Debt and Hormones/Metabolic Syndrome

Although the effects of inpatient short-term single episodes of sleep deprivation on brain functioning have been extensively studied, the consequences of chronic sleep restriction (insufficient sleep for multiple days) as experienced by millions of people, have received much less attention. During the past 5–6 years, however, a set of studies has demonstrated that the effects of sleep restriction is not limited to the executive performance and alertness functions of the brain, but also affects the entire body. Elegant studies have shown that sleep curtailment impacts the somatotropic (GH), corticotropic (cortisol) and thyrotropic (TSH) axes [8]). Interestingly, they also showed under a sleep restriction protocol, that leptin is decreased and ghrelin is increased, reducing the feeling of satiety and increasing the feeling of hunger [9]. Another group of studies, showed that short sleep duration is associated with reduced leptin, increased ghrelin and increased body mass index (BMI, an index of obesity) [10]. Taken together, these results suggest a causal relationship between sleep debt and metabolism impairment that has large implications for the health of sleep restricted individuals in industrial societies, in which the rate of obesity and metabolic illnesses such as type II diabetes is increasing dramatically.

Conclusions

This chapter highlights the wide variety of relationships between sleep and hormonal activity. PRL and GH are increased during sleep (SWS in particular) and

mainly driven by sleep. In contrast, the circadian timing system is the main driving force of the 24-h rhythm of melatonin and cortisol, with, for the latter hormone an additional influence of the internal sleep structure on its pulsatile release. TSH lies on the boundary of these classes of hormones, as its 24-h rhythm is generated by the circadian system and by modulated (inhibited) by sleep (SWS).

Because of the intricate relationships among hormones, sleep, and the circadian timing system, alterations of hormonal release can impact sleep and its structure. Similarly, sleep loss and circadian misalignment, either due to pathologies (sleep apnea, ►insomnia, etc.) of real life situations (voluntary or socially induced sleep curtailment, jet lag, ►shift work) can have a detrimental impact of many endocrine systems. Further work is needed to detail the neuroanatomy and molecular mechanistic links between sleep and hormones that result in the observed interactions.

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Sleep – Motor Changes

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Synonyms

Descending Drive to motorneuron pool; Motor responsiveness; Sleep Movement Disorders

Definition

Sleep associated motor changes reflect neurophysiological alterations in descending excitatory and inhibitory drives to the alpha ►motorneuron pool. Integration of descending excitatory and inhibitory drives determines net motor output during sleep.

Characteristics

Sleep is characterized by specific postural changes, reductions in muscle tone, and changes in excitatory and inhibitory inputs to ►motorneurons that influence the likelihood of an action potential and therefore motor output. Motor output characteristically changes across wakefulness and sleep states such that muscle activity is highest during active wakefulness, decreases during quiet wakefulness and ►Non-REM sleep (NREM) sleep, and is minimal or absent during ►rapid eye movement (REM). Thus, measurement of gross motor activity, i.e., inactivity, has often been used as a proxy to assess wakefulness-sleep timing [1].

Changes in Descending Drive to Motor Neurons During Sleep

In most mammals, activities of alpha motorneurons that innervate skeletal and respiratory ►muscle fibers may or may not be reduced during NREM sleep relative to quiet wakefulness, whereas during REM sleep motorneuron activity is actively reduced or inhibited. However, compared to active wakefulness when the ►alpha motorneuron membrane potential is most easily raised above threshold for the generation of action potentials, the membrane potential of motor neurons are ►hyperpolarized during NREM sleep. Motorneuron membrane potential becomes even more hyperpolarized during REM sleep making it even less likely that an action potential will occur. Sleep related changes in membrane potential are thought to be caused at least in part by a reduction or removal of excitatory drive to the motorneuron pool (i.e., ►disfacilitation) and by increased inhibitory drive at the level of the ►postsynaptic membrane. Excitatory drive is reduced to the greatest extent during REM sleep. Reductions in ►monoaminergic neuronal activity emanating from ►brain stem raphe serotonergic neurons and ►locus

coeruleus noradrenergic neurons are hypothesized to contribute to reductions in the excitatory drive to the motorneuron pool during sleep compared to wakefulness [2]. REM state specific activation of brain stem ►cholinergic neuronal cell groups and reductions in brain stem serotonergic and noradrenergic activity are reported to contribute to ►muscle atonia during REM sleep [3,4]. Findings from lesion studies indicate that damage to cell in the peri locus coeruleus [4] or ►sublaterodorsal tegmental nucleus [5] of the brainstem can result in a release from muscle atonia during REM sleep and as a result, animals appear to act out their dreams [6,7]. ►Gultamatergic cells within the sublaterodorsal tegmental nucleus of the brain stem are reported to project to ►spinal cord interneurons [5], and to actively inhibit alpha motor neuron action potentials though release of ►glycine and ►GABA [2,4,5]. In addition, during REM sleep there is an increase in small amplitude spontaneous as well as sensory stimulated ►inhibitory post synaptic potentials (IPSPs) in the motorneurons. These small amplitude IPSPs and REM state specific large amplitude IPSPs are reported to be associated with responses to sensory stimulation and ►pontine-geniculo-occipital (PGO) waves [8].

Although reduced, supraspinal excitatory drives to the motorneuron pool remain active even during REM sleep. Inhibitory drives generally predominate during REM sleep and thus muscle activation does not typically occur. However, twitches in skeletal muscle fibers take place during REM sleep and these brief increases in muscle activity are thought to be due to a temporary predominance of excitatory over inhibitory drives. Phasic muscle twitches that occur during REM sleep are reported to be associated with phasic activity in other systems such as rapid eye movements, PGO waves, and middle ear muscle activity. Some species, such as dogs and perhaps aquatic mammals like dolphins, appear to have less muscle inhibition during REM sleep.

Behavioral Responses to Environmental Stimuli During Sleep

In humans, it has been demonstrated that behavioral responsiveness to stimuli can occur in all stages of sleep; however, the likelihood of a behavioral response is generally reported to be greatest in stages 1 and 2 sleep (reviewed in [9]). Behavioral responsiveness to stimuli during sleep is dependent on changes in sensory ►thresholds as well as the ability to perform and complete the behavioral response. For example, a button press in response to a tone is less likely to occur during the muscle atonia of REM sleep whereas taking a deep breath in response to an ►auditory tone can take place during REM sleep. In some cases, aborted attempts to respond with a button press can be observed in the ►electromyographic (EMG) activity of hand and forearm muscles during sleep. Findings from such studies demonstrate that complex motor behaviors are possible during sleep.

Sleep Movement Disorders and Motor Phenomena During Sleep in Humans

A number of sleep movement neurological disorders have been identified. Examples include, periodic limb movements of sleep (PLMS), sleep bruxism, REM sleep behavior disorder (RBD), sleep walking, sleep related eating disorder, and obstructive sleep apnea. Periodic limb movements during sleep are characterized by periodic (i.e., every ~20–90 s), rapid flexion of the foot or knee and hip, or the extension of the big toe. Although less common, movements of the arms can also occur during sleep. Sleep bruxism – grinding or clenching of the teeth during sleep – has been reported to occur during all sleep stages but most predominantly in stages 1 and 2 of NREM sleep. Patients with REM sleep behavior disorder exhibit episodes of REM sleep without muscle atonia and therefore these patients appear to act out their dreams. Often, REM sleep behavior disorder can be seen in patients with neurological disorders such as Parkinson's disease. Sleep walking is an arousal out of deep NREM sleep and neurophysiologically the cortical EEG shows signs of wakefulness and sleep. Presumably, sleep related eating disorder is similar to sleep walking. Reductions in respiratory muscle activity during REM sleep also contribute to the cessation of breathing that is observed in the sleep disorder obstructive sleep apnea [10]. Sleep apnea is often worst during the muscle atonia of REM sleep. Many of the complex motor behaviors that take place during sleep are often unremembered because formation of "new" memories appears to be inactive during sleep. Effective treatments are available for patients with movement disorders during sleep. One last sleep related motor phenomena to be mentioned is the hypnagogic jerk, also referred to as a sleep start. The hypnagogic jerk is a sudden, non-periodic, involuntary contraction of the appendicular and/or axial muscles of the body during the transition (►transitions) from wakefulness to sleep. Hypnagogic jerks are usually considered to be benign motor behavior unless they occur multiple times per night and cause sleep onset insomnia. The common sensation of falling during a hypnagogic jerk may be the reason for the colloquialism "falling asleep." The neurophysiology of hypnagogic jerks is not well understood but is likely to be related to changes in inhibitory and excitatory drive to the motorneuron pool.

In summary, motor activity during sleep is determined by the summation of excitatory and inhibitory inputs to ►motorneurons. Inhibitory influences generally predominate during sleep. Furthermore, muscle activity is actively inhibited during REM sleep. Odd motor behaviors during sleep may be related to neurological disorders.

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Sleep – Sensory Changes

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Synonyms

Sensory Information Processing; Sensory Responsiveness

Definition

Sleep associated changes in sensory physiology reflect neurophysiological alterations in ascending arousal systems and activation of sleep promoting systems.

Characteristics

Sleep was once thought to be caused by a lack of environmental stimulation and sensory systems were thought to be relatively inactive during sleep. We now know that sleep is actively promoted by the brain and that processing of sensory information remains active during sleep [1–3]. However, neurophysiological changes during sleep are associated with alterations in sensory information processing and reductions in responsiveness to external stimuli. For example, arousal ►thresholds are higher during sleep than wakefulness and sensory physiology is different between stages of ►non-REM (NREM) and ►rapid eye movement (REM) sleep. In general, arousal thresholds progressively increase from light stage N1 through deep stage N3 of NREM sleep whereas arousal thresholds during REM sleep have been reported to be similar to those observed during deep NREM sleep or lighter stage N2 sleep depending on the amount of prior deep NREM sleep, time of night and/or ►circadian time [4,5].

Brain Sensory System Activity During Sleep

The vast majority of studies that have examined the activity of sensory systems during sleep have examined exposure to ►auditory stimuli. In the 1930s, Loomis and colleagues first described ►electroencephalographic (EEG) activation and the ►K-complex EEG response to environmental stimuli during sleep [6]. More recent studies have reported that a meaningful stimulus, such as the person's name, produces more K-complexes than do less important stimuli. Brain imaging studies indicate that activation of the auditory ►cortex, the ►thalamus and the ►caudate nucleus occurs in response to auditory stimuli during NREM sleep [7] suggesting that some level of cortical processing takes place during sleep. Exposure to most odors alters EEG activity during sleep even if the odor is below detection threshold during wakefulness. Exposure to painful stimuli such as electric shock, hot and cold water applied to the skin, and infusion of saline into muscle have been reported to result in EEG ►arousals and increased heart rate responses during sleep (reviewed in [2]). Behavioral button switch press responses to photic flash stimuli during stages 1 and 2 sleep and also REM sleep have been reported. To date, brain EEG arousals have been reported in response to auditory, ►olfactory, ►somatosensory, ►visual, and ►taste stimuli.

Sensory Information Processing During Sleep

The finding that sensory information can be processed during sleep is also supported by findings from evoked or ►event related potential studies. Early components of the ►evoked potential are linked to the sensory processing of stimuli and later components are linked to cognitive processing of stimuli. In general, the early ►brain stem components of the evoked potential

are similar between sleep and wakefulness whereas the later cognitive components are altered by sleep [8]. The cognitive evoked potential referred to as the ►P300 is elicited during wakefulness when stimuli are both detected and attended. The P300 is present during sleep but the latency of the P300 is delayed and the amplitude is reduced [9]. Other auditory evoked components such as the ►N1 and ►P2 are altered during sleep compared to wakefulness [8]. Changes in evoked potentials measured by EEG and ►magneto-encephalography (MEG) [3] between wakefulness and sleep and among NREM and REM sleep stages have been reported in response to auditory, somatosensory and visual stimuli. Although sensory processing can occur during sleep the neurophysiology of sleep does not appear to be conducive to the formation of new memories, with the exception of ►classical conditioning [2].

Synaptic Excitability During Sleep

Neurophysiologically, the intrinsic and ►synaptic excitability of cortical and thalamic neurons changes between wakefulness and sleep, and between NREM and REM sleep. Wakefulness and REM sleep are associated with EEG activation caused by brainstem and ►forebrain arousal systems, whereas during deep NREM sleep the EEG is characterized by ►slow oscillations and ►synchronization. Relatedly, the transmission of sensory information from the thalamus to the cortex is enhanced during wakefulness and REM sleep compared to NREM sleep [10]. ►Field potentials between the thalamus and cortex that are evoked by stimulation of sensory pathways are reduced during NREM sleep. In addition, when a ►sleep spindle is generated – spindles are a hallmark of NREM stage N2 sleep in humans – there is an inhibition of sensory information transfer from the thalamus to the cortex. Such blockade of sensory information transfer during NREM sleep appears to occur at the level of the thalamus and ►GABA is thought to be a primary neurotransmitter involved in this process.

Inhibition of Ascending Arousal Systems During Sleep Influences Sensory Information Processing

Reductions in activity of a multitude of brain stem, ►midbrain and forebrain arousal systems critically involved in attention and memory processes, likely contribute to alterations in sensory processing during sleep. In general, sleep promoting regions of the brain actively inhibit activity of ascending arousal systems including ►locus coeruleus noradrenergic neurons, ►raphe serotonergic neurons, ►basal forebrain and brain stem ►cholinergic neurons and ►hypothalamic orexigenic and histaminergic neurons (►histamine). Activities of ►monoaminergic neurons are even further reduced, if not completely silent, during REM sleep, whereas ►REM on cells actively promote REM sleep.

In summary, all sensory systems studied to date show that sensory processing take place during sleep, yet information processing and behavioral responsiveness to external stimuli are altered during sleep. Information transfer from the thalamus to cortical areas is blocked during synchronizing events, such as the generation of sleep spindles, during NREM sleep. Furthermore, there exist differences in sensory processing among NREM and REM sleep states that are likely related to changes in modulatory neurotransmitter brain stem, forebrain and midbrain arousal systems, which widely innervate cortical and subcortical structures.

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Sleep Apnea

►Obstructive Sleep Apnea

Sleep Brain Wave Activity

►EEG in Sleep States

Sleep Cycle

Definition

One sleep cycle lasts about 90 min and is comprised of one set each of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Most people repeat this cycle four times a night.

►Non-REM Sleep
►Rapid Eye Movement (REM) sleep
►Sleep States
►Sleep-wake Cycle

Sleep Electroencephalograpy (EEG)

►EEG in Sleep States

Sleep Generating Mechanisms

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Synonyms

Sleep regulating mechanisms; Sleep onset mechanisms

Definition

Neuronal and neurochemical mechanisms that actively promote sleep onset, function to maintain sleep continuity, and regulate sleep depth in response to homeostatic and circadian demands.

Characteristics

Sleep as an Active Process

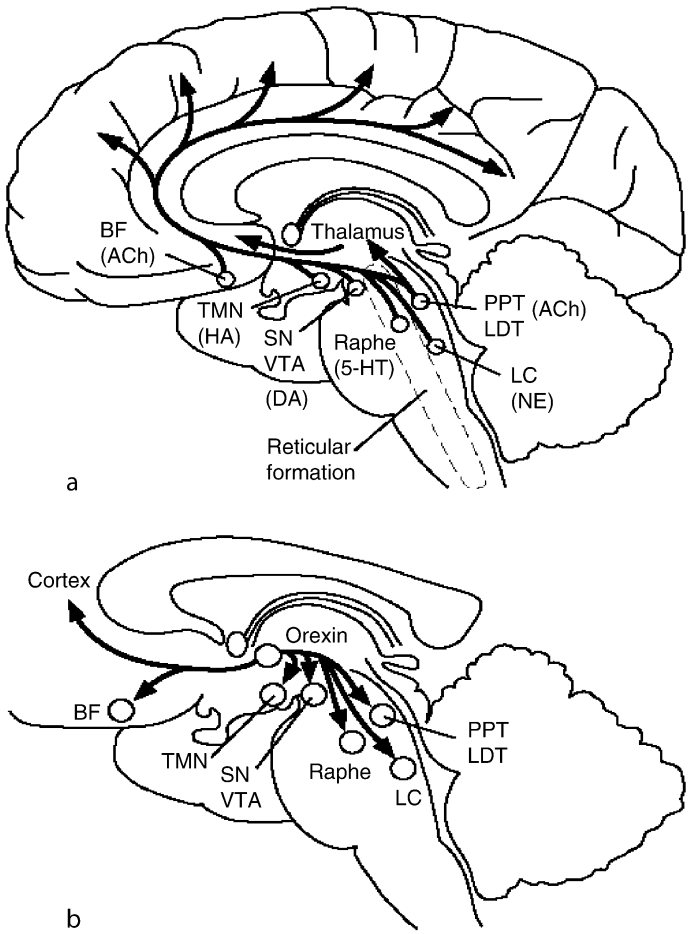
The prevailing view among physiologists during the first half of the twentieth century was that waking brain activity depended upon sensory stimulation. ►Sleep was believed to occur as a passive consequence of diminished sensory input that accompanied instinctual sleep preparatory behaviors (e.g., behavioral rest, eye closure, selection of a warm, quiet environment, etc.). Within this conceptual framework, then, the existence of brain mechanisms that actively generated sleep was not required [1].

This concept of sleep as a passive process was undermined by the following findings (i) sleep consists of an active cycling between ►nonREM and ►REM sleep, (ii) electrical stimulation of the midline thalamus or of the basal forebrain elicits sleep and (iii) brainstem transactions at the midpontine level or discrete lesions of the rostral hypothalamus cause chronic sleep suppression [2]. As will be described in this essay, the existence of neuronal mechanisms that function to actively generate and maintain sleep is now firmly established.

Sleep Generation Entails Coordinated Inhibition of Arousal Systems

During the past 50 years, researchers have focused on identifying specific neuronal groups and pathways in the brain that interact to generate arousal states. Multiple chemically-defined neuronal systems located in the brainstem and posterior hypothalamus function to promote both behavioral and electrographic aspects of arousal. These arousal systems include monoaminergic neurons in the rostral pons, midbrain and posterior hypothalamus, cholinergic neurons in the brainstem and basal forebrain, dopaminergic neurons in the ventral tegmentum and ►orexin - (hypocretin-) containing neurons in the lateral hypothalamus (Fig. 1) [3]. Most of these arousal systems are characterized by localized aggregations of cell bodies with long axonal projections that have widespread forebrain targets, including the thalamus, limbic system and neocortex (Fig. 1). Descending projections from the arousal systems (not all of which are shown in Fig. 1) regulate muscle tone and autonomic nervous system activity at the level of the brainstem and spinal cord.

The characterization of these neuronal groups as "arousal systems" is an over-simplification, as each regulates various aspects of waking brain function. However, the collective activity in these neuronal systems during waking imparts a tonic background level of arousal/activation that is reflected in low voltage, fast frequency cortical EEG patterns. Neuronal activity in these arousal systems is characterized by high levels of tonic or phasic discharge during ►waking behaviors, and comparative quiescence during sleep.



Sleep Generating Mechanisms. Figure 1 Ascending arousal systems in the brainstem and posterior hypothalamus. (a) Schematically depicted are (i) acetylcholine (Ach) neurons in the pedunculopontine and laterodorsal tegmental areas (PPT/LDT) and the basal forebrain (BF); (ii) noradrenergic (NE) neurons in the locus coreuleus (LC); (iii) serotonergic (5-HT) neurons in the dorsal raphe nucleus; (iv) histamine (HA) neurons in the tuberomammillary nucleus (TMN); (v) dopamine (DA) neurons in the substantia nigra and ventral tegemental area (SN/VTA). (b) Localization and projections of orexin neurons in the perifornical lateral hypothalamus From [3] with permission.

Some arousal systems (e.g., cholinergic) exhibit elevated discharge during waking and REM sleep and minimum activity during nonREM sleep. Others (e.g., the monoaminergic systems) display discharge rates during REM sleep that are as low or lower than that observed during nonREM sleep (so-called "►REM-off" discharge pattern) [3,4]. What is common to nearly all of the arousal systems schematized in Fig. 1, is a rapid decline in neuronal activity just prior to, or at the time of sleep onset.

A critical task, therefore, for brain mechanisms that generate sleep is to achieve a coordinated inhibition and/or disfacilitation of these disparate arousal-regulatory neuronal groups. There are three interrelated cellular and neurochemical mechanisms that accomplish this. First, is a system of neurons located in the preoptic hypothalamus that is activated during sleep and that exerts sleep-related inhibitory influences over several of the arousal systems through synaptic connectivity with these systems. Second, are endogenous sleep factors (e.g., adenosine) that exert inhibitory neuromodulatory effects on one or more arousal systems. Third, in all mammals, the timing of sleep and waking is controlled by the circadian clock in the brain. Thus, a third aspect of sleep generation involves regulation of the excitability of the arousal systems by the circadian clock in the ►suprachiasmatic nucleus of the hypothalamus.

Sleep Generating Neurons in the Preoptic Hypothalamus

The preoptic area of the hypothalamus was initially identified as a potential site of sleep generating mechanisms on the basis of stimulation and lesion studies. Electrical or chemical stimulation of this area can

acutely evoke sleep onset and experimental damage to the preoptic hypothalamus yields profound and persistent insomnia [4]. Recordings of neuronal activity during natural sleep and waking identify neurons in the preoptic area that display elevated discharge rates during nonREM and REM sleep compared to waking. The activity of these "sleep-active" neurons increases prior to sleep onset during waking to sleep transitions. The sleep-wake discharge pattern of these preoptic neurons is the reciprocal of the REM-off discharge pattern observed in several of the arousal systems [4].

In addition to single unit recordings, sleep-active neurons can be identified by immunostaining for the protein product of the *c-fos* gene. *c-fos* gene expression is a validated marker of neuronal activation. By comparing immunoreactivity for the c-Fos protein in the brains of animals that are predominately asleep or predominately awake during the 1–2 h prior to sacrifice, the anatomical distribution of sleep-active neurons in the brain can be determined. This approach identifies two subregions of the preoptic area in the rat that contain high densities of sleep-active neurons; the ►ventrolateral preoptic area (►VLPO) and the median preoptic nucleus (MnPN) [4,5]. Combined staining for sleep-related Fos protein and neurotransmitter makers reveals that most sleep-active neurons in the MnPN synthesize the inhibitory neurotransmitter GABA, and that sleep-active neurons in the VLPO contain both GABA and the inhibitory neuropeptide, galanin.

Mechanisms of sleep induction by preoptic area neurons entail GABA-mediated inhibition of multiple arousal systems. Anatomical studies demonstrate direct projections from the VLPO and MnPN to all of the ascending monoaminergic arousal systems and to the orexin neuronal system. Particularly dense are the projections from the VLPO to histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus (Fig. 1) [5]. The functional importance of this pathway is demonstrated by the ability of electrical stimulation of the VLPO to evoke GABA-mediated inhibitory postsynaptic potentials in histamine neurons. Activation of sleep-active neurons in the preoptic area by local thermal stimulation suppresses waking activity in serotonergic neurons in the dorsal raphe nucleus. Evidence also supports functional inhibition of orexin neurons by sleep-regulatory cells in the preoptic area. MnPN and VLPO neurons projecting to the orexin neuronal field in the lateral hypothalamus exhibit sleep-related c-Fos expression. Electrical or chemical activation of the MnPN evokes suppression of waking neuronal discharge in the lateral hypothalamus [4]. Collectively, findings support the hypothesis that deactivation of several functionally important arousal systems during sleep is due to GABA-mediated inhibition originating in the preoptic hypothalamus.

A mechanism that may help stabilize sleep-waking transitions arises from mutually inhibitory interactions between VLPO neurons and the monoaminergic arousal systems. VLPO neurons are inhibited by ►serotonin and noradrenalin. Thus, waking-related monoaminergic activity prevents inappropriate activation of VLPO sleep-generating cells during the active phase of an animal's day. At wake to sleep transitions during the rest phase, activation of VLPO neurons is reinforced by disinhibition as monoaminergic activity wanes. The mutual inhibitory interactions between sleep- and arousal-regulatory neurons function like a bi-stable switch (or flip-flop switch), and can help promote rapid and stable transitions between wakefulness and sleep [5].

GABAergic neurons in the preoptic area also participate in regulating homeostatic increases in sleep amount and sleep depth that occur as a consequence of sleep deprivation [4]. MnPN GABAergic neurons are progressively activated during a period of sleep deprivation, as sleep propensity (i.e., the tendency to fall asleep) increases. Activity of VLPO neurons is enhanced during recovery sleep following sleep deprivation.

Endogenous Sleep Factors

Humoral theories of sleep generation have a long history, and are appealing because the cycling between waking and sleep seems consistent with the waxing and waning of an endogenous sleep-regulatory substance [1]. The search for, and characterization of endogenous sleep factors remains an active area of contemporary sleep neurobiology [6]. Most candidate sleep factors are implicated in a key feature of sleep regulation, namely the homeostatic control of sleep. A defining feature of sleep in mammals is that deprivation or restriction of sleep is followed by increased sleep drive (sleepiness) and, when sleep is permitted, rebound increases in sleep amount and sleep depth. There is evidence that putative sleep factors such as adenosine (see below) accumulate during sustained waking and dissipate during recovery sleep, thereby contributing to homeostatic aspects of sleep regulation.

A large body of evidence supports a role for adenosine as a sleep generating neurochemical [6,7]. Acting through the A_1 receptor, adenosine has inhibitory effects on multiple neuronal types in several brain regions. Adenosine is a by product of brain metabolism, and AD levels are elevated in response to intense brain activation (e.g., seizures) and as a consequence of sustained waking. Sleep deprivation is accompanied by elevated adenosine levels in the basal forebrain, followed by a decline in these levels during recovery sleep [7]. Administration of A_1 adenosine receptor agonists promotes sleep and enhances EEG slow-wave activity. The stimulant, caffeine, is an A_1 receptor antagonist. Collectively, these findings impli-

cate adenosine in homeostatic sleep regulation. Sleep generating effects of adenosine entail A_1 receptor mediated inhibition of arousal systems, including basal forebrain cholinergic neurons and orexin neurons in the lateral hypothalamus. Adenosine may activate sleep regulatory neurons in the VLPO as well, due to A_1 receptor mediated disinhibition and to excitatory actions mediated by A_{2A} receptors.

While adenosine is arguably the most completely characterized putative sleep factor, other candidate substances are being actively investigated. Several cytokines, including, interleukin-1β and tumor necrosis factor-α, are sleep promoting and augment EEG slow-wave activity during sleep [6]. Antagonism of these cytokines can disrupt normal sleep and impair homeostatic responses to sleep deprivation. Cytokines are pivotal to the sleep enhancement that accompanies immune system activation and are implicated in normal sleep generation as well. Cellular mechanisms of cytokine-mediated sleep generation are not completely understood, but may involve a combination of arousal system inhibition and activation of preoptic sleep regulatory neurons. Additional candidate sleep factors include prostaglandin-D_2 and growth hormone releasing hormone [3,6].

The Suprachiasmatic Nucleus and Sleep Generation

As Borbely articulated in his two-process model 25 years ago [8], the generation of sleep is under both circadian and homeostatic control. Homeostatic pressure for sleep increases in proportion to prior time awake, but the circadian system regulates the timing of sleep, such that it is largely confined to the species-appropriate time of day. The cellular and neurochemical details of how the mammalian suprachiasmatic nucleus (SCN) interacts with sleep generating mechanisms are far from completely understood. The SCN may regulate the timing of sleep primarily through modulation of activity in one or more arousal systems [9]. Ablation of the SCN in primates, while eliminating free running circadian rhythms in rest and activity, causes a significant increase in daily total sleep time, suggestive of an arousal deficit. The intact SCN has few direct efferent projections to hypothalamic or brainstem arousal systems. SCN modulation of arousal systems may involve neurohormones, since transplantation of SCN tissue can restore rest-activity rhythms in rats with SCN ablation. A multisynaptic pathway, involving the hypothalamic subparaventricular zone and the dorsomedial hypothalamic nucleus (DMH), links the SCN with the orexin arousal system [9]. The final link in this pathway is an excitatory glutamatergic projection from the DMH to the orexin neurons in the lateral hypothalamus [9]. SCN influences on sleep generation may also entail inhibition of preoptic area neurons. GABAergic projections from the DMH to the VLPO could covey inhibitory effects from the SCN [9]. Direct SCN to VLPO pathways may also play a functional role. A recent finding in a horizontal hypothalamic slice preparation, demonstrates that electrical or chemical activation of the SCN evokes inhibition in VLPO neurons [10]. Thus, SCN control of the timing of sleep generation may involve a combination of excitatory modulation of the arousal systems and inhibition of VLPO neurons.

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Sleep Homeostasis

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Synonyms

Homeostatic regulation of sleep need; Pressure; Intensity; Debt; Propensity, or duration; Process S; Sleep recovery process

Definition

Homeostatic regulatory processes strive to maintain physiological variables constant or within an acceptable range thereby ensuring optimal functioning of the

organism. Sleep is thought of as a behavior that subserves a homeostatic process; a need or pressure for sleep accumulates during wakefulness and this need can only be alleviated efficiently during sleep. When sleep need exceeds optimal levels, such as occurs under conditions of sleep loss or sleep restriction, it negatively impacts cognitive performance and ultimately will lead to diminished health and well-being. The effects of sleep loss or sleep restriction can be countered by sleeping longer and/or by intensifying sleep. In particular, the observations that sleep time and/or intensity increase after sleep loss led to the notion that sleep is homeostatically regulated.

Characteristics

The concept of homeostasis was first formulated by the French physiologist Claude Bernard (1813–1878). He stated that the constancy of the internal environment ("*le milieu intérieur*") is the condition for "a free and independent life." The term homeostasis itself was later coined by the American physiologist Walter Cannon (1871–1945). Homeostatic regulation has been extensively documented for, e.g., blood glucose levels and body temperature. The physiology behind sensing and evaluating these variables, as well as how effector mechanisms are activated and act to counter deviations from "set-point," is well understood. Its application to sleep-wake regulation is, however, problematic for several reasons: (i) When describing sleep phenomenology at least three main processes have to be considered that all interact and of which the respective contributions sleep are difficult to separate in normal, daily life conditions. Thus a ►circadian process interacts with the homeostatic process enabling us to stay awake and alert throughout the day and to remain asleep through the night. A third regulatory process underlies the more or less rhythmic alternation between the two main sleep states [i.e., ►rapid-eye-movement (REM) sleep and ►non-REM (NREM) sleep] also known as the NREM-REM sleep cycle. (ii) Both sleep states can be said to be homeostatically regulated since deprivation of sleep leads to increases in the duration of both. However, the regulation of the duration of NREM sleep differs from that from of REM sleep. Furthermore, different aspects of one state, such as the duration and intensity of NREM sleep, are regulated differently. (iii) The regulated variable and the neuro-physiological function of sleep remain elusive which makes it difficult to study the homeostatic control circuitry of sleep. Consequently, most concepts of the homeostatic regulation of sleep have been based on behavioral and EEG studies. The search for the neuro-chemical, neuro-anatomical, and molecular-genetic substrates of sleep homeostasis is the focus of intense research in various organisms. Homeostatic regulation of sleep also has been observed in invertebrates. The fruit fly, in particular, provides a powerful model system to dissect the molecular-genetic underpinnings of sleep function.

The Homeostatic Regulation of NREM Sleep

In mammals, the homeostatic regulation of NREM sleep has been extensively studied and consists of changes in both duration and intensity. One widely used measure of NREM sleep intensity or depth that can be extracted from the electroencephalogram (EEG) is power in the delta frequency range (1–4 Hz). This measure is referred to as ►slow-wave activity (SWA) or ►EEG delta power and quantifies the prevalence and amplitude of slow waves that are characteristic of the NREM sleep EEG. When EEG slow waves are prevalent and SWA is high, arousal thresholds also are high (i.e., it is more difficult to awaken a subject) and sleep is more consolidated (i.e., less brief awakenings). SWA in NREM sleep typically declines over the course of the daily sleep period, increases as waking proceeds and is reduced after excess sleep. These changes in SWA are highly reliable and predictable and can be closely approximated through mathematical simulations. Because of this, much attention has been focused on this aspect of sleep and often the homeostatic regulation of sleep is equated with the sleep-wake dependent changes in SWA. These changes in SWA played a central role in the conceptualization of Alexander Borbély's ►two-process model of sleep regulation [1]. In this influential model a homeostatic process, "►Process S," reflected by SWA, in interaction with a circadian process, "►Process C," regulates the timing and intensity of NREM sleep. Many aspects of sleep regulation can be understood in the context of this model. Among those are the recovery from sleep deprivation, the dependence of sleep duration on circadian phase, sleep during shift work, sleep fragmentation during continuous bed rest, and ►internal desynchronization in the absence of time cues. That SWA can be used to index sleep need has been demonstrated in most, if not all mammalian species investigated to date.

Initially, the state of Process S was monitored only during NREM sleep by quantifying SWA. This measure is interpreted and used to index sleep need. In addition, it is thought that changes in SWA determine the efficiency with which sleep need is recovered during the sleep period. The initial part of the night during which NREM sleep SWA is high and rapidly declines, is therefore considered especially recuperative in terms of reducing the need for sleep. Suppressing EEG slow waves during this part of the night by presenting

acoustic stimuli (that did not awaken the subjects) led to a intra-night SWA rebound in the second, undisturbed half of the night indicating that the recovery process can be delayed and that the expression of EEG slow waves are functionally relevant. Meanwhile, EEG measures reflecting changes in sleep need have also been identified in the waking EEG.

Also the duration of NREM sleep is considered to be homeostatically regulated because increases in time spent in this state are observed after sleep deprivation (provided the experimental protocol allows for sleep extension). These "►rebounds" in NREM sleep duration are, however, usually less precise, depend on circadian phase at which sleep occurs, make up only a fraction of NREM sleep time lost, and can take place over a longer time span as compared to the immediate and highly predictable changes in SWA. Nevertheless, even small increases in NREM sleep duration can importantly affect SWA which poses the question of which aspect of sleep is homeostatically defended. Results of a sleep deprivation study in rats illustrate this issue. Twenty-four hours without sleep resulted in the expected and immediate increase in SWA that quickly subsided over the first 4 h of the recovery period. The duration of NREM sleep was also increased but this increase lasted for most of the 48 h for which recovery was monitored. As a result of the increase in NREM sleep time, SWA fell to values below those reached under baseline conditions (i.e., "►negative rebound"). Although both the positive and negative rebound in SWA in this study could be explained based on the altered sleep-wake distribution, the following question presents itself: If SWA indeed reflects sleep need then why should animals continue to sleep more (compared to baseline) when SWA is below baseline? The issue of the homeostatic regulation of NREM sleep time versus NREM intensity (i.e., SWA) is also relevant in the context of development; rats younger than 24-days old seem not yet able to compensate for sleep time lost by intensifying sleep and, in contrast to older rats, they compensate almost all of the sleep lost by sleeping more.

The Homeostatic Regulation of REM Sleep

Although EEG measures indicative of REMS intensity have been proposed, losses in REM sleep seem to be primarily compensated by increases in REM sleep time as has been observed after selective REM sleep deprivation or total sleep deprivation in a variety of mammalian species. In particular, several studies in rats, cats, and mice indicate that the REMS increase during recovery from REM sleep deprivation, varying in length from 1 to 24 h, is proportional to the loss incurred by that deprivation (for references see [2]). This suggests that the daily amount of REM sleep is accurately regulated in these species. Strong evidence for a homeostatic regulation of REM sleep in humans is less well established as usually only small and/or delayed rebounds have been reported. Based, in part, on these discrepancies among species, James Horne argued that REM sleep is a "default" state and as such its duration is not homeostatically regulated [3]. On the other hand, based on data obtained in rats, Allan Rechtschaffen went so far as to suggest that REM sleep is the only sleep state that is homeostatically defended [4].

The NREM-REM Sleep Cycle

Because both NREM and REM sleep seem homeostatically regulated, because their regulation differs, and because these two states greatly differ in many electro-physiological and neuro-chemical aspects, it is plausible to assume that they fulfill specific functions. During a sleep episode both NREM and REM sleep needs have to be fulfilled, an assumption supported by the observation that the two behaviors seem to compete for expression; i.e., a selective high pressure for one sleep state has repercussions for the expression of the other (reviewed in [2]). The alternation between NREM and REM sleep, i.e. the NREM–REMS cycle, can thus be viewed as a way "the system" ensures that the need for both behaviors is addressed efficiently within the circadian time frame allotted for sleep. The process underlying the more or less regular NREM–REMS alternation during sleep is thought to be a sleep-dependent oscillator; or, in other words, a homeostatic need to express REM sleep increases as a function of time spent in NREM sleep. Evidence for such need is based on the observation that the number of attempts to enter REM sleep increase as a function of the time-spent-asleep without REM sleep.

Homeostatic versus Circadian Processes

Apart from the homeostatic process ("Process S") that is activated by and counters the effects of sleep loss, an equally important, circadian process ("Process C") determines the time-of-day sleep preferably occurs. Their interaction is described in the two-process model [1] and the fine-tuned, opposing influence between the two enables us to stay awake and alert throughout the day and to remain asleep at night [5]. Despite this close interrelationship it is widely believed that the two processes operate independently. This notion is based on observations in animals that lost circadian rhythmicity, sleep deprivation still elicits an intact homeostatic response in sleep time and intensity. Moreover, in humans it has been demonstrated that the daily, sleep–wake dependent variation in SWA is little affected by

circadian factors. More recent observations challenge this notion and suggest a direct cross-talk between the two regulatory systems. Thus, sleep deprivation was found to affect the phase of circadian rhythms and high levels of SWA seem to suppress neuronal activity in the ►supra-chiasmatic nucleus (►SCN), the hypothalamic structure that contains the circadian pacemaker. Finally, animals that lack circadian rhythms through genetic lesioning (i.e., "knock-outs") of one or more core circadian clock genes, also have altered sleep homeostasis (reviewed in [6]).

Functional Considerations

After having established that sleep is homeostatically regulated the next obvious question to ask is what is being regulated or what function does sleep subserve. Given the complexity of sleep and its regulation it is likely that sleep fulfills more than one function. Several functions have been proposed over the years. Most have in common that sleep fulfills a function specifically benefiting the brain (*"Sleep is of the brain, by the brain, and for the brain!"*). This assertion is based on a variety of observations. Prominent among those are the facts that brain electrical and metabolic activity dramatically differs between NREM sleep and wakefulness, that falling asleep is associated with a loss of consciousness, that loss of sleep affects first and foremost cognitive performance, vigilance, and alertness, and that the variable that most reliably indexes the time-spent-awake and -asleep (i.e., SWA) is of cortical and thalamo-cortical origin.

The analysis of SWA reveals that sleep need is a local and use-dependent process [7,8]. SWA exhibits a frontal predominance both under baseline conditions, as well as after sleep deprivation. Local changes in SWA can be induced by engaging volunteers in tasks that activate specific brain areas. Thus vibration of one hand, which stimulates the somato-sensory cortex during wakefulness, leads to an increase in SWA in the contra-lateral sensorimotor cortex. Similarly, in rodents, regional activation of the barrel-cortex by unilateral whisker stimulation is followed by an increase of SWA in the stimulated cortex, specifically. Perhaps the most striking example of SWA's local and use-dependent aspects has been observed in the bottlenose dolphin. This mammal displays unilateral slow-wave sleep (NREM sleep with high SWA) and depriving one hemisphere of slow-wave sleep resulted in an increase in SWA in that hemisphere only. An extension of the use-dependent regulation of SWA is the association between local increases in SWA and the consolidation of particular forms of memory. The highly predictive sleep-wake dependent changes in SWA as observed in the EEG and its local and use-dependent nature gave rise to the notion that slow waves are closely linked to a recovery process that occur during NREM sleep and that this recovery is linked to the neuronal activation during wakefulness.

Neuronal activation during wakefulness is associated with synaptic rearrangement or strengthening at the level of individual neurons and/or at the level of brain micro-circuitry [7,8]. Extended periods of wakefulness would result in levels of synaptic weight that cannot be sustained or allow for further plastic events. The regular hyperpolarizing-depolarizing membrane potentials that underlie slow waves and/or associated changes in growth factors may reverse the detrimental effects of wakefulness on synaptic weight and brain micro-circuitry. Through such mechanisms SWA could restore performance and plasticity for the subsequent wake episode. Such detailed account on the hypothetical restorative function of SWA are still lacking for the other homeostatically regulated aspects (i.e., duration of NREM sleep and of REM sleep).

Molecular and Genetic Correlates

SWA and its regulation by the duration of wakefulness are under genetic control. The dynamics of the sleep homeostatic process in mice were found to differ with genetic background and a QTL (Quantitative-Trait Locus) region on chromosome 13 was identified that could explain 50% of the variance in this trait between two inbred strains of mice (reviewed in [9]). In humans, a polymorphism in the circadian ►clock gene *Period-3* has been show to affect SWA and waking performance. Previously, studies in mice had demonstrated that the clock genes ►*Cryptochrome-1* and *-2*, ►*Bmal1*, ►*Clock*, and *Npas2* affect expression and regulation of SWA and NREM sleep (reviewed in [6]). The involvement of genes that play a key role in the generation of circadian rhythms in the regulation on SWA and NREM sleep seems at odds with the notion that the sleep homeostatic process and the circadian timing system are considered separate processes (see above). These results also demonstrate that genetic factors contribute to the considerable individual differences observed in the expression and regulation of SWA.

With the development of the techniques that allow for high-throughput assessment of gene expression; i.e., "microarrays," (►microarray, DNA Chip) genome-wide expression profiling has been performed to investigate which genes change their expression with time-spent-awake or -asleep. Instead of focusing on individual genes such approach allows for the identification of pathways that are activated with sleep loss. Stress-induced transcripts such as heat-shock proteins, genes encoding molecules involved in synaptic plasticity, and, more general, genes coding for enzymes involved in biosynthesis were found to change expression with sleep and waking in the few available studies. Progress on high-throughput techniques to investigate changes in proteins levels is being made

and preliminary studies using these techniques in sleep research have been published (see [9] for review).

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Sleep Inertia

Definition

Interval of reduced alertness, cognitive performance impairment, grogginess, and tendency to return to sleep, which occurs immediately after awakening. The impairment from sleep inertia is normally mild and short-lived (less than half an hour), and is believed to be affected by the structure of the prior sleep period (non-REM sleep and rapid eye movement (REM) sleep amounts), the sleep stage from which awakening occurs, and the timing of the awakening relative to the circadian cycle. The magnitude and duration of sleep inertia are enhanced by prior sleep loss, such that the effect may become as substantial as the cognitive impairment normally seen after a night of total sleep deprivation and may take up to 2 h to dissipate.

►Alertness Level
►Circadian Cycle
►Non-REM Sleep
►Rapid Eye Movement (REM) Sleep

Sleep Movement Disorders

►Sleep – Motor Changes

Sleep-onset Mechanisms

►Sleep Generating Mechanisms

Sleep-onset REM Period

Definition

Abnormally rapid transition from wakefulness to REM sleep, skipping the period of non-REM sleep that normally characterizes the beginning of the sleep period. Sleep-onset REM periods (SOREMs) are a symptom of narcolepsy and as such can be considered in the diagnosis of this disorder.

►Alertness Level
►Non-REM Sleep
►Rapid Eye Movement (REM) Sleep

Sleep Paralysis

Definition

Sleep Paralysis is an inability to move occurring either at sleep onset or upon awakening from sleep. Episodes last a few minutes and are usually accompanied by intense feelings of fear and/or anxiety. Isolated sleep paralysis can occur in up to 25% of healthy, normal individuals and may be precipitated by sleep deprivation. Sleep paralysis is more commonly found in patients with narcolepsy.

►Narcolepsy
►Sleep Generating Mechanisms

Sleep Phylogeny

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Definition

►Sleep phylogeny refers to the variation in the nature and amount of sleep across species.

Characteristics

A primary motivation for the study of sleep in various animals is to gain some insight into the function(s) of sleep. What aspects of sleep, if any, are present in all mammals? What aspects of sleep differ between animals? Why are there two kinds of sleep, ►REM sleep and ►nonREM sleep?

The amount and nature of sleep are correlated with age, body size and ecological variables, including life in the terrestrial vs. aquatic environment, diet and the safety of the sleeping site. The sleep phylogeny literature suggests that sleep reduces activity to the amount needed for feeding and species reproduction, and maximizes energy conservation, thereby furthering genetic survival. Theories of REM sleep function have suggested that in addition to these functions, this state may have a role in periodic brain activation during sleep, in localized brain and body recuperative processes and in emotional regulation.

Sleep Studies in Terrestrial Mammals

Daily sleep amounts vary substantially throughout the mammalian class. Some animals, such as bats and opossums, sleep for 18–20 h/day, whereas others, such as the elephant and giraffe, sleep as little as 3–4 h/day. One might expect that species in each mammalian order would have a similar pattern of sleep because of their defining genetic, behavioral, and anatomical similarities. However, this is not the case. Primates as a group (or carnivores as a group, or rodents as a group) do not have a characteristic sleep duration. Sleep time in these various orders overlaps extensively and any "order related" contribution to sleep duration must be small relative to other factors [1]. Human sleep does not appear to be quantitatively unique in its duration or in the proportion or absolute amount of REM sleep.

Daily sleep amounts are highest in carnivores, lower in omnivores, and lowest in herbivores. Sleep time is inversely correlated with body mass in herbivores. This correlation is responsible for a significant overall correlation between body mass and sleep time over all mammals studied to date [1].

Most studies of mammalian sleep have been performed on placental (eutherian) or marsupial mammals. The third subclass of mammals is the monotremes, found in Australia and New Guinea. These egg-laying mammals have more genetic and physiological similarities to reptiles and birds than do other mammals and are thought to have more characteristics of the common mammalian ancestor. Both the echidna and platypus show evidence of ►brainstem activation during sleep, with the platypus displaying intense rapid eye, limb, and bill movements periodically during sleep. However, the low voltage neocortical EEG typically seen in placental and marsupial mammals during REM sleep is not consistently present during sleep in either the echidna or platypus during these motor activities. Instead the neocortical EEG may resemble that of nonREM sleep [2,3]. Thus, these "primitive" mammals appear to have a form of REM sleep largely localized to the brainstem.

Sleep in Marine Mammals

All terrestrial mammals show relatively high voltage low frequency (slow) neocortical electrical brain waves (EEG) bilaterally during the behavioral state that is recognized as nonREM sleep. In contrast, cetaceans (whales and dolphins) almost never have high voltage slow waves in both hemispheres at the same time. The eye contralateral to the hemisphere with slow waves is almost always closed while the other eye is almost always open. There have been no published reports documenting REM sleep in cetaceans, making them the only studied mammals in which this state has not been observed.

The bottlenose dolphin (*Tursiops truncatus*), when not floating or resting on the bottom, generally swims in a single direction (usually counterclockwise) even as the brain hemisphere with slow waves alternates. Some smaller cetacean species are rarely, if ever, immobile, moving and avoiding obstacles 24 h a day from birth until death, even during unihemispheric slow wave activity; these animals may never exhibit the immobility that is used in terrestrial mammals to define the state of sleep [4].

Postpartum Sleep Behavior in Cetaceans

Further evidence for the unique properties of "sleep" in cetaceans are the phenomena of a near absence of sleep behavior in neonates and a postpartum reduction of sleep behavior in their mothers [5]. All studied terrestrial mammals have shown minimal activity and maximal total sleep and REM sleep amounts at birth, with sleep gradually decreasing and activity gradually increasing to adult levels as the animals grow to maturity. This is not the pattern in cetaceans. Killer whales (*Orcinus orca*) and dolphins have minimal amounts of sleep behavior (i.e., immobility or eye

closure) at birth, with sleep behavior slowly increasing to adult levels over a period of months. This minimal amount of sleep behavior occurs during the period of most rapid growth of body and brain for the newborn, during a period of bonding to the mother and learning how to nurse, find food, avoid predators, and swim efficiently. The continuous activity of cetaceans has adaptive value in allowing the neonate, which is much less insulated by body fat than the adults, to thermoregulate in cold ocean water. The suppression of sleep behavior also allows the neonate to swim with and be protected by its mother during development. As the animal gains mass and blubber and approaches adult size, adult-like "sleep" or rest behavior, including periods of immobility, emerges. Both mother and calf go without substantial amounts of immobility and without substantial amounts of the eye closure linked to unihemispheric slow waves during the postpartum period. Keeping rats awake for comparable periods is lethal. Neither cetacean mother nor calf show any rebound increase in the amount of sleep behavior following this period.

Neocortical Activity and Sleep

Although neocortical EEG changes are the most easily observed electrical correlate of nonREM sleep, as they are recordable from scalp electrodes in humans and from electrodes placed on the surface of the cortex in other animals, sleep produces large changes in the rates and patterns of neuronal activity in nearly all brain regions. Cortical EEG phenomena are controlled by and reflect activity in thalamic, hypothalamic and brainstem reticular regions. The cellular activity changes underlying the changes in neocortical EEG include calcium fluxes into and hyperpolarization of neocortical and thalamic neurons that are synchronized in large populations, producing high voltage brain waves. But neocortical size does not correlate positively with sleep amount. Both total brain weight and encephalization correlate poorly and negatively with total nonREM and REM sleep amounts [1]. The elephant, which has the largest neocortex of any terrestrial mammal, has one of the smallest sleep amounts. Conversely, the rat and the platypus, which have smooth cortices with small total neocortical volumes, have extremely large amounts of nonREM and REM sleep, with the platypus having more REM sleep than any other animal studied to date [3].

Although neocortical size does not appear to be a major determinant of either nonREM or REM sleep amounts, recent work has indicated that neocortical activity during sleep may be altered by prior waking activity. Some such changes dissipate with continued ►waking, suggesting that localized recuperative processes may occur during either waking or sleep in systems projecting to, or within, the neocortex.

Sleep may be adaptive because it conserves energy and suppresses behavior across portions of the ►circadian cycle, just as ►hibernation does across certain seasons. Large herbivores may have evolved reduced sleep amounts because they are more vulnerable to predators than small herbivores. A second hypothesis is that these grazing animals may need to spend more time awake in order to eat, because of the low caloric density of their food. A complementary hypothesis is that small herbivores and other mammals may need to maximize sleep amounts in order to conserve energy, because their relatively high surface area to body mass ratio makes it costly to maintain their body temperature, but retreating to a warm, protected nest may minimize this cost. A striking feature of sleep in animals with small daily sleep amounts, such as many herbivores, is that sleep depth, as judged by EEG and sensory response threshold, appears to be less than that in animals requiring more sleep; i.e., animals with reduced sleep amounts do not appear to "make up" for reduced sleep by sleeping more "deeply."

Energy conservation may be particularly important in newborns. Their high surface area to body mass ratio and need for rapid growth makes the energy conservation achieved by sleep highly adaptive. Furthermore, animals that are immature at birth benefit from the sleep-induced reduction in exposure to danger. When body size increases and sensory-motor systems mature, young animals derive greater benefits from waking activities and can begin to defend themselves, consistent with the developmental decrease in sleep time.

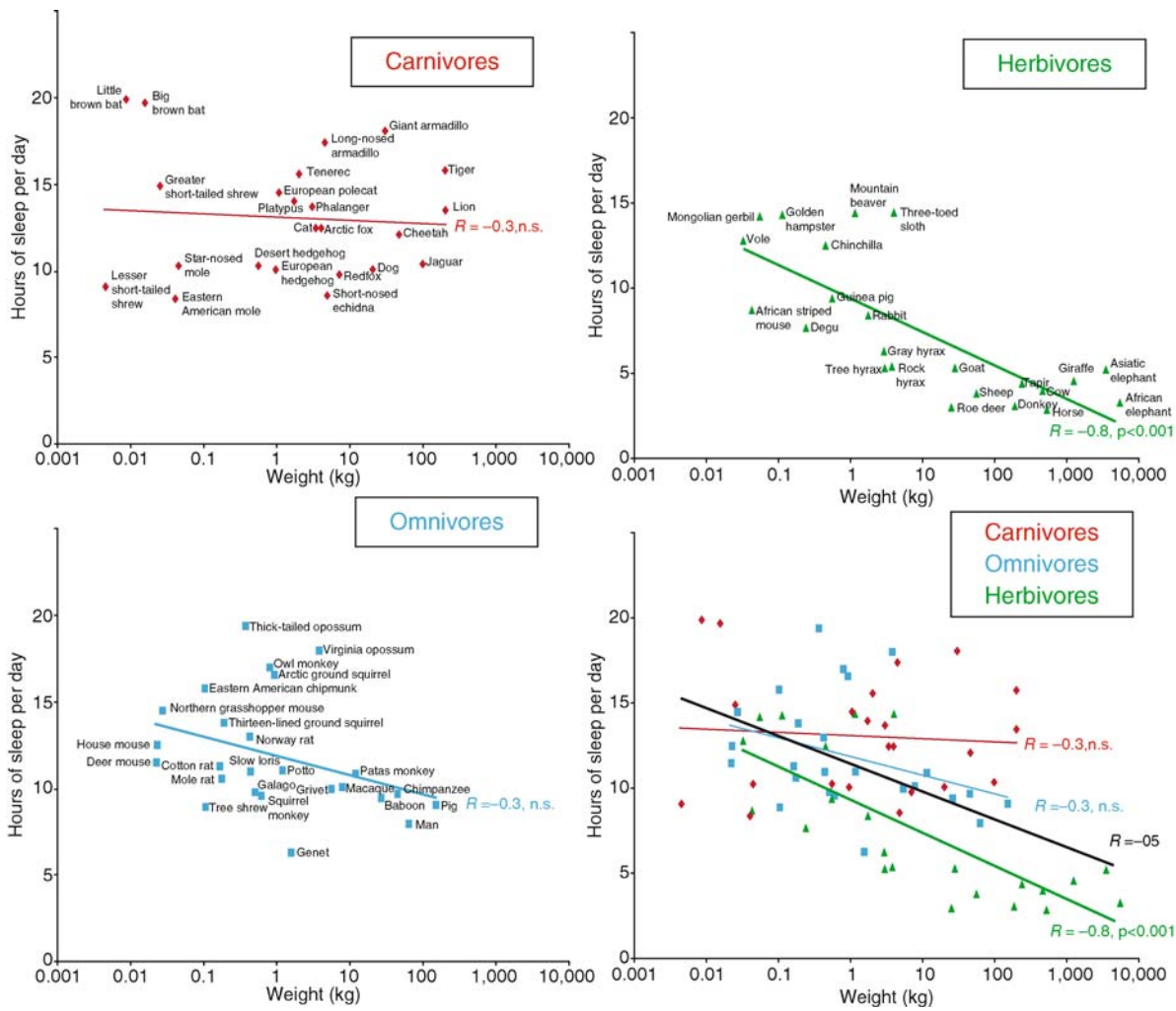
Body Mass, Metabolism and Sleep Control

One of the best established relations in mammalian biology is the inverse relationship between body mass and mass specific metabolic rate. Small animals have high metabolic rates per gram of weight; large animals have low metabolic rates. Brain metabolic rate is correlated with body metabolic rate. Elevated metabolism is linked to a number of biochemical changes, several of which have been linked to sleep control.

Sleep time may be related to defense against oxidative stress. A high metabolic rate results in the generation of high levels of reactive oxygen species (ROS) by mitochondria. This ROS generation has been linked to normal aging. Sleep deprivation in the rat is accompanied by indications of increased oxidative stress and evidence of membrane disruption in the hippocampus, subcortical brain regions and peripheral tissues [6–8]. There appear to be no such changes in the neocortex [7,9]. Higher brain metabolic rates may require longer periods of sleep to interrupt ROS induced damage to brain cells, facilitate the synthesis and activities of molecules that protect brain cells from oxidative stress, allow sufficient time for the repair or replacement of essential cellular components in neurons and glia, and deal with other biochemical consequences of ►waking metabolic activity.

One may hypothesize that the "ratio" of the energy conservation benefit of sleep to the waking metabolic activity-derived need for sleep for brain recuperation varies across species. Carnivores and omnivores, which tend to have more sleep than predicted on the basis of body mass, may make more use of the energy conservation aspects of sleep; their generally safe sleep places and their ability to eat meals with high caloric density may make continuous activity unnecessary. In such a situation, genetic fitness might best be served by energy conservation, which would reduce the need for hunting, aid nurturing of the young, speed development and generally aid in reproductive success.

Protein synthesis in the brain is increased during ►slow wave sleep. New neurons are generated in adult animals in the olfactory bulb, the subventricular zone lining the lateral ventricles, and in the subgranular cell layer of the dentate gyrus of the hippocampus, in a process that produces functional neurons in 3–4 weeks. It has been shown that this neurogenesis is facilitated by exercise and blocked by stress. Short term (2–3 day) total sleep deprivation, even done when controlling for other forms of stress, also blocks subsequent neurogenesis in the dentate gyrus [10]. Thus, sleep may have a general role in allowing or facilitating neurogenesis.



Sleep Phylogeny. Figure 1 Sleep time in mammals: Carnivores are in *red*, herbivores in *green* and omnivores in *blue*. Sleep times in carnivores, omnivores and herbivores significantly differ ($p < 0.0002$, F test, df 2, 68), with carnivore sleep amounts significantly greater than those of herbivores ($p < 0.001$, t test, df 24, 22). Sleep amount is an inverse function of body mass over all terrestrial mammals (*black line*). This function accounts for approximately 25% of the interspecies variance in reported sleep amounts (Regression of log weight against sleep amount, $R = -0.5$, $p < 0.0001$, $N = 71$). Herbivores are responsible for this relation, since body mass and sleep time were significantly and inversely correlated in herbivores ($R = -0.77$, $p < 0.001$, df 24), but were not in carnivores ($R = -0.28$, df 24) or omnivores ($R = -0.25$, df 25).

REM Sleep

REM sleep amount is positively correlated with total sleep amount and negatively correlated with body weight. However, if one statistically controls for body weight or brain weight, REM sleep amount is most strongly correlated with immaturity at birth [1]. Altricial animals, those that are immature at birth, tend to have more REM sleep than animals that are mature at birth, or precocial. This tendency is marked in the neonatal period. But perhaps more remarkable is that altricial mammals continue to have more REM sleep as adults. The platypus has 8 h of REM sleep per day as an adult. The platypus neonate cannot thermoregulate, locomote, acquire food or defend itself at birth, and lives attached to its mother. The ferret, likewise, is immature at birth and the adult has over 6 h of REM sleep per day. In contrast, the guinea pig has only 1 h of REM sleep per day as an adult. The guinea pig is born with teeth, claws, fur and eyes open; it thermoregulates at birth, locomotes within an hour of birth and eats solid food within a day of birth. Similarly, the sheep and giraffe are relatively mature at birth and have little REM sleep (less than one h/day) at maturity [1]. The extremely high levels of REM sleep seen at birth, followed by a slow decrease to adult levels in altricial terrestrial animals, must be an important clue to its function. This time course, combined with the observation that neuronal activity levels are high in REM sleep, led to the hypothesis that this sleep state is involved in the development of the brain.

Dolphins, which can be continuously mobile while having unihemispheric slow waves must have continuous brainstem activity to control this movement, since the brainstem is the final path for motor control. This contrasts with the situation in land mammals, all of which have bilateral slow waves and immobility during sleep and greatly reduced brainstem activity. The absence or reduction of REM sleep in marine mammals displaying unihemispheric slow waves supports the hypothesis that the stimulation of brainstem activating systems is an important function of REM sleep. Similarly, the manifestation of REM sleep in monotremes as a largely brainstem state, without marked neocortical activation, suggests that REM sleep may have evolved as a state of brainstem activation, with cortical stimulation functions added later in evolution. The cold-induced increase in REM-sleep amount in the isolated brainstem, the increased REM-sleep amount at the minimum of the circadian brain, and body temperature cycles and the increase in the temperatures of brain regions during REM sleep are consistent with this brainstem activation hypothesis.

Concluding Paragraph

The nature and duration of sleep are important factors in determining genetic fitness. In sleep, animals realize benefits from reducing energy expenditure, confining behaviors to periods when it is most efficient to find food, avoiding predators and tending to their young. The expression of sleep varies across animals with some being able to sleep deeply and for long durations and others who cannot sleep in safe places evolving to be somewhat responsive for 24 h aday (Fig. 1). Several species are able to greatly reduce sleep time during the postpartum period and during long migrations. Sleep is best viewed as an adaptive state, furthering survival. REM sleep appears to have originated as a brainstem state providing periodic activation of this vital region. In most placental mammals this activation also includes forebrain regions, with increased brain metabolism and neuronal activity. It has been suggested that REM sleep helps maintain neural function during sleep and prepares the brain for rapid awakening [11].

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Sleep Rebound

Definition

Sleep rebound is a term used to describe the increase of a sleep variable above normal (or baseline) levels after a period of sleep restriction or deprivation. Rebounds have been observed for many aspects of sleep (e.g.

electroencephalographic (EEG) delta power, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep duration) and are interpreted as an effort to compensate for the incurred loss of sleep and as proof that sleep is homeostatically regulated. Such initial (positive) rebounds can be followed by subsequent negative rebounds when variables reach below-baseline levels as has been documented for EEG delta power.

►Electroencephalography
►Non-REM Sleep
►Rapid Eye Movement (REM) Sleep

Sleep Recovery Process

►Sleep Homeostasis

Sleep-regulating Mechanisms

►Sleep Generating Mechanisms

Sleep Spindles

Definition

Sleep-related electroencephalographic (EEG) events characterized by 1–2 s burst of nearly sinusoidal 12–15 Hz activity. There is a waxing and waning of amplitude across the duration of the event, giving it a characteristic "spindle" shape. During transitions from waking to stable sleep, sleep spindles are among the first EEG events to appear that exhibit high intra- and inter-hemispheric coherence. Sleep spindles are a defining feature of Stage 2 nonREM sleep in humans.

►Electroencephalography
►Sleep Generating Mechanisms

Sleep States

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Synonyms

Vigilance states; Arousal states

Definition

Sleep states refer to distinct constellations of physiological, behavioral and neurological variables that alternate with wakefulness and are periodically expressed during the 24-h day. The primary defining features of sleep across the animal kingdom include (i) an increase in arousal thresholds; (ii) stereotyped behaviors (e.g., sleep postures, sustained quiescence, avoidance of sensory stimulation); and (iii) homeostatic regulation. Subsidiary features of sleep that are found in some species include (i) changes in autonomic/endocrine function; (ii) alterations in brain rhythms; and (iii) strong circadian regulation [1,2].

Characteristics

Sleep is one of several core behaviors that, like feeding, drinking and reproduction appears to be ubiquitous among higher organisms. It is considered an appetitive behavior vital for life because a need for sleep accumulates in its absence, and prolonged sleep loss is fatal in vertebrate and invertebrate species [3]. In placental mammals and birds, sleep is divided into two principal states of non-rapid-eye-movement (non-REM) and REM (or "►paradoxical") ►sleep. ►REM sleep, however, is not typically observed in reptiles and amphibians or invertebrates which instead display a single sleep state that behaviorally resembles mammalian ►non-REM sleep [1,2]. In most species, sleep is regulated by distinct homeostatic and circadian mechanisms. The homeostat governs the accumulation and compensatory discharge of sleep need; a process commonly detected by increases in sleep time and intensity following extended wakefulness. In contrast, the biological clock provides signals that offset the accumulation of sleep need and influences sleep onset and arousal [4].

Human Sleep

The mammalian states of non-REM and REM sleep can be further divided into sub-stages that are entered and exited in an orderly fashion across the major rest (or inactive) phase. In humans, sleep is entered through non-REM sleep which progresses from "light" to "deep" stages. Each stage is accompanied by a rise in arousal thresholds and characteristic changes in brain

rhythms that reflect increasing levels of neuronal hyperpolarization [5]. These include thalamocortical spindles, a slow neocortical wave, and delta waves. Non-REM sleep is also accompanied by a slowing of respiration and heart rate, a drop in core temperature and a peak in growth hormone secretion [3–5]. The descent into stage 4 sleep is followed by periodic ascents into REM sleep. REM sleep is characterized by several peculiar neurological and physiological changes including paralysis of skeletal muscles, REMs, a "waking"-like electroencephalogram (EEG), suppression of monoaminergic neurotransmission and irregular patterns of respiration and heart rate. REM sleep is sometimes further divided into sub-stages which refer to periods with or without phasic events (e.g. REMs). In healthy humans, approximately 4–5 NREM-REM cycles occur during the night [5].

Phylogenic Studies of Sleep States

The basic properties of sleep observed in humans are also observed in placental and marsupial mammals and birds [1,2]. There are however, important differences as the amounts of total sleep and/or REM sleep vary among different species and the distinct sub-stages of sleep typical of humans are not always observed. In addition, endocrine changes observed in humans are not always detected in other mammals and REM sleep is accompanied by certain types of brain activity (e.g., hippocampal theta rhythms and pontine-geniculate-occipital waves) that may not occur in humans [1,2]. Birds are also quite peculiar in that REM sleep amounts represent a much smaller fraction of total sleep time in comparison to mammals [1].

Sleep has also been studied in several non-mammalian vertebrates, including lizards, snakes, crocodiles, turtles, frogs and salamanders [1,2]. In these species, a state that exhibits the primary features of sleep has been observed, but no convincing signs of REM sleep have been reported. Moreover, the brain rhythms typical of mammalian sleep are absent and instead sleep is accompanied by bursts of neuronal activity that appear as a train of unitary spikes in the EEG. In other cases a slow oscillation is occasionally observed that bears some resemblance to the mammalian slow wave. Similar phenomena are reported during sleep in terrestrial invertebrates (insects and arachnids) [2,6]. Overall, however, neurophysiological changes in sleep in these species are not as distinct as those reported in mammals and birds. This may reflect the fact that these species lack the neurological structures necessary for the generation of mammalian brain rhythms.

Ontogenetic Studies of Sleep States

There are dramatic changes in sleep expression and regulation across the lifespan [7]. These can be summarized as follows. First, recordings of EEG and autonomic activities in very young, developing mammals do not reveal clear signs of REM and non-REM sleep, reflecting the extreme immaturity of the nervous system. Second, once sleep emerges its amounts are very high and then decline with subsequent development. In mammals, these changes are predominantly due to an initial abundance of REM sleep, which is progressively replaced by non-REM sleep. Sleep amounts eventually stabilize by early adult-hood at which time REM sleep and "deep" non-REM sleep begin to slowly decline, reaching their nadir in senescence [5]. A similar pattern has been reported in fruit flies, where newly hatched flies have much more sleep than adult flies [6]. Third, circadian regulation and homeostatic regulation are quite different in early life. Infant animals do not respond to sleep loss as adults do and circadian rhythms are absent until a certain stage of development [7].

Sleep State Mechanisms

Non-REM and REM sleep are generated by distinct neural circuits and brain regions. Although the precise mechanisms have not been completely determined, there is consensus that non-REM sleep is generated by hypothalamic and forebrain regions whereas REM sleep is chiefly controlled by brainstem circuits [8]. The forebrain contains populations of neurons that secrete the inhibitory neurotransmitter GABA onto other neurons important in maintaining arousal. The hypothalamus contains several nuclei (e.g. the ►VLPO) that induce sleep when stimulated or in some cases, when warmed (i.e., are temperature sensitive) [9]. These nuclei secrete the inhibitory neuropeptide Galinin onto posterior hypothalamic structures also important in arousal [10]. Within the brainstem are regions that when stimulated produce REM sleep in its entirety, or separate components of REM sleep. These regions include cholinoceptive neurons and glutamatergic and GABAergic circuits. Stable state expression appears to be controlled by the peptide hypocretin/►orexin because in its absence the normal alternation of sleep and wakefulness is highly disturbed (e.g., in ►narcolepsy) [9,10].

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Sleep-Wake Autonomic Regulation

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Synonyms

Sleep-wake modulation of visceral function

Definition

Across the ►sleep-wake cycle, functions of the viscera (internal organs) are modulated together with those of the soma (body) in an integral manner. Visceral functions (involving smooth muscles of blood vessels, bronchi, gastrointestinal tract and glands) are generally regulated in an automatic or involuntary manner by the autonomic nervous system. In contrast, somatic functions (involving the skeletal muscles) can be controlled in a voluntary manner through input from the brain to the somatic motor neurons. The autonomic nervous system serves to maintain ►homeostasis (constant state) of the internal milieu, including blood pressure, O_2/CO_2 concentrations, osmolarity and sugar, while responding to metabolic needs for energy within the organism. In this process, it regulates the cardiovascular, respiratory, endocrine and digestive systems. These in turn also allow the maintenance of a relatively constant body temperature and associated basal metabolism in mammals and birds. The autonomic nervous system controls these systems through its two reciprocally functioning components: the sympathetic and the parasympathetic. Generally, the sympathetic system supports action of the somatic system by catabolism and mobilization of energy stores to increase energy supply to the skeletal muscles for movement. In contrast, the parasympathetic system functions during rest of the somatic system and is responsible for anabolism and restoration of energy stores. Across sleep-wake states, the sympathetic and parasympathetic systems assume different levels of control and activity such that sleep-wake cycles, as well as their ►circadian organization, permit periods of maximal action during wake and periods of maximal rest during sleep for long term homeostasis of the organism.

There are three distinct states in mammals and birds: ►wake (W), ►slow wave sleep (SWS) and ►paradoxical sleep (PS) or ►rapid eye movement sleep (REMS). Through these states, homeostasis is maintained within an appropriate range of physiological parameters by afferent feedback from receptors and efferent adjustments through the sympathetic or parasympathetic systems. During W, autonomic regulation depends upon behavior, foraging, fighting, fleeing, breeding or eating and resting. During SWS, it is predominated by the parasympathetic division which supports rest and restoration. During PS or REMS, despite continued parasympathetic activity, storms of sympathetic activity occur. Moreover, whereas feedback control is generally robustly exerted during W and SWS, it is blocked or dampened during PS or REMS. This state is called "paradoxical," since despite inactivity and maximal rest in the somatic postural muscles, phasic bursts of activity occur in the somatic eye, facial and distal flexor muscles in the form of twitches and in the cardiovascular system in the form of blood pressure surges. This phasic activity is similar to bursts of somatic and sympathetic activities which can occur during waking behaviors and thus could reflect ►dreaming activity.

Characteristics

Autonomic regulation occurs in an integrated manner across multiple peripheral systems and in parallel with somatic systems across sleep-wake states due to coordination by the central nervous system [1–3]. Nonetheless, the regulation of those systems across states can be most easily considered for each system, including principally cardiovascular [4,5], respiratory [6,7], thermal [8], endocrine [9] and digestive [10] regulatory systems.

Cardiovascular Regulation

Heart rate and blood pressure as well as circulation are regulated during waking by the autonomic nervous system, such that they respond to the demands of activity to be high, stimulated by adrenergic sympathetic input, during walking or running, for example, and attenuated to be low by cholinergic parasympathetic input, during

resting. These autonomic responses occur in parallel with voluntary commands to the somatic system in association with different behaviors. For running, for example, excitation of particular sympathetic ganglia and inhibition of parasympathetic ganglia would stimulate an increase in heart rate and blood pressure and be responsible for an increase in blood flow to the skeletal muscles and decrease in blood flow to the viscera. Adjustments also occur as a function of feedback, positive and negative, to the central nervous system. Thus, a drop in blood pressure upon standing stimulates a compensatory increase in blood pressure through the sympathetic outflow to the heart and major arteries. Excessive increases in blood pressure on the other hand can evoke negative feedback to decrease pressure by inhibiting the sympathetic and exciting the parasympathetic outflow. Cardiovascular regulation during waking is thus a function of behavior and feedback control mechanisms that allow a physiological range of values for action while maintaining healthy homeostasis. An active waking state is stimulated and maintained by ►arousal systems in the brain which in turn promote activity in both the somatic and sympathetic motor systems. Of these, central noradrenaline (NA)-containing ►locus coeruleus (LC) neurons and ►orexin/hypocretin (Orx/Hcrt)-containing hypothalamic neurons are known to excite somatic motor and sympathetic (preganglionic) motor neurons, such that movement and activity are supported by increased cardiovascular function and appropriate circulation.

During SWS, heart rate and blood pressure are on average lower than during waking. It is a state of rest for the body and brain. The sympathetic input to the heart and blood vessels is dampened or silent. The parasympathetic input predominates. Sleep is generated by neural systems in the brain which act to dampen central arousal systems and promote peripheral parasympathetic activity. Of these, neurons in the solitary tract nucleus and surrounding region of the medulla, where vagal afferent and efferent fibers arrive and emerge, have the capacity to promote SWS by central projections, while also evoking decreases in heart rate and blood pressure through peripheral vagus outflow. This circuit can be reflexively triggered by extreme increases in blood pressure that by baroceptor feedback propagate a vagal-mediated drop in blood pressure and an associated loss of consciousness and muscle tone, or syncope. Neurons in the basal forebrain and ►preoptic area also promote sleep along with parasympathetic changes in heart rate and blood pressure, as evidenced by the effects of electrical stimulation of these regions.

During PS or REMS, heart rate and blood pressure are irregular and manifest sudden surges upon relatively low base levels continuing from SWS. These surges are caused by sudden increases in sympathetic nerve activity upon a background of more continuous parasympathetic activity. Interestingly, blood vessels to skeletal postural muscles are constricted by sympathetic nerve activity, whereas blood vessels to the viscera and genitals are dilated by inhibition of sympathetic nerve activity, indicating differential sympathetic control and resulting circulation during this state. PS is promoted in the ►brainstem by discharge of cholinergic neurons in the pontomesencephalic tegmentum while other neurons of the arousal systems, importantly the NA and Orx/Hcrt neurons, are silent. The cessation of activity in the latter neurons results in a disfacilitation of sympathetic as well as somatic motor neurons. Particular GABAergic and glycinergic neurons are additionally responsible for tonic inhibition of the somatic postural motor neurons. At the same time, other glutamatergic reticulo-spinal neurons discharge in phasic bursts, stimulating rapid eye movements and twitches of facial and distal flexor somatic motor neurons. Such phasic excitation is presumably also transmitted in parallel to certain sympathetic (preganglionic) motor neurons in the spinal cord to stimulate blood pressure surges and tachycardia.

Respiratory Regulation

During ►waking, respiration is regulated as a function of activity and the corresponding need for oxygen uptake and carbon dioxide dissipation. With increasing use of muscles stimulated by locomotion, for example, respiration is increased. This response involves both the somatic and visceral motor systems; the diaphragm and intercostal muscles are striate muscles and under voluntary control through somatic motor neurons for breathing, and the bronchial dilator muscles are smooth muscles and under involuntary control of the autonomic nervous system. There is also feedback control through the vagus which stimulates respiration in response to changes in oxygen or carbon dioxide. During active wakefulness, arousal systems in the brain facilitate respiratory motor neurons in the spinal cord for increased ventilation and excite preganglionic sympathetic neurons to dilate the bronchial muscles for greater gaseous exchange in the lungs. There is also a facilitatory influence upon the respiratory rhythmic pattern generator neurons in the medulla. On the other hand, some behaviors can be associated with voluntary breath control and holding that can override to a certain extent the rhythm pattern generator and feedback control.

During SWS, respiration is rhythmic and slow. Feedback mechanisms function to increase rate in response to changes in oxygen or carbon dioxide, although the threshold for this response is slightly higher.

During PS or REMS, respiration can be irregular, somewhat like it can be during waking, particularly during periods of phasic twitches and rapid eye movements. In parallel with the atonia of the postural

muscles, there is also a relative loss of tone in the muscles of the air passages. And there is a relative inhibition of sensory-motor reflexes in the visceral as in the somatic systems, such that the threshold for arousal and increased ventilation with decreasing oxygen and increasing carbon dioxide concentrations in the blood is greatly increased. For these reasons, PS can be associated with relative hypoxia and hypercapnia. In normal animals or humans on the other hand, this state is perhaps not entirely different from certain waking periods in association with particular behaviors and thus might reflect dreaming activity.

Thermal Regulation

In most mammals and birds, body temperature is maintained in a fairly narrow range. For this purpose, energy is expended and thus metabolism increased for warming the body in cold ambient temperatures or for cooling the body in hot ambient temperatures. These regulatory changes are effected through the somatic and autonomic nervous systems which by integral adjustments stimulate changes in behavior and physiological processes. These include included adoption of heat conserving postures (curled), shivering, cutaneous vasoconstriction and shallow breathing for warming in cool environments or adoption of heat dissipating postures (outstretched), cutaneous vasodilatation, sweating and panting for cooling in warm environments. All of these mechanisms function through feedback control during waking behaviors. Generally, increases in somatic motor activity are associated with increases in metabolic rate and temperature up to a point at which cooling mechanisms are activated. The regulatory centers and neurons for temperature sensing and adjustment are in the ►hypothalamus and preoptic area where they overlap with sleep-wake promoting systems.

During SWS, body and brain temperature along with metabolism are lower than during waking due not simply to reduced activity, but also to a change in the thermostatic set point of the thermal regulatory system. A thermal regulatory posture is adopted in SWS which is thus dependent upon the ambient temperature, curled in cold or outstretched in hot environments. Other autonomic adjustments to changing temperatures also function as during waking, however at a lower body temperature. In fact with the onset of sleep, cutaneous vasodilatation occurs and is associated with cooling of the body and brain by ~1° or so during SWS. These changes are promoted by warm-sensitive, sleep promoting neurons in the preoptic area.

During PS or REM sleep, thermal regulatory systems do not function in the same way they do in most periods of waking or SWS. The feedback circuits are closed and somatic along with many sympathetic motor neurons are inhibited, so that shivering or sweating cannot be induced during PS by changes in ambient temperature. On the other hand, given surface and muscle vasoconstriction and visceral vasodilatation (above), core body temperature is well conserved during PS and brain temperature actually increases along with the increases in activity and metabolism that occur in the brain during this state.

Endocrine Regulation

Through multiple endocrine systems, which release various hormones into blood and body fluids to act on target cells in different organs, metabolism and temperature along with many functions of the body and organism are kept within a healthy range. Collectively, they maintain the nutrient, mineral and water fluxes of the internal milieu and also serve special functions for growth and reproduction. These hormonal systems are in turn regulated by the autonomic and central nervous systems. Several important hormones show sleep-wake, as well as circadian, changes or regulation in their release. The corticosteroids, cortisol in humans, which mobilize energy stores for catabolism to support increased metabolism for activity, are maximal in association with or anticipation of waking periods, starting in the early morning for humans, and minimal during sleep, particularly SWS in the first part of the night for humans. Conversely, release of growth hormone and prolactin, which mobilize energy stores for restorative protein synthesis and growth, is maximal during SWS in the first part of the night for humans. In hydromineral regulatory systems, plasma renin which stimulates through angiotensin, retention of sodium and water by the kidney, increases during periods of SWS in response to SWS-associated decreases in blood pressure and volume. ►Melatonin is high throughout the night, but is absent in daytime.

Digestive Regulation

Digestion is obviously a function of eating, which is done during waking, but the gastrointestinal system and associated endocrine systems are regulated across the sleep-wake cycle as well. Digestion is controlled by the enteric nervous system, which is influenced by the autonomic nervous system but can also function almost independently in the process of digestion, particularly digestive peristalsis. Nonetheless, the parasympathetic system is importantly involved in the secretion of digestive juices, including saliva and gastric acid, and in visceral motility. Selective and reciprocal changes in sympathetic and parasympathetic components are also responsible for diverting circulation from the skeletal muscles to the smooth muscles of the viscera to support gastrointestinal activity. Similarly, the parasympathetic system through ►acetylcholine stimulates insulin release from the beta cells, whereas the sympathetic through noradrenaline inhibits insulin release from the beta cells and stimulates glucagon release from the alpha

cells of the pancreas. Insulin promotes uptake of glucose and its storage as ►glycogen in liver and muscle cells. Glucagon prevents these and stimulates glycogenolysis for mobilization and use of glucose. Thus during waking, dependent upon consumption of a meal, the parasympathetic system stimulates digestion and an anabolic state of replenishing energy stores during periods of rest, whereas the sympathetic system inhibits digestion and promotes a catabolic state of energy mobilization and expenditure during motor activity.

During SWS as during rest, when the parasympathetic system predominates, digestion of food can continue. Generally, however, food is digested prior to sleep onset, and digestive activity is relatively quiescent during sleep. Nonetheless, gastric acid secretion continues. Insulin release is quite high during the night in humans. Insulin release is highest in the early part of the night during SWS when growth hormone release is also high, rendering this period and state of rest a maximal anabolic state, since the release of insulin together with growth hormone would stimulate uptake of amino acids and protein synthesis in multiple tissues.

Relatively little is known concerning changes in digestive or metabolic processes during PS or REMS, relative to SWS. However, given the storms of sympathetic activity that occur during PS, many digestive and hormonal processes can be differentially affected during this state.

Summary of Physiological Regulation Across Sleep-Wake States

During waking, homeostatic processes involving positive and negative feedback maintain the body in a relatively balanced state while permitting activity to modulate various systems within a healthy range. Under conditions of high activity involving locomotion, fight or flight, central arousal systems activate both somatic and sympathetic motor systems. These systems are also activated by hunger and promotion of food seeking behaviors. Blood pressure, heart rate, blood supply to muscles, respiratory rate, temperature, cortisol and glucagon release are all increased for supply of energy in these catabolic states. At the same time, blood supply to the viscera, digestive processes, growth hormone, prolactin and insulin release are all decreased and energy storage thus prevented. Following consumption of a meal, an anabolic state of rest usually follows during which the sympathetic nervous system is inhibited and the parasympathetic nervous system activated. This condition allows for digestion by facilitation of gastrointestinal activity along with secretion of acid and digestive juices. Release of insulin is stimulated and promotes uptake of glucose and replenishment of fuel stores.

SWS also is a state of rest but one which allows maximal rest and restoration of fuel stores. This anabolic state is characterized by somatic inactivity and a predominance of parasympathetic activity in the periphery, centrally promoted by sleep promoting systems in the brainstem and preoptic area. Blood pressure, heart rate, respiration, body temperature and basal metabolism along with corticosteroid release are all at their lowest levels. Digestive processes are relatively quiescent as digestion of food has usually been completed. On the other hand, insulin is high along with growth hormone and prolactin release which collectively stimulate amino acid uptake and protein synthesis for repair and growth along with replenishment of energy stores in multiple tissues. SWS is thus an anabolic state allowing for large homeostatic adjustments in all physiological systems for reestablishing and maintaining balance in energy stores and a healthy condition of tissue in adult organisms, as well as growth in immature organisms.

PS or REMS is truly a "paradoxical" state since it is also an anabolic state of sleep and continued rest for the antigravity skeletal muscles, yet is a catabolic state with high activity for the brain and some rapid or twitching muscles, along with the sympathetic nervous system through which surges in heart rate, blood pressure, and respiration occur. During this state, the feedback mechanisms which are fundamental to homeostasis are inhibited, such that cardiovascular, respiratory and thermal regulation are blunted. Such changes may reflect conditions which can also occur with active behaviors during waking and thus dream activity or processes during this "paradoxical" state.

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Sleep-Wake Cycle

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Synonyms

Sleep-wake rhythms; Wake-sleep cycle

Definition

The rhythmic alternation between two behavioral states: sleep and wakefulness. The rhythmic regulation of the alternation between these two states usually refers to rhythms with a circadian period.

Characteristics

Sleep and the Sleep-Wake Cycle

The defining behavioral characteristics of sleep that are used to identify sleep in many animals are: (i) a species-specific posture; (ii) reduced responsiveness to external stimuli; (iii) rebound after deprivation see [1].

The assessment of a species-specific posture requires around-the-clock behavioral observations. In most species, sleep will be accompanied by behavioral quiescence. In some species, such as dolphins, sleep verified by electrophysiological recordings has been observed while the animal is behaving.

Variation in responsiveness across putative sleep and wake states can be assessed by quantification of arousal thresholds for standardized tactile, auditory, or other stimuli. Animals can be deprived from sleep by continuous stimulation through handling or engagement of the animal in activities such as exploration or forced locomotor activity. A rebound of the putative sleep state after a period of deprivation is indicative of homeostatic regulation of sleep and is considered a characteristic that differentiates between a simple circadian rhythm and a homeostatically regulated state.

NREM and REM Sleep

In mammals and birds sleep can be subdivided in two very different sleep states: ►non-rapid-eye movement (NREM) sleep and ►rapid-eye movement sleep (REM) see [1,2]. The two states are identified by simultaneous recording of the ►electroencephalogram (EEG), the electroculogram (EOG) and muscle tone (►electromyogram, EMG). NREM sleep is characterized by low frequency, high amplitude EEG patterns and absence of rapid eye movements. In mammals, ►sleep spindles and slow waves (also referred to as ►slow-wave activity, SWA, or delta waves) are defining EEG characteristics of NREM sleep. In humans, NREM sleep is subdivided in stages 1–4 which contain progressively more SWA. During REM sleep, the EEG patterns resemble those of quiet wakefulness, while at the same time rapid eye movements and atonia in skeletal muscles are observed. The major neuromodulatory systems, including the noradrenergic, serotonergic, histaminergic, cholinergic, and orexinergic systems, are implicated in the alternation between the three vigilance states, NREM, REM and wakefulness. NREM and REM sleep alternate with an ►ultradian periodicity within the sleep episode. The period of this ultradian rhythm varies both within and between species and is proportional to brain size. The ultradian rhythm in REM sleep is generated by the reciprocal interaction of neuronal populations in the upper brain stem and hypothalamus.

Homeostatic Regulation of Sleep and its Function

When animals are provided with *ad libitum* sleep opportunity following a period of enforced wakefulness, i.e., total ►sleep deprivation, an increase in sleep is observed see [3–5]. In mammals, total sleep deprivation leads to an increase in total sleep time, an increase in SWA in NREM sleep and an increase in REM sleep time. Selective deprivation of REM sleep is followed by an increase in REM sleep, and selective deprivation of ►slow-wave sleep (SWS) or SWA leads to a selective enhancement of SWA. SWA in NREM is under strict homeostatic control and mathematical models describing its dependence on the sleep-wake history are available for rats and humans. SWA is also affected by specific experiences during wakefulness, such as explorative behavior, intense somatosensory stimulation and learning. This accurate control of SWA has led to the hypothesis that slow waves are an important aspect of sleep and that they reverse non-specific detrimental effects of wakefulness on the central nervous system. Current hypotheses on the function of sleep for the central nervous system

emphasize the role of SWS in reversing the increase in synaptic strength and the role of both REM and NREM sleep in consolidation of procedural and declarative memories.

Circadian Regulation of Sleep

In nocturnal species such as rats and mice, wakefulness predominates during the night and sleep during the day see [6–9]. In ►diurnal species, such as humans and fruit flies, wakefulness occurs primarily during the day and sleep at night. This association between the ►light-dark cycle and the predominance of sleep is, in itself, not sufficient to conclude that it is regulated by endogenous circadian rhythms. Involvement of circadian process in the regulation of sleep can be ascertained by quantifying its occurrence while the organism is studied under constant environmental conditions, i.e., in the absence of rhythmic variations in variables such as light and temperature. If sleep and wakefulness are not uniformly distributed but the probability of their occurrence varies with a periodicity in the circadian range, then it is safe to assume that circadian processes are involved.

In all species in which sleep has been identified, circadian processes play a role in its regulation. In mammals the role of circadian processes has been studied by ablation of the ►suprachiasmatic nuclei (SCN) of the hypothalamus, which are the locus of the ►pacemaker driving circadian rhythms in physiology and behavior. SCN lesions abolish neither the occurrence of sleep, nor its homeostatic regulation. Although specific aspects of sleep structure, such as REM sleep, and EEG phenomena, such as ►sleep spindles, are modulated by circadian processes, the circadian regulation of sleep primarily concerns its timing. Whereas in the intact animal the distribution of sleep and wakefulness is circadian, in the SCN-lesioned animals sleep and wakefulness are distributed uniformly across the 24 h period. The SCN exert its influence on sleep through indirect projections via the dorsal medial hypothalamus to areas involved in the generation of sleep and wakefulness which are located in the hypothalamus, the thalamus and the brainstem. The SCN also modulate sleep propensity through their influence on the circadian rhythms in other variables, such as body temperature and the pineal hormone ►melatonin.

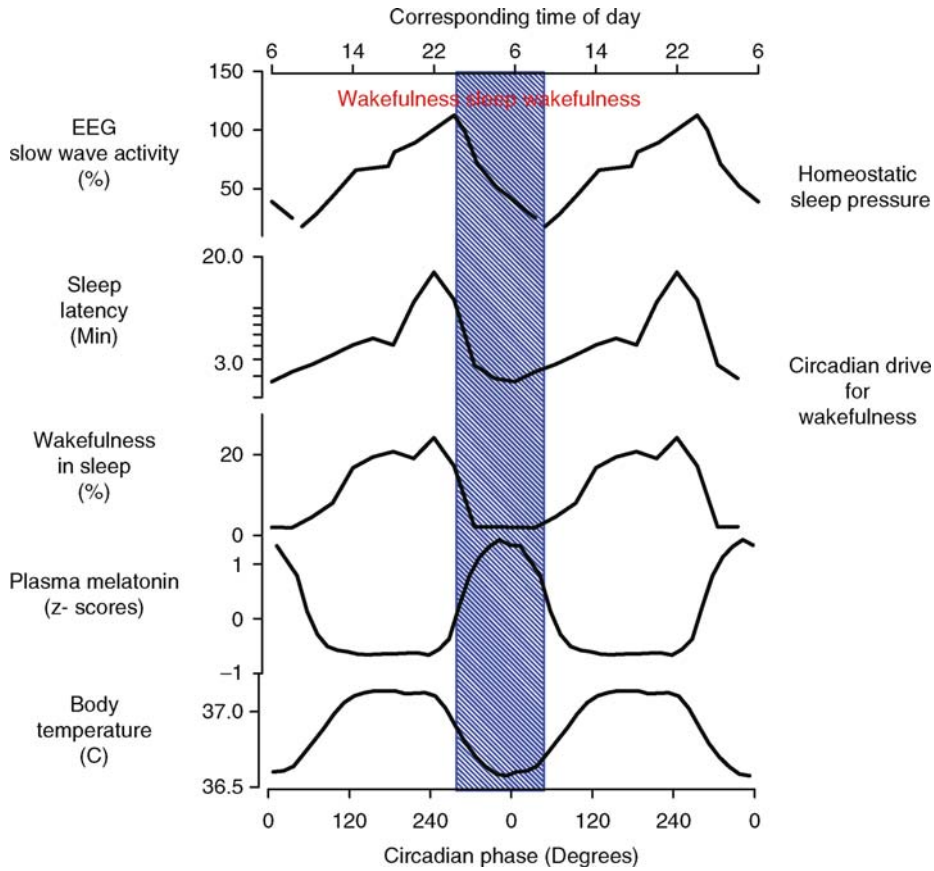
Alterations of some of the core ►clock genes involved in the generation of circadian process do not abolish sleep or the homeostatic response to sleep loss but lead to modifications in total sleep time, sleep structure and the homeostatic regulation of sleep in animals and humans. For example, in mice devoid of the *Cry1* and *Cry 2* genes, EEG SWA, which is a primary marker of sleep homeostasis, is enhanced and total sleep time is increased. In humans, a polymorphism in the *PER3* gene is associated with an enhancement of SWA in NREM sleep, and theta and alpha activity in the EEG in wakefulness and REM sleep.

Interaction of the Homeostatic and Circadian Regulation of Sleep-Wake Cycles in Humans

The interaction of sleep regulatory and circadian processes has been studied in detail in humans see [6,10]. Early experiments by Aschoff and Wever in Germany and Czeisler and Weitzman in the US established that the human sleep-wake cycle persists with a near 24-h period in the absence of an externally imposed light-dark or clock time cycles. These observations demonstrated the endogenous circadian nature of the ►sleep-wake cycle also in humans. Furthermore, both research groups reported that the sleep-wake cycle can dissociate from the endogenous circadian rhythms of other variables, such as core body temperature and urine volume. This phenomenon, which was called spontaneous ►desynchrony, demonstrates that the sleep-wake cycle is generated by the interaction of two oscillatory processes, which in the two-process model of sleep regulation are referred to as a circadian and a homeostatic ►oscillator.

According to this standard model, the circadian oscillator regulates the preferred timing of sleep and the homeostatic oscillator tracks sleep debt, which increases during wakefulness and dissipates during sleep. The deep circadian oscillator is synchronized to the 24-h geophysical cycles primarily through circadian variation in its sensitivity to ocular light exposure. The mechanisms underlying the synchronization between the homeostatic and circadian oscillator are not well understood. Under normal, entrained conditions, when we are active during the day, and sleep at night, the two oscillators are in synchrony.

Desynchrony between the two oscillators occurs during ►shift work and ►jet-lag and has been induced in the laboratory in forced-desynchrony experiments. Under these conditions the circadian oscillator can be tracked by the rhythm of melatonin, and has been shown to oscillate with a period of approximately 24.2 h. Circadian wake propensity, as assessed by the latency to sleep onset (Fig. 1b), or the intrusion of wakefulness in scheduled sleep episode (Fig. 1c), is greatest just prior to the onset of nocturnal melatonin secretion, which under entrained conditions occurs at approximately 22:00 h (Fig. 1d). Circadian sleep propensity is strongest at the nadir of the core body temperature rhythm, which in healthy individuals is located at approximately 06:00 h (Fig. 1e). The homeostatic oscillator can be tracked by slow EEG oscillations in the sleep and wake EEG. Homeostatic sleep pressure increases during the waking day (Fig. 1a), in parallel to the increase in the circadian drive for wakefulness and declines during the nocturnal sleep episode, in parallel to the increase in the circadian



Sleep-Wake Cycle. Figure 1 Circadian and homeostatic regulation of sleep and wakefulness in humans. Panel A: Increase of homeostatic sleep pressure during wakefulness and its dissipation during sleep as reflected in EEG SWA during daytime naps and nocturnal sleep. Circadian variation in wake/sleep propensity as reflected in the latency to sleep onset (Panel B) after 18 h:40 min of wakefulness and wakefulness (Panel C) in sleep opportunities, measured during forced desynchrony of the sleep-wake cycle and endogenous circadian rhythms of melatonin (Panel D) and core body temperature (Panel E).

drive for sleep. It is through these opposing homeostatic and circadian processes that the sleep-wake cycle remains consolidated when the two oscillators are sycnchronized during ►entrainment. During disruption of this desynchrony, as occurs during shift work, jet lag and in circadian sleep disorders, sleep consolidation and waking performance are compromised.

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Sleep-Wake Mechanisms

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Synonyms

Sleep-wake neurochemical substrates

Definition

Mechanisms comprising the neural systems and their neurotransmitters which generate the three major states of mammals: wake (W), slow wave sleep (SWS) and paradoxical sleep (PS) or rapid eye movement sleep (REMS).

Characteristics

The sleep-wake mechanisms comprise the neural systems and their neurotransmitters which generate the three major states of mammals: ►wake (W), ►slow wave sleep (SWS) and ►paradoxical sleep (PS) or ►rapid eye movement sleep (REMS) (see Fig. 1). W is a behaviorally active and responsive state with phasic and tonic activity on the electromyogram (EMG) recorded from the postural muscles, and fast activity (gamma, 30–60 Hz) on the electroencephalogram (EEG) recorded from the cerebral cortex. SWS is a behaviorally quiet state with low muscle tone on the EMG and large slow waves (delta, 0.5–4 Hz) on the EEG. PS or REMS is a "paradoxical" state because it is characterized by muscle atonia on the EMG of the axial postural muscles, yet by rapid eye movements and small twitches of the facial and distal flexor muscles. It is also characterized behaviorally by a lack of responsiveness, typical of sleep, yet by fast (gamma) activity on the EEG, typical of cortical activation and W.

The neural systems generating these states are located through the ►brainstem, hypothalamus and basal forebrain (BF) and give rise to either descending projections to the spinal cord, by which they influence movement and muscle tone (recorded on the EMG), or ascending projections to the cerebral cortex, by which they influence cortical activity (recorded on the EEG) (see Fig. 1).

The different neural systems utilize different chemical neurotransmitters, which include most importantly: ►glutamate (Glu), GABA, ►acetylcholine (ACh), noradrenaline (NA), ►histamine (HA) and ►orexin (►Orx or ►hypocretin, ►Hcrt) (see Fig. 1). Since except for Glu and GABA, these chemicals serve as neuromodulators upon specific receptors on specific cells, they can generate specific states or the specific EMG or EEG activities of those states.

Specific neural groups with particular projections and neurotransmitters discharge during particular states or in association with particular EMG or EEG activities of those states such as to exert their influence in a state selective and determining manner (see Fig. 1).

Neural Systems and Their Neurochemical Substrates

Arousal Systems

The Reticular Formation (RF) and Glutamate (Glu)

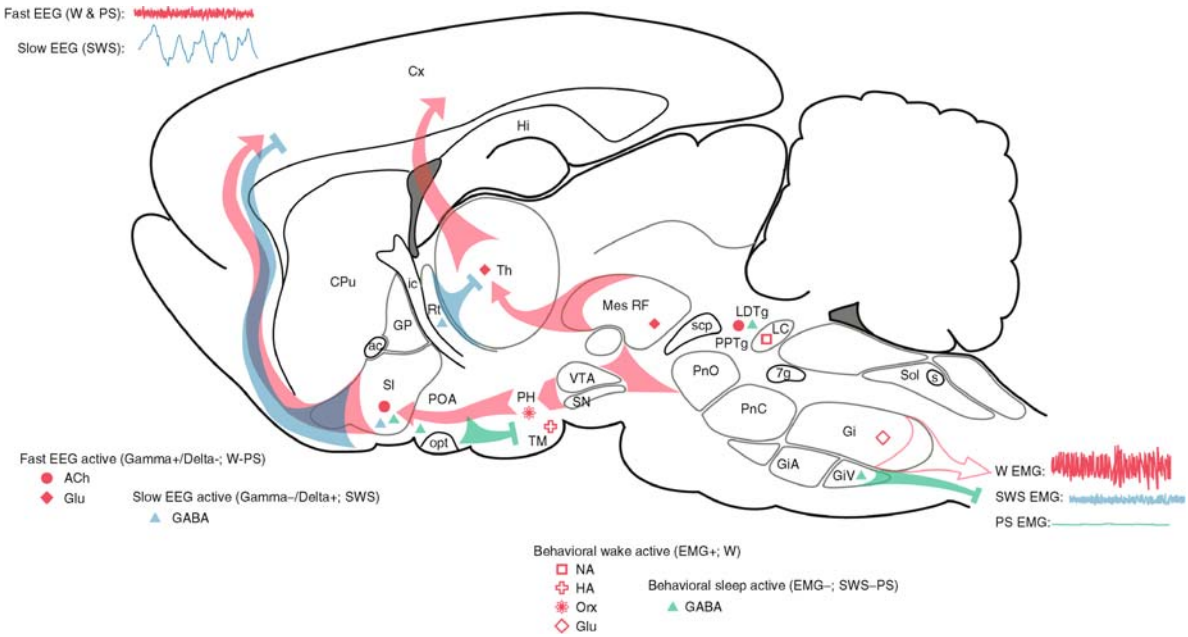
Since the early studies of Moruzzi and Magoun, it has been known that the RF, which is a netlike web of cells and passing fibers in the brainstem, is essential for the ►maintenance of wakefulness, as its destruction by large lesions results in a comatose state [2]. Neurons of the RF give rise to descending projections into the spinal cord by which they influence movement and muscle tone or to ascending projections into the forebrain by which they influence through other relays, cortical activity (see Fig. 1). Through a dorsal pathway, the RF neurons project onto midline and intralaminar neurons in the thalamus, which project in turn in a widespread manner to the cerebral cortex, as the nonspecific thalamo-cortical projection system. Through a ventral pathway, the RF neurons project to and through the hypothalamus and up to the BF from where other neurons also project in turn in a widespread manner to the cerebral cortex, as the basalo-cortical projection system.

Most projection neurons in the RF likely utilize Glu as a neurotransmitter and would accordingly excite their target neurons in the spinal cord or forebrain (Fig. 1).

Neurons in the caudal pontine and medullary RF with predominantly descending projections discharge maximally during waking and in association with movement and muscle tone. Those more concentrated in the oral pontine and mesencephalic RF with predominantly ascending projections discharge maximally during waking and in association with cortical activation. Collectively, these RF neurons stimulate and maintain by their activity and release of Glu, behavioral ►arousal with muscle tone and cortical activation.

Cortical Activation and Acetylcholine (ACh)

From very early studies, ACh has been known to play a very important role in cortical activation [1–3]. Drugs which enhance or mimic cholinergic transmission, such as physostigmine and nicotine, enhance cortical activation, whereas those which block ACh receptors, such as atropine, diminish fast cortical activity, which is replaced by slow wave activity. Interestingly, however, blocking cortical activation with atropine does not prevent movement or behavioral arousal and so produces a dissociation between cortical activity and behavior. Moreover, ACh release from the cortex is high in association with cortical activation during both W and PS. And, injections of the cholinergic agonist,



Sleep-Wake Mechanisms. Figure 1 Sleep-wake state neurochemical substrates. Sagittal schematic view of the rat brain depicting neurons with their chemical neurotransmitters and pathways by which they influence cortical activity or behavior across the sleep/wake cycle. Wake (W) is characterized by fast gamma activity on the cortical EEG (upper left) and high postural muscle tone on the neck EMG (lower right); slow wave sleep (SWS) by slow delta EEG and low tone on the EMG; and paradoxical sleep (PS) by fast gamma EEG and atonia on the EMG. Neurons which are active during waking (red symbols) include cells with ascending projections toward the cortex which stimulate fast cortical activity and cells with descending projections toward the spinal cord which stimulate postural muscle tone and behavioral waking. Those with predominantly ascending projections discharge in association with fast EEG activity (gamma+) and cease firing with delta activity (delta−) to be active during both W and PS (filled red symbols); they include cholinergic (ACh) and glutamatergic (Glu) neurons. Those with more diffuse or descending projections discharge in association with behavioral arousal and EMG activity (EMG+) and cease firing with muscle atonia to be active during W and silent during PS (empty red symbols); they include noradrenergic (NA), histaminergic (HA), orexinergic (Orx) and some putative glutamatergic (Glu) neurons. Neurons which are active during sleep (blue and aqua symbols) include cells with ascending projections toward the cortex which dampen fast cortical activity and those with descending projections toward the brainstem and spinal cord which diminish behavioral arousal and muscle tone. Those with projections to the cortex discharge in association with slow EEG activity (gamma−/delta+) during SWS (blue triangles) and include certain GABAergic neurons in the basal forebrain (BF) and preoptic area. Also shown are GABAergic neurons of the nucleus reticularis in the thalamus that discharge in bursts with sleep spindles and slow waves to inhibit and pace thalamocortical relay neurons. In the BF and preoptic area, presumed GABAergic neurons with descending projections increase their firing as muscle tone progressively decreases (EMG−) during SWS and PS (aqua symbols). Also shown are GABAergic (and/or glycinergic) neurons in the ventral medulla that project directly to the spinal cord where they could inhibit neck and other motor neurons during sleep. Abbreviations: *7g*, genu 7th nerve; *ac*, anterior commissure; *ACh*, acetylcholine; *CPu*, caudate putamen; *Cx*, cortex; *EEG*, electroencephalogram; *EMG*, electromyogram; *Gi*, gigantocellular RF; *GiA*, gigantocellular, alpha part RF; *GiV*, gigantocellular, ventral part RF; *GP*, globus pallidus; *Hi*, hippocampus; *ic*, internal capsule; *LC*, locus coeruleus nucleus; *LDTg*, laterodorsal tegmental nucleus; *Mes RF*, mesencephalic RF; *NA*, noradrenaline; *opt*, optic tract; *PH*, posterior hypothalamus; *PnC*, pontine, caudal part RF; *PnO*, pontine, oral part RF; *POA*, preoptic area; *PPTg*, pedunculopontine tegmental nucleus; *PS*, paradoxical sleep; *RF*, reticular formation; *Rt*, reticularis nucleus of the thalamus; *s*, solitary tract; *scp*, superior cerebellar peduncle; *SI*, substantia innominata; *SN*, substantia nigra; *Sol*, solitary tract nucleus; *SWS*, slow wave sleep; *Th*, thalamus; *TM*, tuberomammillary nucleus; *VTA*, ventral tegmental area (Modified from [1]).

carbachol into the brain and particularly into the oral pontine RF produce a state with cortical activation in association with muscle atonia or the state of PS. ACh and cholinergic neurons thus elicit cortical activation in the presence or absence of behavioral arousal and thus likely stimulate cognitive processes during both W and PS. They may even elicit attenuation of movement or muscle tone along with attentive immobility during waking or with dreaming during PS.

Cholinergic neurons are located in the brainstem, where they are clustered in the dorsolateral pontomesencephalic tegmentum within the laterodorsal and pedunculopontine tegmental nuclei (LDT and PPT). The LDT and PPT neurons project locally into the brainstem RF and rostrally to the thalamus, hypothalamus and BF. ACh excites thalamo-cortical projection neurons to promote their tonic discharge and thus to promote through them, fast cortical activity or cortical activation [4]. Cholinergic neurons are also located in the BF, where they comprise the magnocellular basal nucleus of Meynert within the substantia innominata (SI, see Fig. 1). In the rat brain, they are distributed as well within the magnocellular preoptic nucleus (MCPO), nucleus of the diagonal band of Broca (DBB) and medial septum (MS). Collectively, the BF cholinergic neurons innervate all of the neocortex and hippocampus. ACh excites pyramidal cells in the cortex and thus promotes therein fast cortical activity while blocking slow wave activity [4].

Immunohistochemically identified cholinergic neurons have to date only been recorded in the BF. The BF ACh cells discharge in association with fast cortical activity (gamma+/delta−) during W and PS (as W-PS active cells) (see Fig. 1). Presumed cholinergic neurons in the LDT and PPT discharge in a similar manner. They can thus collectively stimulate cortical activation during both W and PS.

Behavioral Arousal, Noradrenaline (NA) and Dopamine (DA)

The catecholamines, NA and DA have been known to stimulate arousal since early pharmacological studies [2,3,5]. Amphetamine, which releases both NA and DA, evokes prolonged wakefulness characterized by cortical activation and behavioral arousal.

NA-containing neurons are located in the brainstem and clustered in the ►locus coeruleus (LC) in the pons (see Fig. 1). The LC neurons give rise to highly diffuse projections. They project into the brainstem and spinal cord and directly innervate and excite motor neurons. They project into forebrain subcortical relay stations of the thalamus, hypothalamus and BF and also directly up to the cerebral cortex. In the thalamus, NA excites the thalamo-cortical projection neurons and in the BF, it excites the cholinergic basalo-cortical neurons. In the cortex, it also excites pyramidal cells to stimulate fast cortical activity [4]. When NA neurons discharge and NA is released, they would thus stimulate both behavioral arousal and cortical activation. LC neurons discharge selectively during waking and at highest rates during active waking. They decrease and cease firing during SWS and PS.

DA-containing neurons are located in the diencephalon and mesencephalon, being most numerous in the substantia nigra (SN) and ventral tegmental area (VTA). The latter cell groups project into the forebrain, particularly the striatum, amygdala, BF and prefrontal cortex. Both through pharmacological studies and clinical studies of Parkinson's patients, suffering from degeneration of DA neurons, DA is known to play an important role in movement. However, their influence in this domain occurs through forebrain centers, including limbic structures and thus by promoting movement but not directly stimulating it through action upon motor neurons. Given its release by many addictive drugs, DA is also known to be positively rewarding. Upon recording, presumed DA neurons were surprisingly found to discharge during waking and sleep, although in different patterns. They discharge in bursts with rewarding stimuli during W and they do so during PS, perhaps underlying the emotional components of ►dream activity.

Behavioral Arousal and Histamine (HA)

HA has been known to stimulate waking since antihistaminergic drugs diminish cortical activation and produce sleepiness [2,5,6]. The HA neurons are located in the ►tuberomammillary (TM) nucleus of the hypothalamus (see Fig. 1). They give rise to highly diffuse projections into the forebrain and also though to a lesser extent the brainstem and spinal cord. HA excites neurons in the thalamus, BF and cortex, stimulating cortical activation. They discharge during waking and cease firing during sleep.

Behavioral Arousal and Orexin (Orx)/Hypocretin (Hcrt)

Following its discovery ~10 years ago, Orx/Hcrt was found to be essential for the maintenance of waking and behavioral arousal, since in its absence or that of its receptor, ►narcolepsy with cataplexy occurs in mice, dogs and humans [1,5–7]. In humans, this condition is characterized by excessive daytime sleepiness, sleep onset REMS, paralysis and hallucinations. Cataplexy or sudden loss of muscle tone is often triggered by strong emotions and particularly laughter. Given the almost direct entry into REMS or loss of muscle tone accompanied by hallucinations, this disorder is thought to be a disorder of REMS. Its appearance in absence of Orx/Hcrt indicates that Orx/Hcrt neurons sustain behavioral arousal with postural muscle tone, particularly under conditions of strong emotion when other systems, perhaps cholinergic (above), precipitate a loss of muscle tone. The neurons which contain Orx/Hcrt are located in the posterior hypothalamus (see Fig. 1) and like NA LC neurons give rise to highly diffuse projections through the forebrain, brainstem and spinal cord. In the spinal cord, they innervate and excite motor neurons. In the brainstem and forebrain, they innervate and excite the neurons of the other arousal systems, including the ACh LDT/PPT and BF neurons, the NA LC neurons, and the HA TM neurons, together with neurons of the diffuse

thalamo-cortical projection system and deep layers of the cortex. They also directly excite somatic and sympathetic motor neurons. Their discharge would thus be associated with cortical activation and behavioral arousal with increased muscle tone and sympathetic activity. Immunohistochemically identified Orx/Hcrt neurons were indeed found to discharge during active waking, decrease firing during quiet waking and cease firing during sleep, including PS.

Sleep Systems

GABA

GABA has long been known to be important in promoting sleep, since the major hypnotic drugs and many anesthetics act by enhancing GABAergic transmission [1,5,8]. GABAergic neurons are located through all regions of the brain and of course are critical for normal functioning during waking of all neural circuits. However, particular GABAergic neurons are responsible for inhibiting and/or shaping the discharge of neurons of the arousal and activating systems.

As learned in early studies, there are neurons concentrated in certain regions of the brainstem RF which through descending projections to the spinal cord inhibit movement and muscle tone (see Fig. 1). These RF neurons utilize the inhibitory neurotransmitters, GABA and glycine. These amino acids are responsible for inhibiting motor neurons in the spinal cord and brainstem during PS [9]. Such RF neurons discharge selectively during sleep and maximally during the muscle atonia of PS.

GABAergic neurons through the brainstem RF also become active with sleep and are likely responsible for inhibiting other RF projection neurons. GABAergic neurons in the oral pontine and mesencephalic RF can inhibit neighboring Glu forebrain projecting neurons to diminish their discharge with sleep. Such GABAergic neurons also inhibit the LC NA neurons to allow sleep and PS with muscle atonia to occur (Fig. 1).

In the thalamus, GABAergic neurons, located in what is called the thalamic reticular nucleus, surround and innervate the specific and nonspecific thalamo-cortical projection neurons (see Fig. 1). By their specific properties and pattern of discharge, they not only inhibit, but also shape the discharge pattern of the thalamo-cortical relay neurons [10]. When released from excitatory inputs from the RF, the GABAergic thalamic reticular neurons discharge in bursts to drive spindle and then delta activity in the thalamo-cortical neurons. This activity is transmitted through the thalamo-cortical-thalamic pathways to generate the slow wave patterns which characterize and define SWS.

Other GABAergic neurons are found in the BF and preoptic area (including the ventrolateral preoptic area), (POA) which also play important roles in generating sleep (see Fig. 1) [1,7,8]. Among these, some GABAergic neurons discharge in association with cortical slow waves which they could accordingly promote during SWS. The discharge of these SWS-active cells is negatively correlated with gamma EEG activity and positively correlated with delta EEG activity (gamma−/delta+). Some may project directly to the cortex, others locally onto neighboring cholinergic BF neurons, which have a reciprocal profile of discharge (above). Other presumed GABAergic BF and POA neurons discharge at progressively higher rates through SWS into PS, as SWS/PS-active cells. Their discharge is negatively correlated with EMG. Such cells likely correspond in part to GABAergic neurons giving rise to descending projections to the posterior hypothalamus and innervating Orx/Hcrt neurons, which are inhibited by GABAergic inputs during sleep.

Adenosine

►Adenosine has long been thought to play a role in promoting sleep since one of the major stimulants, caffeine, acts as an antagonist of adenosine receptors [3]. It is potentially released from all nerve terminals, since it is a product of ATP, the major energy source contained in terminals and their synaptic vesicles. Its levels are progressively increased with sleep deprivation, presumably as more ATP would be utilized and metabolized by actively discharging neurons. Adenosine inhibits many neurons in the brain, including importantly the cholinergic BF neurons.

Orchestration of Neural Systems Generating Sleep-Wake States

The three states of mammals are generated by concerted or reciprocal discharge of hodologically and chemically distinct cell groups through the brain. W is stimulated and maintained by spinally projecting and forebrain projecting Glu RF neurons, which are in turn facilitated and reinforced in their action by diffusely projecting NA, HA and Orx neurons. These systems collectively promote motor activity along with muscle tone for behavioral arousal with cortical activation. GABAergic neurons in the brainstem, preoptic area and BF inhibit the neurons of these arousal systems to shut them off during sleep and thus prevent behavioral arousal while diminishing muscle tone. Other GABAergic neurons in the thalamus and BF inhibit thalamo-cortical and cortical neurons respectively, while also pacing them to elicit spindle and slow wave activity in the cortex during SWS. Discharging during W and PS, cholinergic neurons in the brainstem and BF stimulate cortical activation along with attention during W and perhaps ►dreaming during PS, when in absence of the influence from other arousal systems, most importantly Orx/Hcrt neurons, they also provoke a loss of muscle tone.

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Sleep-wake Modulation of Visceral Function

►Sleep-Wake Autonomic Regulation

Sleep-wake Neurochemical Substrates

►Sleep-Wake Mechanisms

Sleep-wake Rhythms

►Sleep-Wake Cycle

Sleep Walking

Definition

Sleep walking, also known as Somnambulism, consists of a series of complex behaviors that are initiated during sudden arousals from Non-REM sleep, and usually from slow-wave (delta) sleep, which culminate in walking around with an altered state of consciousness and impaired judgment, with absent or poor subsequent recall. In some adults there is associated dreaming.

►Non-REM Sleep

Sleepiness

Definition

The subjective report of the drive for sleep, or likelihood of falling asleep. Objectively it can be measured by the time it takes to fall asleep in a standardized test: the multiple sleep latency test.

►Alertness Level
►Sleep-wake Cycle

Sleeping Sickness

Definition

Infectious parasitic disease carried by tsetse flies and characterized by inflammation of the brain and the covering of the brain (meninges). An alternative name is African trypanosomiasis. Sleeping sickness is caused by two organisms, T. brucei rhodesiense and T. brucei gambiense.

Slice Preparation

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Synonyms

Acute brain slice

Definition

Thin sections (~400 μm thick) of part of the brain kept in oxygenated ►artificial cerebrospinal fluid.

Purpose

In the mammalian central nervous system (CNS), pharmacological studies were seriously hampered by the presence of the blood brain barrier (BBB). Direct infusion of drugs into the small brain regions is technically difficult *in vivo*, and it is rather hard to estimate the actual concentration of the drug at the recording site. In order to develop alternative *in vitro* experimental systems enabling pharmacological studies in a quantitative manner, in the mid 1960s, Yamamoto and McIlwain, devised a novel way to keep intact neuronal networks in thin slices of anterior piriform cortex [1,2]. Afterwards, it was revealed that this method is applicable to many cortical areas including neocortex, cerebellum, hippocampus, *etc* (Figs. 1 and 2).

Slice preparation retains intact structures and functions of CNS synapses, and use-dependent synaptic plasticity such as LTP and LTD can also be induced in these experimental systems. Currently, slice preparation is one of the most widely-used techniques to study the mechanism of synaptic transmission and plasticity *in vitro*. It also provides useful experimental models for the study of the pathological mechanisms underlying epileptogenesis and generation of seizure discharges. Slices are also widely used for studies of ischemic cell damage following hypoxia and hypoglycemia.

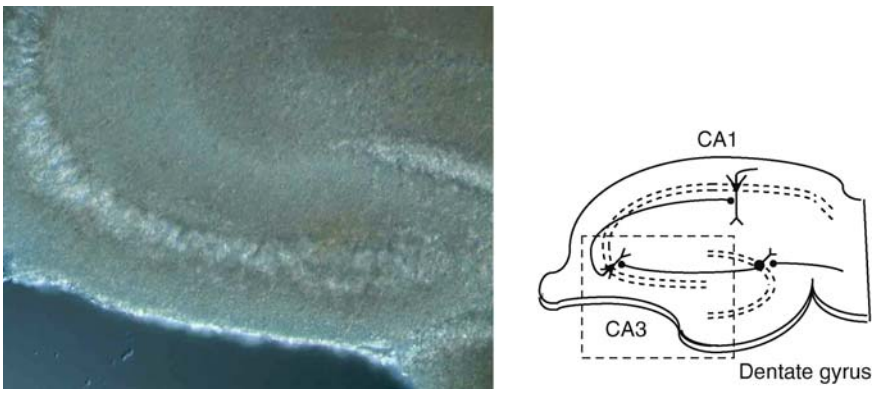
Principles

In principle, slice preparations can be made from any brain regions by cutting them into thin sections.

However, in practice there are several technical limitations to this method. Slices are usually continuously perfused with artificial cerebrospinal fluid (at a rate of ~2 ml/min) bubbled with 95% O_2 and 5% CO_2. Neurons in slice preparation are nourished with oxygen and glucose exclusively by penetration from the surface, and therefore the thickness of the slice is limited and must be thinner than ~400 μm. In addition, several conditions are critical for preparing "healthy" slices. Generally, slices should be cut quickly following removal from the skull in order to avoid ischemic neuronal damage. Cooling of tissues before and during slicing improves viability of neurons and is practically essential. Using a ►cutting solution also improves the viability of neurons, especially when slices are prepared from older animals. Since cell damage is mainly due to an influx of Ca^{2+} from the cut end or by activation of Ca^{2+} channels and NMDA receptor channels, a low Ca^{2+} and/or Na^{+} solution remarkably reduces cell death during slicing. After cutting slices, it takes approximately one hour to recover metabolisms of neurons from cooling and subsequent depletion of ATP. Slices can be kept alive for up to 10 h, but their activity gradually diminishes due to the breakdown of important molecules such as proteins, nucleotides and lipids, because artificial cerebrospinal fluid does not supply sources for synthesis of those macromolecules.

Advantages and Disadvantages

Slice preparation offers innovative experimental approaches for cellular and molecular neuroscientists. As discussed above, the most important advantage of this method is that quantitative pharmacological experiments of CNS neurons become feasible. In addition to pharmacological application, slice preparation is well suited for detailed cellular neurophysiological studies of CNS. Neurons are readily visible under the



Slice Preparation. Figure 1 Hippocampal slice preparation. *Left panel*: Surface image of the slices. Transverse slices of mouse hippocampus (~400 μm thickness) were prepared using a ►vibrating slicer (see Fig. 2) and viewed under microscope with DIC optics. A photograph was taken from the boxed area shown in the schematic drawing (*right panel*). Note that some of the neuronal cell bodies can be seen in the cell layer (translucent layer). Hippocampal slice retains intact neuronal networks of tri-synaptic circuit, which are thought to be important for mnemonic function of the hippocampus.

Slice Preparation. Figure 2 Vibrating slicer. Conventional vibrating type slicers for fixed tissues can be used for cutting living brain slices. A block of brain tissue was glued to the bottom of some metal dishes, and continuously submerged in an ice-cooled artificial cerebrospinal fluid gassed with 95% O_2 and 5% CO_2. After slicing using a horizontally oscillating razor blade, the metal dishes were lifted for the desired thickness (~400 μm) and cut another plane to obtain the slice.

microscope with DIC optics, and movement due to pulsation is absent. Therefore, slice preparation is adopted for many *in vitro* neurophysiological studies of ion channels, synaptic transmission, and local neuronal networks. Patch clamp recordings are also possible [3], even from fine cellular processes such as dendrite [4], axon [5], and presynaptic terminal [6] (►blind patch-clamp, slice patch-clamp). On the other hand, serious disadvantages of this method are that slices are short-lived and cannot be used for longer period than days. Therefore, acute slices are not usually suited for the molecular biological experiments using heterologous gene expression. In order to overcome this disadvantage, Gähwiler developed an ►organotypic slice culture that enables cultivation of slices for many weeks to months [7]. Thereafter, a much simpler method was revised for cultivating slices [8]. Currently, organotypic slice culture has been widely adopted for experiments requiring gene delivery either by using virus vector or by biolistic method. Combining GFP imaging with multiphoton laser microscopy, movement of glutamate receptors following high-frequency stimulation can be monitored in a real time manner [9]. Recently, activity-dependent changes in spine shape were also shown using a similar experimental strategy [10]. Another inevitable limitation of slice preparation arises from the slicing procedure itself. Although slices retain cytoarchitecture of the tissue of origin, only a fraction of the neuronal networks is kept intact because of thickness limitation (~400 μm). Therefore, it should be noted that natural inputs from presynaptic neurons are largely diminished or abolished in slice preparation.

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S

Sliding Filament Theory

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Definition

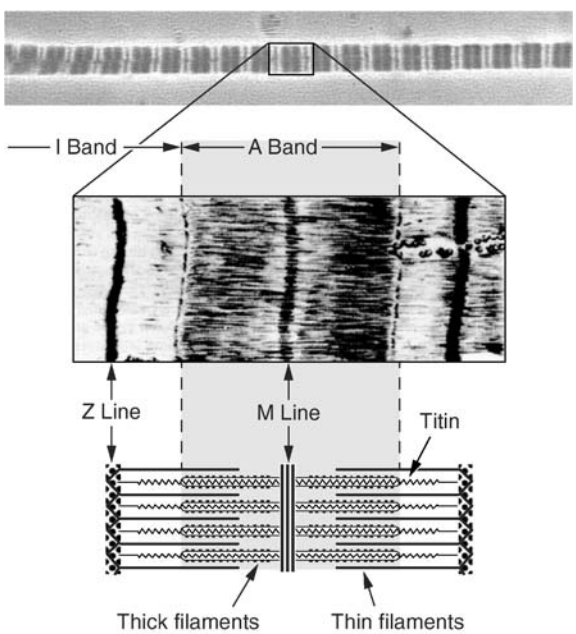
According to the sliding filament theory, muscle contraction occurs through the relative sliding of two sets of filaments (►actin and ►myosin). This sliding is produced by cyclic interactions of sidepieces from

the myosin filament (►cross-bridges) with specific sites on the actin filament. Each such interaction is associated with a cross-bridge ►power stroke whose energy is derived from the hydrolysis of adenosine-triphosphate (►ATP), one ATP per cross-bridge cycle.

Characteristics

Prior to the 1950s, muscle contraction and force production was associated with the shortening of myosin filaments. Myosin filaments can be seen with microscopy as the dark bands (the so called A-bands) in the striation pattern typical for skeletal and cardiac muscle (Fig. 1).

However, in 1954, Andrew Huxley and Rolf Niedergerke [1] in single fibres and Hugh Huxley and Jean Hanson [2] in isolated myofibrils showed independently that the A-band was not shortening when their preparations were activated and contracted. They speculated that muscle contraction and shortening was not caused by A-band (or myosin) shortening, but rather by the sliding of actin filaments relative to the myosin filaments. This sliding was proposed to be powered by so called cross-bridges (sidepieces arising from the myosin filament) that attach cyclically to actin and pull the actin past the myosin filament.

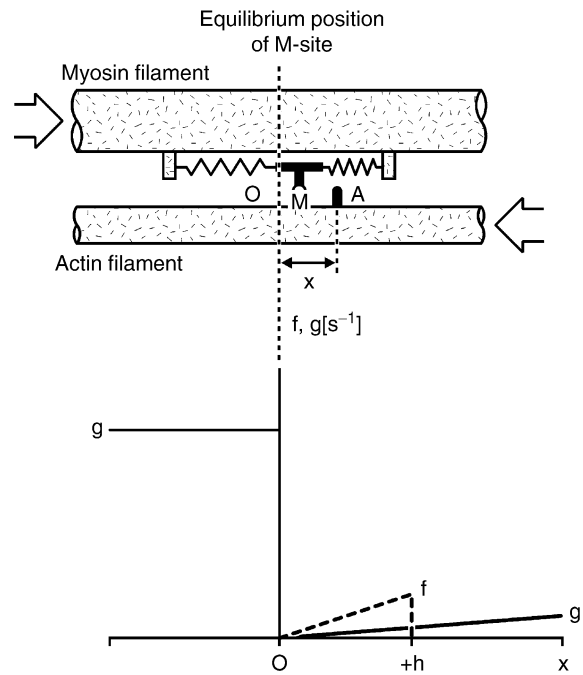


Sliding Filament Theory. Figure 1 Micrograph of a series of sarcomeres from an single myofibril (*top panel*), an isolated sarcomere bordered by the z-lines and containing myosin (or thick filaments) in the A-band region and actin (or thin filaments) in the I-band region (*middle panel*), and schematic representation of an isolated sarcomere with z-lines, thick filaments, thin filaments and titin identified (*bottom panel*).

The 1957 Cross-Bridge Theory

In 1957, Andrew Huxley [3] was the first to describe in precise mathematical terms how muscle contraction might occur and how the myosin and actin filaments might interact to cause muscle contraction. Huxley [3] proposed that cross-bridges were uniformly arranged along the myosin filament, and that there were uniformly arranged attachment sites for the cross-bridges on actin. Cross-bridges were assumed to be attached to myosin through a linearly elastic spring and they were moving around an equilibrium point through thermal agitation (Fig. 2).

Attachment and detachment of cross-bridges to actin was determined by a set of attachment and detachment rate functions that depended exclusively on the location of the cross-bridge equilibrium point relative to the nearest attachment site ("x" in Fig. 2). The attachment and detachment functions were asymmetric with respect to the cross-bridge equilibrium point, thus enforcing that force production was unidirectional, muscles can pull and exert tension, but they cannot push (Fig. 2). The 1957 theory contains

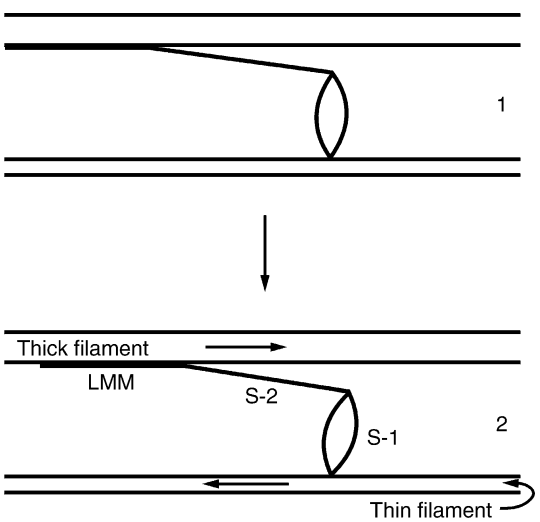


Sliding Filament Theory. Figure 2 *Top*: Schematic illustration of the 1957 cross-bridge model with the cross-bridge head (*M*) oscillating around its equilibrium position through thermal agitation until it may become attached to its nearest attachment site on actin (*A*) *Bottom*: Rate functions of attachment (*f*) and detachment (*g*) as defined by Huxley [4]. Note that the rate functions are exclusive functions of x, the distance from the cross-bridge equilibrium position to the nearest actin attachment site. (Adapted from [3] with permission).

two cross-bridge states, an attached and a detached state. The action of each cross-bridge is independent of other cross-bridges and the force is given by the stretch of the elastic element that connects the cross-bridge to the myosin filament. Each cross-bridge cycle (attachment and detachment) was associated with the hydrolysis of one ATP.

The 1969 Cross-Bridge Theory

Hugh Huxley [4] showed that the spacing between actin and myosin filaments behaves isovolumetrically, like that observed in whole muscle. Therefore, when ►sarcomeres are stretched from 2.0 to 2.8 μm, myofilaments approach each other and the distance between them decreases by about 18%. Huxley [4] argued that this is too great a range for protein interactions that must produce specific conformational changes associated with the regulation of enzyme activities. Based on further structural evidence, Huxley [4] suggested that the light meromyosin (LMM) part of the cross-bridge was bonded to the backbone of the filament (Fig. 3).The linear portion of the heavy meromyosin S-2 component (S-2) was assumed to be attached to the LMM portion through a flexible joint. The cross-bridge head (heavy meromyosin S-1) was also assumed to be attached to the heavy meromyosin S-2 portion through a flexible joint (Fig. 3), thus cross-bridges can interact with actin through a great range of ►lattice spacings without changing their orientation. Huxley [4] provided further structural evidence suggesting that the cross-bridge head could rotate and so produce force and sliding of actin. Thus the swinging lever arm theory was born.



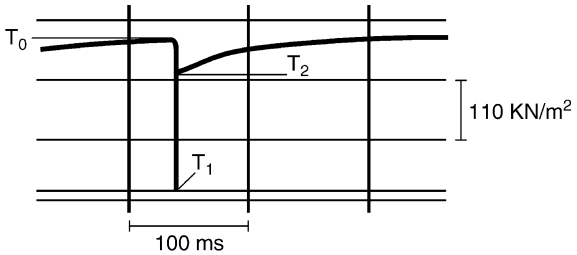
Sliding Filament Theory. Figure 3 Schematic illustration of the mechanism of force generation according to Huxley [4]). Note that in the 1969 model, the cross-bridge head (S-1) can rotate around its attachment point on actin (thin filament).

The 1971 Cross-Bridge Theory

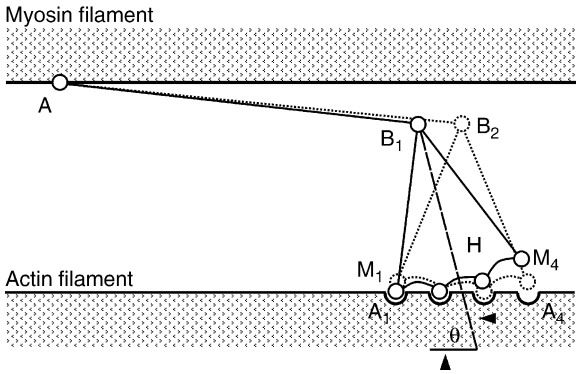
A characteristic of muscle contraction that could not be predicted adequately with existing models was the force transients following quick length changes. When a muscle fibre is shortened rapidly, force drops virtually simultaneously with the length change and then recovers quickly at first (1–2 ms) and more slowly later (Fig. 4).

In order to account for the force transients following stepwise length changes and to avoid losing the good predictive power of earlier cross-bridge models, Huxley and Simmons [5] introduced the concept of different attachment states for cross-bridges, thereby allowing the cross-bridges to perform work in a small number of steps. Going from one stable attachment configuration to the next was associated with progressively lower potential energy. Furthermore, Huxley and Simmons [5] assumed that there was an elastic element within each cross-bridge which allowed for cross-bridges to go from one stable attachment configuration to the next without a corresponding relative displacement of the actin and myosin filaments (Fig. 5).

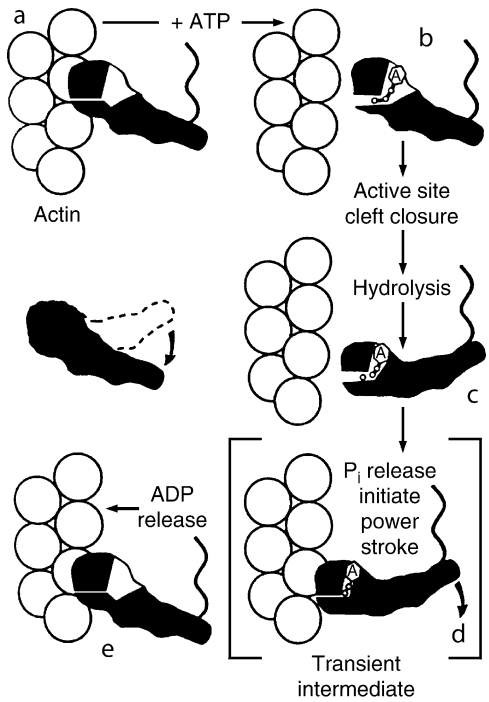
The force transients during a quick release could now be explained as follows. The virtually instantaneous drop in force with a quick shortening step was associated with the elastic cross-bridge element. The quick force recovery was associated with a rotation of the cross-bridge head from a position of high to a position of low potential energy, thereby stretching the elastic link connecting the cross-bridge to the filament and increasing force. Finally, the slow recovery of force was associated with the normal attachment/detachment



Sliding Filament Theory. Figure 4 Force-time trace of an isolated muscle fibre preparation that is shortened rapidly by approximately 6 nm/half-sarcomere. When the fibre is shortened, force drops instantaneously because of the elastic attachment of the cross-bridge to the myosin backbone. Force then recovers, first rapidly because of a quick rotation of attached cross-bridge heads, then slowly in accordance with the normal attachment/detachment kinetics of cross-bridges (Adapted from Ford et al. (1977); with permission).



Sliding Filament Theory. Figure 5 Schematic representation of the cross-bridge model according to Huxley and Simmons [5]. In this model, the cross-bridge head rotates about its attachment site on actin in several discrete steps (Adapted from [5] with permission).



Sliding Filament Theory. Figure 6 Schematic representation of the mechanism of contraction according to Rayment et al. [6, 7]. In this model, the part of the cross-bridge that attaches to actin remains fixed, while rotation of the "cross-bridge" is associated with a conformational change of the light chain binding domain around a hinge in the myosin head (Adapted from Rayment et al. [6] (1993); with permission).

kinetics of the cross-bridges. Thus, cross-bridge models went from two states (attached and detached) to multiple state models with at least one detached and at least two attached states.

Current Thinking

One further step in the development of cross-bridge models deserves attention. In their 1971 explanation of multi-state cross-bridge models, Huxley and Simmons thought that rotation involved the entire cross-bridge head and occurred around the attachment sites on actin. However, based on structural studies of the cross-bridge head (HMM S-1) and the corresponding attachment site on actin, Rayment et al. [6,7] suggested that the attachment of the cross-bridge head on actin was fixed, while the actual "cross-bridge" rotation was associated with a conformational change of the light chain binding domain around a hinge in the myosin head (Fig. 6).

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Sliding Mode Control

Definition

An approach to the synthesis of feedback controllers for nonlinear control systems, where the system trajectories are forced to reach is finite time a certain desirable surface in the state space.

►Nonlinear Control Systems

Slits

Definition

Secreted proteins that exert attractive or repulsive effects via receptors of the Robo family. A prominent role of slits is the guidance of commissural axons at the ventral midline and in axon pathfinding at the optic chiasm.

►Growth Inhibitory Molecules in Nervous System
►Development and Regeneration

Slow Oscillation in Non-REM Sleep

Definition

Slow (<1 Hz) alternation between hyperpolarization and depolarization of cortical neurons during NREM sleep.

►Non-REM Sleep
►Sleep – Motor Changes
►Sleep – Sensory Changes

Slow-wave Sleep (SWS)

Definition

The component of mammalian non-REM sleep that is accompanied by maximal amounts of high-amplitude electroencephalogram (EEG) slow-wave activity in the 0.3–4 Hz frequency range (also known as delta waves). In humans, SWS is synonymous with Stage 3/4 sleep. SWS is regarded as the deepest and most restorative stage of nonREM sleep, and slow-wave activity in the EEG is an accepted measure of homeostatic sleep need.

►Electroencephalography
►Non-REM Sleep
►Sleep Generating Mechanisms

Slowly Adapting Pulmonary Stretch Receptors

►Respiratory Reflexes

Slowly Adapting Type I Mechanoreceptors

Definition

A mechanically sensitive sensory ending in the skin that adapts slowly to a sustained indentation and therefore is sensitive to static events; it is also dynamically sensitive. It has small, well-defined receptive fields and the sensory terminal is believed to innervate the Merkel-cell neurite complex. Also known as SAI (slowly-adapting type I) afferents in humans and SA receptors in the cat and primate.

►Cutaneous Mechanoreceptors
►Functional Behavior
►Electric Fish

Slowly Adapting Type II Mechanoreceptors

Definition

A mechanically sensitive sensory ending in the skin that adapts slowly to a sustained indentation and therefore is sensitive to static events; it is also dynamically sensitive. It has large, poorly-defined receptive fields and the sensory terminal is believed to innervate the Ruffini ending. Also known as SAII (slowly-adapting type II) afferents in humans and other animals.

►Cutaneous Mechanoreceptors
►Functional Behavior
►Electric Fish

SMA (Supplementary Motor Area)

Definition

►Supplementray Motor Area

SMAD Signaling

►BMP Signaling and Synaptic Development

Small Pit Organ

Definition

Electroreceptive sensory organ described in catfishes, and that is part of the octavolateral system. Functionally equivalent to the ampullary electroreceptor organ in sharks, sturgeons and some other non-teleost fish.

►Electric Fish

"Smart"

►Nootropic Drugs

Smell

►Odor

Smell Disorders

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Synonyms

Olfactory disorders; Dysosmia

Definition

Olfactory disorders are states where the normal human olfactory function is altered. This might happen physiologically with age, but is mainly the consequence of a pathological event. The most frequent causes of olfactory disorders are head trauma, upper respiratory tract infections or sinunasal diseases. Other causes, assessing methods and therapy options are discussed.

Characteristics

Anatomy

Olfactory perception starts at the level of the olfactory epithelium in the roof of the nasal cavity. ►Olfactory receptor neurons (ORN) are embedded within the respiratory epithelium and send their axons through the cribriform plate towards the olfactory bulbs. From there, most fibers directly project to the piriform and entorhinal cortices as well as to the amygdalae (all structures formerly subsumed under the term "limbic system") whereas a minority of fibers project through the thalamus towards the orbito-frontal cortex. Compared to other sensory modalities the olfactory system has some particularities. First, the majority of the olfactory fibers do not cross but project ipsilaterally in the brain. Second, most olfactory fibers bypass the thalamus and project very rapidly and directly in the pyriform cortex, amygdalae, and entorhinal cortex which are implicated in emotional and memory processing.

Chemicals Senses

Although this essay focuses on the olfactory system, it is necessary to mention briefly, taste and ►trigeminal function. Together with olfaction, taste and trigeminal function are called the "chemical senses." All three systems can be stimulated by chemicals, and they provide us with different information. The trigeminal system is the somato-sensory innervation of the nasal mucosa. The main modalities supplied by the trigeminal system are temperature, pain, touch, and irritation. Since most odorous compounds stimulate trigeminal nerve endings, at least at higher concentrations, this system is almost always co-activated in the perception of odors. With few exceptions almost all odorants have

been shown to exhibit trigeminal activation to some extent [1] (e.g., mint has a somewhat fruity odor, but also evokes a typical cooling effect which is mainly trigeminally mediated). The gustatory system provides the five basic tastes; sweet, sour, salty, bitter, and umami (glutamate). The latter, which resembles mainly the taste of chicken soup, has long been claimed in the Asian literature to be a basic taste quality, whereas the western scientific community considered umami mainly as a "taste enhancer." This controversy was resolved when monosodium glutamate receptors were found on the tongue surface acting as specific taste receptors [2]. Taste receptors are located within the taste buds, which are situated on all papillae except the filiform type. The highest densities of taste buds are found on the tongue and palate but they are also found throughout the entire oral cavity, hypopharynx and larynx. The facial, glossopharyngeal, and vagal nerves provide neural supply for these cells. Like olfaction, taste fibers project ipsilaterally into the brain stem. All gustatory fibers (facial, glossopharyngeal and vagus) innervating the oral-pharyngeal cavity converge into the nucleus solitarius within the brain stem. In most situations of the daily life (e.g., eating) all tree chemical senses are stimulated concomitantly.

Retronasal Olfaction

"Retronasal olfaction" encompasses the perception of odors emanating form the oral cavity during eating and drinking. It is opposed to "orthonasal olfaction" which occurs during sniffing. The retronasal olfactory pathway, contributing to the flavor of foods or drinks, is commonly associated with "taste." Clinically, most patients with olfactory dysfunction complain of both, loss of smell and taste. Furthermore, this "taste" loss has been reported to affect quality of life of most patients with olfactory disorders [3].

Measurement

Olfactory function, like most other sensory systems can be measured by psychophysical or objective techniques. Since the subjects' self assessment of olfactory function is unreliable, testing of olfactory function is necessary [3].

Psychophysical Methods

The basic principle of psychophysical testing of olfaction is to expose a subject to an olfactory stimulus and to interpret the responses or reactions of the tested subject.

The most valuable advantage of psychophysical testing compared to objective testing methods is the rapidity which allows quick screening for olfactory dysfunction. More extensive testing sets, which can also be used for clinical research, allow graduation of the olfactory disorder. Fundamentally, every collection of odors is a potential olfactory test. Whatever a clinical test consists of, it should reliably distinguish between anosmic, hyposmic, and normosmic subjects. Most tests are based on a forced choice paradigm. An odorant is presented at supra-threshold concentration and the subject has to identify the odor from a list of descriptions of odors (e.g., the subject gets rose odor to smell, and is asked whether the perceived odor was "banana," "anis," "rose," or "lilac"). This forced-choice procedure controls the subjects' response bias. It also (potentially) allows the detection of malingerers since even anosmic subjects will produce a few "correct" answers provided in a random selection of items. The result of the test corresponds to the sum of the correctly identified items. This test design is called a ►smell identification test, and is the most widely used way of testing [4]. Another widely used test design are ►threshold tests. The idea of threshold tests is to expose a subject repeatedly to ascending and descending concentrations of the same odorant and to identify the least detectable concentration for this individual odor.

Besides the solid body of literature and its clinical convenience, the psychophysical tests have one main limitation. As soon as the patient's collaboration is not guaranteed, interpretation of test results becomes difficult or even impossible.

Objective Methods

Electro-Olfactogram (EOG)

Electro-olfactograms (EOG) are electrical potentials of the olfactory epithelium that occur in response to olfactory stimulation. The EOG represents the sum of generator potentials of ORN.

Chemosensory Event-Related Potentials (CSERP)

Event-related potentials are EEG-derived poly-phasic signals. They are caused by the activation of cortical neurons which generate electro-magnetic fields. As the EEG is a noisy signal which contains activity from many cortical neurons, ERP need to be extracted from this background activity. The classical approach to this problem involves averaging of individual responses to olfactory stimuli such that random activity would cancel itself out while all non-random activation would remain. Olfactory ERP (i) are direct correlates of neuronal activation, unlike the signals that are seen, for example, in functional MR imaging, (ii) have an extremely high temporal resolution in the range of micro-seconds, (iii) allow the investigation of the sequential processing of olfactory information, and (iv) can be obtained independently of the subject's response bias

Symptoms

Although this distinction is a matter of debate, the discrimination between qualitative and quantitative

olfactory disorder have proven helpful in clinical practice. This distinction is mainly based on the patient's history and psychophysical test results.

Quantitative Olfactory Disorders

Normosmia/Hyposmia/Anosmia

►Normosmia (►Normosmia/Hyposmia/Anosmia) is the subjectively perceived normal olfactory function, usually defined as the ability to detect the great majority of tested odors in a given olfactory test. ►Hyposmia means the decrease of this olfactory function and ►anosmia the total loss of any olfactory function. Beside total anosmia, specific anosmias have been described, where only certain odors are not perceived and most odors are smelt normally [5].

Qualitative Olfactory Disorders

The term "qualitative olfactory disorder" reflects the qualitatively changed perception of odorous sensation. They are frequently, but not necessarily, associated with quantitative olfactory disorders.

Parosmia

►Parosmia describes the distorted perception of smells in presence of an odor source. In other words, parosmias are triggered by odors. This is a symptom occurring particularly often in post-URTI or posttraumatic olfactory disorders. Mostly odors are distorted into unpleasant odors. For example, to parosmic patients, coffee smells like burnt plastic. The exact explanation of the molecular modifications leading to parosmia is as yet unknown. Even the site of parosmia generation (olfactory epithelium, olfactory bulb, or other central-nervous olfactory structures) is not clear. Important clinically, is the observation that most parosmic impressions tend to diminish over months and finally disappear after years.

Phantosmia

►Phantosmia describes the distorted perception of smells in the absence of an odor source. Most often, phantosmias occur after trauma or URTI and consist of unpleasant odors occurring without being elicited through environmental odor sources. Phantosmias also have a tendency to disappear over the course of years.

Causes/Etiologies

Methodological progresses made in the assessment of olfactory function allowed epidemiological studies, which demonstrated that the occurrence of olfactory disturbances is largely underestimated. Almost 15% of the general population suffers from a mild or severe olfactory dysfunction [6].

Most Common Causes

Olfactory Loss Following Infections of the Upper Respiratory Tract (URTI)

Apart from posttraumatic and ►sinunasal origin, post-URTI olfactory loss is among the major causes of olfactory dysfunction. The patient's history typically starts with a cold, during which he loses his sense of smell. Not particularly bothered during the cold, the patient becomes suspicious about the smell loss when, one or two months after all sinunasal symptoms have abated, normal olfactory function does not return. Currently, no good data indicate which agent in such upper tract respiratory infections (URTI) leads to olfactory lesions. It is not even clear whether toxicity originates from a virus or bacteria, or from the immune response directed against olfactory neuroepithelium. In one third of those patients parosmia occurs two to three month after the URTI.

Posttraumatic Olfactory Loss

Posttraumatic olfactory disorders represent approximately 20% of the patients seen in "Smell and Taste Clinics" [7]. The current explanation is that "coup-contre-coup" lesions or tearing of the filae olfactoriae leads to anosmia or hyposmia. Olfactory loss seems to correlate with the severity of the trauma [8], although several authors pointed out the fact that there is considerable individual variability in terms of the vulnerability of olfactory structures. Thus, even minor trauma can lead to anosmia whereas severe brain injuries may not alter olfaction [8]. Probably, the injured parts of the olfactory system are most often the filae olfactoriae which cross the cribriform plate. Similar to post-URTI olfactory impairment, these patients are prone to develop parosmia and phantosmia several months after the trauma.

Sinunasal Causes

Approximately 20% of all patients in smell and taste consultations have lost or impaired olfactory function due to a nasal problem [7]. Chronic inflammatory processes within the nasal and paranasal cavities such as nasal polyposis probably lead to mechanical obstruction of nasal cavity restricting the airflow to the olfactory cleft. During the last two decades, as a result of better olfactory tests, mild olfactory impairments could also be identified in other groups of patients with sinunasal diseases such as allergic and uncomplicated chronic rhinosinusitis.

Neurodegenerative Causes

Olfactory loss is common in patients with idiopathic Parkinson's disease (IPD). This olfactory deficit is so reliable that it can be used as a marker of IPD [9]. In other words; if a patient with normal olfactory function presents

with IPD symptoms the diagnosis should be re-investigated [10]. It can also be assumed that olfactory loss precedes the onset of motor symptoms by 4–6 years so that IPD may be the reason for "idiopathic olfactory loss" in some patients. Olfactory loss is also observed regularly in Alzheimer's disease, but at a much lower frequency and is less pronounced in multiple system atrophy, Huntington's disease, and motor neuron disease. Little or no olfactory deficit is seen in cortico-basal degeneration, progressive supranuclear palsy, or essential tremor.

Idiopathic

In almost 20% of the patients with olfactory disorders, no origin is identified even after extensive workup. These idiopathic (unknown) olfactory disorders seem simply to reflect the poor understanding of factors interfering with olfaction. With further insight and research this percentage should logically decrease.

Less Frequent Causes

Endocrine Diseases

Diabetes has been shown in most studies to cause slight olfactory deficiencies especially at threshold levels. Several other endocrine diseases have been reported to cause olfactory disorders.

Epilepsy

The general findings in epileptic patients were that they perform similar to controls with regard to odor thresholds. In contrast, more centrally believed tasks such as odor identification, discrimination or memory tests revealed that epileptic patients have olfactory impairments predominating on the side of the epileptic focus. This indicates that decreased olfactory function in epileptic patients is primarily due to centrally altered olfactory structures whereby the temporal lobe is the main lesion site.

General Pathologies

Long lists of general pathologies causing olfactory disorders can be found in most reviews and textbooks of smell and taste disorders, whereas only few large studies investigated general disease and olfactory function. Especially kidney and liver affections have been associated with decreased olfactory function.

Drug-Induced/Toxic

Numerous toxins have been implicated as causes of olfactory disorders. Nevertheless, this information has been mainly accumulated on the basis of case reports.

Congenital

Congenital anosmia occurring as an isolated defect or occurring within the context of a syndrome are distinguished. Isolated ►congenital anosmia seems to occur more often than previously believed. Apart from the typical patient history of no odor memories, only MR imaging leads to a more definitive diagnosis showing hypoplasia or aplasia of the olfactory bulbs. Among cases of congenital anosmia as part of a syndrome, the Kallmann-Syndrom is the disorder in which it is most frequently encountered. This is an anosmia associated with hypogonadotropic hypogonadism clinically characterized by infertility and anosmia. Congenital anosmia is typically discovered during early puberty.

Consequences

Compared to deafness or blindness, anosmia is less disabling in terms of typical social functioning. However, beside the associated dangers like eating spoiled food or non recognition of fire and smoke, it considerably impairs quality of life. Recent studies underlined the potential alteration of quality of life consecutive to olfactory impairment [3]. In some patients olfactory dysfunction even leads to depression.

Treatment

The treatments of olfactory disorders mainly depend of its origin. Neither treatment nor ►spontaneous recovery can be expected in age-related and congenital anosmia. Sinunasal smell disorders are mostly treatable with antibiotic and anti-inflammatory drugs such as systemic and topical corticosteroids. In general, treating the underlying nasal disease, either surgically or with medical treatment, improves olfactory function. Toxic- and drug- induced smell disorders may recover once the drug intake is interrupted. For two of the most important causes (post-URTI and posttraumatic) of olfactory dysfunction, no curative treatment exists. However, in contrast to other sensory neurons, olfactory neurons regenerate regularly. Thus, spontaneous recovery after olfactory loss is often observed after posttraumatic and post-URTI olfactory dysfunction. Recovery rates are much better in post-URTI (in ca. 60% of the patients) than in posttraumatic (ca. 15%) patients. Usually the main recovery takes place within the two years after the event causing the olfactory disturbance. Spontaneous recovery often remains partial and rarely complete. Although olfactory neurons have the ability to regenerate, the exact mechanisms favoring such spontaneous recovery are not understood. It is currently impossible to predict an individual outcome with regard to recovery. In contrast to the quantitative olfactory disorders, the qualitative disorders have a far better prognosis of spontaneous disappearance. Parosmias tend to decrease to a bearable level after approximately one year. To summarize, the best current therapeutic attitude towards post-URTI and posttraumatic olfactory disorders is to correctly inform the patient, without removing all hope of recovery.

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Smell Identification Test

Definition

Testing olfactory function can be done by different means. The most popular and widespread one is to use an identification test. The subject is exposed to an odorant in a concentration which is far over threshold concentrations. Then the subject has to identify this odor. In order to facilitate the task he is presented a list of possibilities (usually four) of which he has to decide for one. The number of correct answers is the score of the identification test.

►Smell Disorders

Smooth Pursuit

Definition

Continuous eye movements made to track a moving visual target.

Smooth Pursuit Eye Movements

Definition

Smooth pursuit eye movements are those where subjects intentionally track a smoothly moving object or target using their eyes. The smooth pursuit system attempts to match the velocity of subject's eye movements to that of the target so that the image of the target continuously falls on the fovea.

Because subjects rarely do this perfectly, accumulating position errors are corrected using saccadic eye movements, often called "catch-up saccades". Although movement of the image of the target on the retina (retinal slip) is often a stimulus for smooth pursuit, it is not a necessary one. Subjects can track a target with negligible slip if the target motion is highly predictable, and subjects can correctly track the perception of movement created by object moving behind a narrow stationary slit oriented perpendicular to the motion (i.e., the visible edges of the object also move perpendicular to the actual motion.

Smooth pursuit is distinct from the optokinetic response, which is involuntary and responsive to image motion anywhere on the retina. Animals lacking a fovea exhibit little or no smooth pursuit, but do exhibit an optokinetic response.

►Retinal Slip
►Saccade, Saccadic Eye Movement

Snapback Hairpin

Definition

Snapback hairpin – A short hairpin RNA (shRNA) is a sequence of RNA that makes a tight hairpin turn that can be used to silence gene expression via RNA interference. This is when a single-stranded RNA folds back on itself by pairing with its own complementary strand. Snapback refers to this hairpin formation.

►GAL4/UAS

Snapshot Memory

Definition

The memory of the scene from a goal. Upon reaching a goal for the first time, a subject may make a survey of

the scene from the goal and store this in memory for subsequent use in returning to the goal. This snapshot may be used to mediate a form of navigation back to the goal. This involves moving to minimize the difference between the current snapshot and the one from memory.

A common form of insect navigation is based on snapshot memory, and there is also evidence that mammals use snapshot memory too.

►Spatial Learning/Memory

SNARE Proteins

Definition

Snare proteins are group of proteins located on the membrane of synaptic vesicles and the prejunctional nerve terminal that interact to mediate vesicle docking, fusion and exocytosis of neurotransmitters in a calcium-dependent manner. The proteins on vesicle membranes include synaptotagmin and synaptobrevin (v-SNAREs), with syntaxin and SNAP-25 located on the inner surface of the nerve terminal membrane (t-SNAREs).

►Postganglionic Neurotransmitter

Sniff

Definition

Sniffing is the drawing of air into the nasal cavity with the goal of odor detection. The flow rate observed during a sniff is usually higher than what is seen during quiet inspiration and the initial flow rate is very consistent from sniff to sniff. The higher flow is thought to direct more of the incoming air to the olfactory receptors and it facilitates olfaction by creating a more turbulent flow within the nasal cavity.

►Nasal Passageways

Sniffing Behavior (Mammals)

►Odor-Sampling Behavior

Snoring

Definition

Sound produced by vibration of anatomic structures in the upper airway during sleep. Snoring can be caused by obstruction or narrowing of the upper airway (e.g., obesity, elongated soft palate, relaxation of tissues in the throat) and by sedative drugs (alcohol and some prescription medications including sleeping pills).

Snoring often disrupts the sleep of housemates more than that of the person snoring. However, loud snoring associated with pauses in breathing can be a sign of sleep breathing disorders referred to as sleep apnea and upper airway resistance syndrome. Snoring in children may be related to airway obstruction caused by large tonsils or adenoids.

►Sleep – Motor Changes
►Sleep – Sensory Changes

SNP

Definition

Single nucleotide polymorphism, one base pair sequence difference between alleles.

►Bioinformatics

Social Behavior Network

Definition

Set of interconnected brain areas implicated in the control of multiple forms of social behavior, such as communication and sexual behavior. Each one of these brain areas is a node of the network. These nodes are also characterized by containing receptors to sexual steroids.

►Evolution of Septal Nuclei

Social Chemosignal

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Synonyms

Social odor [1]; Semiochemical [2]; Sociochemical [3]
Related terms: Social olfaction; Social chemosensation; Chemical communication; Semiochemistry [2]; Sociochemistry

Definition

Social chemosignals encompass all types of stimulations exchanged among members of a given species and that are detected through the chemical senses (i.e., olfaction, vomerolfaction, taste, tarsal chemoreception). These are carried by chemicals derived from physiological processes and circumstantially learned as social cues, as well as by specialized signals, termed pheromones, which were evolutionarily selected for communicative purposes.

It should be noted that whereas all pheromones are social chemosignals, all social chemosignals are not pheromones. There is indeed a definitional confusion leading to the indiscriminate use of the pheromone concept to designate any communicative process involving odors. In fact, pheromones may be conceived more as regulating than as informative factors. Thus, the term pheromone should be kept separate to qualify *well-identified chemicals* that fulfill an operational set of functional criteria [4,5]. Pheromones have been proposed to belong to a subclass of (i) chemically simple compounds (single- or multiple-component pheromones made up with a limited set of active compounds in given ratio); (ii) that are exclusive in eliciting (iii) a well-defined and invariant behavioral/physiological response with obvious functional significance (iv) among individuals of the same species; finally, (v) the activity of these compounds should be minimally dependent on learning processes [4,5]. In sum, pheromones represent only a portion of social chemosignals; these latter include more or less additional compounds leading to mixtures that can be exceedingly complex in both chemical (sometimes composed by several hundreds of compounds) and semiotic terms. These social chemosignals elicit responses that can be highly variable as a function of the context or the interacting organisms' internal state, mingle individual as well as supra-individual (colony, caste, species, etc.) information, and depend on prior experience and cognitive processes.

Characteristics

The chemical, physiological and behavioral principles of social olfaction mostly stem from studies in Insects and Vertebrates, especially Mammals [2,6]. Accordingly, these principles may be revised with incoming new knowledge from other taxa. As in any communication system, social odors may be described in the context of the functional loop between an emitting individual carrying the source of the chemosignal that impinges on a recipient organism responding either by attentional mobilization, by an immediate overt behavior or by a covert physiological reaction.

Sources

Social chemosignals are derived from multiple sources, which are either distributed over the tegumentary surface (sebaceous, eccrine and apocrines sweat glands) or collected in more or less specialized scent glands. They can also be emitted by the way of various excretory carriers, such as tears, breath, saliva, mucus, milk, the genital discharges, urine, or feces [2,6]. These biological substrates may transmit an intrinsic distinctive odor or may gain their characteristic odor through the action of bacteria dwelling on the skin surface or in glandular recesses. They are composed of volatile and involatile fractions the interaction of which modulates the temporal dynamics and properties of the final odor stimulus.

These multiple secretory or excretory sources, and hence the odor quality and intensity derived from them, are regulated by the organism's genetic and immunogenetic constitution, but can also be induced by a multiplicity of factors, including endocrine status (linked with age, sex, reproductive stage), metabolism (diet, pathology), and psychobiological state (age, stress, dominance, fitness). The combined action of all these causal pathways leads to the formation of a specific chemical image or of an individual's olfactory fingerprint or signature.

Signals

The chemistry that any organism presents to its conspecifics can be exceedingly complex and versatile, and its total chemical understanding may be unattainable [2]. Many classes of biologically emitted chemical compounds are physically and biologically compatible with chemosensory function. In terrestrial animals, a first partition in this complexity is between volatile and involatile fractions of the chemosignals, leading to ▶odor detection or ▶odor tracking from a distance or to the need for direct contact with the stimulus.

In this way, involatile proteins, lipids or cuticular hydrocarbon can act as fixatives or precursors of volatile cues, as well as contact chemosignals. In aquatic species, chemosignals generally need to be hydrosoluble, and bind with receptors from the olfactory as well as the taste system [7]. A second divide in the complexity of chemosignals is between individual-specific and species-specific compounds in the stimulus. Depending on the behavioral tests used to assess the responses, an

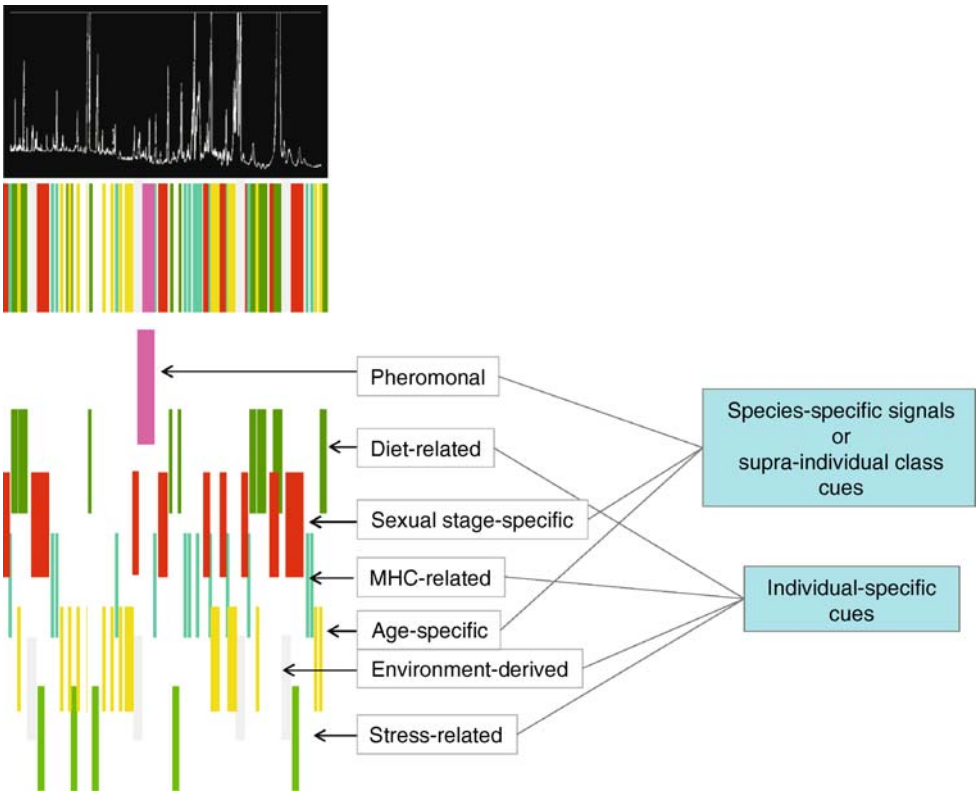
organisms' ability to extract individual or supra-individual meanings can be evidenced in a same chemosignal. Thus, social chemosignals may be conceived as more or less complex stimuli in which multiple levels of information can be nested (Fig. 1).

Little is known on the rules by which information is ciphered in social chemosignals [4,7,8]. A same biological secretion may code for one information or for several, or different secretions may code for the same information. Within a complex secretion, only one or several compounds, or groups of compounds, may carry the signal, the remaining compounds constituting background noise. The term "mosaic signal" has been proposed for such complex signals in which most of the individual compounds do not bear an effect by themselves [8], but are part of a multidimensional chemical signal classified in a multidimensional perceptual space.

Reception and Integration

Animal organisms have evolved several neural systems to detect, analyze, extract and store information from social chemosignals [8,9]. In higher vertebrates, an array of different systems detects chemosignals depending on the volatility and concentration of ligand molecules. From the most to the least volatile stimuli, the main olfactory system, the accessory olfactory (or vomeronasal) system and taste system come into play. The trigeminal system may be drawn in the detection of higher intensity compounds. In these systems, recognition pathways can be narrowly or broadly tuned, leading to specialized versus generalist chemoreception [9]. It was long held in higher vertebrates that some of these neural pathways (e.g., the vomeronasal system) were dedicated to detect social chemosignals of the subclass pheromones. A strict functional exclusivity has been since questioned, and overlap and interactions between specialized and generalist systems of chemodetection now seems to be the rule.

The brain structures involved in higher level processing of social chemosignals remain poorly understood, and offer a promising ground for future advances in cognitive and behavioral neuroscience [9]. So far, we know in rodents some neural structures (e.g., medial area of the amygdala, hypothalamus) that react differentially to complex odors contrasted along sex or individuality,



Social Chemosignal. Figure 1 A bar-code metaphor to nested chemical sources of meanings within a social chemosignal. The complex chromatographic pattern is translated in color bars representing levels of meanings. The decomposed bundles of bars represent compounds that are correlated with a given meaning, and hence with a given communicative function. Note that a pheromone is inclusive to a social chemosignal.

linking social chemosensory inputs to the brain areas involved in neuroendocrine, affective and cognitive processes.

Functions

The chemical senses being operative throughout the animal kingdom, their involvement in social processes is well conserved [1,5,7,10]. This functional ubiquity is reinforced by the fact that chemosignals have specific advantages over visual or auditory signals in terms of pervasiveness: they can operate in obscure (night-time, burrows, turbid water) or noisy (dense colonies) environments, are distributable in space and time (scent-marking) and can outlast for long periods the emitter's presence. Further, these chemosignals can rally attention in other modalities (alerting function) and they can be integrated with the entries from the other sensory systems, leading to the multimodal appraisal of conspecifics (cognitive function) and redundant regulation of behavior.

Social chemosignals can convey a wide range of psychobiological meanings actualized in the varying types and rates of behavioral and physiological responses measurable in appropriate experimental situations [6,7]. The basic requirement of social life being the recognition of particular individuals, or classes of individuals, it is seminal that chemoreceptive cues encode such categories. ►Odor recognition of individuality, or of classes of individuals, has been repeatedly shown in vertebrates and insects, making olfaction a basic organizing system of social life. The recently established role of peptides from the major histocompatibility complex in individuality signals reveals how genotypic information can be externalized and traced in vertebrates. Similar abilities lead to discriminate social categories such as age or gender, or to differentiate kin, family and colony members from out-groups, inducing within-group social selectivity and more or less between-group closure, and strategies to avoid consanguinity.

Social odors are also used as situational cues inscribing the individual in space and time. This is best observed in the frequent marking behaviors involved in the establishment and maintenance of a territory, or trails within it, in the labeling of conspecifics, foods or objects with own odor, or even in self-anointing. Social chemosignals are also involved in the coordination of social interactions. They can elicit recruitment and aggregative responses (as in foraging and reproductive parties), as well as avoidance and dissociative responses (warning signals, *Angstgeruch, Schreckstoff*). Finally, chemosensory correlates can be traced to decode indices related to psychological state (mood, stress), fitness (dominance, aggressiveness), and diet and health status (pathologies, parasite load) [1,7].

Social chemosignals have been investigated most extensively in the context of reproductive processes [5–8]. They guide the appraisal of mate quality, and hence direct mate choice and recognition, provide mutual indications on male sexual state and female stage of receptivity, and in concert with the other senses orchestrate courtship and copulation. In species that take care from their young (social insects, mammals), females are sensitive to the odor cues emitted by their offspring. Brood, amniotic and neonatal chemosignals determine the rapid onset of selective responses of females directed toward the young [10]. Reciprocally, at least in mammals, newborns are attracted to odor cues from females, and rapidly develop selective attachment responses to their mother. Further, mammalian females emit odor signals near the mammary glands or in milk, which have the effect of boosting neonatal motivation and of providing guidance to the nipples. In addition to the orchestration of behavior, data from rodents, ungulates and primates also indicate that social chemosignals modulate the physiological coordination of reproduction within groups. For example, urinary volatiles of reproductively-active males accelerate the attainment of puberty in young females, or induce estrus, block pregnancy, or synchronize ovarian cycles in mature females [5,7,9].

Finally, it may be highlighted that social chemosignals remain active in species that have developed higher cognitive processes, ideation, and communication systems dominated by vision and audition. Although it has been proposed that improved visual abilities in primates made olfaction redundant, social chemosignals remain actively involved in inter-individual exchanges [10]. For example, men and women can distinguish gender and recognize their mates and genetic relatives. Likewise, infants single out the individual odor of their mother from that of other females; but, in addition, infants display general attraction to the breast odor of any lactating woman and to the odor of conspecific milk. This is a well documented situation where individual and supra-individual cues can be extracted from a same chemosignal. The fact that social chemosignals make a notable contribution to the perceptual world of humans is further underlined by their universal use of extraneous odorants, adding culturally shaped complexity to the odors produced by species-specific chemo-emission.

Development: How Odors Become Social Signals?

The most obvious means by which odors become socially relevant is through acquisition processes, i.e., direct familiarization, associative learning, or conditioning [7,10]. Odor familiarization can be already set on in ovo or in utero, while embryos are exposed to genotype- or phenotype-related (dietary) compounds transmitted by the maternal organism. This explains how newly emerged insect larvae and vertebrate newborns can already be biased in their responses to maternal chemosignals against homologous signals from other conspecifics. Afterwards, the range of

stimuli that become salient in social contexts is rapidly, and sometimes lastingly, expanded through odor exposure during early sensitive periods. In this way, the females' constitutional odors, as well as circumstantial odorants from the environment associated with her, can be imprinted as chemical templates against which future allies or mates are selected. Further, indirect familiarization, by which familiar individuals (kin) can be used as standards against which others are compared, can also come into play in the discriminative value of chemosignals. In this case, individuals or categories of individuals are discriminated not because of previous contact, but as a function of phenotypic resemblance to relatives (or self) with whom one is acquainted (phenotype matching). Lifelong learning processes mediated by social interactions occur further in juveniles and adults, especially in emotion-primed contexts. Another recently-evidenced way to engage the learning of social chemosignals is through the intrinsic reinforcing impact of pheromones. In certain cases, these compounds promote the rapid learning of any odorant that is associated with them, rendering initially inactive odorants functionally similar to them, and thus engage circumstantial odorants into communicative actions. In this way, predisposed and plastic cognitive processes may cooperate in attuning individuals to the local conditions of their present and future social networks.

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Sodium Channels

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Synonyms

Voltage-dependent sodium (Na^+) channel; Voltage-gated Na^+ channel; Voltage-sensitive Na^+ channel; Voltage-activated Na^+ channel

Definition

Sodium (Na^+) channels are ►membrane glycoproteins (►Cell membrane – components and functions) that form Na^+-selective voltage-gated pores across the plasma membranes of excitable cells, such as neurons and muscle fibers. When these pores are in an open configuration, Na^+ cations flow through them. This flux is usually into the cell, and thus creates a voltage change across the cell membrane that is the basis of the propagating electrical signal known as the action potential (►Action potential; Action potential propagation). (Note: These voltage-gated channels are not to be confused with non-voltage-gated epithelial Na^+ channels (ENaCs) that are found in a variety of epithelial tissues, such as kidney, colon, and lung.)

Characteristics

Voltage-gated Na^+ channels are the primary molecular entities that initiate the propagating action potential of nerve axons, the fundamental electrical signal that underlies communication in the nervous system. Due to their central role in the function of the nervous system, a variety of natural toxins have evolved that affect them, while several clinically important drug classes target Na^+ channels, such as local anesthetics, chronic pain medications, and anti-seizure (►Seizures) drugs. Finally, genetically-based changes in the function of Na^+ channels can give rise to a number of human diseases, e.g. certain forms of cardiac long Q-T syndrome and epilepsy (►Epilepsy), and the periodic paralyses of muscle (►Familial periodic paralysis). For these reasons, Na^+ channels have been well studied in the past and will continue to be a focus of major investigative efforts for some time to come.

As with many other proteins, within a given organism Na^+ channels are encoded by a number of genes, giving rise to channel ►isoforms. In addition, additional diversity in channel types may derive from variations in the RNA processing of any gene transcript, while posttranslational modifications can vary the functional properties of the expressed gene product itself [1,2]. Consideration of the biological significance

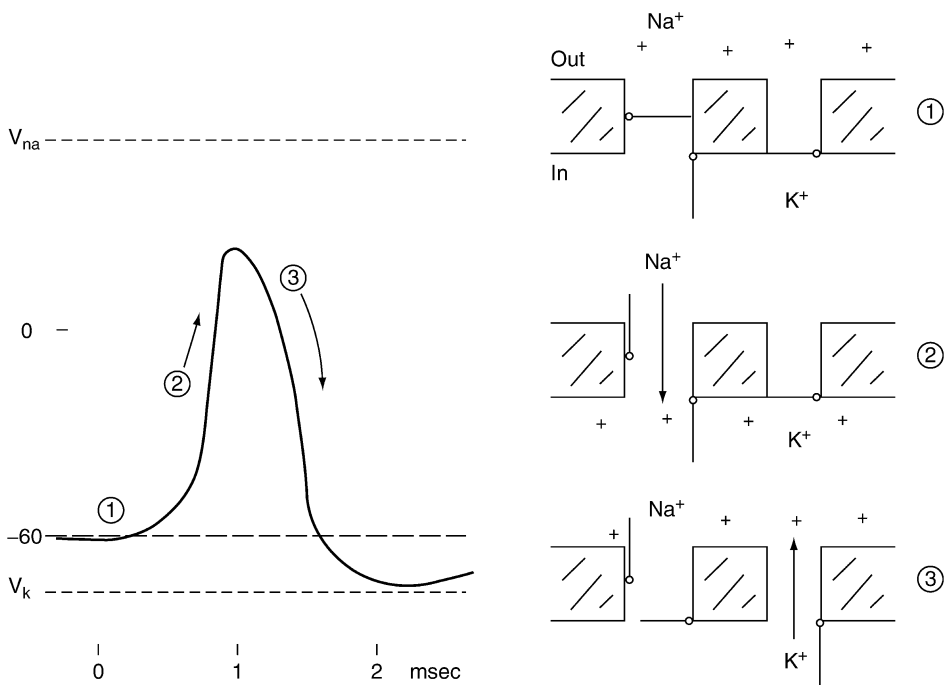
of such structural and functional variations among Na^+ channel isoforms is a major focus of current research.

Basic Physiological Functions of Na^+ Channels

Role in Generation of Propagating Action Potentials (►Action potential)

The study of the functional properties of Na^+ channels in generating action potentials has a long history and is described in detail in a number of texts (e.g. [3]). In its simplest terms, the action potential is a brief, propagating change in the transmembrane voltage across the neuron axon. As originally elucidated by the classic work of Hodgkin and Huxley (see [3]), this waveform is generated by the coordinated flux of Na^+ and K^+ ions across the cell membrane (Fig. 1). Subsequently it has been established that these ion fluxes are mediated by discrete molecular pores known as voltage-gated Na^+ and K^+ ►ion channels N euronal potassium channels). In particular, these channels are closed in the resting state, but are opened by any stimulus (e.g. by a ►postsynaptic potential at a ►synapse or a ►generator potential in a ►sensory receptor) that ►depolarizes the negative resting membrane potential (i.e. decreases it towards zero), past a characteristic threshold level. Initially, this voltage change causes Na^+ channels to open or ►activate, allowing Na^+ ions to flow passively into the cell driven by their ►electrochemical gradient (►Membrane potential – basics). This influx of positive charge further depolarizes the transmembrane voltage, and causes the initial rising phase of the action potential (Fig. 1), which goes toward V_{Na} (i.e. the Na^+ ►equilibrium potential as approximated by the ►Nernst equation for Na^+). In reality, V_{Na} is never quite reached because of two subsequent limiting processes: (i) Na^+ channels ►inactivate, thus shutting off the further influx of Na^+ ions; (ii) K^+ channels slowly open, which allows the outward flow of K^+ ions from the cell driven by their own electrochemical gradient, thus returning (►repolarizing) the membrane potential to its original resting level. After a brief delay (the ►refractory period), during which Na^+ channels recover from inactivation and K^+ channels close, another action potential may be generated.

The basic description above allows one to explain certain fundamental properties of the action potential, namely the "all-or-none" nature of its amplitude and its propagation. Both phenomena are related to the fact that in excitable tissues the influx of Na^+ ions through the



Sodium Channels. Figure 1 Ionic flows involved in generation of the action potential. The left part of the panel shows the action potential waveform, while the right part shows the gating state changes in Na^+ and K^+ channels that shape the action potential. Thus in the resting state (i), both Na^+ and K^+ channels are in the closed, nonconducting states. In (ii), a suprathreshold voltage stimulus causes Na^+ channels to open rapidly (i.e. activate), and the resultant influx of positively charged Na^+ ions causes the positive-going "►depolarizing" phase of the action potential. In (iii), the upstroke of the action potential ceases due to the entry of Na^+ channels into their "►inactivated" state, while the delayed opening of K^+ channels allows the efflux of K^+ cations to return the membrane potential to its starting value.

first few opening Na^+ channels causes an increased local depolarization that accelerates the opening of some of the surrounding channels; influx of Na^+ through these channels in turn further depolarizes the membrane, thus increasing the opening rate of more Na^+ channels, and so on. This "regenerative" effect quickly becomes the dominant stimulus for Na^+ channel activation, hence overwhelming the influence of the original stimulus. As a result, all subsequent processes in the action potential (e.g. Na^+ channel inactivation, K^+ channel opening) are obligatorily entrained by the regenerative phenomenon, and thus the action potential amplitude and shape are independent of the initial depolarizing stimulus. This explosively regenerative upswing in the membrane potential also propagates in a domino-like fashion, as channels adjacent to this activation zone are recruited into a conducting state (►Action potential propagation). In addition to this the process of "continuous conduction" characteristic of unmyelinated nerve fibers found in most animals, Na^+ channels also mediate the process of fast saltatory ("jumping") conduction that is found in the ►myelinated axons of vertebrates through the formation of very high densities of channel clusters at nodes of Ranvier.

Role of Na^+ Channels in the Initiation of Action Potentials and in Integrating Multiple Synaptic Signals at Dendrites

In addition to their classical role in generating action potentials, it has more recently been appreciated that Na^+ channels also are involved in initiating action potentials and in responding to more graded signals such as stimuli transduced by sensory receptors or synaptic potentials in neuron dendrites.

One essential role of Na^+ channels is to reinitiate the action potential on the postsynaptic side as a result of synaptic transmission. Thus in the motor endplate, Na^+ channels are located in the folds of the postsynaptic membrane (►Neuromuscular transmission). Both the high density of channels and the geometry of the folds themselves allow endplate potentials to initiate reliably a propagating action potential in the postsynaptic membrane. In neurons, Na^+ channels are present at high density in the ►axon hillock and ►initial segment of the axon. These channels initiate an action potential only when synaptic inputs at dendritic synapses summate sufficiently to depolarize the membrane potential in the peri-somatic axonal membrane. Clearly, in both of these cases the voltage-sensitivity of the Na^+ channels will determine the strength of synaptic signal required to fire an action potential in the postsynaptic cell. In addition, a very low and non-uniform density of Na^+ channels has been inferred to exist in the dendrites themselves. These channels are thought to be part of the mechanism by which dendrites perform signal processing of multiple synaptic inputs to produce an appropriate output at the axon hillock. Finally, Na^+ channels are found in certain sensory receptors, e.g. those for pain (►Pain), taste (►Chemical senses), and sound (►Hearing), where they are part of the transduction mechanisms that amplify weak sensory stimuli.

In summary, recent work shows that Na^+ channels play a number of important yet different roles in neuronal communication and sensory transduction. The multiplicity of such functions suggests that functionally distinct Na^+ channel types (i.e. isoforms) will serve in these different roles.

The Molecular Basis for Na^+ Channel Function

Basic Functional Properties of Na^+ Channels

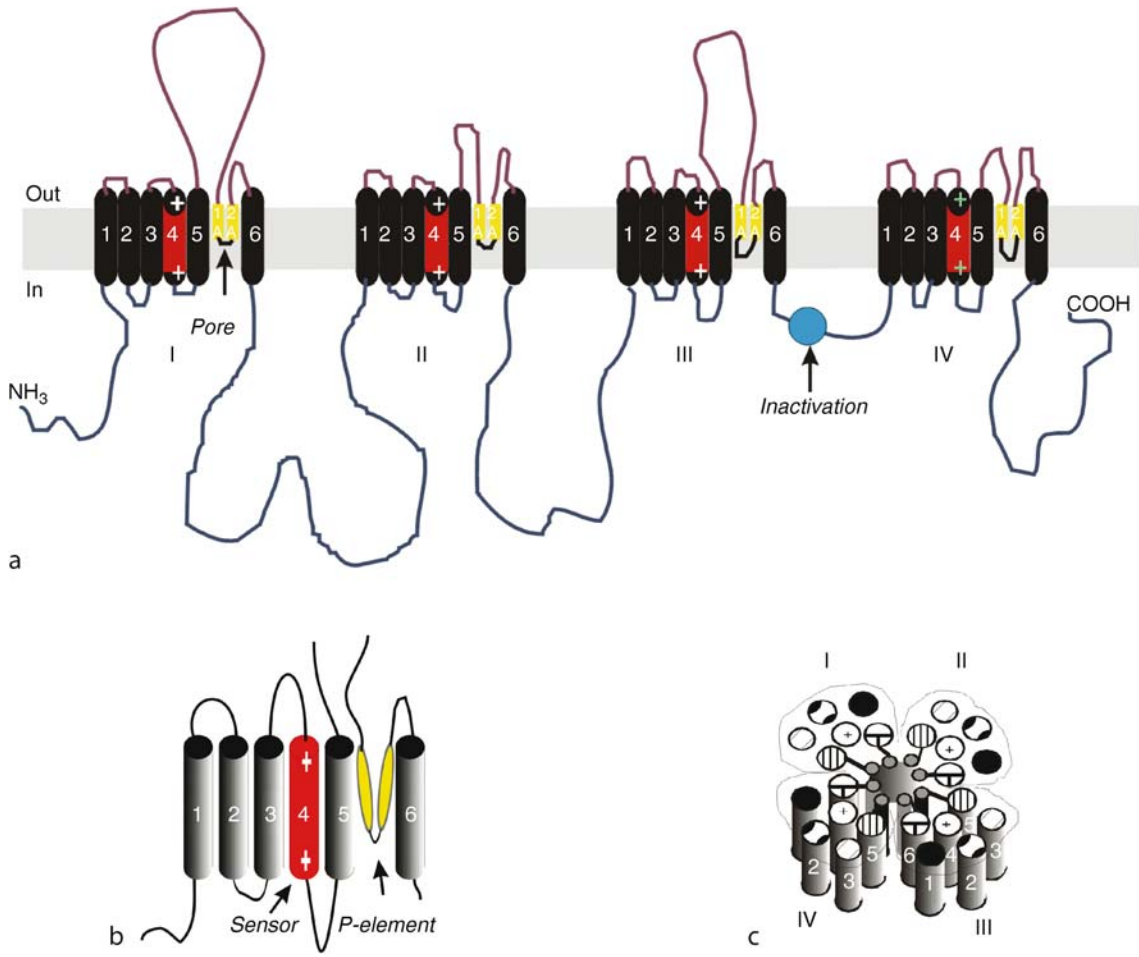
The microscopic functional properties of individual Na^+ ion channels that underlie its role in electrical signaling phenomena may be conveniently broken down as follows. First, Na^+ channels must have a *transmembrane aqueous pore* that allows the passage of ions across the plasma membrane. Second, access to this pore pathway must be regulated by a mechanism for *ion selectivity* that allows the channel to choose Na^+ over other ions in physiological solutions (e.g. K^+, Cl^-, Ca^{2+}). Lastly, there must be *voltage-sensitive activation and inactivation gates* that allow channels to assume the various closed, open, and inactivated states that occur in response to changes in membrane voltage (Fig. 1).

Subunit Composition and Amino Acid Sequence of Na^+ Channels

The basic molecular mechanisms of Na^+ channel operation (i.e. that which forms voltage-gated, ion selective pores) are contained within a single large polypeptide (usually designated as an "α" subunit). These are very large proteins of approximately 2,000 amino acid residues in length whose amino acid sequences have been determined largely from cloned cDNAs (see [1] for a description of the strategies and methods used). Naturally, models of the secondary and higher order structure could then be constructed from a combination of ►hydropathy and secondary structure prediction analysis.

Such a predictive model for the Na^+ channel structure is shown in Fig. 2. First, hydropathy and ►secondary structure constraints predict that Na^+ channels consist of four transmembrane domains (I, II, III, IV), each of which consists of six hydrophobic α-helices (S1–S6). Second, this architecture suggests that the four domains might contain segments (i.e. the α-helices) of highly (but not completely) conserved sequence homology to one another. These "internal repeats" have been confirmed by homology analysis.

In addition to these primary α subunits, many channels are associated with one or several "accessory" β subunits. While not directly part of the actual pore, selectivity or gating structures, there is increasing evidence that such



Sodium Channels. Figure 2 (a) Predicted secondary structure of a typical Na^+ channel α subunit. (b) Enlarged view of a transmembrane homology domain, showing segments postulated to comprise the voltage sensor and the selectivity filter in the pore lining ("p-element"). (c) Transmembrane "staves of a barrel" tertiary architecture involved in pore formation by α subunit homology domains.

subunits play important roles in regulating channel numbers, localization, and gating [4].

Sodium Channel Molecular Mechanisms

Pore formation: The four-fold pseudo-symmetry of Na^+ channel domains has been taken to imply that transmembrane pores are formed by an arrangement in which each internal repeat domain forms one quarter of the pore structure (Fig. 2). This architecture is highly similar to that of many other ion channels as described in other articles, e.g. K^+ channels that are formed by a four-fold association of individual subunits shown (►Neuronal potassium channels). A variety of ►mutagenesis studies have confirmed this "staves of a barrel" architecture.

Ion Selectivity: Classic biophysical studies provided evidence for thinking that the ion selectivity apparatus lay within the lining of the transmembrane pore itself, and consisted of a narrowing of the pore to form a "selectivity filter" (see [3]). It is currently thought that fully hydrated ions are too large to pass through the filter by themselves, and that the role of the selectivity filter is to remove their associated water, thus the naked ion would then be small enough to move past the barrier. Selectivity among ions would thus occur through differences in their relative affinity for water-removing selectivity filter. Such a view has largely been confirmed for other ion channels, and such a mechanism is assumed to operate for Na^+ channels.

The amino acid sequences responsible have been identified in Na^+ and other voltage-gated channels, and reside in the sequences between helices S5 and S6 termed the "P-element" or "P-loop" (Fig. 2). Thus Na^+ channels are postulated to contain four such loops, each one of which forms a quarter-sector of the cylindrical pore lining, and mutagenesis of the four P-loop segments in Na^+ channels has identified the region as crucial to the selectivity properties. In particular, two negatively charged glutamate residues have been

localized in this region that are thought to be responsible for binding the Na^+ cation, causing the Na^+ water of hydration to dissociate and allowing the ion to pass the selectivity barrier [5].

Voltage-sensitive gating (►Ion channel gating): The transmembrane segment S4 contains a strikingly unusual motif that consists of a repeated triad of two very hydrophobic amino acids (usually leucine, isoleucine, or valine) followed by a positively charged amino acid (arginine or lysine) [1,3,6]. This structure is found in all voltage-gated cation channels, and it is highly suggestive of a ►voltage sensor lying within the transmembrane electrical field. The basic idea is that sufficient changes in transmembrane potential will cause motion of the S4 structure in the membrane, and it is this motion that is then mechanically coupled to other parts of the channel structure to open (i.e. activate) the pore. Thus mutagenic substitution of the positively charged amino acids for either neutral or negatively charged residues usually alters the voltage-dependence of channel opening. More recently, elegant biophysical experiments have been done in which fluorescent reporter probes have been introduced into these segments and surrounding structures [6]. These studies provide strong support for the identification of these S4 segments as voltage sensors in Na^+ channel gating, while they illuminate the actual molecular movements that give rise to activation gating.

The mechanism of Na^+ channel inactivation has also been successfully addressed in structure-function mutagenesis studies (see [6]). Evidence from a large number of classic electrophysiological studies suggested that inactivation for ion channels generally occurred through a mechanism in which the inactivation gate is a protein "ball" that enters and blocks the open channel from the inside of the membrane. For Na^+ channels, this "ball" lies in a highly conserved cytoplasmic sequence between domains III and IV, and is thus tethered to the channel by a "chain" formed by amino acid residues at both ends. This model has been elegantly confirmed in a series of mutagenesis experiments that have identified the critical residues this "ball and chain" mechanism. Mutagenesis and biophysical experiments have also identified candidate sites within the channel to which the ball binds to occlude the pore.

Molecular Diversity of Na^+ Channels: Isoforms

As described earlier, Na^+ channels consist of a large polypeptide "α subunit" that forms the pore and gating structures, along with a variable number of accessory β subunits. Nine genes that code for Na^+ channel α subunits and four β subunits have been identified in mammals. The nomenclature that evolved for the different α isoforms was awkward and inconsistently used, thus a simpler nomenclature has been proposed that is now accepted in which individual α polypeptides are designated as $Na_v1.x$, where "x" ranges from 1 to 9. In addition, a rather mysterious Na^+ channel-like protein has been identified from cDNA clones and has been termed an "atypical" Na^+ channel, or Na_v2 in the current nomenclature. Based on difficulties in studying its functional properties, it is still uncertain whether it is a functional Na^+ channel in vivo. Lastly, the four β subunits, designated as β1 through β4, have similar structures consisting of a single transmembrane domain with a short cytoplasmic tail and an extracellular domain that has ►immunoglobulin-like motifs [4].

Finally, although there has been no systematic study describing all the molecular isoforms generated by each Na^+ channel gene, it is likely that each gene gives rise to a geometric increase in protein isoforms due to alternative splicing and editing of mRNA, to posttranslational modifications, and to different combinations of subunits. The physiological significance of such potentially great molecular diversity of Na^+ channels has only recently started to become clearer.

Physiological Significance of Na^+ Channel Diversity

Functional Variations Among Na^+ Currents in Cells and Tissues in vivo

In addition to their central role in mediating the propagating action potential, Na^+ channels have been recently recognized to play an increasing number of roles in sensory transduction and in signal processing events (see above). These different roles would seem to require different functional forms of Na^+ channels to serve each one of them. However, it has been difficult to study the functional properties of different channel isoforms in actual nervous tissues because multiple isoforms are nearly always co-expressed in a given neuron. Thus such studies have often utilized ►heterologous expression systems in which cDNAs encoding a specific channel isoform are introduced into a cell line that has no (or nearly no) Na^+ channels of its own.

In any case, significant functional differences in basic voltage gating behavior have been found among isoforms. For example, the $Na_v1.6$ isoform generally displays very rapid kinetics, which is assumed to be adapted to its role as the primary isoform involved in fast *saltatory conduction* of frequency-encoded information over myelinated fibers (►Action potential propagation). On the other hand, peripheral nervous system isoforms such as $Na_v1.7$ and $Na_v1.8$ display slow kinetics of gating, which are thought to be somehow important to their role in the transmission of pain information from the site of injury [7] (►Voltage-gated sodium channels: multiple roles in the pathophysiology of pain).

In addition, when co-expressed with various α isoforms, β subunits cause significant alterations to Na^+ channel function to occur, the details of which depend on the specific combination of α and accessory subunits in the complex [4]. For example, association of β4 with

$Na_v1.6$ results in a Na^+ channel with highly unusual inactivation properties that appear to be required for the spiking behavior of the ►Purkinje neurons in which it is expressed. Thus differential association of accessory subunits is a basis for generating additional functional diversity among Na^+ channel isoforms.

Sodium Channel Isoforms are Differently Modulated by Intracellular Signaling Cascades

Sodium channels are substrates for biochemical modification by protein kinases (i.e. PKC, PKA, RPTPβ), and such modifications result in significant changes to the functional properties of channels in vivo [2]. Such dynamic, cell signaling-related changes are known collectively as ►ion channel modulation. Recent work has established that modulation effects are isoform-specific. For example, PKA appears to reduce the number of Na^+-conducting $Na_v1.2$ channels while it otherwise specifically affects the gating kinetics of the $Na_v1.8$ isoform. Overall, it appears that Na^+ channel isoforms may indeed be differentially modified by a variety of mechanisms, and this may serve as the basis for the specific regulation of Na^+ currents within individual cell types and tissues.

Differential Expression and Localization of Na^+ Channel Isoforms in Tissues: Targeting and Clustering

The above suggests that functional and regulatory differences among Na^+ channel isoforms allow the tissue-specific expression and modulation of electrical signaling properties. Thus it has been found that Na^+ channel isoforms are differentially expressed among excitable tissues. Figure 3 summarizes information derived from ►immunocytochemical studies (►immunocytochemistry) regarding the selective localization of Na^+ channels in excitable tissues. It would seem that the expression of individual Na^+ channel isoforms is highly tissue/cell specific (see Fig. 4 for examples). Thus two isoforms are selectively expressed in muscle, while three appear to be peripheral nervous system specific. Nonetheless, there are a few recent reports of expression of these isoforms in the central nervous system, so the tissue-selective expression of some isoforms is still uncertain.

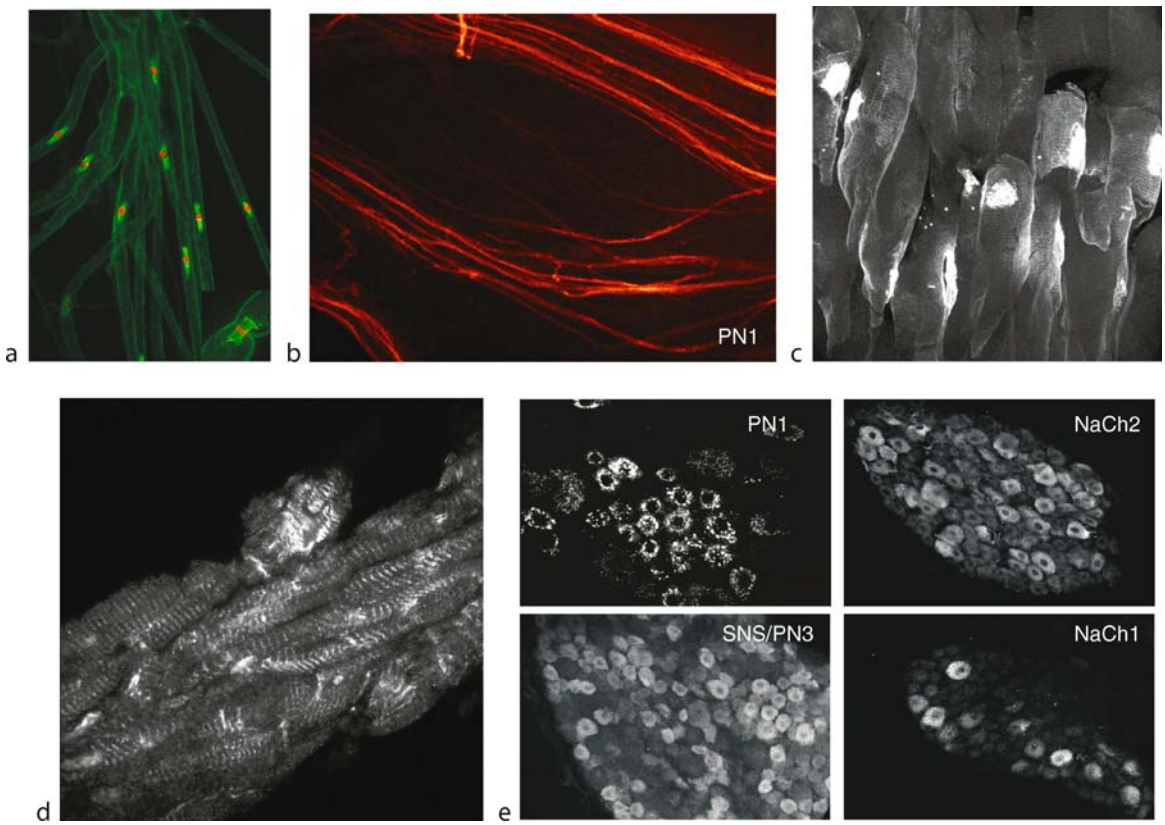
In addition, even within a given cell, different isoforms are usually selectively targeted to different specializations, such as dendrites or the axon hillock. For example, in retinal ganglion cells (►Retinal ganglion cells), the $Na_v1.2$ isoform is expressed in the unmyelinated segment of the neuron axon within the retina itself, whereas $Na_v1.6$ is selectively clustered at ►nodes of Ranvier in the ►optic nerve. Thus there must be cellular targeting mechanisms to achieve the differential distribution of these two isoforms in the same axon. At present the mechanisms behind the selective targeting of Na^+ channels are being actively investigated.

The formation of high-density clusters of Na^+ channels at nodes of Ranvier is one aspect of Na^+ channel targeting and clustering that is being actively studied by a number of laboratories. These clusters are essential to the mechanism of high-speed saltatory conduction in myelinated nerve axons (►Action potential propagation). Here the neuron must precisely target the $Na_v1.6$ isoform to the minute domains of the nodal gaps, and it must do this for nodes that may be many thousands of cell diameters remote from the soma where the channels are synthesized. How might such a spectacular process of transport, targeting, and clustering be achieved?

Sodium channel isoforms

$Na_v1.1$ (Type I)	*Dendrites*
$Na_v1.2$ (Type II/IIA)	*Unmyelin. initial segments*
$Na_v1.3$ (Type III)	*Early neuronal development*
$Na_v1.4$ (SkM1, μ1)	*Skeletal muscle (mature)*
$Na_v1.5$ (H1, SkM2, μ2)	*Heart, Immature Skel. musc.*
$Na_v1.6$ (Cer3, PN4)	*Nodes, synapses, dendrites*
$Na_v1.7$ (PN1, hNE-Na, Nas)	*Unmyelinated PNS (pain)*
$Na_v1.8$ (SNS, PN3)	*Unmyelinated PNS (pain)*
$Na_v1.9$ (NaN, SNS2)	*PNS – free nerve endings*
$Na_v2.x$ (ret1, NaG, *atypical*)	*Nonmyelinating Schwann c.*

Sodium Channels. Figure 3 Sodium channel isoforms and their known distributions in excitable tissues. Also given are older alternative isoform protein designations: Genomic nomenclature is also sometimes used, but is not shown here.



Sodium Channels. Figure 4 Images of the subcellular localization of various Na^+ channel isoforms as seen using isoform-specific immunofluorescence techniques. (a) $Na_v1.6$ channels (red fluorescence) at nodes of Ranvier. These are mouse sciatic nerve axons co-labeled for caspr (green), a protein found in paranodal glia-axonal junctions. (b) $Na_v1.7$ (a.k.a. PN1) isoform expression in unmyelinated fiber bundles of mouse sciatic nerve. (c) $Na_v1.4$ expression in rat skeletal muscle. Note the intense labeling of postsynaptic Na^+ channel clusters, while weaker labeling of t-tubules is also apparent (as seen in the z-line labeling pattern). (d) $Na_v1.5$ expression in rat cardiac ventricular myocytes. Note intense staining of intercalated discs between myocytes and the t-tubule staining pattern. (e) Expression of isoforms in the dorsal root ganglion. Isoforms are identified by the older nomenclature. Note that expression of isoforms varies among different sized subpopulations of neurons, i.e. smaller neurons express PN1 and SNS ($Na_v1.7$ and 1.8), while larger neurons express $Na_v1.1$ and $Na_v1.2$.

Part of the answer to this question appears to be that myelinating glia (i.e. ►Schwann cells in the peripheral nervous system, ►oligodendrocytes in the central nervous system) assist the neuron by specifying where nodal clusters are to be formed. In particular, immunocytochemical studies show that when glia start to form compact myelin during development, Na^+ channel clusters quickly form at the ends of the myelinating glial cell. Further, as the myelin sheath extends along the axon, these clusters appear to move with it at the edge of the growing glial processes. This motion continues until adjacent myelin sheaths come close to one another; at this point the adjoining clusters appear to fuse to form a stable nodal cluster [8].

At the other end of the nodal clustering process, a number of proteins have been described that define the nodal membrane domain, while others have been identified as being part of the actual Na^+ channel cluster complex (see [9]). In particular, ►ankyrinG is thought to be the link that joins Na^+ channels to the axonal cytoskeleton, but this interaction seems to take place between ankyrinG and the β1 subunit.

Roles of Na^+ Channels in Human Disease: Na^+ Channelopathies

Finally, a growing number of human disorders have been identified with defects in Na^+ channel function or expression [10] (see ►Channelopathies; ►Voltage-gated sodium channels: multiple roles in the pathophysiology of pain). Best characterized are the periodic paralyses (►Familial periodic paralysis) and certain myotonias (►Myotonia) of muscle and certain heritable forms of long Q-T syndrome of the heart; these involve $Na_v1.4$ and $Na_v1.5$ isoforms, respectively. In the

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nervous system, several forms of ►epilepsy and pain disorders have been linked to genetic defects in the functional properties of Na^+ channel isoforms, particularly $Na_v1.1$ and $Na_v1.7$ (►Voltage-gated sodium channels: multiple roles in the pathophysiology of pain). In addition, a form of epilepsy has been associated with a defect in β1 expression. No doubt other human disorders will be identified as Na^+ channelopathies of other isoforms, especially since animal diseases have been associated with such defects (e.g. $Na_v1.6$ channelopathies in mice).

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Sodium (Na^+) Channel Activation

Definition

The transient opening of a Na+ channel upon application of a depolarizing stimulus, which allows the selective inflow of Na^+ ions down the electrochemical gradient.

►Action Potential
►Sodium Channels

Sodium (Na^+) Channel Fast Inactivation

Definition

Rapid inactivation (within milliseconds) of the channel which is accomplished by the structural rearrangement that cause blocking the cytoplasmic end of the channel's pore by the inactivation gate residues, thus terminating the inflow of Na^+ ions.

►Action Potential
►Sodium Channels

Sodium (Na^+) Channelopathies

Definition

Pathologies linked to mutations in genes encoding voltage-gated Na^+ channels, or to dysregulation of these channels under pathological conditions.

►Voltage-gated Sodium Channels: Multiple Roles in the Pathophysiology of Pain

Soft Determinism

Definition

The thesis that determinism is true and is compatible with free action.

►Freedom of Will

Solitary Nucleus

Synonyms

►Nucl. solitarius

Definition

Long cell column in the floor of the fourth ventricle, at the level of cranial nerves X, IX and VII. The nucleus has two parts:

- Solitary nucleus, gustatory part
- Here terminate relevant fibers of cranial nerves X, IX and VII.
- Solitary nucleus, cardiorespiratory part Here terminate mucosa-innervating sensory fibers from cranial nerves VII, IX, and X. Efferents go to the dorsal nucleus of the vagus nerve, medial parabrachial nucleus and to the dorsal tegmental nucleus. Direct fibers to the spinal cord course via the soiitariospinal tract.

►Myelencephalon

Solitary Tract

Synonyms
►Tractus solitarius

Definition
The solitary tract comprises afferent fibers of cranial nerves VII, IX and X, which after entering the brainstem embark on a rostrocaudal course to gradually terminate in the solitary nucleus.

►Myelencephalon

Soluble NSF Attachment Protein Receptor (SNARE)

Definition
A protein which facilitates the binding of NSF to the SNARE complex. Isoforms of this protein are identified by a Greek letter (e.g. α-, β- or γ-) before the term. They can form a complex called the SNARE complex which is important for the process of exocytosis. In synaptic terminals the key SNAREs are: syntaxin, synaptobrevin and SNAP-25.

►Non-synaptic Release
►SNARE Proteins
►Soluble NSF Attachment Protein Receptor (SNARE)

Soma

Definition
Soma is the synonym of cell body.

Soma-Soma Synapse

Definition
Synapse formed between two neuronal cell bodies.

►Synaptic Transmission: Model Systems

Somatic Features

Definition
For a diagnosis of major depression with somatic features, the individual must display at least four of the following: marked loss of interest or pleasure in activities that are normally pleasurable; lack of emotional reaction to events or activities that normally produce an emotional response; waking in the morning 2 hours or more before the usual time; depression is worse in the morning; marked psychomotor retardation or agitation (observed by other people); marked loss of appetite; weight loss (5% or more of body weight in the past month); marked loss of libido.

►Major Depressive Disorder

Somato-Autonomic Reflex

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Synonyms
Somato-visceral reflex

Definition
A somato-autonomic reflex is a reflex elicited by stimulation of somatic tissue (strictly speaking, tissue of

the musculoskeletal system and the dermis of the skin), and manifesting as an alteration in autonomic nervous system function. Altered autonomic nervous system function may or may not subsequently lead to changes in the function of dependent organs, in which case one could properly refer to the phenomenon as a somato-visceral reflex. However, one should also keep in mind that somatic stimulation may evoke mechanisms external to the autonomic nervous system which, nonetheless, impact visceral function and would therefore constitute somato-visceral reflexes. Such mechanisms include humoral, immune and non-autonomic neurological processes. Thus, while the terms somato-autonomic and somato-visceral are often used interchangeably, there are differences in nuance.

Characteristics

Quantitative Description

A great variety of somato-autonomic reflexes has been described in the research literature, and a number of these reflexes have considerable clinical importance. In conscious subjects, somatic stimulation is likely to lead to somatic sensation and to emotional responses that add a further level of complexity to somato-autonomic interactions. Hence, it is extremely challenging to isolate somato-autonomic reflexes in conscious humans and animals. In anesthetized animal preparations, however, somatic stimulation has been clearly shown to elicit responses in autonomic efferent nerves and, thereby, in the functions of various organs. Indeed, a comprehensive review of the literature [1] has revealed somato-autonomic reflexes arising from noxious and innocuous thermal, mechanical and chemical stimulation of virtually all somatic structures investigated, and manifesting in, for example, the cardiovascular, digestive, urogenital and endocrine systems.

Higher Level Structures

►Central structures regulating autonomic function [link to essay "Central Regulation of Autonomic Function" by Dr. Benarroch] have been described comprehensively elsewhere in this text. Important centers for autonomic output, such as the nucleus tractus solitarius (►NTS [link to glossary item "Nucleus of the Solitary tract" by Dr. Benarroch]) and rostroventrolateral medulla (►RVLM [link to glossary item "Rostral Ventrolateral Nucleus (RVLM)" by Dr. Kannan]), receive inputs from higher centers and thus are influenced by, for example, emotional state. These same centres also receive visceral sensation which contributes to the generation of ►viscero-visceral reflexes [link to glossary item "viscero-visceral reflex" by Dr. Budgell] such as the ►baroreceptor reflex [link to glossary item "Baroreceptor reflex" by Dr. Dampney]. Additionally, autonomic nuclei in the brain stem receive relays from centres which receive noxious input, including noxious input from somatic tissues. Thus, somatic pain influences central autonomic function indirectly, through emotional responses to pain, and also through less circuitous relays [2]. Important within the context of somato-autonomic reflexes, is the more recent demonstration of direct inputs from somatic afferents to central autonomic motor nuclei; see, for example [3].

Lower Level Structures

The lower level structures contributing to somato-autonomic reflexes are somatic afferents, and sympathetic, parasympathetic and enteric motor neurons. The afferent limbs of somato-autonomic reflexes include group II, III and IV afferent fibers entering the spinal cord via the spinal nerves, and entering the brainstem via the trigeminal nerve. There is also emerging evidence to suggest that group Ia or Ib afferents (from muscle spindles and Golgi tendon organs) modulate some autonomic reflexes [4].

Higher Level Processes

The importance of central regulation of autonomic function is brought into sharp focus by the distressing and even life-threatening manifestations of ►disease effecting these structures [link to essay "Autonomic Insufficiency" by Budgell]. Furthermore, while a simplified view would hold that noxious stimulation increases sympathetic output, while innocuous stimulation decreases it (with the inverse effects on parasympathetic output) [5], clinical observations and laboratory experiments demonstrate that the higher autonomic centres are much more discriminating. As mentioned above and described in detail elsewhere in this text [link to essay "Central Regulation of Autonomic Function" by Dr. Benarroch], ►autonomic centres in the brain receive divergent input allowing the integration of emotion, information concerning the internal environment, and somatic sensory information. This permits them to generate not simply stereotypical responses, such as "►fight or flight response" [link to glossary item "fight-or-flight response" by Dr. Passatore], but rather responses which are specific to the immediate needs of the organism. Hence, by way of example, there will be occasions on which the higher level structures dampen what might otherwise be exuberant sympathetically-mediated hypertensive responses to pain. The adaptive importance of this discriminative potential becomes obvious in patients with high spinal cord injuries, and in laboratory animals subjected to experimental spinal cord lesions.

Lower Level Processes

In subjects with an intact nervous system, autonomic reflex responses may include excitation or inhibition of motor neuron activity, depending, in part, on the somatic afferent modalities involved; see for example [6]. Classically, noxious somatic stimulation has been

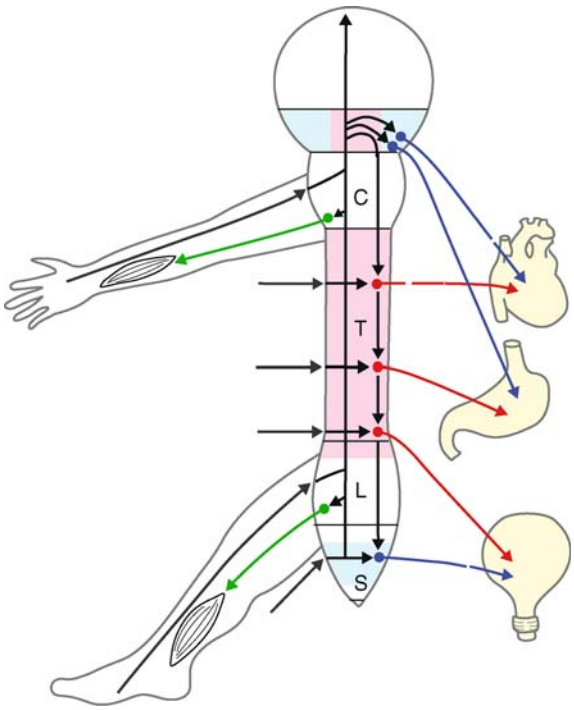
thought to increase the activity of peripheral autonomic nerves, and any number of experimental studies support this generalization; see, for example [7]. However, in animals subjected to spinal lesions, one can observe the native reflex activity of peripheral autonomic nerves below the level of the lesion in the absence of modulating influences from autonomic centres in the brain. In such animals, the peripheral autonomic motor neurons seem to be capable of only excitatory responses to stimuli [6]. Furthermore, these reflexes exhibit a clear segmental organization [7,8]. That is to say the reflex output of an autonomic motor neuron is likely to be greatest when the stimulation is conveyed by a sensory nerve which enters the same spinal cord segment. By way of example, noxious pinching of upper thoracic skin may preferentially excite the cardiac sympathetic nerves which originate in the upper thoracic region, and this leads to reflex ►tachycardia [link to glossary item "tachycardia" by Budgell]. On the other hand, noxious pinching of abdominal skin may preferentially excite the renal sympathetic nerves which originate in the lower thoracic and upper lumbar spinal cord of the rat, and this leads to increased blood pressure.

Process Regulation

It would appear that there are a number of parallels between somato-somatic and somato-autonomic reflexes. To use the patellar reflex as an example of a somato-somatic reflex, when one strikes the patellar ligament and stretches the quadriceps muscles, somatic information enters the spinal cord, synapses immediately with somatomotor neurons at the same level(s), producing an excitatory response – the leg jumps. Furthermore, it appears that this reflex is normally dampened by inhibitory influences descending from the brain, such that the reflex often becomes exhuberant with brain or spinal cord injury. Similarly, it appears that somatic information entering the spinal cord may synapse with autonomic motor neurons originating in the same region of the cord, producing an excitatory response – for example, an increase in heart rate or blood pressure. As with the somato-somatic reflex, it appears that such somato-autonomic reflexes are often dampened by inhibitory influences descending from autonomic centres in the brain.

This model of somato-autonomic reflexes is both attractive and logical, but has been slow to emerge due to the complexity of autonomic anatomy and physiology. In particular, early experimentation into somato-autonomic reflexes often employed noxious stimulation of limb afferents; a model which obscures the segmental organization of autonomic function. This is because somatic sensory information from the forelimbs and hind limbs enters the spinal cord at the cervical and lumbar enlargements, respectively. In these regions of the spinal cord, there are many somatic motor neurons to control limb movement, but relatively few autonomic motor neurons. Hence, autonomic reflex responses to limb stimulation are necessarily mediated primarily at the supraspinal level, and so are abolished by transection of the upper cervical spinal cord. It was only with systematic investigation of thoracolumbar stimulation that the segmental organization of somato-autonomic reflexes became apparent.

The thoracolumbar region of the spinal cord (exclusive of the lumbar enlargement) and the sacral region contain abundant ►preganglionic autonomic motor neurons [link to glossary item "preganglionic neurons" by Dr. Gabella]. In humans, preganglionic sympathetic neurons are concentrated in the intermediolateral and intermediomedial columns between, approximately, the first thoracic and the second or third lumbar segments. Preganglionic parasympathetic neurons form the intermediate columns in the second to fourth sacral segments. Hence, somatic afferents entering the spinal cord at these segmental levels have the potential to elicit local, spinally-mediated reflex responses, and may also synapse with projections to higher supraspinal centers (Fig. 1).



Somato-Autonomic Reflex. Figure 1 Schematic diagram of the reflex pathways for the somato-somatic and somato-autonomic reflexes (from Sato A. et al. 1997 [1]). Somatic stimulation of limb tissues elicits reflexes mediated primarily at the supraspinal level (in the brain), whereas somatic stimulation within the distribution of the thoracolumbar spinal nerves (the trunk region) has the potential to elicit both spinally-mediated and supraspinally-mediated reflexes.

Thus, stimulation within the distribution of the thoracolumbar and second to fourth sacral spinal nerves may elicit "segmentally-organized" somato-autonomic reflexes. That is to say, the stimulation may preferentially elicit responses in visceral organs receiving autonomic efferent innervation from the same (or adjacent) segmental level(s) as the involved afferents. Moreover, the segmental organization of these reflexes is likely to manifest itself more clearly when released from descending inhibitory influences, as for example when the cervical spinal cord is transected.

Clinical Implications

A number of somato-autonomic reflexes have well established roles in clinical practice. For example, ►paralytic ileus [link to glossary item "Paralytic Ileus" by H. Katayama] may be an important clue to the presence of local disease such as an occult fracture of the lumbar spine. Similarly, the ciliospinal reflex may be used to assess the extent of injury to the cervical sympathetic trunk. More recently, ►autonomic dysreflexia, [link to glossary item "autonomic/enteric dysreflexia" by Budgell] exhuberant autonomic reflex activity in patients with spinal injury, has emerged as an important clinical challenge. Historically, somatic stimulation has also been used in a variety of health care practices, including acupuncture and spinal manipulation, to manage visceral disease. Clinical and basic scientific studies suggest that somato-autonomic reflexes may account for at least some of the therapeutic effects achieved with these therapies [9].

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Somato-cardiovascular Reflexes

►Cardiovascular Reflexes

Somatosensory Cortex, Plasticity

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Definition

Somatosensory ►cortex is the part of neocortex of the forebrains of mammals that is activated exclusively or mainly by somatosensory stimuli. Somatosensory cortex is plastic in the sense that it can change in internal organization so that the response properties of neurons in the cortex are altered. Most notably, neurons that lose their major source of somatosensory activation following nerve or nervous system injury typically become responsive to remaining sources of activation.

Characteristics

Somatosensory cortex is divided into a number of functionally distinct regions called areas. Typically, each area represents cutaneous or (and) deep tissue (muscle and joints) receptors of the contralateral body in a systematic (somatotopic) pattern. Areas depend on inputs from the somatosensory ►thalamus and other somatosensory areas for activation. The loss of a source of activation, such as afferents from the hand, is typically followed by neurons developing responsiveness to remaining inputs, such as those from the face or arm. Sensory experiences can also alter the response properties of neurons, often in ways that they become more selective for the experienced stimuli. These plastic changes in somatosensory cortex are mediated by the growth of axons and the formation of new synapses

in the somatosensory system, as well as by cellular changes that influence the sensitivities of neurons to neurotransmitters.

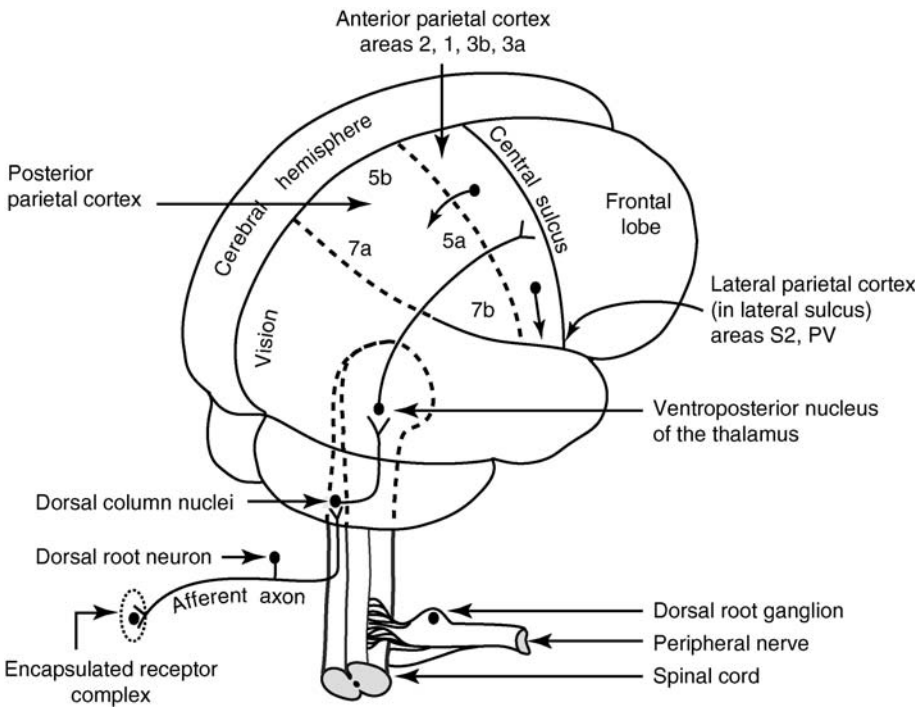
Plasticity in the Somatosensory System

Neural ►plasticity has often been observed during the development of the nervous system, in that the early loss of some input, such as that from the whiskers of the face in rats, will alter the course of development so that parts of somatosensory cortex that represent the whiskers fail to develop properly. Thus, sensory experience is essential for the normal development of the somatosensory system and somatosensory cortex.

The somatosensory systems of mature mammals are also plastic, but the mature system responds somewhat differently. In adult mammals, the response properties of cortical neurons are reversibly altered by sensory experience, often in ways that makes them more sensitive to relevant stimuli. Such changes in neuron response characteristics appear to mediate long-lasting improvements in sensory and perceptual abilities that are called ►perceptual learning. In addition, damage to the mature nervous system usually results in some reorganization of the system so that remaining neurons partially compensate for the loss, allowing some behavioral recovery. However, a major loss of sensory inputs results in an extensive reactivation of deactivated portions of somatosensory cortex by remaining somatosensory inputs in ways that result in misperceptions, such as feeling ►touch or pain in a missing (phantom) limb. Researchers are trying to understand the mechanisms of neural plasticity so that useful forms of plasticity can be promoted, and harmful types of plasticity can be prevented.

The Organization of the Somatosensory System and Somatosensory Cortex

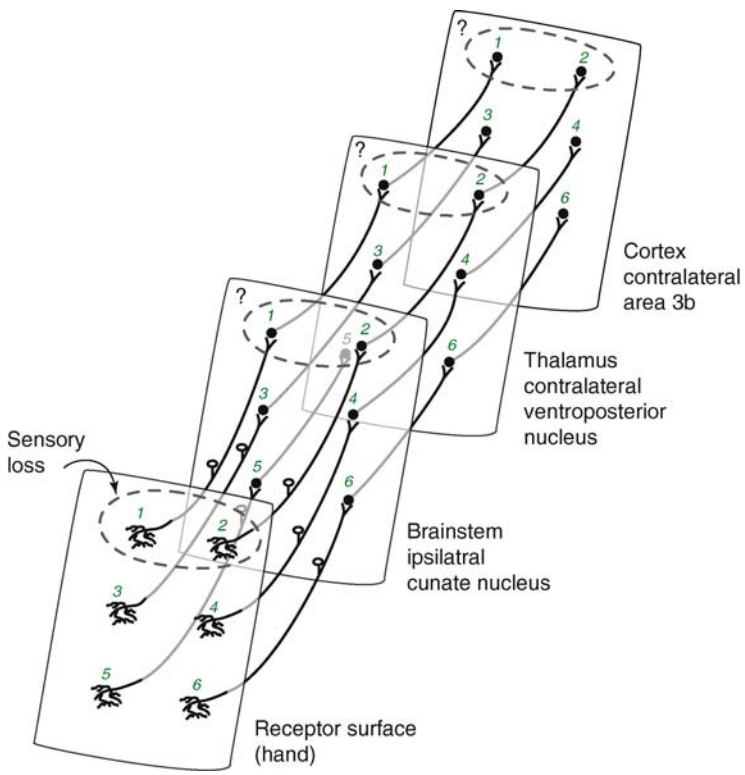
While the somatosensory system is complex, and involves several afferent pathways [1] nearly all of the studies of plasticity in the somatosensory system have focused on the major pathway that starts with encapsulated, low-threshold mechanoreceptors in the skin and reaches primary somatosensory cortex via the dorsal column-trigeminal nuclear complex in the ►brainstem and the ventroposterior ►nucleus in the thalamus (Fig. 1).



Somatosensory Cortex, Plasticity. Figure 1 The somatosensory system for tactile discriminations in humans. Afferents in peripheral nerves enter the spinal cord or brain stem and send branches to the dorsal column-trigeminal nuclear complex where the contralateral body surface is represented somatotopically. Neurons in these nuclei project to the ventroposterior nucleus of the thalamus of the contralateral cerebral hemisphere, where neurons project to primary somatosensory cortex (area 3b). Information is then relayed to other somatosensory areas. Cortical regions are numbered according to current use of the numbering system of Brodmann. *S2,* the second somatosensory area; *PV,* the parietal ventral area.

Much of the research in the plasticity of the mature somatosensory system after injury has involved alterations of the representation of the glabrous hand in area 3b (primary somatosensory cortex) of anterior parietal cortex. According to Bolanowski and coworkers [2], tactile experience in humans depends on combinations of neural activity in four peripheral nerve channels that appear to correspond to the two slowly adapting and two rapidly adapting classes of low-threshold mechanoreceptor afferents. These afferents enter the spinal cord and course rostrally in the dorsal columns to the dorsal column nuclei, including the cuneate nucleus for afferents from the upper limb, the gracile nucleus column nuclei for the lower body, and the trigeminal nucleus for the head. These nuclei of the lower brainstem project to the ventroposterior nucleus (VP) in the contralateral thalamus. The ventroposterior nucleus, in turn, projects densely to layer 4 of area 3b, and to layer 3 of area 1 in anterior parietal cortex. Area 3b distributes tactile information to areas 1, 2, and 3a of anterior parietal cortex, and to the second somatosensory area, S2, and the parietal ventral area, PV, of lateral parietal cortex in the lateral sulcus. These areas distribute tactile information to additional areas in lateral parietal and posterior parietal cortex, as well as to motor cortex. The subcortical nuclei and most of the ►cortical areas of the somatosensory system contain systematic, topographic (somatotopic) representations of the body, including the glabrous hand. Thus, at least the early stages of the ascending somatosensory processing hierarchy of nuclei and areas can be portrayed schematically as a series of surfaces where the order of the distribution of receptors in the skin is preserved in representations of the skin at each level (Fig. 2).

While the representation of the fine grain of the receptor array is degraded somewhat from level to



Somatosensory Cortex, Plasticity. Figure 2 A schematic of the early stages of the portion of the somatosensory system that processes tactile information from the mechanoreceptor of the skin. In this schematic, the surface of the hand is portrayed as a simple sheet, with subsequent targets in the nervous system as similar sheets. The important point is that the order of afferents subserving receptors of the hand is preserved as they terminate in the cuneate nucleus of the brainstem, and the order is further preserved as neurons project successively to the thalamus and cortex. Thus, removing some of the afferents, such as those from positions 1 and 2 (*dashed lines*) immediately deprives neurons at the 1 and 2 positions at subsequent levels of their sources of tactile activation. Plasticity is demonstrated when any of these deprived zones of nuclei or cortical areas recover responsiveness to any of the preserved inputs.

level, as receptive fields for neurons become larger, orderly ►somatotopic representations are found at each stage up to and beyond area 3b to also include the representations in areas 3a, 1, 2, S2, PV and elsewhere. In rats, and many other mammals, similar processing hierarchies exist, but they are less elaborate at the cortical level. In rats and other mammals, primary somatosensory cortex, S1, corresponds to area 3b of primates.

The Immediate Consequences of Sensory Loss

In either monkeys [3] or rats [4], the immediate consequence of removing a portion of the tactile afferents from the body is to completely deactivate the corresponding portions of each successive representation in the hierarchy. Thus, if afferents from skin locations 1 and 2 in Fig. 2 are eliminated by sectioning them in the dorsal columns of the spinal cord, neurons in locations 1 and 2 in the brainstem, thalamus, and primary somatosensory cortex will no longer respond to tactile stimulation on skin locations 1 and 2, or any other place on the body. In some higher order representations such as S2, where the convergence of inputs creates larger receptive fields that include locations 3 and 4 as well as 1 and 2, neurons in partially deprived cortex will respond only to touch on locations 3 and 4 and not 1 and 2, thereby having smaller receptive fields. This complete or partial deactivation of neurons is exactly what one would expect from the diagram in Fig. 2, but the brain is not stable like the diagram, and the somatosensory system immediately starts to recover from the damage. What occurs depends in part on the species (rat or monkey) and the age of the animal at the time of injury. Also, the type of recovery is more dependent on the magnitude of the sensory loss rather than the way the loss occurred. Thus, similar recoveries can occur after damage to peripheral sensory nerves, the section of the dorsal roots of sensory serves as they enter the spinal cord, section of ascending branches of afferents in the dorsal columns of the spinal cord, or even the loss of a limb via therapeutic amputation.

Plasticity after Sensory Loss in Mature Primates

After a sensory loss in primates, a process begins that starts to reactivate the deactivated neurons via remaining afferents [5]. If the loss is limited, such as the loss of afferents from part of the glabrous hand via section of the median nerve, reactivation proceeds rapidly over the course of 2–3 weeks, with most of the deprived neurons acquiring new receptive fields on the dorsal, hairy surface of the hand and digits. The reactivation is complete or nearly complete at the level of the cortex, nearly complete at the level of the thalamus, and partial, but extensive, at the level of the cuneate nucleus in the brainstem. As afferents from the back of the hand terminate in the cuneate nucleus very close to those from the glabrous hand, the critical mechanism of reactivation is likely to be the local sprouting of preserved afferents in the cuneate nucleus to synapse on and activate denervated neurons. Although the reactivation of neurons in the cuneate nucleus is incomplete, these reactivated neurons project to the ventroposterior nucleus of the thalamus where the activity is amplified to include more neurons at the thalamic and cortical levels via the divergence of projections in each relay, and the lateral (horizontal) connections in cortex. In addition, there is likely to be some axon sprouting and the formation of new connections at the thalamic and cortical levels to further promote reactivation. Reactivation is also promoted by self-regulatory cellular mechanisms such that deprived neurons produce less inhibitory neurotransmitters and fewer receptors for inhibitory neurotransmitters, thereby making them more sensitive to remaining inputs.

If the sensory loss is such that all inputs are sectioned from some digits, but at least a few inputs remain from other digits, deprived cortex becomes completely or nearly completely reactivated by preserved inputs from the hand, including those that were so sparse that initially they failed to activate any cortical neurons [3,6]. This reactivation results in a considerable recovery of hand use in skilled behavior, such as in retrieving food. Thus, the cortical reactivation is clearly useful. This recovery of cortical activation and behavior occurs over a period of weeks to several months, and again it depends on the growth of new connections in the dorsal column cuneate nucleus, and possibly in the thalamus and cortex.

A greater sensory loss, such as the loss of all the afferents from an arm after an injury and therapeutic amputation, or after extensive damage to the dorsal roots of nerves subserving the arm, is followed after months of recovery in the reactivation of the deprived parts of somatosensory cortex. Cortex that is normally devoted to the hand can be reactivated by inputs from the stump of the amputated limb or from the face [7,8]. Similar, but possibly less complete reactivations of the deactivated portions of the ventroposterior nucleus of the thalamus have been observed in both monkeys and humans. As with more limited sensory losses, the growth of new connections at the level of the brainstem, and the amplification of those effects at higher levels, seems to be critical to the cortical reactivation. Such extensive reactivations appear to be largely maladaptive, as patients with arm amputations report feeling touch on the fingers of the missing hand after being touched on the face or arm stump. A similar reorganization of the pain system could account for the feeling of pain in missing limbs of patients after amputations (phantom pain). Thus, not all outcomes of brain plasticity are good, and

we need to learn how to promote types of plasticity that restore lost abilities while preventing types of plasticity that lead to misperceptions and pain.

Plasticity of the Somatosensory System in the Developing Brain

The effects of sensory loss can be quite different in developing and mature brains. The section of somatosensory afferents of the forelimb in the spinal cord of the developing brain of rats around the time of birth can cause a rapid degeneration of the relay neurons in the cuneate nucleus of the brainstem and a loss of the normal modular organization of the nucleus that reflects the normal somatotopy [9]. Most of the deprived neurons in the brainstem apparently die before they are reinnervated by the sprouting of preserved tactile inputs. As a result, the deprived portion of the ventroposterior nucleus fails to develop, and even much of deprived primary somatosensory cortex (S1) fails to histologically develop or acquire a source of somatosensory activation. However, preserved afferents from the anterior upper arm may activate forelimb cortex, and these afferents typically activate a larger than normal portion of S1, including some of the deprived forepaw region, demonstrating that preserved afferents also enlarge their cortical territory in the developing somatosensory system. Similar results have been obtained after forelimb amputation in neonatal rats. In addition, after forelimb amputation, some hind limb afferents grow into the cuneate nucleus to activate and preserve neurons.

Presently, little is known about what happens to the somatosensory system after sensory loss in newborn primates. However, the degeneration of the deprived portions of the brainstem relay nuclei would remove one site that is important in the reactivation of cortex in adults.

Plasticity Following Somatosensory Experience

Sensory experience and learning produce changes in somatosensory cortex that are often called "use-dependent plasticity." During development, the extensive use of a part of the sensory surface can lead to an over-representation of that surface, while the disuse of a surface can result in an under-representation of that part. Such sensory experience, or lack of experience, can alter the course of development so that changes in representation are difficult or impossible to reverse after the brain matures.

Sensory experience also changes the organization of the somatosensory system in mature mammals. In contrast to the usual outcome of developmental plasticity, changes induced by experience in the mature somatosensory system can be rapidly reversed. The changes are largely at the level of single neurons and small groups of neurons, and therefore they are not expressed as large changes in somatotopy. For example, neurons in somatosensory cortex of rats that respond mainly to the movement of a single whisker on the face typically increase their responsiveness to an adjoining whisker, if the two whiskers are repeatedly stimulated together (called whisker pairing). Similar changes in the response properties of neurons in somatosensory cortex of monkeys have been shown to follow training and sensory experience. Over periods of disuse or altered use, the changed properties of cortical neurons typically reverse. The ability of neurons to change how they respond to stimuli apparently depends cellular mechanisms that alter synaptic strengths, and they often depend on co-activations of neurons by sensory inputs and by neurotransmitter systems that modulate neural activity [10]. As perceptual skills improve with training, and training changes the properties of cortical neurons in ways that would enhance the detection of the stimuli rewarded during training, such perceptual learning is often attributed to local regions of experience induced plasticity in somatotopic cortical representations.

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Somatosensory Cortex I

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Synonyms

Primary somatosensory cortex; First somatosensory cortex, SI

Definition

The cortical area first found to be specifically involved in somatosensory processing. It is in the postcentral gyrus in primates and in the postcruciate gyrus in cats. The human somatosensory cortex was defined earlier as the regions where electrical stimulation provoked subjective somatosensory experiences. In animals, cortical evoked potentials were recorded by electrical stimulation of the body surface to determine the location of the somatosensory cortex.

Characteristics

The somatosensory cortex I (SI) was located in the postcentral gyrus in primates. In humans, electrical stimulation of the postcentral gyrus evoked subjective somatic sensation and the somatotopic maps of the body representation over the cortical surface were drawn. In monkeys, cortical evoked potentials were recorded with shortest latency after stimulation of the periphery, either skin or nerves. Analogous somatotopic maps of the body representation were also drawn in various other mammals [1].

Cytoarchitectonic Subdivisions of SI

Brodmann assigned three different cytoarchitectonic areas in the postcentral gyrus of primates, areas 3, 1 and 2. Later area 3 was subdivided into areas 3a and 3b.

Thalamic Inputs to SI

SI receives direct projections from the thalamic ventrobasal complex, the specific somatosensory relay nuclei that mainly convey somatosensory signals from the periphery through the dorsal column-lemniscal system, and some through the spinothalamic tract. Sensory signals from deep tissues, muscles or joints project mainly to area 3a, while those from the skin or intra-oral mucous membrane, project mainly to area 3b. The projections from the ventrobasal complex also go to areas 1 and 2, but less heavily than to area 3. Area 2 receives some additional projections from the thalamic association nuclei such as the posterior nuclei.

Cortico-Cortical Association Connections of SI

The gray matter of the neocortex is composed of six layers. Axons of neurons in layer III project to other cortical areas as cortico-cortical association fibers. In SI, areas 3a and 3b project to areas 1 and 2, and area 1 to area 2. Areas 3a, 1 and 2 project anteriorly to the motor cortices. Areas 1 and 2 project posteriorly to areas 5 and 7. Areas 3b, 1 and 2 project to the second somatosensory cortex (SII) [2].

Callosal Connections of SI

Among neurons in layer III, some neurons send axons to the other hemisphere through the corpus callosum. Through these callosal fibers homotopic cortical regions of two hemispheres are connected. Generally speaking, the callosal fibers are scarce in the primary sensory areas. In SI, it is in 50 area 3b, the hand or foot region, in particular. They are seen only in the face or trunk region in area 3b. The callosal connections are denser in area 2 and more posterior in area 5, seen even in the hand or foot region [2].

Corticofugal Connections from SI

Neurons in the cortical layers V and VI send axons down to subcortical structures. Neurons in layer V send axons to the brain stem and spinal cord while those in layer VI send axons to the thalamus [2].

Somatotopic Representation of the Body Surface

SI is characterized by a topological (somatotopic) representation of the body over the cortical surface. In SI of the primate, the oral cavity, face, hand, arm, trunk, leg, and foot are represented orderly in the lateral-medial direction over the postcentral gyrus. Penfield and Boldrey (1937) invented a homunculus to describe such an arrangement. Maps of somatotopic representation of the body over the cortical surface were demonstrated in various other mammals by recording evoked potentials. The cortical tissue devoted to each body-part representation is not equal. The part of the body which is most exaggerated in the somatotopic map differs among animals. In primates, the cortical region for the oral cavity, face, hand, or foot is much larger compared to that of the trunk or the proximal part of the arms or legs.

Plastic Changes in the Somatotopy

It has been reported that amputation of a digit in macaques resulted in modification of the cortical representation map in a way to cover the representation area of the lost digit by that of adjacent digits. After extensive training to use certain digits this resulted in the enlargement of the representation of adjacent digits. Furthermore, in owl monkeys after extensive use of three digits together, neurons emerged with multidigit receptive fields, which were never seen in untrained animals in area 3b [3].

Blind persons who use three fingers together to read Braille frequently misperceive which of the fingers

actually touches the text. In these subjects an expansion and dislocation of SI hand representation were found by magnetic source imaging techniques [4]. The representation area of fingers measured by magnetic source imaging increased in the left hand in string players possibly as the result of extensive training [5].

Columnar Structures of SI and Diversity of Neuronal Receptive Field along a Perpendicular Array

There has been a hypothesis that the neocortex is columnar in its structure. The idea of columnar organization of the cortex in a physiological sense was first proposed in the cat somatosensory cortex by Mountcastle (1957). He described that neuronal receptive field locations tended to be similar among neurons recorded along an electrode track perpendicular to the cortical surface. He thought the phenomenon reflected the anatomical structure of vertical neuronal arrays in the cortex proposed by Lorente de No (1949). The columns were thought to be basic and elementary structures for the localization of functions in the neocortex.

The columnar structure in its original proposal was based on the assumption that a cortical locus represents a locus in the periphery faithfully, that is, the cortex is somatotopic. Receptive field characteristics of neurons in a single column could share a common thalamocortical input. It was thought that the barrel cortex in the rodent is a typical example: each barrel represents a single whisker hair there. However, recent studies show that it is not so simple in the barrel field (ref to Essay by Ebner). In other cortical areas in SI of monkeys that are more associative, such as areas 2 or 5, what is represented in the putative unitary structure is not clear-cut, because receptive field characteristics are not necessarily the same nor are they similar among neurons in a vertical array. Neurons in deep layers tend to have larger and more complex receptive fields [6,7].

Receptive fields of neighboring neurons diversify in conjunction with an increase in receptive field size and the complexity of neuronal properties in the crown of the postcentral gyrus, areas 1 and 2. In that sense, some investigators doubt that the cortex is modular. There are synonyms of column: mini-columns, modules, slabs, stripes, bands, barrels, beads, blobs, patches, puffs, lattices etc.

Hierarchical Processing in the Hand Region

Modern microelectrode techniques to record single neuronal activity in waking animals enabled scientists to analyze detailed organization of the enlarged cortical finger representation in the monkey [1]. The most important principle of information processing in SI is a hierarchical processing, that is, information each neuron bears becomes progressively more complex along the rostro-caudal axis of the postcentral gyrus [6]. In the finger region of area 3b in the monkey, the neuronal receptive field is small, often representing only a part of a phalange of a single finger. Functionally unique parts of fingers (i.e. tips, ventral glabrous surfaces, and dorsal surfaces) are represented separately, forming different subdivisions of area 3b. These subdivisions provide a basis for inter-digital integration of information in the more caudal regions of SI, areas 1, 2 and 5.

In areas 1 and 2, progressive inter-phalangeal or inter-digital integration takes place, and receptive fields of neurons become larger, covering more than one phalange of a finger, or more than one finger. The inter-digital integration is more remarkable in the ulnar fingers than in the radial ones. There are unique types of neurons in areas 1 and 2 with selectivity to specific features of stimulus, such as the direction of a moving stimulus; the presence of an edge or rough surface; those that are activated better or solely by the monkey's active hand movements, including reaching; or those facilitated or inhibited by attention.

Vertical Neuronal Arrays Representing Active Touch

Diversity in the receptive field of cortical neurons was also pointed out in conjunction with a perpendicular array of neurons [7]. Receptive fields of neurons recorded along a perpendicular penetration were often variable, but the largest receptive fields usually covered the others, and were found mostly in the infragranular layers. Often they included inhibitory receptive fields that were arranged side-by-side to the excitatory ones, and also some of them responded to both skin stimulation and joint manipulation. The key stimulus common to neurons in a perpendicular penetration was the contact of an object to the receptive field achieved during an animal's active behavior to manipulate objects. Thus the largest receptive field was designated as functional surfaces. They could be regarded as a functional assemblage that deals with a set of information concerning one of various aspects of active touch.

Bilateral Representation of the Body in SI

The hierarchical integration proceeds to combine information from the bilateral sides in the higher stages of hierarchical processing: a substantial number of neurons with bilateral or ipsilateral receptive fields are found in the caudalmost part (areas 2 and 5) of the postcentral finger region, and also in other body parts.

Neurons in SI usually have receptive fields on the contralateral body. Several studies reported the presence of neurons with bilateral receptive fields (Manzoni et al. 1989). According to these studies, these exceptional bilateral activities were limited to the body midline including the dorsal or ventral trunk, occiput, perioral face, or oral cavity. The midline structures are activated bilaterally in normal body use and thus have good reason to be represented bilaterally. From the

same functional standpoint however, even the distal and other body parts such as hands, shoulders, or feet should also be represented bilaterally. It had been generally thought such bilateral integrations were postponed to SII and the parietal association cortices.

Indeed, such bilateral activities have been found in the postcentral gyrus of macaque monkeys (Iwamura et al. 1994, 2001) [8]: bilateral hands, arms/shoulders and trunk, girdles, and feet neurons have been found in the caudalmost part of the postcentral gyrus (areas 2 and 5) in the dorsal bank of the intraparietal sulcus. These neurons were found systematically and nearly somatotopically. The bilateral receptive fields are large and the most complex types found in this gyrus. The distribution of the bilateral receptive field neurons roughly corresponds to that of callosal connections in this gyrus.

Hierarchical Processing in the Hand Region of Human Somatosensory Cortex

Recent progress in technology of investigating human brain activity such as MEG, PET, fMRI, TMS etc. enabled the confirmation that the organization of the human somatosensory cortex (SI) is based on the same principles as those found in macaque as described in the previous section. Precise cytoarchitectonic structures of the human SI have been described. Representation of single finger in multiple sites of the hand region, overlapping representation of different fingers, the increasing rostral to caudal convergence of finger representation, integration of cutaneous and kinesthetic information in the caudal region were described, and thus the presence of hierarchical processing of information was confirmed in the hand region of the human somatosensory cortex [9]. Inui et al. (2004) compared the latency of SEF potential and found that it becomes progressively longer as the recording site moves caudally in the postcentral gyrus, from area 3b to 1 and 2, and areas 5 and 7.

Attributes of Tactile Perception Represented in Cortical Activity

Cortical activities representing spatio-temporal patterns of tactile skin stimulation such as flutter-vibration, motion, direction, length, velocity of tactile stimulus, surface texture, spatial form, and so on, have been studied [1]. Studies of single cells in the somatosensory cortex SI have shown that responses reproduce essential object features presented to the skin and show response patterns similar in many cases to the primary afferent input signals. For example, the configuration of embossed dot ensembles is clearly evident in the response patterns across arrays of single cortical units. Some single cortical units have characteristics that appear to combine response characteristics of more than one afferent type, e.g. SAI and FAI afferents, providing an additional layer of information. DiCarlo et al. (1998) indicated that area 3b neurons act as local spatio-temporal filters and may contribute to form and texture perception.

Lesions placed in the caudal postcentral region cause disturbances in the discrimination of size, form and roughness of tactile objects. Neurons were found in the caudal part of the SI of monkeys that were activated by the contact of either round or elongated objects with edges (Iwamura & Tanaka 1978). These neurons were considered as neuronal correlates of stereognosis.

In human brain the presence of systematic and hierarchical organization to discriminate texture or object shape was shown [9].

Representation of Pain in SI (See Pain Section)

Single-neuronal recordings in the monkey established that nociceptive pathways project to area 3b and 1 of the somatosensory cortex SI. SI may be involved in the sensory-discriminative aspect of pain, especially stimulus localization. Intensity may be coded in other somatosensory cortical areas as well [10]. Pain has a strong emotional component, in addition to the sensory component, and is therefore processed by further distributed multiple cortical loci.

Pathology

Lesions of SI produce deficits in somaesthesia, including simple light touch, two-point discrimination, position sense, vibration sense and complex perceptual abilities such as tactile object recognition and visuo-tactile matching. In contrast, patients with lesions of the posterior parietal cortex (posterior S1 and areas 5 and 7) are particularly impaired on complex tasks. Some of these patients also show difficulties in generating exploratory and manipulative finger movements within the context of active touch, called limb kinetic apraxia (Liepmann 1910). Such observations suggest that the posterior parietal cortex is a key station in generating and executing exploratory movements utilizing both efference copy and sensory feedback.

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Somatosensory Cortex II

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Synonyms

Secondary somatosensory cortex; The second somatosensory cortex; SII

Definition

The cortical area involved in the somatosensory processing in the parietal operculumin in primates and in the lateral cortical region in the cat. It has been defined as a separate cortical region from SI based on the presence of an independent somatotopic representation of the body. The extent of SII and its functional role are still in debate.

Characteristics

Adrian (1940, 1941) found the second representations of the contralateral paw and toe being close to each other in a small portion of the lateral cortex of the cat. Penfield suggested the presence of the second somatosensory cortex (SII) in the human in the parietal operculum, in the Sylvian fissure (Rasmussen & Penfield 1947, Penfield & Rasmussen 1950): somatic sensations referred to the limbs or other body parts of either side (though more often the contralateral side) were obtained by electrical stimulation of the cortex. Woolsey (1958) later confirmed the presence of SII in various mammals [1].

Location of SII in Terms of Brodman's Cytoarchiteconic Areas

SII can be included in Brodmann's area 43, but they do not correspond to each other since the area 43 encompasses the postcentral face region of areas 3 and 1, and reaches the insula. Posterior to area 43, Brodmann identified area 40. Area 40, known as the posterior parietal association cortex, could include a part of SII [1].

Thalamic Projections to SII

Major thalamic nuclei projecting to SII are VPI (nucleus ventralis postero-inferior in the ventrobasal complex), PO (the posterior nuclei), and CL (nucleus centralis lateralis in the intralaminar nuclei). Sensory modalities reaching to the SII region are innocuous cutaneous, proprioceptive, and nociceptive.

Cortico-cortical Inputs to SII

SII in the primate receives ipsilateral cortico-cortical projections from each of the three cytoarchitectonic subdivisions of SI, areas 3b, 1 and 2, and areas 5 and 7 in the parietal cortex [1]. SII receives callosal inputs from the contralateral SI and SII.

Subdividing of SII Region

Monkey Studies

Based on single neuronal recording in monkeys (after halothene administration was discontinued), Whitsel et al. (1969) divided the second somatosensory area into two parts, rostral and caudal. They defined the rostral area as a true SII (SII/r) where neurons were activated solely by one modality of somatic stimuli from the contralateral side (thus the body representation was somatotopic), while in the caudal area the neuronal receptive fields were large (thus the body representation was not somatotopic) and some neurons were activated by visual or auditory stimuli. Robinson & Burton (1980) did more extensive microelectrode mapping in unanesthetized monkeys in SII and the surrounding areas. They found a rather complex somatotopic representation of the contralateral body in SII. Burton et al. (1995) divided SII into two parts, based on the labeled corticocortical connections from area 3b and 1 to the SII region: two somatotopic maps were in mirror image. Krubitzer et al. (1995) recorded multi-units in anesthetized monkeys and proposed that the lateral somatosensory cortex should be divided into two parts, SII and PV (parietal ventral area). One of the common findings in these mapping studies was that the distal limbs occupy the central and largest part of the SII region [1].

Recently, Fitzgerald et al. (2004) reported that the SII hand region comprises of three adjoining fields: posterior, central and anterior, by receptive field

analysis of single units recorded from unanesthetized macaque brain [2]. The central field receives cutaneous inputs only while the other two fields receive both cutaneous and proprioceptive inputs. The authors speculate that the three fields play different roles in tactile perception.

Human Studies

Disbrow et al. (2000) based on fMRI data proposed that the subdividing of SII cortex with the nomenclature of SII and PV proposed by Krubitzer et al. (1995) for monkeys was applicable to the human SII region. Mima et al. (1997) demonstrated two representations of the hand by recording SEPS and SEFS directly from the cortical surface of the human perisylvian cortex (SII).

Eickhoff et al. (2006) histologically mapped the SII cortex of human postmortem brains and identified four cytoarchitectonic areas: OP1–4 (for Operculum, 1–4 in caudal to rostral sequence) [3]. The authors claim that this cytoarchitectonic heterogeneity corresponds to results of fMRI studies on the human SII cortex.

Bilateral Body Representation

Earlier studies in monkeys pointed out the presence of neurons with bilateral receptive fields (Burton 1986, Manzoni et al. 1986, Whitsel et al. 1969), but survey for the bilateral representation have not been extensive. More recent studies in human using magneto-encephalography or neuroimaging techniques confirmed that the representation is bilateral in SII [4].

SII is a Higher Stage of Serial Information Processing

Monkey Studies

The notion that SII is hierarchically higher than SI in the information processing network was proposed on the basis of their anatomical relationships: SI sends projections to SII, while SII projects back to the superficial layers of SI (Burton et al. 1995, Caulier et al. 1998) [1]. Physiological studies have shown that SII neurons tend to have larger and more complex receptive fields, including bilateral ones [1]. SII has been viewed as being composed of at least two parts, with area 3b having greater connections to the anterior part (Burton et al. 1995). It was proposed that there is a hierarchical relationship between the two parts of SII with regard to the receptive field properties of their neurons. Jiang et al. (1997) have shown that neurons in SII signal a change in texture but not its magnitude; thus, SII neurons are of a higher-order than SI neurons, which show a graded change in discharge when the spatial periods of test gratings are increased [5].

On the other hand, neural activity in SII of the marmoset monkey and cat is not completely abolished by reversible inactivation of SI (Zhang et al. 1996, Rowe et al. 1996), leading to the suggestion that the strict serial processing scheme might be in need of revision. Zhang et al. (2001) concluded that SI and SII occupy a hierarchically equivalent network for tactile processing [6].

Human Studies

Inui et al. (2004) compared the latency of SEFs evoked by transcutaneous electrical stimulations applied to the dorsum of the left hand, just on the first metacarpal bone, and found that it becomes progressively longer as the recording site moves caudally in the postcentral gyrus, from area 3b to 1 and 2, and areas 5 and 7. The latency was even longer further in SII, indicating the presence of serial hierarchical processing from SI to SII [7].

SEFS evoked by median nerve stimulation have been recorded in SI, posterior parietal, parietal opercular (SII), and frontal regions (Mauguiere et al. 1997). On the basis of latency differences, it was assumed that the higher-order areas receive signals from SI through serial feedforward projections.

Huttunen et al. (1996) recorded SEFs in response to median nerve stimulation so as to measure changes in responsiveness during finger movements. The changes did not parallel those in SI, suggesting that the changes depended on additional modulatory inputs to SII rather than those from SI. The long latency component of SEF in response to stimulation of the posterior tibial nerve is affected by movement imagery of a toe in bilateral SII. Painful stimulation first activates contralateral SI and then bilateral SII, although it is not clear whether SII receives signals through SI or directly from the thalamus. SEFS in response to median nerve stimulation in SII are enhanced during thenar muscle contraction, possibly by decreasing inhibition from SI. Enhanced SII activation might be related to the tuning of SII neurons towards the relevant tactile input arising from the muscle.

Young et al. (2004) found that separation of hand and foot representation was clear in SI but less and less clear in SII in the order of OP4, OP2 and OP1. Instead, the rostralmost area (OP4) showed task-related enhancement [8].

Attention to Tactile Objects Alters Responsiveness of SII

Recent studies have identified neurons in the monkey somatosensory cortex with enhanced sensitivity and selectivity for stimuli to which an animal is directing its attention (Sinclare & Burton 1993, Hsiao et al. 1993, Burton et al. 1997). The authors argue that SII, rather than SI, plays a role in tactile attention because a larger number of neurons in SII is related to attention. Burton et al. (1997) found that tactile and auditory cues correlate with enhanced or suppressed average firing rates of SII or area 7b neurons (45–50% of neurons) in response to vibrotactile stimuli. These modulations are consistent with a model of possible neural mechanisms associated

with selective attention and confirm earlier suggestions that SII plays a role in tactile attention. The authors also suggest that area 7b might play a similar role.

Nelson et al. (2004) confirmed in a human fMRI study that SII was activated more often during an attention demanding tracking task compared with passive vibration.

Chapman et al. (2005) in the study to record neurons in monkeys that were activated by a texture discrimination task, concluded that the attentional mechanisms were dual, one involved both SI and SII, while the other was more specific to SII [9].

SII Neurons Activated by Decision-Making

Romo et al. (2002) found that some SII neurons were activated specifically at decision- making. They trained monkeys to compare two mechanical vibrations applied sequentially to the fingertips and to report which of the two had the higher frequency.

Activity of some SII neurons were correlated with monkey's decision-making to judge which of two stimuli (remembered and current) is higher in their vibration frequency [10].

SII for Proprioception

Fitzgerald et al. (2004) [2] reported by receptive field analysis of single units recorded from unanesthetized macaque brain, that the central field receives cutaneous inputs only while the other two, the anterior and posterior fields, receive both cutaneous and proprioceptive inputs. The authors speculate that three fields play different roles in tactile perception. Alary et al. (2001) in a human SEF study suggested that human left SII plays a predominant role in proprioceptive processing.

Projection of Pain in Human SII

Feretti et al. (2003) found in an fMRI study that the activity for the painful stimulation was localized more posteriorly compared to that for the nonpainful stimulation. Bingel et al. (2004) in an fMRI study showed that both SI and SII encode spatial information of nociceptive stimuli independent of tactile ones, and proposed the concept of a redundant representation of discriminative stimulus in somatosensory cortices. Marihofner et al. (2006) in an fMRI study concluded that SII plays an important role in the discrimination dimension of pain rather than the affective-motivational ones.

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Somatosensory Projections to the Central Nervous System

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Synonyms

Somatic Sensory Projections to the Central Nervous System

Definition

►Somatosensory projections arise from ►sensory receptors and nerve fibers distributed throughout the body as a whole, as distinct from those arising from the highly specialized sense organs for vision, hearing, balance, taste and olfaction. They are therefore concerned with the sensory modalities of touch, pain and thermal sensation, and the kinaesthetic sense which is the sense of body position and movement.

Characteristics

The Sources of Somatosensory Information

Much of the information contributing to the different modalities of somatic sensation is derived from sensory

receptors or nerve endings in the skin, in particular, for touch and thermal sensations. However, for kinaesthesia, the information is derived from receptors in muscles and joints, and to some extent, from those within the skin because, as fingers or limbs are moved, the cutaneous mechanoreceptors are subject to perturbation in association with the stretch or compression of the skin in the vicinity of the joints being moved. In the case of pain sensations, the input may be derived from almost any site in the body, including, of course, the skin, but also from muscles and joints, for example, in association with muscle injury or inflammatory diseases of joints. Inputs for pain sensation may also arise from pathophysiological disturbances in our internal organs and give rise to ►referred pain in which the pain is associated with an external body part, such as the left shoulder or arm, in the case of coronary-induced cardiac pain. The pattern of pain referral is crucial for differential diagnosis at a clinical level, and, in terms of its explanation, is thought to reflect convergence or overlap within the central nervous system (CNS) projections of nociceptive afferent nerve fibers arising from the affected visceral organ and from the somatic site to which the pain is referred.

The Nature of Somatosensory Receptors and Associated Afferent Nerve Fibers

The receptors and sensory nerve fibers responsible for the four modalities of somatic sensation fall into two broad groupings. First, the mechanoreceptors for tactile and kinaesthetic sensation are specialized transducer structures in which the sensory nerve ending has a complex association with non-neural cells. In contrast, thermal and pain information appears to be derived from naked sensory nerve endings in which the peripheral endings of the sensory nerve fibers, whether in the skin, muscles, joints or viscera, have some physicochemical specialization that enables them to act as transducers that convert the thermal or a variety of noxious stimuli into the electrical signals that are conveyed over the sensory nerve fibers to the CNS. A further distinction among these four modalities of somatic sensation exists over the diameter and conduction velocity of the sensory nerve fibers responsible for each modality of somatic sensation. These somatic sensory nerve fibers are usually classified into four major groups on the criterion of the cross-sectional diameter of the nerve fiber (or axon) and range from as fine as <1 μm in diameter (the group IV fibers, or C fibers as they are also known, that lack a fatty-insulating layer of ►myelin around the conducting cable of the nerve fiber) up to diameters of ~20 μm (the Group I fibers, which, like the Group II and III fibers, are said to be myelinated, because the nerve axon is ensheathed by a myelin layer that helps confer a faster signaling speed on the fiber. The largest and fastest conducting fibers (Gr. I and II) carry kinaesthetic and tactile information, whereas the Gr. III and IV fibers carry information for pain and thermal sensations. Fiber diameter correlates with the conduction velocity at which impulses are propagated along these somatic sensory nerve fibers, with velocities exceeding 100 m/s in Gr. I fibers, and ranging from ~40–70 m/s in Gr. II fibers, ~10–30 m/s in Gr. III fibers, and ~0.5–2 m/s in Gr. IV fibers. It should be emphasized that a peripheral somatic nerve such as the ulnar nerve (which is the one that passes close to the humerus bone near the elbow, and which, if bumped, generates pain and the pins-and-needles sensation) contains thousands of individual nerve fibers and includes not just the sensory, or afferent fibers, but also nerve fibers that convey signals outwards from the CNS to bring about muscle contraction, and others, the autonomic efferent fibers, that control blood vessel diameter and sweat gland activity.

The Projection of Somatosensory Information From the Periphery to the CNS

Somatosensory information for touch, kinaesthesia, pain and thermal sensations is carried from all parts of the body to the CNS via vast numbers of nerves that finally enter either the spinal cord or the brainstem, depending on their source in the body. Those arising below the head enter the spinal cord via a series of paired posterior nerve roots that extend all the way from the upper cervical levels of the cord down through thoracic, lumbar and sacral levels. Each pair of spinal nerves supplies a particular band of skin, known as a ►dermatome, and associated subcutaneous somatic or visceral structures. Inputs from the feet and legs enter at lumbo-sacral levels while those from the trunk, arms and hand enter at progressively higher levels of the spinal cord. Somatosensory information from craniofacial regions enters the brainstem directly via the fifth cranial nerve, known as the trigeminal nerve, and therefore mediates tactile and kinaesthetic sensations upon which we rely for the complex sensori-motor mechanisms involved in facial expression, speech and eating, together with pathophysiological ones associated with toothache and headache.

Projection of Somatosensory Information Within the CNS

Upon entering the CNS, somatosensory nerve fibers may project, as a result of branching in their axons, into more than one target site at which they make synaptic connections with neurones of the CNS. In this way, incoming signals may be distributed in parallel for different processing purposes, supplying, first, intraspinal nerve networks for the reflex regulation of posture and movement; second, central structures, such as the cerebellum, for the regulation of voluntary movements; and third, ascending pathways, crucial for conscious

sensory and perceptual experience, that convey the information to somatosensory areas of the cerebral cortex, in particular, the primary and secondary somatosensory areas of cortex (SI and SII respectively) located in the postcentral gyrus and the Sylvian fissure of the human cerebral cortex. In each of these cortical areas, the somatic inputs are projected in a so-called ►somatotopic pattern that retains the spatial relations of the body parts, but with the area of representation of those body regions being proportional to the density of somatosensory innervation of the region.

CNS Pathways for Ascending Projections of Somatosensory Information

There appear to be at least three major pathways within the spinal cord for conveying somatosensory information to higher centers of the brain for somatic sensation and perception. The first of these is the Dorsal Column (DC) system, made up, to a great extent, of Gr. I and II tactile and kinaesthetic sensory axons that project directly up the spinal dorsal columns before synapsing with neurones in the ►dorsal column nuclei (DCN) at the junction of the spinal cord and brainstem. Although inputs from the upper body, including the hand, project directly to the cuneate nucleus division of the DCN, those from the leg are conveyed over both direct and indirect paths to the gracile nucleus division of the DCN and a further division, known as nucleus Z, located just in front of the gracile nucleus [1]. Output from the DCN is projected across the midline of the brain and ascends via the medial lemniscus to the level of the ►thalamus, in particular, the ventralposterior (VP) nucleus, for further synaptic processing before the next stage of projection takes place to the SI and SII areas of the cerebral cortex.

The second principal ascending spinal cord pathway for ascending somatosensory information is the ►spinothalamic tract (STT) which arises from neurones of the spinal dorsal horn, and which, in contrast to the DCN, receives direct input from Gr. III and IV afferent nerve fibers responsible for signaling pain and thermal information [2]. However, there are also substantial inputs to this STT system from collateral branches of larger tactile afferent fibers. STT axons project from the dorsal horn across the midline of the spinal cord, ascending in the anterolateral columns of the cord, and project to a number of different nuclei of the thalamus.

The third of the major ascending somatosensory pathways at the spinal level is the ►spinocervical tract (SCT) system which, like the STT, arises from dorsal horn neurones [3]. However, the SCT axons project into the ipsilateral dorsolateral columns to the upper cervical cord where they synapse with neurones of the lateral cervical nucleus whose axons, in turn, project across the midline to ascend in association with the dorsal column-lemniscal pathway to the thalamus. The SCT system, whose input comes predominantly from tactile and nociceptive sources, is most prominent in carnivores, but is present in primates, including human beings [1,3].

Somatosensory information may also be conveyed to higher centers of the brain over less direct pathways, in particular, involving spino-reticular pathways (►spinoreticular tracts) whose functions are not entirely clear, but are probably not of major importance for the signaling of detailed discriminative information for sensory experience.

Role of Ascending Somatosensory Pathways Based Upon Experimental Surgical or Clinical Evidence

Lesions, whether in experimental animals, or in human patients, do not provide an unequivocal account of the functional role of each of the major ascending somatosensory pathways, principally because of the difficulty of confining the disruption selectively to the intended ascending pathway. Nevertheless, observations of this type, coupled with a knowledge of the inputs reaching each of these systems, have identified the DC system as the principal ascending pathway for tactile and kinaesthetic information, while the STT appears to be the principal path for pain and thermal signaling. This knowledge has been utilized at times for the alleviation of intractable pain in patients, by means of surgical interruption of the spinal anterolateral tracts [2]. Inferences about the function of the SCT system are especially difficult to derive from lesion data as the dorsolateral columns of the cord contain a mixture of different fiber tracts.

Function of Ascending Somatosensory Pathways Revealed by Electrophysiological Studies

Electrophysiological recordings from STT neurones, in particular, by Willis' group in Texas [2], have demonstrated that a great many are involved in nociceptive processing. However, some are responsive to gentle touch and may therefore contribute to the residual tactile sensory capacities that can survive if the DC pathway is damaged [4]. However, as the SCT is also involved in processing innocuous tactile information [3,5], it also remains a candidate for this role.

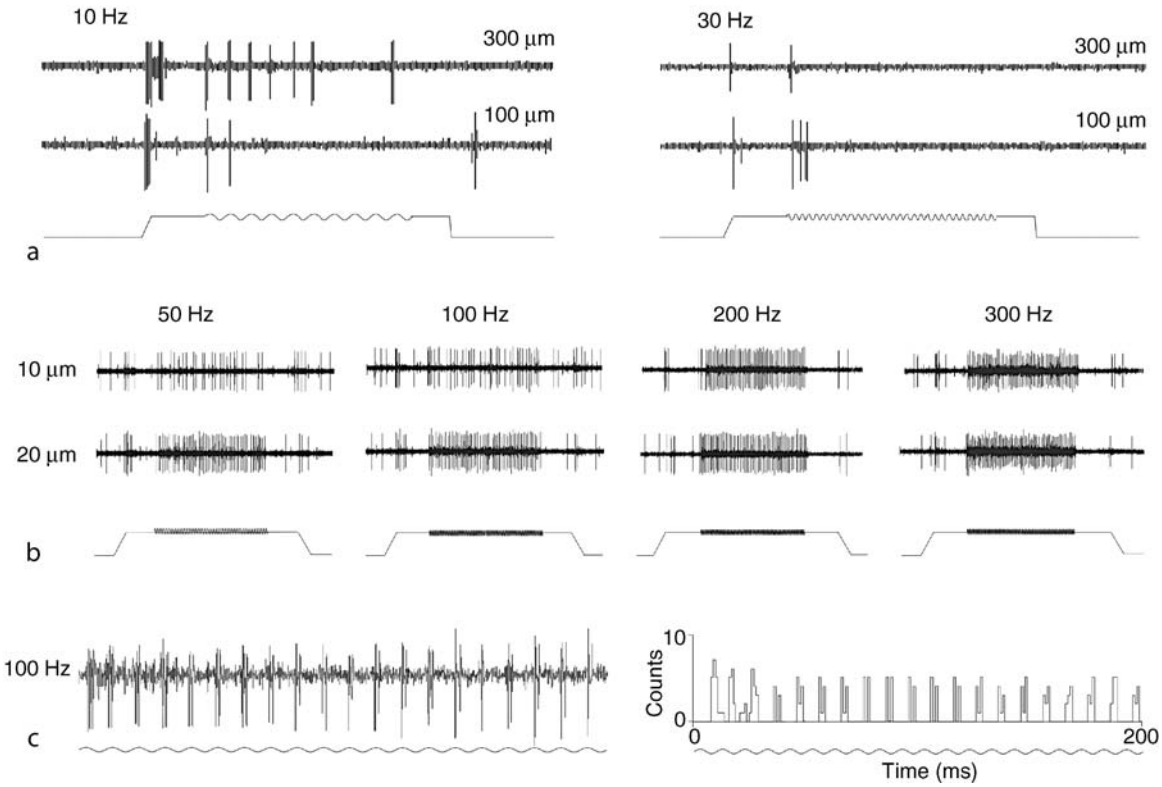
Differential Representation of Different Body Regions Within Ascending Somatosensory Projection Pathways

Recent detailed analysis of the function of these ascending tactile systems has clarified to a great extent the differential capacities of these pathways and why such marked differences exist among them in their contributions to tactile sensibility. *First*, it is now

recognized that there are important differences in the regional representation of the body within the different ascending systems. For example, there is a restricted representation of glabrous skin inputs from the limb extremities in both the SCT [3] and STT systems [2], in contrast to the DC system which clearly serves as the pre-eminent pathway for tactile information from these crucial prehensile regions of the limb extremities [6–8]. However, for tactile inputs from the more proximal, hairy regions of skin on the limbs and trunk, there is a prominent representation within all three of these ascending pathways [2,3,5,8–10]. One might therefore ask whether there are differences in the signaling of tactile information from these sources over the three parallel pathways. In order to evaluate this issue in a quantitative way it has been necessary to employ reproducible forms of cutaneous stimulation, for the most part involving precise step indentations or sinusoidal vibrotactile stimuli delivered to the skin by means of feedback-controlled mechanical stimulators (Fig. 1).

Quantitative Analysis of Tactile Coding Capacities for Neurones of the DC Ascending Somatosensory Pathway

In the case of the DC system, the individual neurones display a striking capacity to code reliably for the various parameters of tactile stimuli whether these are applied to the glabrous skin [6,7] or to hairy regions of skin [9,10] (Fig. 1b and c). These DCN neurons display sensitively graded stimulus-response relations as a function of changes in the intensity of both vibrotactile stimuli and static forms of skin indentation, and, in addition, retain a tightly phaselocked pattern of response to vibrotactile stimuli over a broad bandwidth of vibration frequencies extending up to ~400 Hz [6–8,10] (Fig. 1c). The high security of synaptic transmission between tactile afferent fibers and their DCN target neurons [7,10] enables the DCN neurons to retain, in their rates and patterns of impulse activity, a reliable signal of the intensity and periodicity parameters of vibrotactile perturbations encountered in either the glabrous or hairy skin.



Somatosensory Projections to the Central Nervous System. Figure 1 Vibrotactile responsiveness of representative neurones of the SCT system (a) and DCN-lemniscal system (b and c). (a) the paired impulse traces show the limited responsiveness of a typical SCT neurone to 1s-long trains of skin vibration at 10 and 30 Hz, at the indicated amplitudes. (b) paired impulse traces show the response behavior of a DCN neurone to 1s trains of skin vibration at 50, 100, 200, and 300 Hz, at the two indicated amplitudes. (c) the expanded impulse trace (on the left hand side) and response histogram of accumulated impulse counts (on the right) show the precise phaselocking of DCN responses to the waveform of a 100 Hz train of skin vibration. (Figure modified from Fig. 1 in [9], and Figs. 5 and 9 in [8]).

Quantitative Analysis of Tactile Coding Capacities for Neurones of Somatosensory Pathways Arising in the Spinal Dorsal Horn

Within the parallel ascending projection systems arising in the spinal dorsal horn, such as the spinocervical tract (SCT) pathway, there have also been reports of secure transmission between tactile afferent fibers and the post-synaptic neurons [3,5]. However, these studies of transmission characteristics were based upon very brief input signals. With recent study using vibration stimulus trains that generate a sustained input, it has become clear that SCT and other dorsal horn projection neurons are fundamentally limited in their capacity to sustain a response beyond the transient, onset component (Fig. 1a), in contrast to the neurones of the DCN [8,9]. Furthermore, as a consequence, the response levels of these dorsal horn neurones are very low and stimulus-response relations display only a very coarse and poorly-graded signal of vibrotactile stimulus intensity, in contrast to DCN neurones [8,9], demonstrating that their capacity to signal intensive changes in vibrotactile disturbances is vastly poorer than that of individual neurones of the DCN-lemniscal pathway. As spinal dorsal horn neurones are limited in their bandwidth of vibrotactile responsiveness to no more than 5–10 Hz [9] (Fig. 1a) there is a dramatic difference in functional properties, with DCN neurones displaying a vibrotactile bandwidth effectively 40 times broader than that of dorsal horn neurones in systems such as the SCT and STT [2,6,7–10] (Fig. 1). In addition, DCN neurones retain great precision in the temporal patterning of their impulse activity in a way that enables them to reliably signal information about the periodicity inherent in vibrotactile stimuli, at least up to frequencies of several hundred Hertz [6–8,10] (Fig. 1c). In contrast, even at very low vibration frequencies (up to 5–10 Hz) that SCT and other dorsal horn neurones can follow, the phaselocking of responses is poorer than in DCN neurones [9]. The limitations revealed by these quantitative measures suggest that ascending pathways from the dorsal horn, such as the SCT system, could, in contrast to the DCN system, serve as little more than coarse *event detectors* for tactile sensory experience [9].

Evolutionary and Comparative Roles of Dorsal Horn and DC Tactile Projection Systems

The limited capacities of SCT and other dorsal horn neurones in tactile signaling raises the question of why these ascending systems should operate in parallel with the far more discriminative DC system. From an evolutionary perspective, one finds that both systems appear to be present in amphibians, reptiles and birds, as well as in mammals. However, it is unclear whether the tactile signaling capacities of the dorsal horn somatosensory projection systems and those of the DC-lemniscal systems have remained consistently different across generic and species borders. Perhaps the existence of both these major systems represents, at least in the tactile signaling capacities of the dorsal horn outflow projection system, a form of redundancy in the evolution of sensory systems. Alternatively, subtle differences in projection targets of each system at higher levels of the nervous system may confer some differential and unique role in tactile sensibility upon the two systems.

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Somatosensory Reorganization

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Synonyms

Somatosensory representational plasticity; somatosensory remodelling

Definition

Tactile inputs from the body surface are sequentially processed at various subcortical stages (spinal cord,

brain stem, thalamus) before this information reaches the primary somatosensory cortex (SI) and the following other cortical areas.

Each of these processing levels is characterized by a topographic representation of their respective sensory epithelial surfaces. The result is a somatotopic map of the body surface (called ►homunculus), where neighbouring neurons respond to tactile stimuli at neighbouring skin sites. The size of the representations of different body parts within these maps is related to their behavioural relevance, the receptor density, and the amount of tactile sensations within these body parts. Consequently, certain body parts, like the tongue and single fingers, are over represented relative to much larger body parts like the abdomen.

However, cortical representations are not fixed but continuously modified throughout life in response to use, learning, skill acquisition, or lesions. Thus, somatosensory reorganization describes lasting changes in the layout of topographic representations of the body surface, allowing developmental and adult adaptation to individual and dynamically changing sensory input patterns that are not specified by genetic constraints.

Although somatosensory reorganization is best described for the ►primary somatosensory cortex (SI), which is located in the postcentral gyrus, it occurs at all afferent subcortical levels and is not restricted to cortical areas.

Characteristics

Higher Level Structures

The classical experiments in monkey somatosensory cortex, performed by Merzenich and colleagues, demonstrated that immediately after peripheral nerve section or digit amputation a large portion of the respective cortical representation was unresponsive to any stimulation, but over the course of a few weeks, this unresponsive area came to be excited by inputs from neighbouring skin surfaces. The recent development of ►non-invasive imaging techniques made it possible to perform similar studies in humans. These studies consistently revealed that neurons in the SI hand or forelimb representation, having lost their inputs due to amputation, became reactivated by inputs from the stump or the face [1].

Other experiments demonstrated that the somatosensory cortex could dynamically allocate areas in a use-dependent manner. In monkeys, extensive training in a tactile discrimination task resulted in an expansion of the respective cortical representation of the trained skin surface [2]. In professional string players, the cortical representation of the left string-fingers are substantially enlarged as compared to the fingers of the right hand. Similarly, blind Braille readers have increased representations of their reading fingers, which are accompanied by superior tactile spatial acuity with these fingers [3].

Moreover, it is also possible to induce lasting changes in sensory performance by passive induction of cortical reorganization without conscious attention and feedback. For example, in humans, a few hours of synchronous tactile stimulation of separated ►receptive fields on single fingers also leads to an increase of the related representational areas and their overlap in primary somatosensory cortex, paralleled by improvement in spatial two-point discrimination [4]. However, the improvement is completely reversible within hours after termination of the stimulation protocol. Therefore, stability of the reorganization is closely related to the time course of induction, and original representations reoccur after exposure to the original sensory input statistics.

Lower Level Components

Topographic changes as well as changes in single neuron response characteristics, synaptic properties, and biochemical processes can be found months or years after peripheral deafferentiation at all subcortical afferent stages [1]. However, it seems to be most pronounced at the somatosensory cortex. One reason for that might be the system of divergent and convergent afferents, leading to increasing ►magnification factors from the periphery to the cortex. Thus, small changes at the brain stem level would induce much larger changes in the cortex. However, the extent of cortical reorganization goes far beyond the boundaries of thalamocortical afferents favouring far-reaching intracortical horizontal connections in being the substrate for these effects. Moreover, tactile training experiments in monkeys revealed cortical receptive field changes, which were not paralleled by similar changes in the thalamus [1]. Using microstimulation to induce short-term plasticity in the SI cortex and thalamus, without involving more peripheral levels of sensory processing could demonstrate that reorganization in the thalamus can be induced by stimulating the cortex, but in contrast, no thalamocortical transfer was found. What is more, the largest map changes were observed in the cortex after ►intracortical microstimulation. These results direct to the cortex as main substrate for somatosensory reorganization.

Higher Level Processes

►Hebbian-based learning rules relate to the detection of temporally correlated inputs and are often used to explain the formation and plasticity of representational maps. In the case of topographic representations of sensory epithelia, peripheral inputs that fire in close temporal proximity are more likely to represent neighbouring points on the peripheral sensory sheets.

Animal and human data have always pointed to the behavioural significance of input timing [1]. In monkeys, artificially induced ►syndactyly, aimed to

enhance indirectly the degree of synchronicity of inputs across two merged fingers, led to a fusion of the respective cortical representations. In human subjects, after surgical reversal of congenital syndactyly, and therefore reduction in synchronous tactile inputs, cortical representations of the respective fingers that had been strongly overlapping before surgery, became rapidly separated.

Even enhancement of synchronous usage of different fingers in monkeys during training in a tactile discrimination task, resulted in an integration of the representations of those parts of the fingers that received temporally coincident inputs [1]. In humans, examination of the cortical hand representations of blind Braille readers who use three fingers of each hand in synchrony for reading [3], revealed a distortion of the normal cortical topography due to an increase of overlap of the respective finger representations.

On the neuronal level, in freely moving rats, clipping and pairing whiskers for several days led to increased neuronal responses to the paired surround receptive field whiskers which had experienced temporally correlated activity, and decreased responses to the clipped whiskers in which activity was temporally de-correlated to the neuron's principle whisker [5].

More recently, imaging experiments in humans [4] revealed consistent effects of synchronous coactivation characterized by an enlargement of the respective somatosensory cortical representations and their overlap. On the other hand, segregation of cortical representations could be induced by asynchronous coactivation [6].

Interestingly, coactivation-induced somatosensory reorganization was accompanied by alterations in perceptual capacities: after synchronous coactivation, two-point discrimination performance was improved, while frequency discrimination and localization became impaired. On the other hand, segregation of cortical representations induced by asynchronous coactivation was paralleled by an impairment of two-point discrimination, but an improvement of localization abilities on the stimulated skin sites.

Lower Level Processes

Reorganization can be observed on different time scales from minutes and hours to days, weeks, months, and even years, indicating different mechanisms being involved. After extensive remodelling of sensory afferents and cortical representational areas during maturation, only very few changes in the anatomical connections can be observed in the adult individual. Local growth of axons and dendrites, as found months or years after severe central or peripheral lesions, cover only very short distances (several micrometers) and cannot account for far reaching map reorganization of several millimetres to centimetres. Possible other mechanisms are the unmasking of previous silent, subthreshold, or actively inhibited synaptic connections. Increased numbers of $GABA_A$-receptors after chronic injury might be interpreted as response to immediately decreasing levels of the inhibitory neurotransmitter ►GABA, leading to disinhibition and hyperexcitability extending over several millimetres within minutes after deafferentiation [1].

Changes within the existing network based on cellular and synaptic mechanisms may play a crucial role, also underlying short-term somatosensory cortical reorganization after training or extensive tactile stimulation. This might be alterations in synaptic strengths and efficacy, changes in the balance of excitatory and inhibitory intracortical connections, as well as structural processes resulting in the formation of new synapses and an increase in spine density. In a Hebbian sense, the importance of stimulus timing and the amount of synchronicity of different stimuli point to the relevance of spike timing-dependent processes like ►long-term potentiation (LTP) and ►long-term depression (LTD) [7]. This view is supported by the finding that input-dependent plasticity can be facilitated or blocked by either ►NMDA-agonists or antagonists, respectively [7].

Process Regulation

Cortical plasticity allows adaptation to changing sensory environments and demands. However, sensory reorganization influences perception and may interfere with the need for stable percepts of the outer world. Thus, it is important that changes in the amount of sensory inputs causing reorganization are behaviourally relevant. Interestingly, Recanzone and co-workers found changes in the somatosensory hand representation of monkeys after extensive tactile finger stimulation only when the monkey had to attend the stimuli to get a reward but not with passive stimulation [2]. The ►nucleus basalis (NB), a subcortical structure receiving inputs from limbic and paralimbic regions and sending excitatory projections to the entire brain, seems to play a key role in estimating the behavioural relevance of particular stimuli and the control of selective attention [8]. Nevertheless, as shown above, cortical plasticity is controlled not only by top-down directed processes like attention or reinforcement, but somatosensory reorganization can also be induced in a bottom-up fashion purely by the statistics of the sensory inputs. The application of tactile stimuli with high frequency for several hours, resulting in a total number of stimuli that is much larger than that used in most training experiments, might yield an intrinsic behavioural significance of these stimuli relative to others.

Function

Functional recovery after damage seems to be one major role of somatosensory reorganization. However,

since processes of axonal and dendritic sprouting, as occurring after deafferentiation, are very slow and would not have direct evolutionary advantages, the main role of somatosensory reorganization might be founded on its strong relationship to tactile learning processes. Further, whereas physical growth during maturation establishes the gross layout of the somatosensory map, adult plasticity allows the ongoing adjustment of cortical information processing to changing demands.

Pathology

Somatosensory reorganization not only takes part in tactile learning or rehabilitation after lesions. It may also be related to maladaptive phenomena like ►phantom limb pain (PLP) or ►focal dystonia [3].

In upper arm amputees, the neighbouring representations of the face and shoulder invade the representational area of the lost arm. A significant relationship was found between the amount of reorganization in the primary somatosensory cortex, and the occurrence of phantom sensations and even phantom limb pain that were perceived to be emanating from the now missing extremity.

Focal dystonia – a motor disorder often leading to loss of motor control of one or more fingers – is frequently observed in musicians like pianists or string players who extensively do repetitive, synchronous movements of their fingers. Motor impairment is associated with somatosensory cortical reorganization: Assumable as a consequence of synchronous inputs from multiple skin sites at unusually high rates, topographic order is disturbed and cortical representations of the fingers are more overlapping than in controls.

Therapy

One kind of therapy for patients suffering from PLP as well as from focal dystonia is to reverse cortical reorganization. Huse and colleagues treated upper arm amputees suffering from PLP with asynchronous tactile stimulation of the stump and the face for several months, and found a decrease in PLP accompanied by a disintegration of the face and stump representations [9]. Tactile discrimination training had a similarly beneficial effect on both the cortical topography and PLP [10].

Whereas some researchers also suggested sensory discrimination training for the treatment of patients suffering from focal dystonia, Elbert and co-workers used a different approach: they fixed single fingers with a splint so that the other fingers could be moved independently. After both kinds of therapy, a normalization of the map layout and a decrease of dystonic symptoms occurred [3].

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Somatosensory Representation

Definition

A cortical area or a subcortical nucleus where neurons are activated, when receptors of the body (skin and deep tissues) are stimulated, in a spatial pattern that reflects (represents) the locations of the receptors in the body.

►Somatosensory Cortex I (SI)
►Somatosensory Cortex II (SII)
►Somatosensory Cortex, Plasticity
►Somatosensory Reorganization

Somatosensory Representational Plasticity

►Somatosensory Reorganization

Somatosensory Senses

Definition

Body senses of pain, touch, temperature and the position of muscles and joints.

►Sensory Systems

Somatosensory Trigeminal System

►Evolution of the Trigeminal Sensory System and its Specializations

Somatostatin

Definition

A peptide hormone that inhibits growth hormone release from the pituitary and affects neurotransmission and cell proliferation.

►Neuroendocrinology of Psychiatric Disorders

Somatotopic Map

The ordered projection of a sensory surface to one or more structures of the central nervous system.

Somatotopic Organization

Definition

The localization of function for different body parts to separate regions of the cerebral cortex or brain area. Somatotopic organization exists for both motor output from the brain in the form of movements as well as sensory input to the brain from the body surface.

►Motor Cortex: Output Properties and Organization
►Somatosensory Projections to the Central Nervous System
►Somatosensory Reorganization

Somato-visceral Reflex

►Somato-Autonomic Reflex

Somniloquy

Definition

Somniloquy, also known as Sleeptalking, consists of expressing speech during any stage of Non-REM or REM sleep. The speech can be fragmented and unintelligible, or it can be clear, coherent, and lengthy and mimic an actual conversation, including emotional tone. The content of the talking can be meaningful or random.

►Non-REM Sleep
►Rapid Eye Movement (REM) sleep

Somnogens

Definition

Endogenous substances that increase sleepiness or promote sleep. Examples of somnogens in the sleep research literature include prostaglandin D2 (PGD2), Interleukin-1 (IL-1), Muramyl peptides, and adenosine.

Various substances classified as somnogens may have different effects on NREM and REM sleep stages and thus they may be best characterized by indicating their affects on wakefulness, NREM and REM states.

►Non-REM Sleep
►Rapid Eye Movement (REM) sleep
►Sleep – Motor Changes
►Sleep – Sensory Changes

Song Control System

Definition

An interconnected chain of brain areas that controls song production and sensory-motor learning.

►Song Learning of Songbirds

Song Learning

Definition

Bird calls are, in general, acquired by inheritance. However, two orders of birds are able to learn vocalizations: parrots and passerines. These birds inherit only a very general motor program. They modify this program in two steps: first they hear their father singing. They store this information in a template. When they start to sing by themselves they compare their own singing with the stored template.

Song Learning of Songbirds

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Definition

Songs of songbirds (order Passeriformes, suborder oscines) are sequences of frequency-amplitude-modulated sounds and intervening silent intervals. First, songs can be characterized by the phonology of the sounds, which are named elements. Second, songs can be characterized by its syntax, the rules with which elements and silent intervals are combined to form longer temporal sequences. For example, in some species such as the great tit the songs of a male can be classified into distinct song types, characterized by unique sequences of elements. In other species such as the sedge warbler songs consist of sequences of randomly assembled elements, rarely repeated in the same order. Intra- and interspecies differences in song phonology and syntax are in part due to auditory-motor learning, i.e., songs are cultural trades much like human language.

Characteristics

Song Learning: Consideration from Behavioral Experiments

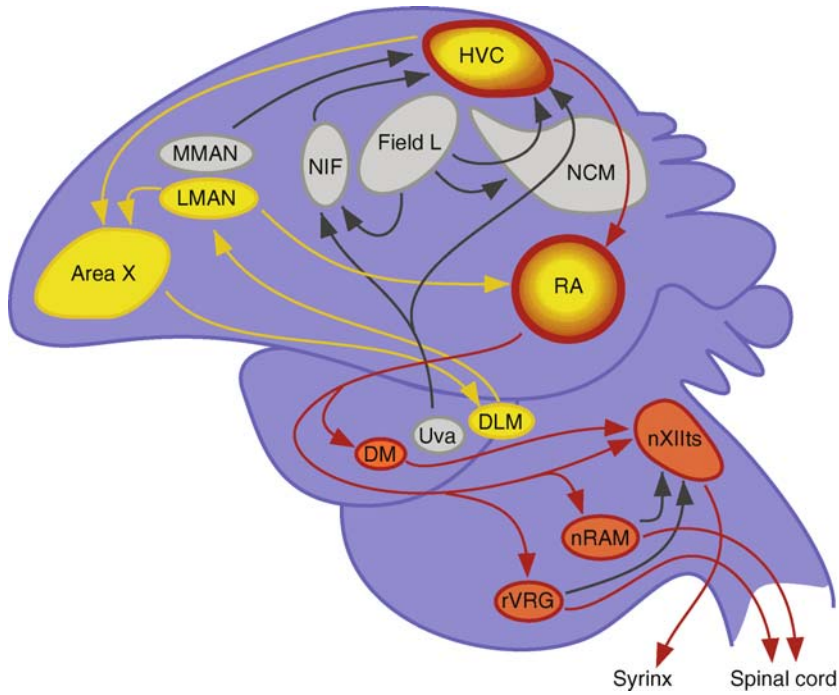
During development young birds first listen, guided by innate auditory preferences for conspecific song, and memorize the song of an adult tutor during the ►sensory phase. The overlapping or subsequent sensory-motor phase starts with the onset of singing at a species typical age. In the sensory-motor phase, the juveniles first produce immature vocalizations that they gradually refine and approach towards the memorized tutor song. Konishi [1] developed the concept of an acquired auditory ►template or memory as the basis of song learning in songbirds. He showed that deafening of non-learning species (e.g., chicken) shortly after hatching had no effect on their vocal development. In contrast, deafening in songbirds such as the white-crowned sparrow disturbed song development dramatically depending on the age at which the surgery took place. Males that were operated upon before onset of singing developed highly abnormal songs, while those deafened after establishing of a stable (crystallized) song pattern maintained their songs. This pioneering and subsequent works [1,2,3] suggest that: (i) innate motor programs are only sufficient for the development of parts of the song, (ii) a combination of innate and acquired auditory templates guides song development, and (iii) self-generated auditory feedback is essential for the conversion of innate and acquired templates into songs. Although the timing and the amount of learning from external models might vary considerably between species, vocal learning appears a general feature of songbirds while the song features (e.g., the phonology, the syntax) to be learned are species-typical.

These behavioral studies suggest neural circuits for the following processes [3–5]: (i) the generation of the motor commands that give rise to the songs, (ii) the sensory learning of sounds, and (iii) the comparison of self-generated sounds and auditory memories and subsequent error correction mechanisms during sensory-motor learning. Despite the large diversity of song pattern among songbirds, the neurobiological mechanisms of vocal learning detailed below are derived, mainly for technical reasons, from a few species, primarily the zebra finch.

The Song Control System Produces Learned Vocalization

In songbirds, neural vocal control is achieved by a chain of anatomically discrete, interconnected brain areas in the fore-, mid-, and hind-brain [6] (Fig. 1).

These areas can be subdivided in the descending motor pathway (HVC, RA, nXIIts) and the anterior forebrain pathway (AFP). The AFP is a forebrain-basal-ganglia loop that connects HVC with RA via three intervening areas (LMAN, DLM, Area X). Besides



Song Learning of Songbirds. Figure 1 A schematic parasagittal view of the song system of songbirds indicating the major projections (*arrows*). The descending motor control pathway (*red*) includes the HVC, RA and syringeal motonucleus nXIIts as well as respiratory premotor areas. HVC and RA are further the beginning, respectively, and the end of the anterior forebrain pathway (▶AFP) (including Area X, LMAN, DLM) (*yellow*) that is likely involved in sensory-motor learning. Thus, HVC and RA (*red* + *yellow*) might be involved in motor control and sensory-motor learning. Sensory input (*grey*) comes via the UVA (somatosensory) and via the Field-L complex and NIF (auditory) into the HVC. Song perceptual learning might first take place in the Field-L complex and NCM. The role of MMAN is not studied in detail. Abbreviations: *DLM*, nucleus dorsolateralis thalamis, pars medialis; *DM*, nucleus dorsomedialis; *HVC*, Nucleus HVC of the nidopallium; *LMAN*, Lateral magnocellular nucleus of anterior nidopallium; *L*, Field L; *MMAN*, Medial magnocellular nucleus of anterior nidopallium; *NCM*, Caudal medial nidopallium; *NIF*, Nucleus interface of the nidopallium; *nRAM*, nucleus retroambigualis; *nXIIts*, pars tracheosyringealis of hypoglossal nucleus; *RA*, Robust nucleus of arcopallium; *rVRG*, rostroventral respiratory group; *UVA*, nucleus uvaeformis.

the AFP, there are further recursive loops between song areas and sensory input comes from the somatosensory and the auditory system. Although the flow of auditory information into the vocal areas is not entirely worked out, the avian primary auditory cortex (Field L-complex) appears to connect with NIF and HVC (Fig. 1) [4,6].

The production of learned vocalizations correlates with the differentiation of forebrain vocal control areas [6] (Fig. 1). These forebrain areas are rudimentary in females of those songbird species such as the zebra finch, in which females produce only innate vocalizations (calls). In suboscine passerines such as the tyrannid flycatchers and in those non-passerine species that do not learn its vocalizations, these forebrain areas are missing entirely. Interestingly, in parrots (order Psittaciformes) and hummingbirds (family Trochilidae, order Apodiformes), the other two avian taxa with vocal learning, the vocal control system too comprises multiple forebrain areas. Since the three groups of song learning birds (songbirds, parrots and hummingbirds) are not closely related, vocal learning evolved independently at least three times among birds.

The Descending Motor Pathway Generates the Motor Commands of Song

Singing involves inspiratory airflow (silent intervals) and expiratory airflow, during which the frequency-modulated sounds are produced involving activity of the syrinx and of suprasyringeal structures such as the trachea, tongue, and beak. The descending motor pathway consists of the HVC, RA and hindbrain areas that innervate the syringeal muscles (nXIIts) and expiratory and inspiratory motoneurons of the spinal cord (Fig. 1) [6]. This pathway generates the motor commands of the song with a hierarchical organization. The premotor activity of HVC correlates with larger vocal sequences and that of RA with the motoric details.

Is the Template Memorized in the Auditory or the Song System?

Despite the comparative evidence that implicates forebrain areas in the production of learned vocalizations, the location of the template, probably a distributed function, is unclear. Since auditory learning is a general characteristic of birds and not linked to the production of learned vocalizations, template formation might occur in the auditory system and/or in the ►song control system. The best experimental attempt to involve the song system, in particular the AFP, in sensory learning has been to reversibly inactivate the LMAN by infusing a NMDA-receptor antagonist during tutoring periods but not during periods of active singing of young zebra finches. Although song learning is somewhat reduced in these males, template formation was not prevented [4,5]. A recent study employing markers of neuronal activity suggests that some auditory responses in the caudomedial nidopallium reflect the song learning experience of individual male zebra finches (Fig. 1). This finding and the lack of song control neurons that are tuned to the ►tutor song before the onset of sensory-motor learning indicates that sensory learning of song occurs first in the auditory cortex rather than in the song system [4,5].

Where does Sensory-Motor Learning Take Place?

During sensory-motor learning, motor circuits need to be gradually shaped by singing-based feedback in order to transform an auditory map into a muscle map. The electrophysiological finding of auditory neurons that become tuned to features of the tutor song, or of the ►birds-own-song,or of both in vocal areas gives anatomical grounds for sensory-motor learning in the song system [4,5]. Such neurons are found in the descending motor pathway (HVC, RA) and in the AFP. Lesion experiments of the AFP suggest that the integrity of this loop is necessary for sensory-motor learning. Although lesions do not locate function and AFP-lesions affect the differentiation of the descending motor pathway, such lesions inhibit the development of aberrant songs that can be induced through certain experimental conditions [5]. This suggests the AFP as part of a comparator that generates a correction signal. Another candidate for sensory-motor learning is the HVC [4]. The auditory properties of HVC (neurons tuned to birds-own-song and tutor song), the separate projections of HVC into the descending motor pathway and into the AFP, and the properties of the local HVC-circuitry put this area in a central position for sensory-motor integration. Thus, we need to consider that sensory-motor learning is a distributed function with various tasks located in various brain areas or neural assemblies.

Hormone-Dependent Differentiation of the Song Control System and Song Learning

The evolution of forebrain song control areas in songbirds is paralleled by the evolution of estrogen (only HVC) and androgen receptor (all song areas) expression [7,8]. During ontogeny, expression of these hormone receptors is one of first neurochemical features of song areas to emerge, i.e., the song system is sensitive to gonadal hormones during periods of sensory and sensory-motor learning.

Androgens and estrogens specify the sexual differentiation of brain and behavior upon brain-intrinsic genetic mechanisms. In this process, the hormones first specify the global development of the song control system, which provides the crude substrate for song development. Some of these hormone-sensitive global anatomical features, in particular the size of the vocal areas and its neuron numbers, are proposed to relate to the amount of song motor memories, i.e., to the amount of ►sensory motor learning [7,8]. However, since the overt motor memories do not in all cases represent the total learned repertoire such correlations are controversial. For example, adult male canaries sing some of their song elements in certain seasons while others are produced year-round. Similarly, the selective production of song units after initial overproduction due to socio-sexual interactions, coined action-based-learning by Marler [2], does not mean that unused motor memories are deleted.

Next to the overall differentiation of a functional song system, androgens and estrogens modify many neural phenotypes (synapse density, synaptic proteins, neurotrophins, neurotransmitter receptors) that are potentially involved in the formation of neural circuits during song learning. In relation, circumstantial evidence suggests hormonal modification of sensory-motor learning: High levels of testosterone induces premature crystallization, i.e., ends sensory-motor learning, while depletion of testosterone delays the closure of sensory-motor learning. Similarly, seasonal periods of sensory-motor learning in adult canaries coincide somewhat with periods of low testosterone production. These findings need, however, to consider that testosterone increases singing activity. Thus, it remains to be seen if sex hormones affect the production of motor commands, or auditory properties or the comparison between birds-own-song and the song template. The presence of further types of hormone receptors (e.g., melatonin) in the song system as well as the expression of receptors of the ascending monoaminergic systems (e.g., dopamine receptors) suggest that song learning is modulated by a number of signaling systems that reflect environmental conditions. Such modulatory action is to be expected since learned songs are under sexual selection pressure [7,8].

Sensory and Sensory-Motor Learning at the Circuit Level

After the onset of singing, i.e., during the period of sensory-motor learning, neurons that are tuned to birds-own-song or to the tutor song or to both emerge in various parts of the song control system. Thus, it is likely that the template is first formed outside the song control system and subsequently shifted to (multiple) sites of the vocal system during the sensory-motor period of song learning, a process reminiscent of memory translocation in visual imprinting. Syringeal deafferentiation that hampers the birds to gradually copy the tutor model indicates that the neural representation of the tutor song in vocal areas requires the process of sensory-motor learning [5].

The transformation of the auditory template into a motor representation in the song system requires comparison. The comparator circuit would evaluate auditory feedback of the birds-own-song in the context of the template. Differences between the actual song and the model would result in an error signal that modifies the song control system so that subsequent song better matches the template. One scenario is that premotor-linked inhibition and auditory-evoked excitation of Area X-projecting HVC neurons might constitute an estimate of the error signal. The inhibition is through inhibitory HVC interneurons, which are activated by RA-projecting HVC neurons. In relation, Area X-projecting HVC neurons can respond to various sounds including birds-own-song, but are silent during the singing of adult males, i.e., these neurons might only be active in the case of non-matching auditory feedback but otherwise cancel out auditory feedback. Such error estimates could also be produced in the AFP, since the AFP also contains neurons tuned to the birds-own song and/or the tutor song and is active during singing. The song related activity of the AFP might constitute an efference copy of premotor activity, which results (as detailed above) from the patterned inhibition of X-projecting HVC neurons during singing. This inhibition of the input to Area X could activate LMAN circuits through disinhibition of a thalamic relay (DLM), similar to mammalian cortex-basal-ganglia circuitry. Although there is much progress in understanding the properties of the vocal circuitry in relation to song learning, the central problem of how an error signal modifies the motor network is unsolved [4,5]. However, since the AFP and the HVC excite the same RA neurons with a time difference of about 60 msec, delayed excitation could be used as a reinforcement signal to the descending motor pathway. Lastly, since song areas of sleeping animals show discharge patterns that are remarkably similar to patterns generated during singing, off-line rehearsal might play a role in sensory-motor learning or maintenance of motor memories [3–5]. This would solve some problems of the above scenarios resulting from fast sound production.

Cellular Mechanisms of Sensory and Sensory-Motor Learning

In general, we don't need to expect any "songbird-special" cellular mechanisms of learning, seen in the similarities of song learning to other types of sensory-motor learning [9]. Thus, the songbird-specific feature is grounded in the anatomy and connectivity of the vocal system itself. One speciality of song learning might, however, be seen in the ample recruitment of new neurons into certain song areas (see below) [10].

Changes of the vocal system during sensory-motor learning have been best studied in the AFP. Refinements of topographic projections between LMAN and RA, elimination of synaptic contacts in LMAN, faster NMDA currents at the DLM to LMAN synapse, and loss of activity-dependent synaptic potentiation and depression in LMAN have been reported. It is difficult to establish if such regression and refinement underlie sensory-motor learning, since the song system still undergoes maturation during the sensory-motor period that is independent of learning. To separate maturation from learning related events, zebra finches are raised under special conditions, e.g., without tutor. Although this approach indicates that certain developmental observations such as synapse elimination in LMAN are linked to song learning, the findings might rather reflect the social isolation than the lack of learning [9].

An unusual type of mechanism involved in sensory-motor learning might be the recruitment of new neurons during both development and adulthood [10]. Various factors including testosterone, auditory input, or singing are thought to affect the addition of new neurons in HVC. Although, fascinatingly, these new neurons are integrated into neural circuits, clear evidence that they are required for song learning is missing. In female canaries, the number of new neurons can be increased by testosterone treatment, which is otherwise known to induce song crystallization. If the new neurons indeed play a role in this behavioral process needs to be seen since neuron recruitment is subsequent to testosterone-induced angiogenesis in HVC. The latter certainly has a number of consequences next to facilitating neuronal recruitment that could underlie song development [10].

Function of Song Learning

Song learning might facilitate the adjustment of vocal development to local ecological demands or socio-sexual experiences. However, evolutionary related groups of birds (the ►suboscines) are successful without the evolution of song learning. Among ►songbirds, song learning is an additional criterion upon which sexual selection works, seen in the function of learned song in the realm of reproduction (mate choice, territorial defence). Mate choice based on singing not only considers the actual physiology such as high levels

of sex hormones of the advertiser, but also considers the life history of the singer, i.e., its physiological conditions during song learning periods [7].

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Sonomicrometry

►Measurement Techniques

Sound

Definition

Sound is an oscillation in pressure, stress, particle displacement, particle velocity in a medium with mass and inertia.

►Acoustics

Sound Intensity (I)

Definition

The average rate of sound energy transmitted in the specified direction through a unit area normal to this direction at the point considered. For cases in air, I ¼ p2=_0c , where p is pressure, ρo is the density of the medium, and c is speed of sound in the medium.

►Acoustics

Sound Localisation Pathways

►Binaural Pathways and Processing

Sound Pressure Level (SPL)

Definition

The decibel level expressed relative to 20 μPa (micropascal), which is approximately the lowest sound pressure that humans with normal hearing can detect.

►Acoustics

Sound Representation

►Tonotopic Organization (Maps)

Sour Taste

Definition

►Taste - Sour

Source Amnesia

Definition

When one can recall a fact or an idea, but cannot recall the source of the information. In other words, the person can recall the fact, but cannot remember where or when the fact was learned. It has been linked to frontal lobe dysfunction.

►Amnesia

Source Monitoring

Definition

Source monitoring refers to the process of identifying the origin of memories and knowledge, such as when, where, or from whom they were obtained, independent of the knowledge on what information and knowledge one has in own memory storage.

►Metacognition

Southern Blot

Definition

Southern Blot is used to identify a particular DNA in a sample. Genomic DNA is isolated from a population of cells, separated on the basis of size by gel electrophoresis, and the DNA transferred to a membrane. A radioactive (or fluorescent/chromogenic) complementary DNA or RNA probe is then used to detect the DNA.

Space Adaptation Syndrome Drugs

►Anti-Motion Sickness Drugs

Space Motion Sickness

Definition

Space motion sickness is a condition resembling motion sickness on Earth but encountered during early exposure of astronauts to microgravity in space. Symptoms consist of nausea, vomiting, headache, vertiginous sensation etc.

►Autonomic Function in Space
►Motion Sickness
►Anti-Motion Sickness Drugs

Sparse Coding

►Combinatorial Coding

Spasm

Definition

Brief, non-sustained contraction of one or more muscles.

Spasm-like Electromyographic (EMG) Activities

Definition

The generation of single unit potentials and compound motor action potentials that were evoked by noxious chemical stimulation of visceral afferent fibers.

►Electromyography
►Viscero-Somatic Reflex

Spasmodic Torticollis

Definition

Also known as cervical dystonia, is characterized by abnormal sustained muscle contraction causing twisting, turning, and abnormal posturing of the neck. Botulinum toxin injections are the first line of therapy for most focal dystonias such as torticollis.

Spasmophilia

Definition

Idiopathic normocalcemic ►tetany, which may be hereditary of acquired.

Spastic Ileus

►Bowel Disorders

Spasticity

Definition

Spasticity results from damage to motor nerve fiber systems descending from supraspinal to brainstem and spinal structures. However, lesions limited to the pyramidal tract (e.g., the pyramids in the medullar oblongata) entail a Babinski reflex and paresis (i.e., temporary weakness and loss of dexterity), but neither spastic dystonia nor permanent weakness. The pathophysiology is complicated, therefore, also due to the fact that (i) depending on damage site, there are several clinical syndromes with potentially different pathogenic mechanisms (cerebral spasticity vs. spinal spasticity, which can be symmetric or asymmetric), (ii) descending fibers and afferent sensory fibers show a complex convergence onto motoneurons and interneurons in brainstem and spinal cord. In varying combinations, symptoms include *positive symptoms* such as *hypertonia* (velocity-dependent resistance of skeletal muscle to stretch); *hyperreflexia* (enhanced tendon reflexes and clonus); *enhanced cutaneous reflexes*; *contractures*; *autonomic hyperreflexia*; and *negative symptoms* including *paresis*; *synkinesia*; *lack of dexterity and enhanced fatiguability. Hypertonia* probably has several intertwined causes. First, muscle compliance may change due to changes in collagen tissue, tendons and joint capsules, thus entailing a higher passive stiffness. Second, the histochemistry and morphometry of spastic muscle may change. *Hyperreflexia:* The tendon reflexes and the fast dynamic reflex responses to maintained muscle stretches, as well as the H-reflex (Hoffmann reflex), are enhanced. *Clonus* is thought to result from increased stretch reflex excitability and consequent tendency towards oscillation. The *enhanced tendon jerk* can probably not be accounted for by augmented γ-motoneuron activity. α-Motoneurons might become hyperexcitable due to changes in biophysical properties or synaptic inputs. Recurrent inhibition has been found changed in spastic patients, but in different ways, partially dependent on disease state. Reciprocal inhibition is often disrupted and mostly reduced in spastic patients, which might disrupt the orderly alternation of agonist/antagonist activity during rhythmic movements such as locomotion. Changes in reflex pathways from Golgi tendon organs could alter reflex excitability. The presynaptic inhibition of group Ia fibers from muscle spindles appears reduced in amyotrophic lateral sclerosis, multiple sclerosis and patients with spinal cord injury. Spinal *reorganization*: Short- to long-term plastic changes may re-organize spinal operations so as to increase the cord's excitability. Mechanisms might include the unmasking of existing but hitherto ineffective synapses, collateral sprouting, reductions in pre- and postsynaptic inhibition, and changes in postsynaptic sensitivity ("denervation hypersensitivity"). *Flexor spasms:* Flexor spasms are another facultative sign that occurs especially in spinal cord-injured patients. They probably represent the augmented form of normal flexion reflexes as they are used during locomotion and the withdrawal reflex. They may be elicited by excitation of small-diameter, mechanically sensitive muscle afferents (maybe including group II muscle spindle afferents), joint and cutaneous afferents. In cerebral spasticity, short-latency cutaneous reflexes may be suppressed, while spinal spasticity often goes along with a particularly prominent enhancement of the

long-latency flexor withdrawal reflexes, with a reduced threshold, prolonged duration and irradiation. *Spastic Gait:* The traditional concept of spastic gait disorders envisages exaggerated reflexes as the primary change underlying spastic movement disorders and thus promotes anti-spastic drugs as means to reduce the reflex activity. The new concept emphasizes the loss of functionally more important long-latency reflexes (leading to reduced muscle activity during movements despite increased short-latency stretch reflexes) and changes in non-neural factors that compensate for the loss of supraspinal drive, which would argue against anti-spastic drugs in mobile patients. In children with early supraspinal motor lesions, e.g., in *cerebral palsy* children, the usual maturation of gait does not take place so that the co-activation of antagonist leg muscles persists. In adults with spasticity acquired after the age of four years, the reciprocal pattern is developed, but temporal overlap of antagonist muscle activities is pronounced. Functionally important polysynaptic and long-latency reflexes are diminished, leading to reduced proprioceptive contributions to the leg muscle activations, which are less well modulated and less well adapted to the ground conditions. One problem in making spastic patients walk more easily is to overcome the destructive flexor spasms. Modern treatment strategies rest on combinations of physiotherapy, locomotor training, electrical stimulation (e.g. of spinal cord and peripheral afferents), and drug therapy (e.g., with α_2-agonist clonidine) to support rhythmic spinal activity generation, provided by spinal central pattern generators (CPGs), while attempts at repairing the spinal lesions are in the experimental phase.

►Amyotrophic Lateral Sclerosis (ALS)
►Babinski Reflex
►Central Pattern Generator
►Clonus
►Golgi Tendon Organ
►H-reflex (Hoffmann Reflex)
►Multiple Sclerosis
►Muscle Spindle
►Presynaptic Inhibition
►Reciprocal Inhibition
►Regeneration

Spatial Abilities

►Spatial Memory

Spatial Attention

Definition

The process of selecting stimuli on the basis of spatial location. Items in the selected region then receive further cognitive processing.

►Spatial Cognition
►Visual Attention

Spatial Coding

►Combinatorial Coding

Spatial Cognition (Category: Others)

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Definition

The representation of location, orientation, and action with respect to the self, others, objects, or the environment. Spatial cognition may be studied in the context of sensory information, motor control, frames of reference, scale, maps, imagery, attention, language, and memory. Approaches include developmental, neural, cognitive, and cognitive neuroscience investigations of both humans and nonhuman animals. The study of spatial cognition crosses disciplines of psychology, ethology, geography, information science, and computer science.

Characteristics

Multiple Sources of Spatial Information and Integration

There are multiple sources of information for spatial orientation. External, or allothetic, information includes visual, auditory, olfactory, or tactile cues for position. Internal, or idiothetic, information includes proprioceptive and vestibular sources that change as a result of self-movement. Research has addressed the relative contribution and integration of sensory information for

the perception of self-motion and spatial localization within one's environment. Nonhuman animals have been shown to integrate allothetic and idiothetic cues in a flexible manner, using both route-based and landmark-based references. For example, given an environment with visual, olfactory, and internal motion cues, rodents will rely first on vision, next on olfaction, and third on motion-based path integration (see below). However, given unreliable or the lack of visual and olfactory cues, the animals will navigate through path integration alone [1]. Humans have been shown to dynamically calibrate perceptual and motor information. There is consistent covariation between action and perception as an observer navigates through space. For example, when a person walks along a straight path (translation), visual perspective translates as well. Rieser and colleagues [2] demonstrated that changing this perception-action coupling will lead to systematic recalibration of representation-action coupling, or how one dynamically updates spatial orientation without vision.

Action, Path Integration, and Spatial Updating

A common goal for all organisms is to act in their environment, making action critical to defining spatial cognition. Moving in space provides information about spatial location through efferent feedback of the motor system, afferent proprioceptive cues linked to limb movement, and vestibular cues of linear acceleration and rotation. ►Spatial updating is the process of updating representations of the locations in the environment with respect to the self and others. It potentially involves two broad sources of information. The first is path integration, in which velocity- or acceleration-based self-motion information from the visual, vestibular, and proprioceptive systems is used to update one's spatial displacement. The second is the recognition and use of landmarks within the environment. Path integration is typically tested in both human and nonhuman animals with a return-to-origin or path completion task in which the observer follows an outbound path and then travels back (or points or turns) to the origin of the path without the use of positional landmarks. Although organisms such as the desert ant and rodents are quite skilled at path integration, it has been suggested that humans are imprecise when navigating by path integration alone. In contrast, tasks referred to as visually directed actions, in which an observer typically walks without vision to a previously viewed target, are performed on average, quite accurately up to approximately 20 m.

It has also been proposed that transient action-based responses (necessarily egocentric, see next characteristic) involve a distinct representation of space as opposed to longer-lasting spatial representations that use other spatial frames of reference (►spatial frame of reference) [3]. This "two visual systems approach" suggests that spatial characteristics may be processed independently depending on the goal of the observer, defining a long-term conscious system for "what" or identification versus an immediate unconscious system for "how" or guiding actions. However, other research supports the claim that some visually directed actions and cognitive response measures are informed by the same spatial representations.

Frames of Reference and Structure of Space

Spatial frames of reference are a means of representing spatial locations relative to some spatial framework. Generally, frames of reference are defined relative to the viewer, *egocentric*, or relative to something other than the viewer, *allocentric*. More specifically, the egocentric frame of reference involves a ►first person perspective and may be subdivided into spatial relations to body-parts, such as oculocentric, headcentric, and bodycentric, specifying spatial locations relative to the eye, head, and body, respectively. Allocentric representations include the object-relative frame which defines space relative to two or more objects and the environmental frame which defines space relative to cardinal directions of north, south, east, and west. The gravitational frame of reference specifies up and down relative to gravity.

Regions of space defined relative to the observer have been characterized in the context of the utility of information for space perception and action-relevant goals. In the context of space perception, Cutting and Vishton [4] defined *personal space*, which extends slightly beyond an arm's reach from the observer, *action space*, within which we can rapidly locomote and extending from the boundaries of personal space to approximately 30 m from the observer, and *vista space* beyond 30 m from the observer. In a somewhat different context of how people think about space, Tversky [5] categorized *space of the body* as the understanding of positions and relations of body-parts, *space around the body* as the space within which one can immediately see and reach to things, and *space of navigation* as space that is explored and too large to see all at once.

Imagery and Spatial Transformations

The human ability to imagine spatial transformations is important for accomplishing many daily goals such as action planning, object recognition, spatial navigation, and problem solving. Much of the early work on ►spatial imagery and mental rotation focused on the human ability to make a decision about the congruency of one rotated object with respect to another. Shepard

and Metzler [6] found that the time required to make a decision about the similarity of the structure of two rotated objects was a function of the angular disparity between the two objects. This monotonic rotation function was upheld for rotations in the picture plane and in depth. Much mental rotation work has focused on 2D or 3D objects but other related research has involved imagined transformations of hands and bodies using both cognitive and neuroimaging approaches.

Mental transformations of bodies and body-parts may serve to facilitate planning of actions, predicting or understanding other's behavior, or other complex tasks of spatial reasoning. Parsons' [7] work with imagined spatial transformations of biological objects such as hands, feet, and bodies indicated that the response time to make a left-right decision about the hands or feet (given no explicit instructions on a strategy to use) was highly correlated with the time required to imagine a limb movement (without the left-right decision). Both types of judgments were also highly correlated with participant's ratings of the awkwardness of moving into a given limb orientation. This work relates to the concept of body schema, knowledge of the spatial relations among the parts of the body that can be used to represent oneself and others, as well as ►self perception.

A related paradigm has compared object- and perspective-based transformations in the context of spatially updating external objects. Several studies have directly compared both cognitive and neural mechanisms involved in mental transformations of objects versus egocentric (or viewer) perspective [8]. When participants are given a spatial updating task to name an object in a given location after a specified imagined transformation, a large systematic performance advantage has been found for viewer versus object/array transformations.

Spatial Attention

►Spatial attention is the process of selecting stimuli on the basis of spatial location. Often this process relies on visual stimuli and is referred to as ►visuospatial attention. Items in the selected region then receive further cognitive processing. Attentional mechanisms may operate early or late in processing. In a spatial cuing paradigm, a "cue" preceding a target either predicts (valid trial) or does not predict (invalid) the target's spatial location. Typically, valid trials lead to facilitation of responses to the target, although this effect can be reversed when the time interval between the cue and the target is increased. Neglect is a disorder of spatial attention typically a result of damage to the right posterior parietal lobe. Patients with neglect fail to attend to the side of space opposite the brain lesion are typically unaware of stimuli falling on the left side of egocentric or object-centered space.

Spatial Language

►Spatial language uses verbal description to represent objects and locations with respect to multiple coordinate systems or frames of reference. Both the scene characteristics and the speaker's perspective and goals influence schematization of spatial relations in language. Spatial language can be used effectively to communicate spatial layout and directions. Furthermore, mental representations of space based on verbal descriptions have been shown to be functionally similar, and accessed and updated as those based on visual information [9]. However, some recent work has shown that language-based responses of direction lead to different spatial updating performance than body-based responses such as turning or pointing.

Cognitive Maps, Place Cells, and Spatial Knowledge

Historically, the term ►cognitive map has been used to refer to a mental map of space represented in an allocentric framework. The hippocampus is one brain region which has been defined as integral to spatial memory and a cognitive map theory in animals. Identified within the hippocampus were place cells, neurons that fire in response to specific locations in an environment regardless of the animal's movement or perspective. This pattern of neural activity specific to spatial positions led to the proposal of the hippocampus as supporting an allocentric environmental map, distinguished from other brain regions that might support more egocentric representations of space. Recent data shows that in addition to place cells, neurons throughout the limbic system encode nonspatial experiences and viewing orientation (head direction cells), suggesting a more general navigation system. This conjecture is also supported by human lesion research in which patients with hippocampal damage are impaired in path integration. More generally, human cognitive mapping defined from cognitive psychology and geography involves extracting information from large-scale environments to store in some type of mental representation of space [10].

A distinction between route and survey perspectives has been made both in spatial learning and memory. Route-based perspectives involve egocentric representations from the viewpoint of the observer navigating in an environment. Survey-based perspectives involve map-like or global "birds-eye" spatial representations without a specific viewer orientation. Although these types of representations may be distinguished clearly in spatial cognition, human neuroimaging data suggests that the neural substrates supporting these representations overlap.

Neural Representations of Space

Two dominant regions of the brain that are implicated in spatial cognition are the parietal cortex and the hippocampus. Evidence for the strong role of the parietal cortex in spatial cognition comes from a variety of domains such as single-unit recording of neurons in the monkey for different spatial frames of reference, lesions in humans associated with neglect and other spatial deficits, and functional neuroimaging of spatial decisions, imagery, and navigation with healthy humans. The hippocampus has been implicated in large-scale spatial navigation, allocentric representations and spatial memory for the configuration of objects. Hypotheses differ in how the parietal cortex and hippocampus interact.

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Spatial Cueing Paradigm

Definition

►Visual Attention

Spatial Frame of Reference

Definition

A means of representing spatial locations relative to some spatial framework. Broadly, frames of reference are defined relative to the viewer, egocentric, or relative to something other than the viewer, allocentric. Specifically, the viewer-centered reference frame can be sub-divided into head, limb, or body reference frames. The allocentric reference frame includes objector environment-relative frameworks.

►Spatial Cognition

Spatial Hearing

►Neuroethology of Sound Localization in Barn Owls

Spatial Imagery

Definition

A quasi-pictorial representation of spatial knowledge in the absence of immediate sensory input that emphasizes the location and orientation of objects or parts of objects.

►Spatial Cognition

Spatial Language

Definition

A means of representing objects and locations through verbal description with respect to multiple coordinate systems or frames of reference.

►Spatial Cognition

Spatial Learning/Memory

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Synonyms

Navigation

Definition

Spatial learning and memory refers to the set of behaviors and processes through which information about external environmental space is acquired, stored, organized, and used. These phenomena provide a paradigm to systematically study the neural basis of cognition.

Characteristics

Background

While gathering nuts, a squirrel spots a threatening hawk overhead. Quickly, it runs at top speed in a direct path towards the safety of the nest. How is this done? How does the squirrel process its current sensory information, combine that with memory, and rapidly choose the best path for survival?

Animal ►navigation has been studied for over 100 years in the laboratory. For several decades in the early twentieth century, animal psychologists argued about whether rats solved complex maze (►maze learning) tasks by means of "place" or "response" strategies. Tolman, the leader of the "place" group argued that the maze behavior of rats could only be explained if a rat possessed a "cognitive map" of the maze. Such a map would describe the spatial relations among major ►landmarks.

The brain has two types of representations of space: egocentric and allocentric. An egocentric spatial representation refers to a representation using body-centered coordinates (the ego or self). Examples of egocentric neural maps are ►retincocentric (retina-centered) maps in the ►visual and ►parietal cortices, and ►somatotopic (body-centered) maps in the ►somatosensory or ►motor cortex.

Allocentric representations have coordinate frames that are not centered on the body. The simplest example is a road map. Significantly, Tolman's cognitive map is allocentric. Later in this article we will describe several examples of neuronal representations that are allocentric. Since the data the brain uses to construct these maps enters via body-centered sensory channels, allocentric representations seem complex in that they involve transforms to-and-from egocentric frames. Although allocentric representations are difficult to construct, they permit important efficiencies.

Spatial Navigation Strategies

Navigation is the process of planning and going to a specific location. Its function is to make efficient use of scattered resources. There are four principal mechanisms: (i) ►Beaconing is taxic movement towards a landmark. Animals may use a wide variety of strategies to reach a beacon, ranging from simple ►chemotaxis to complex processes such as ►echolocation. One form of beaconing may involve moving to minimize the difference between the current visual snapshot and a previously memorized snapshot taken from the goal. (ii) Homing is the process of returning to a place by reverse summation of the outbound movement vectors. (iii) Route learning is a memorized series of ►local cue response rules. An example might be "at the big rock, turn left; next, at the fallen tree bear right…". Route learning is also called "response chaining" and in animals is typically acquired through operant conditioning. Route learning can work effectively in a static environment, but is inflexible. (iv) Cognitive mapping is a navigational strategy where behavior is optimized by using a two- or three-dimensional representation of the environment.

A cognitive map can be thought of as a bird's-eye representation. These are economical representations of the many relationships among environmental features. Importantly, unless we are referring to birds, these global representations of relationships among landmarks have never been seen; that is, they are transformations of sensory data. Using a cognitive map permits taking direct paths from any location to any other location on the map. Start and stop points may or may not be the locations of important landmarks. The gold-standard test of whether an animal is using a mapping strategy has been to see whether it can take a novel route to an unmarked goal. Such a route would rarely occur if the animal is navigating with other strategies.

This article will focus on neural mechanisms that contribute to map-based navigation. The mapping strategy is sometimes referred to as the locale navigation strategy in contrast to a ►route navigation (►or taxon navigation) strategy. We will be focusing on the mechanisms that have been studied in the laboratory over the past 30 years, chiefly in the hippocampus and chiefly in rats. There are other well-studied aspects of animal navigation whose neural substrate is being explored. These include trail following in a variety of animals, ►chemotaxis, path integration and snapshot navigation in insects, migration in birds and other animals, ►magnetic sensation, food caching, and flocking. These will not be covered.

There are two parts to the cognitive mapping process: creating the map and using the map. The process of map creation is associated with ►exploratory behavior. At the neuronal level, this is the plastic stage when the map is created, filled out and stabilized. Usage is when an animal can take an efficient route or exhibit other behavioral efficiencies. Presumably, during usage the brain map is read-out and utilized.

It is important to note that the hippocampus, the focus of this article, is commonly associated with the plasticity during the storage of ►declarative (generic) memories. Although it seems likely that map learning and ►declarative learning have much in common, the relationship remains problematic. Nonetheless, it is clear that modification of hippocampal circuits is involved in both declarative learning and spatial learning. In addition, long-term potentiation (►LTP), the favored model for memory, is a prominent feature of hippocampal circuits and is involved in both declarative learning and acquiring spatial maps.

Measuring Spatial Learning and Memory in the Laboratory

Three sets of techniques comprise the great majority of laboratory approaches to navigational behavior. For the first half of the twentieth century, studies of rat cognition employed a wide variety of alleyway mazes. Some of the most familiar are the Hebb-Williams maze set, the sunburst maze, the T maze and the plus maze. Famously, Tolman and Hull used a variety of these to demonstrate that rats either did or did not use a cognitive map in navigation. In 1976 Olton and Samuelson introduced the ►radial-arm maze. In this, apparatus arms are baited at the ends, and a rat or mouse will forage using an innate win-shift strategy to visit each arm only once. Although a number of effective strategies are possible, such as a rat avoiding its own odor trace, rats spontaneously use an apparent mapping strategy, avoiding a previously-visited arm because of its association with the spatial arrangement of distal landmark cues. Although an inherent problem with the radial-arm maze is that it can be solved by a variety of strategies, it remains popular due to ease of use and the relative ease of combining navigational problem solving with electrophysiological recordings. The water maze, introduced by Morris in 1981, is a circular swimming pool with a stationary slightly-submerged escape platform [1]. On initial trials a rat is introduced near a wall and swims until it bumps into the submerged platform. On subsequent trials when the rat is introduced from various start locations it will take shorter times and more direct routes to the platform. After a few dozen trials a typical rat will take direct escape paths from any start location. The water maze provides the clearest example that a rat can take a novel route to an unmarked goal.

In ship navigation, two strategies are commonly used to determine a vessel's location: The first is "►fixing a position by sighting", where the navigator records angles and distances to distal objects (stars, landmarks), and, with the aid of a map, determines the ship's position. The second is "►dead reckoning" where the navigator uses knowledge of the ship's motion (speed, direction, time) to update position on the map. Although sightings are critical, in certain situations, such as fog, navigators rely completely on dead reckoning. Rodents appear to use both types of strategy for navigation. In rats ►self-motion cues (►idiothetic cues) are generated from motor commands and sensory cues generated from self motion, such as vestibular activity, optic flow and proprioception. Sighting cues (allothetic cues) are not exclusively visual, as rodents also rely heavily on their auditory, tactile and olfactory senses.

The Spatial Theory of the Hippocampus

A salient clue that the hippocampus might be involved in navigation was provided by the ►theta rhythm, a highly regular 6–10 Hz EEG oscillation generated in the ►hippocampus. In rats, theta is present whenever the animal walks or interacts with external objects [2]. Both hippocampal principal cells and interneurons fire in register with the theta rhythm, with the firing of certain interneurons (►theta cells) dramatically entrained. Several theories have suggested that the theta rhythm plays a role in navigational behavior, but all are speculative. It was the subsequent observation of place cells in the hippocampus [3] and the ►cognitive map theory that followed, which first convincingly linked the hippocampus to navigation.

In 1978 O'Keefe and Nadel published the cognitive map theory as a book ►The Hippocampus as a Cognitive Map [4]. The book was the birthing event in the neuroscientific approach to navigation. This book contained five important features. First, it summarized O'Keefe's discovery of hippocampal ►place cells. Place cells initiated the notion that the hippocampus was part of navigational machinery. Second, it placed navigational problem solving in a historical/philosophical context, notably invoking Kant and Tolman as the sources for the idea that the brain had an inborn, map-like representation of the world. Third, most remarkably, it reviewed the rat hippocampal lesion literature and made a convincing argument that the deficits reported in virtually all studies could be attributed to failures of a brain map. Fourth, it established the first of many computational models for how hippocampal place cells are formed and how they might aid in route finding. And, finally, it speculated on the relationship of the hippocampal map to learning. Although there remains intense debate over the degree to which the rat or human hippocampus is devoted to spatial problem solving, this book,

and the questions it raised, remains the touchstone of these key issues.

Hippocampal lesions have been the principal tool of establishing a causal relationship between this structure and navigation. In the 1970s and 80s it was repeatedly established that hippocampal lesions eliminated use of locale (mapping) strategies on the plus maze, the radial arm maze and the water maze. After hippocampal damage rats either relied on cue strategies, response strategies or apparently random goal selection. Particularly stark, early results were obtained with the water maze. After several training sessions an intact rat will swim directly towards the goal from any start location. A rat given hippocampal lesions and similar training is more likely to swim in circles [5]. It is important to realize that lesions to several other parts of the brain, including the ►subiculum, and the ►entorhinal, ►medial prefrontal, ►parietal, and ►cingulate cortices also impair navigation in the water maze, suggesting a network of structures mediate navigation by mapping. Lesion studies have provided additional insights. For example, when rats are trained in a plus maze, they will initially use hippocampus-dependent locale strategies (e.g. go to a particular part of the room). After more extensive training, rats will switch to a hippocampus-independent response strategy (e.g. turn right). Another important line of work involves ►acoustic fear conditioning. Several labs have demonstrated that a rat requires an intact ►amygdala to form a tone-shock association. On the other hand, a rat must have an intact hippocampus for the global environment (►context) to influence the tone-shock association or for the rat to learn a direct relationship between context and shock. Although these fear-conditioning studies do not involve navigation directly, there is a fascinating connection. If we view the enclosure that a rat is tested in as a large "place", rats with hippocampal damage are exhibiting a form of spatial deficit. These studies suggest a continuity between place and context.

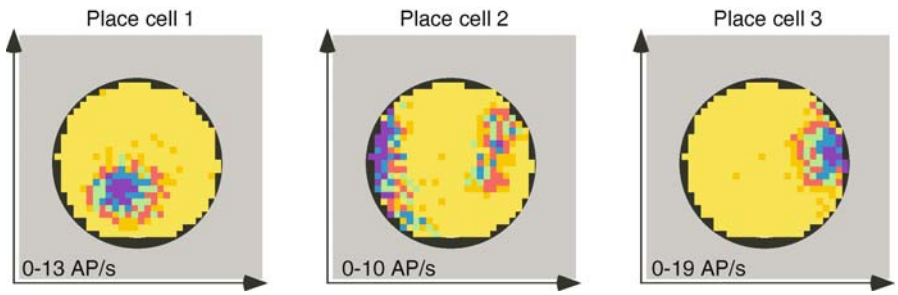
Pharmacological, genetic, and molecular imaging studies also implicate the hippocampus in navigation. Anticholinergic drugs like atropine disrupt the theta rhythm. Like other manipulations that disrupt theta, such drugs also impair spatial navigation in the water maze. Similarly, specific forms and phases of spatial learning are impaired by drugs and genetic manipulations that interfere with the induction of ►LTP such as treatments that impair *N*-methyl-D-aspartate (►NMDA) glutamate receptor function. The imaging of memory-related and activity-related molecules like immediate early genes also suggest the hippocampus is a key structure in spatial learning and memory. However, it is important to keep in mind that to-date essentially all pharmacological and genetic treatments that impair spatial behavior also interfere with both the information processing and storage functions of the brain, and thus far, molecular imaging has not distinguished between the potentially distinct processing and storage functions of a brain area.

The Neurophysiology of Allocentric Spatial Information

The specific information processed by a part of the brain can be discovered by recording the action potential discharge of individual neurons from a freely-behaving subject and then by correlating the neural activity with well-defined sensory, motor, and cognitive variables. Projecting neural discharge onto representations of a freely-moving subject's position and direction revealed that the activity of individual neurons in three connected mammalian brain networks contain allocentric positional and directional information that may be the basis of the cognitive map.

Place Cells

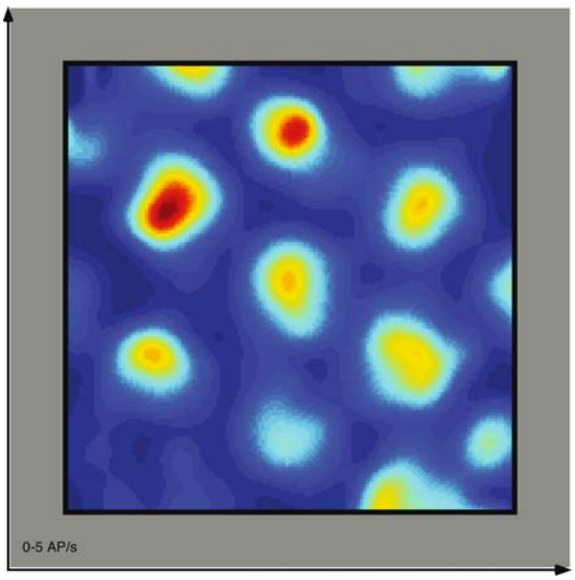
Place cells are hippocampal ►pyramidal neurons with strong location-specific firing. An individual place cell fires rapidly almost only when the animal is in discrete regions of the environment termed "►firing fields". Typically, a place cell will have zero, one or a few firing fields in a few scattered locations (Fig. 1). An animal's location can be predicted, within a few centimeters, from the activity of an ensemble of a few hundred place cells [6].



Spatial Learning/Memory. Figure 1 Firing rate maps from three simultaneously recorded place cells. The recording was made while the rat was foraging for food on a 82-cm disk. The maps are depicted in real-world space; thus, they are allocentric. The color code is that yellow codes regions of zero firing rate, while the colors orange, red, green, blue and purple represent higher rates. The range of rates is given for each cell in units of action potentials/sec.

Grid Cells

Grid cells, discovered by the Moser lab in Norway, are cells that show intense location-specific firing. Unlike the firing patterns of place cells, however, grid cells firing patterns are spread over an environment [7]. The pattern appears as a regular, hexagonal grid (Fig. 2). Grid cells are found in the dorso-caudal part of the medial ►entorhinal cortex.

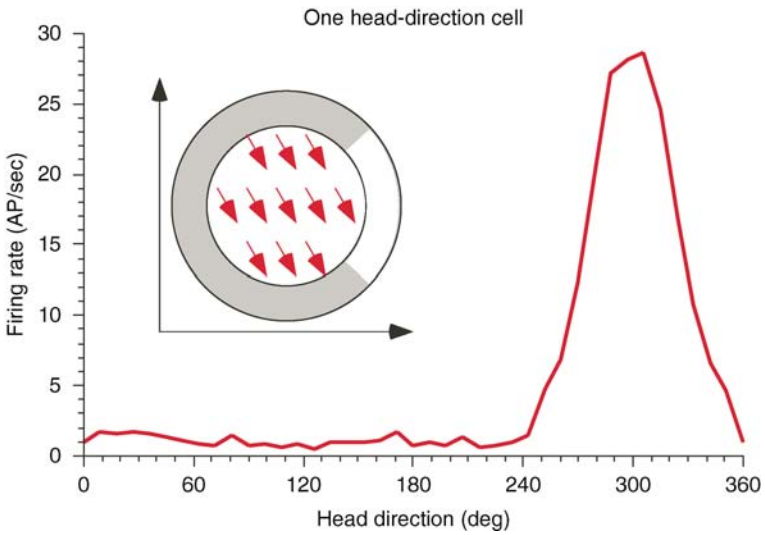


Spatial Learning/Memory. Figure 2 The firing rate map from a grid cell recorded from a rat foraging in a 1.5 m square black box with a white card on one wall. Again, the map coordinates are in real-world, allocentric space. The color code is blue for 0 AP/s and red for 5 AP/s. Figure courtesy of Jonathan Whitlock, May-Britt Moser and Edvard Moser.

Head-direction Cells

Head-direction cells are neurons that fire when the rat's head is pointed in a particular direction with different cells tuned to different directions (Fig. 3). The directional tuning is independent of a rat's location. (Therefore, if mapped on a floor projection, the tuning of a head-direction cell is a set of parallel vectors). Originally discovered by Ranck [8] during recordings of the post-subiculum (part of the hippocampal formation), head-direction cells can be recorded in several areas including the anterior and lateral dorsal thalamus and mammillary bodies. These regions, which resemble the Papez circuit, have interconnections with various parts of the hippocampal formation.

Place cells, grid cells and head-direction cells have important similarities. The best spatial discharge correlate of each cell class is a map-like feature of allocentric space. Activity within each class of representation tends to be internally coherent so that the firing of individual neurons is constrained to remain in register with the discharge of other neurons in the representation. The spatial discharge of each cell class also tends to stay in register with external sensory orientation cues, but firing is also controlled, at least in part, by other inputs like self-motion. Several models describe how these three neuron classes together represent an animal's location and orientation in allocentric space [9].



Spatial Learning/Memory. Figure 3 This plot of data from a head-direction cell depicts firing rate as a function of head angle. Data were collected while the rat collected food pellets in a 76-cm gray cylinder with a white card on the wall. Head angle is with respect to east, and is therefore allocentric. The inset is an idealized representation of the preferred head angle at different regions of the cylinder.

Local and Global Space

We've described the fundamental local spatial discharge correlates of place cells, grid cells, and head-direction cells, as animals move within a single environment, but additional features of these networks can be revealed by comparing their discharge in distinct environments. The across-cell pattern of place cells and grid cells in two distinct environments can "remap", meaning the spatial relations amongst place fields and grid peaks is scrambled, as if reset between environments [10]. ►Remapping radically changes which principal cells can be simultaneously active. In contrast, conditions that trigger remapping typically cause all head-direction cells to reorient as a cohesive unit, perpetually preserving which cells do and do not discharge together. As a rat moves within a single environment, the rat's local position and direction is signaled by a unique across-cell, ensemble discharge pattern that changes smoothly within the place cell, grid cell, and head-direction cell networks. Remapping implies that the ensemble activity of each cell class can switch abruptly when a rat is moved between two environments. Under special conditions this switch may also occur within a single environment, suggesting these networks may signal global space or context as well as local space.

Conclusion

Returning to our initial question, how does the squirrel know the best path? How does the map work? We still do not know. Over the past three decades scientists have used ingenious methods and advanced tools to observe the map in action. We now have a good description of the brain map and how it is formed. We see a rich ever-changing array of spatial data. But we don't know how brain networks use these data to calculate an optimal path and organize behavior. A few simple models have been developed, but they need extensive work. Understanding how the brain solves spatial challenges like the squirrel's appears to be a tractable cognitive problem. Understanding the operation of the cognitive map is a challenge for the next decade.

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Spatial Memory

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Synonyms

Spatial cognition; Spatial abilities; Spatial navigation; Cognitive map; Way finding

Definition

From an evolutionary perspective, spatial memory is crucial to foraging and reproduction but, at the same time, multiplies the risks of getting lost, being killed or consumed by other animals (predation). Thus, survival of mobile species depends on their ability to reach a feeding location, return home quickly and safely, find shortcuts and avoid dangerous places. These basic behaviors are crucial for successful interactions with the environment and call upon effective spatial navigation skills.

The capacity to move through space may appear to be a very simple behavior consisting in maintaining a body trajectory from a place to another. However, getting from place to place is more than a body displacement. Indeed, ►navigation is an action oriented by a goal that at least involves knowing where I am and where I go. Such knowledge requires the encoding and the gathering of multimodal information concerning our body position relative to the position of other objects. This ability – called spatial memory – is now considered as analogous to human ►episodic memory (memory of personal, experiential events) since both rely on the coding, storing and retrieving of events in a spatio-temporal context (e.g. [1]).

Characterizing spatial orientation and spatial memory skills requires an understanding of how cognitive and neural mechanisms underlie adaptive behavior to environmental requirements. The following section summarizes the basic concepts and findings issued from this research effort.

Characteristics

Reference Frames

Fixing and maintaining a trajectory from place to place is done through the establishment of a relationship between subject and object. This relationship is commonly categorized in egocentric and ►allocentric reference frames.

Frameworks centered on the subject (e.g. body parts such as head, trunk, arm, or receptor surfaces such as retina) are called ►egocentric reference frames. Such ►reference frames allow the subject to directly estimate the position of an object relative to their own body. However, the egocentric bearing is not invariant with respect to the subject's orientation and position. Frameworks centered outside of the body, on a fixed point in the environment (e.g. mountain, corner of a room or individual object), are allocentric reference frames. Such reference frames provide two main advantages: (i) to be invariant with respect to the subject's position and orientation in the environment, and (ii) to represent the relative location of objects independently from the subject's viewpoint.

Although these two systems of knowledge allow navigation, their respective weight depends on learning. Indeed, if a local or egocentric frame is immediately available even for naive subjects, a relational or allocentric frame depends on the development of spatial skills.

Spatial Navigation Strategies

Spatial cognition is assumed to be a hierarchical set of reference frameworks -or maps- containing landmarks, routes, locations, and configurations that integrate relative information about landmarks, routes and locations in a coherent structure. It is based on what information is perceived, represented and processed by the subject to solve navigation tasks. Adaptive spatial behavior relies on the flexibility in the use of reference frames depending on the problem to be solved. This involves the capability to choose among different cognitive possibilities that are referred to as spatial strategies.

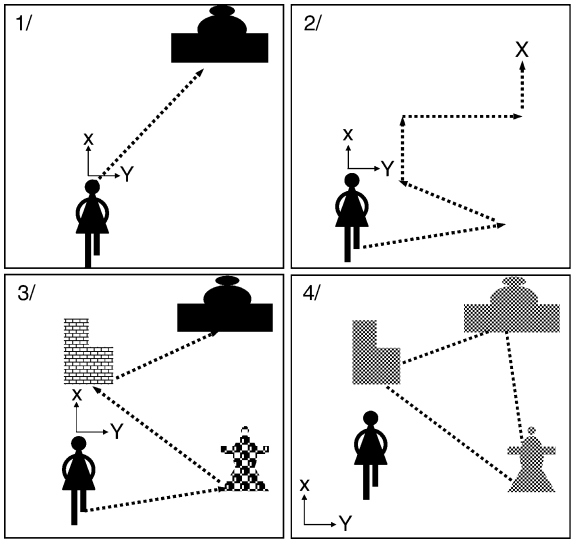
A four-level hierarchy of ►spatial navigation strategies based on a large range of researches [e.g. 2–4] can be resumed as following (fig. 1):

►Taxon navigation strategy (level 1) is used when a location coincides with a conspicuous cue. In such case, approaching a goal location is easy if the latter is either directly visible or identified by a visible cue. Such behavior does not require spatial memory per se, but rather an association between the cue and the goal to initiate a guided movement.

►Praxis navigation strategy (level 2) is used when a subject can navigate towards a hidden goal by executing a specific motor sequence acquired by extensive training. For example, if the goal is never moved and the individual always starts at the same location and with the same orientation, it can easily learn the appropriate of taxon and sequence of movements leading to that goal.

►Route navigation strategy (level 3) is a more complex strategy where the subject has learnt to associate a direction of movement to each sensory view. This strategy is appropriate, when a goal is identified by a sequence of specific sensory cues. Then, instead of single cue guidance, the subject can use more elaborate chaining sequences of taxon and praxis strategies.

Relational or configural strategy (►Relational or configural navigation strategy) (level 4) is based on the coding of relations between attributes of the environment into an internal ►spatial representation. An important property of this representation is that it offers a flexible spatial behavior adapted to each situation. In a familiar environment for example, subjects can get to a place from different starting points, as well as choose a novel path when the usual one is unavailable.



Spatial Memory. Figure 1 Egocentric and allocentric reference frames. The egocentric reference frame (1 taxon, 2 praxis and 3 route navigation strategies) is centered on the subject (x and y arrows) whereas the allocentric reference frame is centered outside the body (4 relational or configural strategy).

To summarize, taxon, praxis and route navigation strategies are based on an egocentric frame of reference

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depending on sensory-action associations where the position of the goal is directly estimated with respect of body-based references. They are inflexible in the sense that they prevent the taking into account that different paths may join the same place. Relational or configural strategy is based on an allocentric reference frame (a spatial representation of the environment) where the relationships between stimuli are maintained invariant with respect to the subject's position.

Multimodal Sensory Information

The establishment of an efficient spatial representation relies on the integration of multimodal sensory information that has been divided into allothetic (►allothetic information) and idiothetic (►idiothetic information) categories.

Stimuli provided by environment-like visual, olfactory, sound, tactile stimuli- are allothetic signals providing spatial information to the subject. Orientation based on allothetic stimuli allows, for example, identifying a place through visual features of a particular object.

Stimuli provided by the body-like vestibular, proprioceptive and motor command efferent copies are idiothetic signals providing information about continuous changes of the subject position and orientation. Orientation based on idiothetic stimuli allows deriving the subject's current position in relation to a starting position by the integration of its angular and linear displacements. This ability to keep track of spatial location relying on self-motion information is referred to as ►path integration (e.g. [5]). Although path integration is available in all types of environments (unknown, absence of landmarks, darkness), its use is limited by its vulnerability to cumulative non-systematic errors over distance. However, when allothetic landmarks are available, path integration can be reset in order to maintain orientation.

Therefore, prevention of ambiguous information relies on the combination of different sensory information that is encoded within different reference frames. Thus, multisensory integration requires the integration of different reference frames into a unified spatial framework, and the hippocampus appears to be the brain region in charge of such process.

Spatial Coding and Hippocampal Brain Area

Studies of the hippocampal formation occupy a central position in the advance of theories concerning episodic and spatial memory. Early experimental evidences for location-sensitive neurons in the rat hippocampus called "place cells," and the "►cognitive map theory" promoted by O'Keefe and Nadel [6] make out the hippocampus as the brain area that mediates allocentric spatial coding. Hippocampal function appears to be required in spatial representation, path integration and exploration (e.g. [7]) concerning the encoding of trajectories, single cell recording data suggests that the hippocampus represents the animal's position in the context of a trajectory through space while the enthorinal cortex represents regularities across different trajectories that could allow for generalization across experiences. Apart from the hippocampal area, the posterior parietal cortex seems to be in charge of egocentric spatial coding that represents body location related to subject's environment. It has been hypothesized that the multiple egocentric representations from sensory receptors and motor effectors converge from the parietal cortex onto the hippocampal formation where they are translated into an allocentric spatial reference frame. This postulate is based on findings showing strong neuronal connections between the posterior parietal cortex and the hippocampal formation, and between the hippocampal formation and the parahippocampal region. Thus, it could be postulated that spatial memory and flexible navigation requires the combination of both egocentric and allocentric components of the task, which is based on the cooperation of parietal cortex and the hippocampus respectively. This hypothesis is supported by a large convergence of data from experimental psychology, comparative anatomy and field research (for reviews see for example [8–10]).

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Spatial Navigation

►Spatial Memory

Spatial Orientation

Definition

Orientation of the head and body in space. Inputs from the vestibular, visual and somatosensory systems provide critical information about the spatial orientation. Once information from two sensory inputs conflicts, disorientation and vertigo are brought about.

►Anti-Motion Sickness Drugs
►Vertigo

Spatial Receptive Field (SRF)

Definition

The region of space from which a sound can evoke a response in auditory neurons.

►Neuroethology of Sound Localization in Barn Owls

Spatial Representation

Definition

Synonym of cognitive map, internal representation where the coding of relations between attributes of the environment are maintained invariant with respect to the subject's position.

►Spatial Memory

Spatial Resolving Power

Definition

The detection of light energy by the eye based on the spacing of the detector elements i.e. photoreceptors, retinal ganglion cells. Typically expressed in either cycles per degree or minutes and seconds of arc, spatial resolving power may be partly dependent on the optical resolution of the lens.

►Photoreceptors
►Retinal Ganglion Cells

Spatial Rule of Multisensory Integration

Definition

The principle that multisensory stimuli from will be integrated depending on their relative spatial locations. Typically, stimuli presented from the same spatial location will result in enhanced multisensory integration, while stimuli presented from different spatial locations result in decreased multisensory integration, or multisensory inhibition.

►Multimodal Integration

Spatial-temporal Transformation

Definition

Many sensory regions of the cerebral cortex and brain stem receive information from the outside world via a topographic and in many cases a point-to-point relationship between the physical stimulus (e.g., visual, auditory, somatosensory, etc) and the target neural structure. However, the actions of the organism are carried out by effectors (e.g., muscle) that require temporal signals to control the rate and amplitude of the movement as well as maintain its final position. Exactly how the brain performs the conversion from topographic maps into the appropriately timed neural signals is under intensive investigation. This transformation from spatial coordinates (i.e., topographic maps) to temporal

activity (e.g., muscle contraction) is called the spatial to temporal transformation. It has been studied extensively in the oculomotor system.

Spatial Updating

Definition

The process of updating representations of the locations in the environment with respect to the self and others after the observer or objects have moved.

►Spatial Cognition

Spatial Vision

Definition

Information about the structure of the visual scene as opposed to unstructured information like overall light levels.

►Blindsight
►Visual Space Representation for Action
►Visual Space Representation for Reaching
►Vision

Spatiotemporal Learning Rule LTP STLR

►Synaptic Plasticity

Spatiotopic

Definition

It makes reference to topographic arrangements of sensory pathways that reflect the spatial localization of sensory stimuli.

►Evolution of the Optic Tectum: In Amniotes

Species-specific Defense Reaction (SSDR)

Definition

Bolles (1970) first characterized SSDRs as innate defensive reactions in response to aversive stimuli. Bolles stated that animals undergoing aversive conditioning are more likely to learn reinforced responses related to their innate SSDRs then other behaviors (e.g., freezing vs. lever pressing). The Blanchards experimentally validated the SSDR theory, broadening the spectrum of known defense reactions and redefining the term as "species-typical defense reactions," due to a cross-species generality of defensive behaviors.

►Aversive Learning

Specific Anosmia

Definition

Specific anosmia is selective inability to smell one particular odor. This anosmia may be genetically based.

►Smell Disorders

Specificity of Learning

Definition

The improvement of discrimination, classification, or discrimination achieved through training does not transfer to similar (classes of) stimuli.

►Sensory Plasticity and Perceptual Learning

Spectral

Definition

Refers to the frequency (pitch) aspects of the speech signal.

►Hearing Aids

Spectral Reflectance

Definition

In vision, the proportion of photons at different wavelengths in the visible spectrum which are reflected by a given object in the visual field. Spectral reflectance is the inverse of spectral absorption.

►Color Processing
►Retinal Color Vision in Primates

Spectral-shape Cues in Hearing

Definition

In the ear canals of humans and other mammals, certain frequencies are attenuated or boosted in a manner that is highly characteristic of the position of the source along the midsagittal plane. For instance, when a sound with a flat spectrum at the speaker is placed overhead, the 8 kHz band is found to have been boosted in the ear canal, due to the shape of the human head and ear. Humans appear to use these bands, collectively called spectral shape cues, for vertical sound localization. (Humans use interaural differences in time and level to localize sounds in the horizontal plane).

Spectrin

Definition

A membrane-associated protein that interacts with a number of other proteins, including actin and ankyrin, to form and maintain the cytoskeletal network or "mesh" found near intracellular membrane surfaces.

►Synaptic Proteins and Regulated Exocytosis

Spectrogram

Definition

A pattern for sound analysis that provides a three-dimensional display of time on the horizontal axis, frequency on the vertical axis and intensity on a color or gray scale.

►Speech Perception

Spectrum in Acoustics

Definition

A description of the relationship between magnitude (pressure or sound intensity), frequency and starting phase of the sinusoidal components of a complex sound wave.

►Acoustics

Speech Perception

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Synonyms

Human speech recognition; Human speech understanding

Definition

Speech perception encompasses an array of sensory and perceptual processes through which listeners can recognize words using sensory signals from the ears and sometimes the eyes.

Characteristics

Speech Production

In many ways, perception of speech is much like other perceptual tasks. However, there is one aspect of speech communication that is not typical of most perception. A tree does not strike a pose that deliberately conveys strength and longevity, but talkers do speak so that they can be understood. Speech sounds are created especially for listeners.

Owing primarily to unique characteristics of supra-laryngeal anatomy, the adult human's sound-producing abilities are unrivaled among other organisms. This capacity is revealed in a grand assortment of over 850 different speech sounds used contrastively by the more than 5,000 distinct languages around the world. In contrast to this diversity, collections of consonants

and vowels used by individual languages are anything but random. One factor that may help determine what combinations of vowels and consonants are commonly used is the ease with which the sounds are produced either in isolation or in sequence with other sounds. Most important for perception is the fact that speech sound repertoires of all languages have developed over generations toward greater communicative effectiveness, with inventories of sounds optimized for acoustic and auditory distinctiveness [1].

Another factor that makes differences between speech sounds perceptually dependable is the complexity and consequent redundancy of the speech signal. Speech ►articulation has multiple acoustic consequences. Often, multiple acoustic attributes are effortless consequences of passive interactions between articulators and/or airflow. Talkers also systematically vary relatively independent articulatory maneuvers to enhance auditory distinctiveness.

Speech Perception

Performances of listeners detecting tones in quiet and detecting small differences in pitch are poor predictors of ability to understand speech. Perceiving distinctions between speech sounds does not rely upon the ability to make fine-grained discriminations bordering on sensory or perceptual thresholds of auditory systems. Differences between even relatively similar vowels, such as [æ] (as in "bat") and [ɛ] (as in "bet"), are easy to detect on the basis of gross spectral and temporal differences. Hence, speech recognition shares little in common with the types of discriminations presented in psychoacoustic studies that demonstrate humans' ability to detect tiny changes between simple signals. Listeners who suffer significant hearing loss can, nonetheless, manage to understand speech until the level of impairment becomes severe. The ability of normal hearing listeners to understand severely degraded speech is particularly impressive.

Because talkers exploit auditory capacities, several observations follow. First, human infants are quite proficient at discriminating differences between speech sounds from a very early age. Three decades of studies document impressive abilities of human infants, some less than one week old, to discriminate a wide variety of consonants and vowels from across many languages. Second, discrimination of speech contrasts by nonhuman animals is quite good, with multiple demonstrations that animals can distinguish human speech sounds with facility. These findings for human infants and for nonhuman animals can be expected, based on the tendency of languages to use acoustically and perceptually robust distinctions [2].

Because nonhuman animals appear to provide an adequate model for simpler aspects of speech perception, many neurophysiological studies have been conducted in the interest of describing neural representation of speech sounds. Most of this work has focused upon neural responses in the auditory (VIIIth) nerve, but there have been a number of studies concerning successive stages of the auditory system such as ventral cochlear nucleus, inferior colliculus, medial geniculate and auditory cortex.

Enough is known about the ability of humans and animals to use the acoustic information necessary for speech perception to make it clear that apparent limitations on the separate contributions of individual neurons, especially at the periphery, do not present obstacles to understanding speech. In part, this is because ample information is conveyed across 15,000 auditory nerve fibers and increasing numbers of neurons at successive levels of the auditory system. In addition, high fidelity representations are unnecessary to convey acoustically robust distinctions between sounds. Subsequent research should better illuminate the contributions of populations of neurons at low and at higher levels in processing the information contained in speech sounds.

Producing and perceiving differences between speech sounds is only a part of understanding how speech is perceived. Speech production gives rise to a host of acoustic attributes; however, matters are complicated by the fact that no single acoustic attribute by itself dependably signals any given consonant or vowel. This is referred to as the classic problem of "lack of invariance," the fact that there are no individually necessary and sufficient cues that uniquely identify speech sounds. Multiple acoustic attributes of the speech signal must be combined to identify speech sounds.

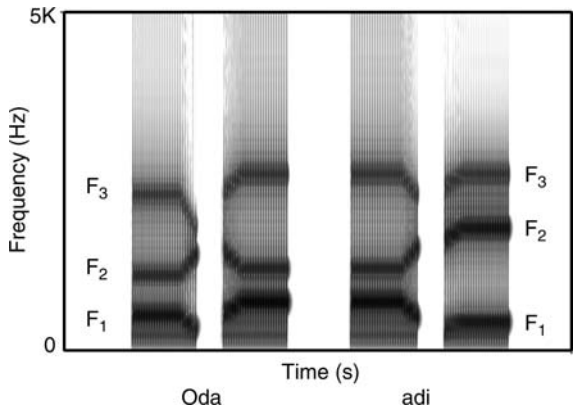
The ability to discriminate speech sounds on the basis of one or more acoustic attributes is *not* synonymous with the functional use of speech sounds. Speech perception requires treating acoustically different complex sounds as linguistically equivalent. Among the many variations in the speech signal, some are relevant to the linguistic message, but many are not. Speech perception requires ignoring irrelevant variation and focusing on linguistically relevant changes. For example, listeners must identify sequences of consonants and vowels despite substantial changes to the speech signal owing to differences in talkers. Other sources of variability that do not affect the linguistic content of speech include acoustic consequences of distance, room reverberation or competing sounds in the environment including the voices of other talkers.

Because so very many speech sounds are used across the languages of the world, perceiving distinctions in one's own language requires becoming tuned to the important distinctions in that language. Acoustic differences that matter critically for one language may be irrelevant or even distracting in another language. Perception must become tuned in such a way that most of the many possible differences between speech

sounds are relatively ignored, while at the same time the relatively few important distinctions between speech sounds that are used by a specific language are preserved or even enhanced.

Even for utterances by the same speaker, acoustic qualities of consonants and vowels vary. Production of consonants and vowels is altered by articulation of consonants or vowels that precede and follow. This process, known as ►coarticulation, results in temporal and spatial overlap in production of successive sounds. One example is the pattern of spectral peaks (►formants F_1, F_2, F_3) for the stop consonant [d] following the vowel [o] ("oh") and preceding [a] ("ah", left) and following [a] and preceding [i] ("ee", right) as depicted schematically in Fig. 1. Due to overlapping production of vowels and consonants, there is no single acoustic quality that signals [d] in both [oda] and [adi].

Explaining perception in the face of context sensitivity and lack of invariance is central to understanding speech perception. It has been shown that auditory processes that increase spectral contrast between successive speech and nonspeech sounds contribute to reversing the assimilative effects of coarticulation [3]. Also, in a way that bears a striking resemblance to visual perceptual constancies, multiple aspects of the speech signal come to be used together through experience with systematic covariation among attributes. One of the things that neural systems do best is to exploit multiple sources of modestly reliable information to reach a highly reliable conclusion. Simulations of neural connectivity and activity in artificial neural networks or connectionist models are designed to mimic the use of multiple attributes and associations between attributes as a function of experience with natural covariation [4]. Some of the most interesting findings to come out of computer simulations of vision have been demonstrations that performance can remain very robust across severe degradations of the signal such as adding noise, spectral filtering or deleting portions of the signal – a close analogy to the robustness of speech perception.



Speech Perception. Figure 1 Pattern of spectral peaks.

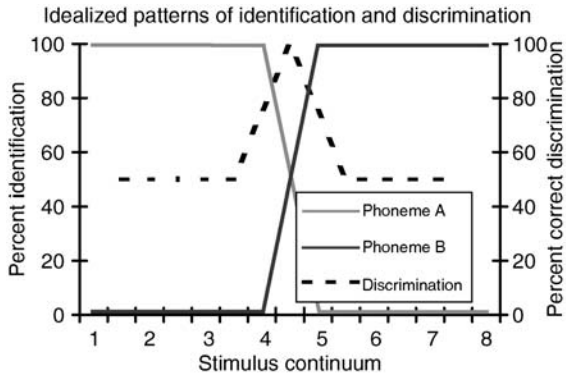
Effects of Experience

Studies on development of speech perception address some of the same issues. Infants' perception of individual speech sounds and words is shaped by statistical regularities across speech sounds heard within even a single listening session. In addition, there have been a small number of studies in which animals, instead of infants or computers, have served as surrogates to reveal how experience with natural covariation between acoustic attributes of speech help to maintain perceptual constancy for speech sounds. In each case, perceptual performance reveals sensitivity to experience with the frequency with which particular sounds occur and with the ways acoustic properties co-occur.

During the first year of life before infants produce much speech, they become increasingly attuned to the differences between vowels and consonants that are functionally appropriate to their language environment [5]. They begin to respond only to acoustic differences that distinguish two sounds in their native language, but not to acoustically equivalent differences that do not distinguish sounds in their language even when those differences are used by other languages. Adult difficulties perceiving differences between sounds in a non-native language develop early. There have been many studies of adult perception and production of contrasts when learning a second language and these show that ease of perception can be predicted on the basis of similarity or dissimilarity with sounds experienced in the native language.

Among experimental phenomena related to speech perception, perhaps none is more widely known than categorical perception. This classic perceptual process is studied using a series of stimuli that vary systematically in one or more acoustic attributes that distinguish between two speech sounds. Listeners label each stimulus as one or the other speech sound, and they discriminate between pairs of speech sounds drawn from different points along the series. Three features define categorical perception, a labeling (identification) function with an abrupt transition between the two categories, discontinuous discrimination performance (near perfect across the identification boundary and near chance when both stimuli are from the same side) and the ability to predict discrimination performance on the basis of labeling data (Fig. 2).

These patterns of data stand in contrast to perception of simple stimuli continuously varying along dimensions such as frequency, intensity, etc. Many additional findings indicate that categorical perception is not unique to humans' perception of speech. As might be expected given the major role of experience in



Speech Perception. Figure 2 Idealized Patterns of Identification and Discrimination.

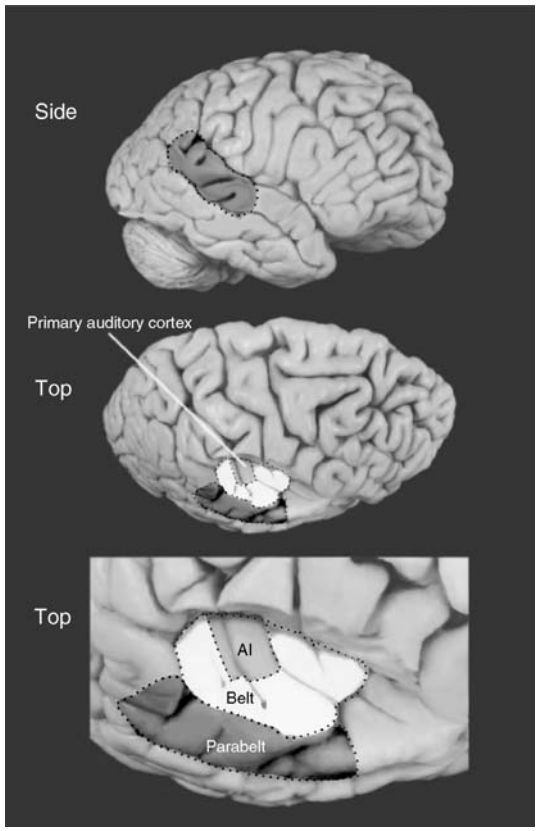
perception of speech, when experience is simulated using artificial neural network models, signature response patterns for categorical perception are emergent properties of learning following exposure to distributions of speech sounds [6]. Consistent with this conclusion, categorical perception has been observed with a number of visual and nonspeech auditory stimuli with which observers and listeners have much experience.

Cortical Processing of Speech

Modern methods of electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are contributing to a greater understanding of cortical functions related to speech perception.

Presentation of sounds of any kind results in activation of primary auditory cortex (AI). Beyond AI, ventral, anterior and posterior, there is a belt of cortex that is activated by more complex sounds (Fig. 3). Ventrally, a second belt, sometimes referred to as a parabelt, can be described. For these belt areas, often referred to as "secondary" or "associational" areas, there is decreasing activation in response to very simple sounds such as sine waves and white noise, particularly when stimuli do not change much over time. In addition to responding to more complex acoustic structure, there is greater evidence of cross-modal encoding (e.g. auditory and visual), particularly in parabelt areas. Activation in response to speech in core, belt and parabelt areas of auditory cortex has most often been found to be relatively balanced bilaterally in the absence of higher-level linguistic effects [7].

Some very recent research suggests that, when listeners discriminate speech sounds such as "ba" and "da", brain areas anterior and ventral to parabelt areas on the superior temporal lobe are more activated relative to very similar nonspeech sounds and this activation is relatively stronger in the left hemisphere [8]. When listeners understand whole meaningful sentences, activation is more clearly lateralized to the left



Speech Perception. Figure 3 Cortical processing of speech.

hemisphere in regions yet further anterior and ventral in the temporal lobe [9].

Although evidence for strong lateralization of cortical speech processing – absent higher linguistic content – is relatively limited, this does not imply that there is nothing special about processing of speech in the human cortex. There are other ways in which processing of speech can be distinguished from perception of other sounds. Cortical organization is critically linked to the amount and nature of experience and there are no acoustic signals with which humans have more experience than speech. One may well expect that, as more becomes known about cortical processing of complex sounds, cortical areas that appear more exclusively dedicated to speech sounds may be revealed.

Evidence for two types of cross-modal organization might also be expected in cortex. First, owing to a wealth of experience simultaneously hearing speech and viewing talkers' faces, one may expect substantial interaction between auditory and visual speech. The so-called McGurk effect, achieved by placing auditory and visual speech information in conflict, provides a powerful behavioral demonstration of this interaction, and there is some brain imaging evidence for cortical areas related to these perceptual effects [10]. Second,

there is some reason to expect evidence of interactions between speech production and perception. In addition to the more dorsal route between posterior temporal and motor cortex via the arcuate fasciculus, there is another connection between temporal and frontal areas of cortex via the uncinate fasciculus, which extends from anterior temporal cortex to inferior frontal gyrus. Thus, anatomical connections are in place to support associations between areas involved in perception of speech with areas involved with production. Given that speech provides an unusual case for which, at least when one is talking, there are simultaneous activities for producing and perceiving one's own speech, the potential for such as an association existing and being significant for speech perception is substantial.

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Speed-accuracy Trade-off

Definition

The rule that the accuracy of a target-directed movement is inversely related to its speed. To increase accuracy, reduce speed.

Speed Profile

Definition

Temporal aspects of the motion along a path, as they are manifested in the profile of the speed as a function of time. The path together with the speed profile over it, define the trajectory.

►Arm Trajectory Formation

Sphingolipids (SLs)

Definition

Ubiquitous, cell- and species-specific components of cell membranes, and together with their metabolites act as signaling molecules involved in cell-to-cell and cell-to-matrix interactions, cell adhesion, differentiation and death, modulation of membrane receptors, signal transduction, and stress responses. Genetic diseases of both the synthesis and degradation of SLs are known. Disease of SL biosynthesis may lead to infantile-onset symptomatic ►epilepsy (►seizures within the first year of life). Defective degradation of SLs and other lipids leads to accumulation of non-degradable material in lysosomes (lysosomal storage disorders). At present, more than 40 lysosomal storage disorders are known, of which 9-10 are due to defective degradation of SLs, among them Fabry disease, ►Gaucher disease and ►Tay-Sachs disease.

►Membrane Components
►Gaucher's Disease
►Tay-Sachs Disease

Spike

Definition

Spike – (also discharge, impulse): another term for the most rapidly changing portion of the action potential.

►Action Potential
►Sensory Systems

Spike Sorting

Definition

Class of techniques and algorithms that use the shape of waveforms collected by one or more electrodes in a neural preparation to distinguish the activity of one or more neurons from background electrical noise – this is also known as "spike detection" – and to assign spikes to different neurons. Extra-cellular electrodes often detect action potentials generated by several neurons in their vicinity. Since the spike shapes are unique and quite reproducible for each neuron, classification of these shapes can be used to distinguish spikes produced by different neurons.

►Computer-Neural Hybrids

Spike Train

Definition

Series of action potentials (or spikes).

►Action Potential
►Sensory Systems

Spin Tensor

Definition

The skew symmetric part of the velocity gradient. Also called vorticity tensor.

►Mechanics

Spina Bifida

Definition

Developmental abnormality resulting from the failure of the caudal ►neural tube to close, which in turn results in disruption of the functions of the lumbar and sacral spinal segments.

►Neural Tube

Spinal Animals

Definition

"Acute Spinal" refers to an animal whose spinal cord is surgically cut with a scalpel on the day of an experiment and is used to record electrophysiological data from muscles, nerves or spinal neurons "Chronic Spinal" refers to spinal animals whose spinal cord is cut at various levels (usually T13 in cats and T8 in rodents) and the animal is kept for a varying number of days, weeks and months to record kinematics, kinetics or EMGs.

►Locomotor Training

Spinal Autonomic Circuit

Definition

Segmental or propriospinal reflex circuit consisting of primary afferent neurons (mostly with small-diameter Aδ- or C-fibers), interneurons and preganglionic neurons. These spinal autonomic circuits are functionally defined by the function of the final autonomic (sympathetic or parasympathetic) pathway (e.g. muscle vasoconstrictor, urinary bladder etc) and the functional type of primary afferent neuron.

►Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Spinal Border Cells

Definition

Spinal border cells are a group of large neurons. similar in appearance to motoneurons, near the lateral border of the ventral horn of lumbar spinal cord segments. They relay proprioceptive information to the ipsilateral side of the anterior lobe of the cerebellum.

Spinal Column

Definition
The longitudinal column of bony rings that surrounds the spinal cord. Also known as the vertebral column or backbone.

►Evolution of the Spinal Cord
►Transplantation of Olfactory Ensheathing Cells

Spinal Cord

Synonyms
►Medulla spinalis

Definition
Spinal cord is surrounded by the spinal meninges, enclosed in the vertebral canal and extends in adults to about the second lumbar vertebra. Here are found primarily conduction pathways, synaptic centers but also motor programs (simple and complex reflexes, movement programs, inter alia).

►Development of Nociception
►Medulla spinalis
►Transplantation of Olfactory Ensheathing Cells

Spinal Cord Stimulation

Definition
Electrical stimulation of the dorsal column with high frequency, low intensity, short duration pulses activate large fibers of the dorsal column. These large fibers excite inhibitory interneurons and modulate the processing of spinothalamic tract cells receiving afferent information that was generated by applying a noxious chemical stimulus to the heart.

►Ascending Nociceptive Pathways
►Somatosensory Projections to the Central Nervous System
►Viscero-Somatic Reflex

Spinal Cord, Cervical Part

Synonyms
►Medulla spinalis; Pars cervicalis

Definition
Cervical cord. The part of the spinal cord comprising the spinal nerves of the cervical vertebral column.

►Medulla Spinalis

Spinal Cord, Gray Matter

Synonyms
►Medulla spinalis; Subst. grisea

Definition
Here are found nuclear regions in which the fibers synapse. Three areas are distinguished:

- Posterior horn
- Intermediate substance
- Anterior horn

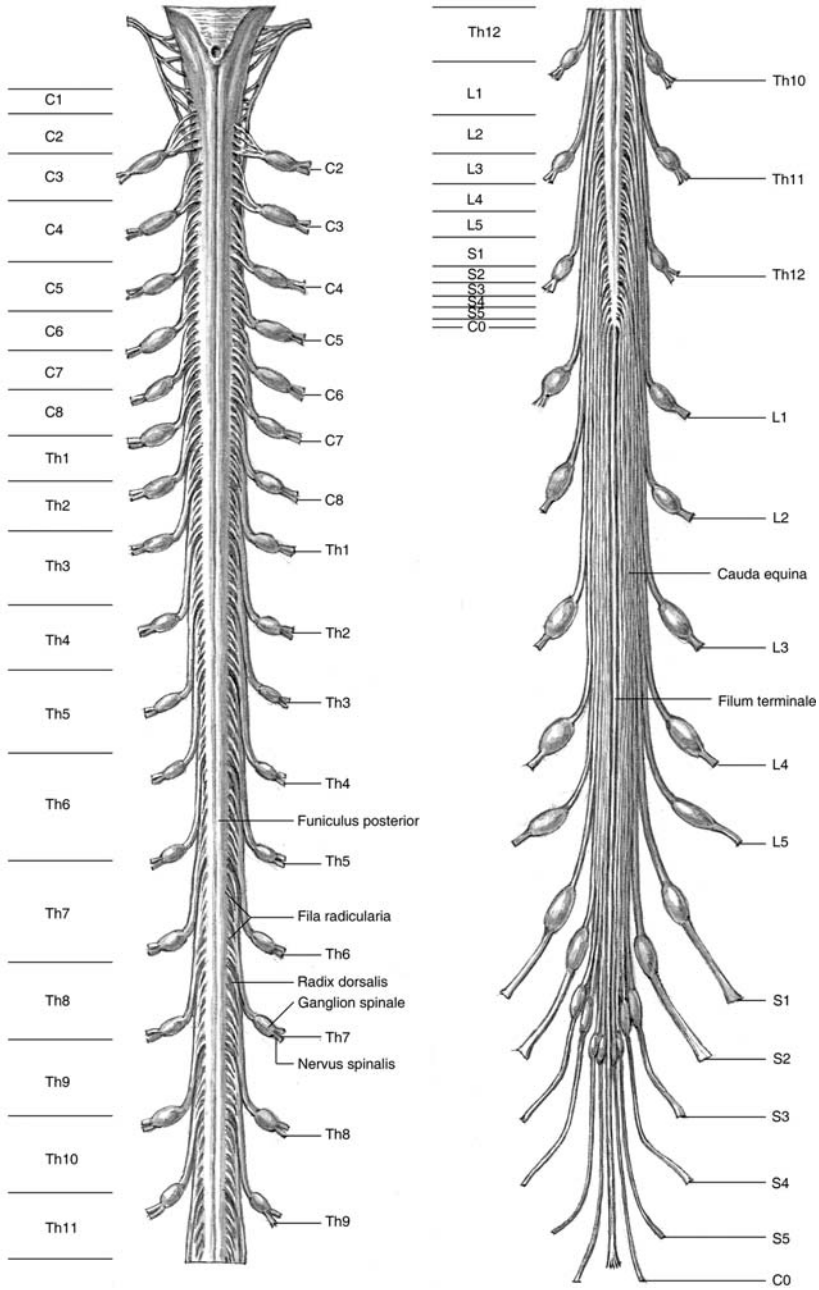
►Medulla spinalis

Spinal Cord, Lumbar Part

Synonyms
►Medulla spinalis; Pars lumbalis

Definition
Lumbar cord. The part of the spinal cord comprising the spinal nerves of the lumbar vertebral column, epidural cavity, which spreads across the entire length of the vertebral column. Cervical, thoracic and lumbar epidural cavities are also called peridural cavity. The peridural cavity plays a decisive role in epidural anesthesia.

►Medulla spinalis



Spinal Cord. Figure 1 Dorsal view of the spinal cord showing attached dorsal root filaments and spinal ganglia. The cervical (*C*), thoracic (*T*), lumbar (*L*), sacral (*S*) and coccygeal (*Co*) spinal nerves have been transected at their site of exit from the intervertebral foramina. The position of the spinal segments is indicated on the *left* side of the cord (2/3×). Original figure 03.14 taken from Nieuwenhuys, R; Voogd, J; van Huijzen, C. (Eds) 2008 "The Human Central Nervous System". Fourth Edition. Springer, Berlin. page 83 with permission.

Spinal Cord, Thoracic Part

Synonyms

►Medulla spinalis; Pars thoracica

Definition

Thoracic cord. The part of the spinal cord comprising the spinal nerves of the thoracic vertebral column.

►Medulla Spinalis

Spinal Ganglion

Synonyms
►Ganglion spinale

Definition
Spinal ganglion is formed by the cell nuclei of vicero-sensory, bi- or multipolar neurons, which project across the dorsal root into the spinal cord, where they mostly synapse directly on viscero-efferent fibers, thus creating the basis for autonomic reflex arcs.

Spinal Hyperexcitability

Definition
Sensitization of spinal cord neurons for peripheral input.

►Hyperalgesia and Allodynia

Spinal Muscular Atrophy

Definition
Disease of spinal ►motoneurons (with some ►demyelination of the ►corticospinal tracts) presenting with wasting and weakness of skeletal muscles, loss of reflexes and ►fasciculations; may be the same disease as ►amyotrophic lateral sclerosis.

►Amyotrophic Lateral Sclerosis
►Corticospinal Tract
►Fasciculations

Spinal Nerve

Synonyms
►N spinalis

Definition
A spinal nerve originates in the spinal cord, unlike the cranial nerve which arises from the cerebrum. A distinction is made between 31 pairs: 8 cervical (C1–C8), 12 thoracic (Th1-Th12), 5 lumbar (L1–L5), 5 sacral (S1–S5), and 1 coccygeal. Each segment pair provides sensory innervation for a clearly delineated skin area (= dermatome). Close to the spinal cord, the spinal nerve divides into a sensory dorsal root and a motor ventral root. External to the intervertebral foramen it divides again into a ventral branch and a dorsal branch.

►Medulla Spinalis

Spinal Nucleus of the Trigeminal Nerve

Synonyms
►Nucl. spinalis n. trigemini

Definition
This nucleus extends from the principal nucleus of the trigeminal nerve to the dorsal column of the cervical cord, which it enters. Afferents are the axons from the trigeminal ganglion, which convey somatotopically organized impulses from the face via the spinal tract of the trigeminal nerve. Efferents come from the caudal nuclear region, decussate to the contralateral side and pass as the lateral trigeminothalamic tract to the ventral posteromedial thalamic nucleus.

►Myelencephalon

Spinal Reflex

Definition
A reflex mediated via neuronal pathways located entirely within the spinal cord.

Spinal Respiratory Neurons and Respiratory Control

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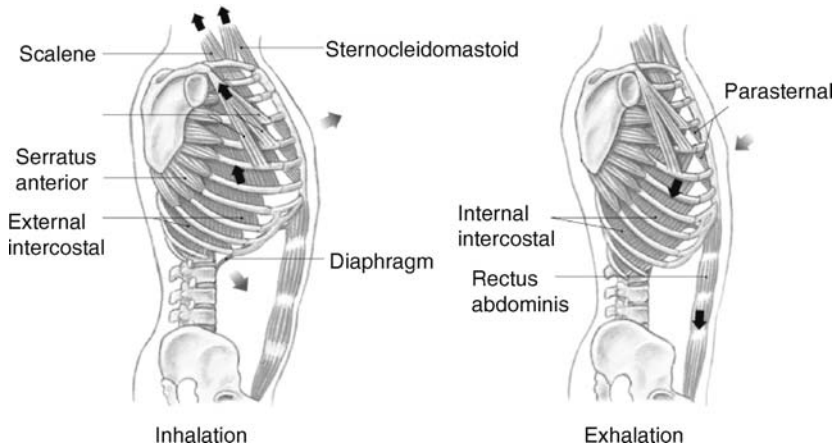
Definition
Air flow in and out of the lungs is regulated by mechanical action of the ribcage moving in axial and radial directions. Inspiration is an active phase controlled by the



Spinal Respiratory Neurons and Respiratory Control. Figure 1 Respiratory muscles innervated by spinal respiratory motoneurons that are recruited during inhalation and exhalation. Levator costae (occupying most rostral regions of each intercostal space), triangularis sterni (underlie parasternal muscles) and other abdominal muscles besides rectus abdominis not shown.

contraction of the diaphragm, levator costae, scalene, parasternal and external intercostals muscles. In addition, the sternocleidomastoid, pectoralis, serratus anterior and trapezius muscles are recruited during forceful inspiration. Expiration is largely passive, except for the recruitment of levator costae muscles. During forced expiration, rib cage movements are also controlled by abdominal and internal intercostal muscles (Fig. 1). Further, the thoracoabdominal muscles play a role in vocalization, various gastrointestinal activities, as well as ribcage stabilization and postural adjustments, particularly during locomotor activities and exercise. Thus, their contribution to airflow generation will vary from breath to breath as it is adjusted to best meet these multiple demands. The motoneurons innervating and controlling these muscles are located within the ventral horn of the spinal cord. This section will provide an overview of the anatomical and physiological properties of spinal respiratory motoneurons. The primary focus will be on ►alpha motoneurons, those that innervate extrafusal muscle fibers. A brief discussion of ►gamma motoneurons which innervate intrafusal fibers of muscle spindles will appear at the end. There a number of excellent reviews that provide more in depth discussions of spinal respiratory motoneurons and the muscles they innervate [1–4].

Characteristics

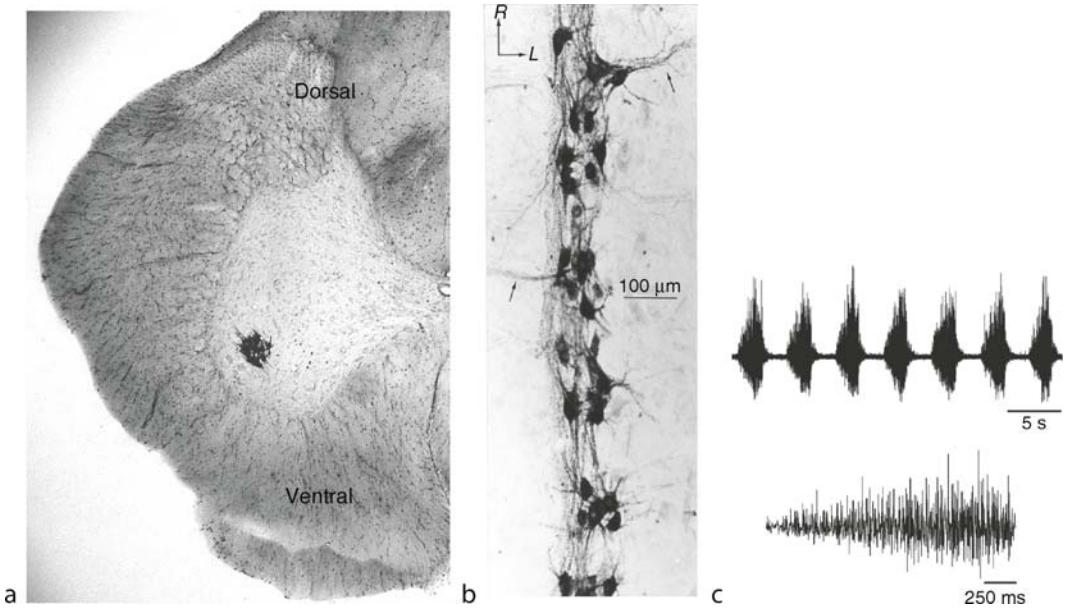
Phrenic Motoneurons

Phrenic motoneurons (PMNs) are the sole source of efferent innervation of the diaphragm muscle, the primary inspiratory muscle controlling thoracic expansion. PMNs have been studied in much more detail compared to other spinal respiratory motoneurons.

Anatomy: PMNs are located in the ventral horn of cervical (C)3-C5 segments of the human and rodent spinal cord. The relative proportion of PMNs residing within each cervical segment varies with species. The PMN nucleus is readily recognizable by its medial position in the ventral horn and the extensive rostrocaudally-oriented dendritic branches (Fig. 2). It has been suggested that these dendritic bundles assist in coordinating respiratory movements by synchronizing the activity of groups of motoneurons. The diaphragm originates from a single embryological structure but is functionally compartmentalized into costal and crural regions via selective recruitment of motor units. PMNs innervating the costal diaphragm are located rostral relative to those innervating the crural diaphragm.

Synaptic input and discharge characteristics: PMNs receive inspiratory drive from bulbospinal neurons located in the ventral nucleus of the solitary tract, referred to as the ►DRG (dorsal respiratory group), and rostral region of the ventrolateral column of respiratory neurons called the rostral ventral respiratory group (rVRG). In the rat, however, the DRG contribution is minor. The connections from the medulla to PMNs are both mono- and poly-synaptic, but monosynaptic connections predominate.

Glutamate is the main neurotransmitter mediating transmission of synaptic inspiratory drive to PMNs. The majority of the glutamate-mediated action is via non- ►NMDA (N-methyl-D-aspartic acid) receptors. However, there is an NMDA-receptor mediated component that accounts for ~10% of the baseline drive and that component may be further enhanced via reflex-mediated synaptic input. PMNs are silent during the expiratory phase due to the combined withdrawal of inspiratory drive and the activation of GABAergic inhibitory synaptic drive. The primary source of inhibitory drive to PMNs arises from expiratory bulbospinal neurons located in the caudal VRG and ►Bötzinger



Spinal Respiratory Neurons and Respiratory Control. Figure 2 (a) HRP labeled PMNs showing distinct clustering and bundling of rostrocaudal projecting neurites. Figures provided by Dr. H. Goshgarian, Wayne State U. (b) Cat phrenic nerve recording showing characteristic ramp-like burst pattern. Figures provided by Irene Solomon, University of New York at Stony Brook.

complex (BötC) located at the rostral end of the ventral respiratory column. Further, PMNs receive GABAergic inhibitory drive concomitant with excitatory glutamatergic inspiratory drive; the balance of each being adjusted to shape PMN discharge pattern and subsequent drive to the diaphragm muscle.

In addition to the fast excitatory and inhibitory inspiratory drives mediated, respectively by the amino acid transmitters glutamate and GABA, a dense plexus of synaptic varicosities converge onto the PMN pool that contain a multitude of neurotransmitters, including serotonin, thyrotropin releasing hormone, noradrenaline, Substance P, metenkephalin, cholecystokinin, galanin, neuropeptide Y and adenosine. The neuromodulators regulate PMN excitability on a slower time scale relative to the amino acid transmitters. In addition, the activity of these modulatory neurons often varies between states (e.g., sleep-wake cycling).

The pattern of phrenic discharge increases in a ramp-shaped pattern during each inspiratory burst (Fig. 2). The increasing discharge is due to the increase in discharge frequency of individual PMNs and recruitment of previously silent PMNs. There is also post-inspiratory discharge amongst a sub-population of PMNs that works in concert with activation of laryngeal expiratory motoneurons to provide a smooth transition from inspiration to expiration by limiting early expiratory airflow. In addition, PMNs receive endogenous rhythmic inspiratory currents with prominent oscillations in the 20–50 Hz and 80–150 Hz ranges. It has been hypothesized that these oscillations control the precise timing of ►action potentials, helping to maximize synaptic drive efficiency by constraining MN firing frequencies to those optimal for muscle contraction [5].

Details of how PMN output in the form of action potentials are determined by the complex interaction of intrinsic and synaptic properties is largely unknown. This requires specific knowledge of several factors including neuronal morphology, type and distribution of multiple types of voltage- and ligand-gated channels, ►second messenger systems and their actions, associated endogenous neurotransmitters and their location on the somatodendritic and presynaptic membranes, and the interactions between various neuromodulators and ionic channels (see [3,10] for review).

Development: Most mammalian motor systems do not become fully functional until they undergo significant postnatal development. While the neuronal and muscular components of the respiratory system mature postnatally, they must be developmentally advanced and functional by birth to generate a rhythm and motor behavior that is sufficient for gas exchange in a highly compliant chest wall but can also to integrate swallowing and other behaviors with breathing. The development of rat PMNs during the perinatal period has been systematically examined (see [7] for review).

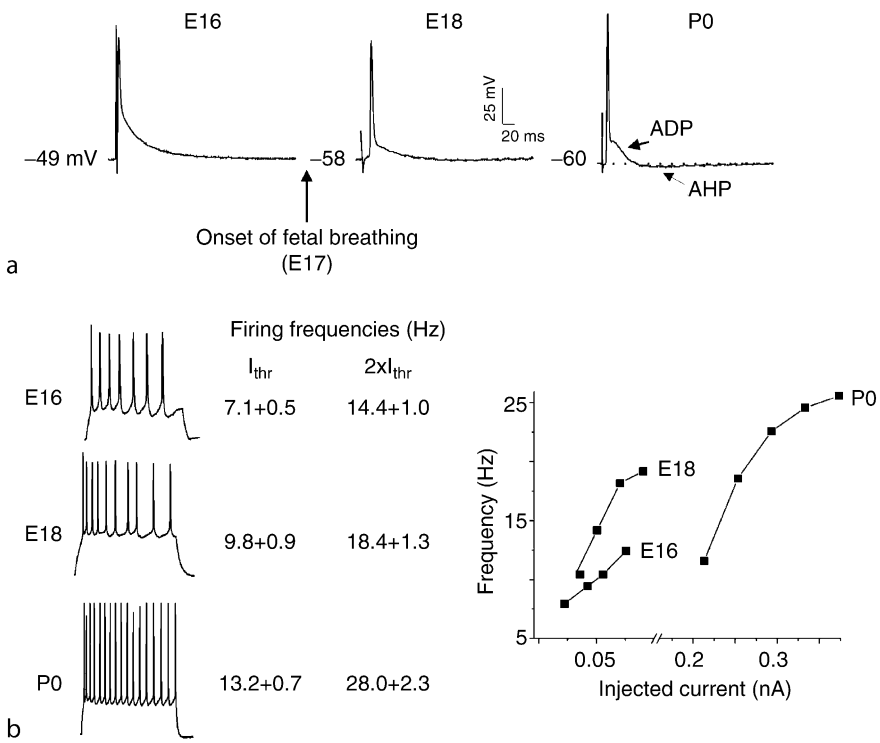
PMNs differentiate and proliferate within the ventricular zone of the neural tube. They are organized into

tightly packed clusters, linked by gap junctions, as they migrate to reach their final position in the ventral horn. During these early stages, the PMN somata and their simple mediolateral neurites align along the processes of radial glia that provide a guiding substrate. The specification of motoneuron identity is thought to be controlled, in part, by the combinatorial actions of transcription factors. The detail of how these operate to specifically define phrenic versus brachial phenotype has not been examined. The axons of phrenic and brachial motoneurons exit via cervical ventral roots and migrate together toward the primordial diaphragm. Under the influence of currently unidentified guidance cues, the two populations, led my pioneer axons, diverge. Phrenic axons continue to grow ventrally toward the diaphragmatic primordium; brachial axons turn laterally to grow into the limb bud. The phrenic nerve initiates branching within the diaphragm when myoblasts in the region of contact with the phrenic nerve begin to fuse and form distinct primary myotubes. As the nerve migrates through the various sectors of the diaphragm, myoblasts along the nerve's path begin to fuse and form additional myotubes.

During these early stages of development from the time of initial axon outgrowth until the diaphragm is fully formed, PMNs are recruited as part of a robust, regular rhythmic motor pattern that is generated along the entire developing spinal cord and brainstem. It has been hypothesized that the spontaneous embryonic rhythmic activity plays a key role in regulating the early development of neuronal circuits and motoneuronal phenotype.

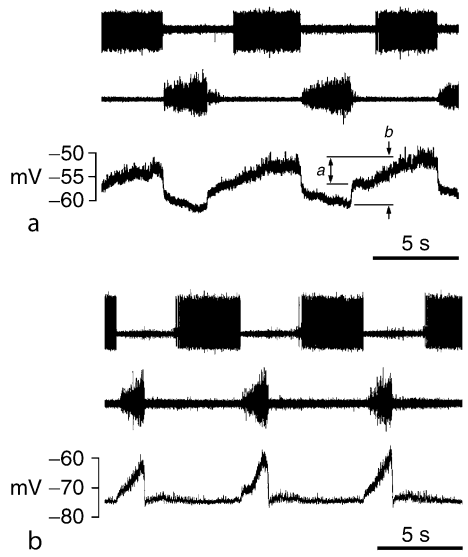
The phrenic nerve intramuscular branching and concomitant diaphragmatic myotube formation is largely complete by embryonic day 17 in the rat and the 10th week of gestation in the human. This is also the time of the commencement of inspiratory drive transmission to PMNs, the inception of fetal breathing movements (FBMs) and the arrival of phrenic afferents to the motoneuron pool.

During the period spanning the inception of FBMs to birth there is dramatic change in PMN morphology, passive membrane properties, action potential characterises and firing properties (Fig. 3). Changes include the following. (i) PMN dendritic branching is rearranged into the rostrocaudal bundling characteristic of mature PMNs, and gap junctions between PMNs decrease. (ii) PMN ►resting membrane potential becomes significantly more hyperpolarized (~10 mV) without a significant change in action potential threshold, whereas



Spinal Respiratory Neurons and Respiratory Control. Figure 3 (a) Typical action potentials recorded from embryonic day (E16), E18 and postnatal (P)0 rat PMNs. (b) *Left panel* shows examples of repetitive firing patterns generated following injection of a depolarizing square pulse. *Right panel* shows representative current frequency plot for PMNs at various ages studied. Adapted from [7].

there are significant decreases in the input resistance (►membrane resistance) (~three times lower) and ►time constant (~1.4 times shorter). Thus, PMNs require significantly less depolarizing current to reach threshold at the inception of inspiratory drive compared with more mature states (i.e., rheobase current is ~2.5 times less at E17 than at birth). Functionally, the increased propensity for reaching firing threshold will compensate for a relatively weak descending inspiratory drive at this age, and thus facilitate the production of fetal breathing movements. (iii) Action potential characteristics change markedly. The amplitude increases by ~12 mV and the duration decreases by ~50%. Calcium conductances emerge which play a large role in the development of after-depolarizing and -hyperpolarizing potentials. (iv) Concomitant with changes in the duration and shape of action potentials, there is a marked change in the repetitive firing properties of PMNs. By birth, PMNs fire at ~ two times the maximum discharge frequency achieved at the onset of FBMs. The net results of the changes in the passive and action potential properties are that by birth, PMNs, while requiring a stronger synaptic drive to initiate firing, are capable of driving the diaphragm musculature to produce greater contractile forces in comparison to those generated in utero.



Spinal Respiratory Neurons and Respiratory Control. Figure 4 Examples of central respiratory drive potentials (CRDPs) in intercostal motoneurons. Records in each panel, from the top: extracellular discharge from an expiratory bulbospinal neuron; efferent discharge in an external intercostal nerve, used to define inspiration; intracellular recording from a motoneuron. (a) expiratory motoneuron, (b) Inspiratory motoneuron. Adapted from [6].

Respiratory Motoneurons Innervating Thoracic Muscles

Motoneurons innervating thoracic muscles are phasically active during inspiratory or expiratory phases to control ribcage expansion. Further, they regulate ribcage stability and therefore improve the efficiency of the diaphragm muscle.

Anatomy: Internal and external intercostal, as well as triangularis sterni and parasternal motoneurons are located in the ventromedial region that corresponds to the intercostal space in which the muscle is located. In the transverse plane, levator costae motoneurons are located in the ventromedial region of the ventral horn, while the parasternal and triangularis sterni motoneurons are located primarily along the lateral edge of the ventral horn. Internal and external intercostal motoneurons are located between these motoneuron groups with external intercostals motoneurons generally being more medial than internal intercostals motoneurons.

Synaptic input and discharge characteristics: Inspiratory drive transmission to thoracic respiratory motoneurons arises from the rVRG and ►DRG. Expiratory drive arises from the cVRG, but likely not the BötC which does not project beyond the cervical spinal cord. Unlike PMNs, there seems to be very little monosynaptic input to thoracic respiratory motoneurons from the medulla. Rather, there is a segmental interneuronal network transmitting reciprocal inhibition between inspiratory and expiratory intercostals motoneurons that provides spinal integration of supraspinal and segmental synaptic inputs (Fig. 4). The neurochemical control of respiratory motoneurons controlling thoracic musculature has not been studied in detail. However, it would appear that the primary inspiratory drive is via glutamatergic synaptic input.

Parasternal, external intercostal and levator costae motoneurons are activated during the inspiratory phase. There is a rostrocaudal gradient of the strength of inspiratory activity in external intercostals muscles. In contrast, there is a tendency for the levator costae motoneurons innervating caudally located muscle to be recruited strongly during inspiration.

Internal intercostal and triangularis sterni motoneurons are activated during the expiratory phase. The majority of triangularis sterni motoneurons commence firing mid-expiration. There is a caudorostral gradient of the strength of expiratory activity in internal intercostals muscles.

Motoneurons innervating muscles in the neck, shoulder and chest region can also contribute to movements of the thorax during respiration. Scaleni motoneurons, located in segments C2-C7, are activated during inspiration. Scalene muscle activity assists with the lifting of the upper ribcage. The sternocleidomastoid, pectoralis, trapezius and serratus anterior motoneurons are not rhythmically active at rest but can be recruited during forced inspiration. Sternocleidomastoid motoneurons are located in segments C1-C3 and trapezius motoneurons extend from C2-C6; both send axons via the spinal

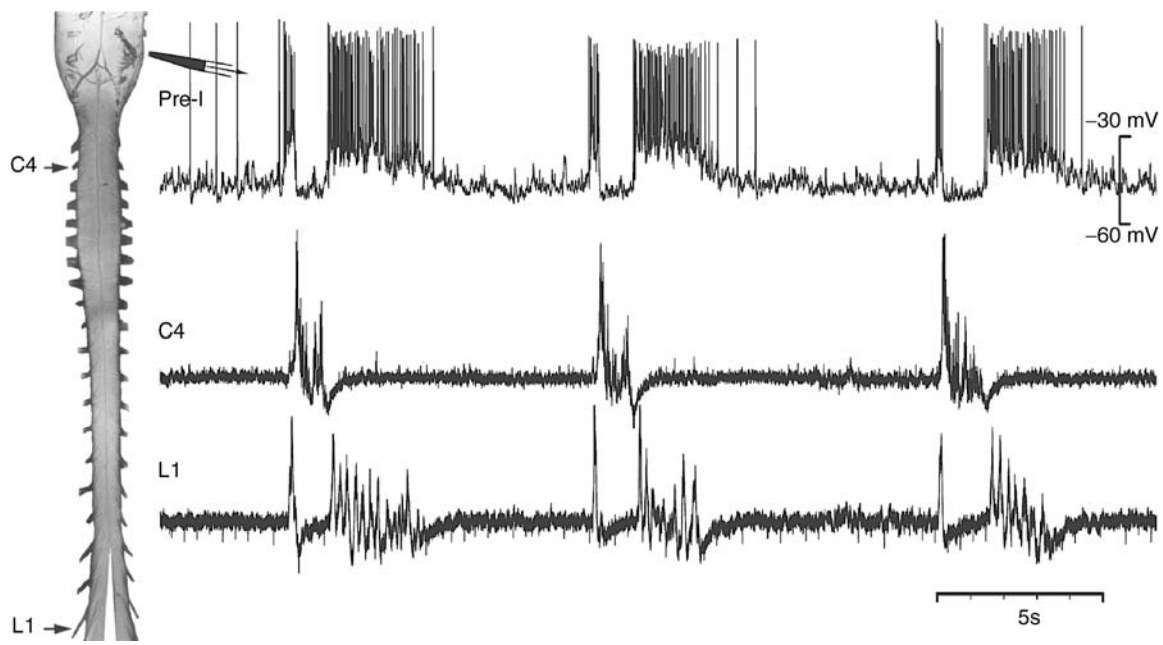
accessory nerve. Notably, there is overlap in the location of caudally located trapezius and PMNs. Pectoralis motoneurons are located within the medial to ventromedial tip of the ventral gray matter of C6-C7. The majority of serratus anterior motoneurons are from C6, with a smaller component located at C7.

Abdominal Motoneurons

The respiratory abdominal muscles comprise two outer (external oblique, EO, and rectus abdominis, RA) and two inner (internal oblique, IO, and transversus abdominis, TA) muscles. Abdominal muscles are primarily innervated by motoneurons located in the lower thoracic and upper lumbar spinal cord; external oblique (T6-L3), internal oblique (T13-L3), transverse abdominis (T9-L3) and rectus abdominis (T4-L3). There is considerable overlap in the positioning of those motoneurons within the ventrolateral region of the ventral horn. Abdominal motoneurons are recruited during forced expirations. Premotoneurones supplying abdominal motoneurones are localized in the caudal part of the ►VRG (ventral respiratory group), within or close to the nucleus retroambiguus. It has been recently hypothesized that preinspiratory neurones located in the rostral ventrolateral medulla close to the ventral surface at the level of the rostral half of the nucleus retrofacialis provide rhythmic drive to those premotoneurons (Fig. 5).

Gamma Motoneurons

Muscle spindles respond to changes in muscle length. The sensitivity and firing rate of muscle spindles is modulated by fusimotor axons. Most fusimotor axons derive from γ-motoneurons that exclusively innervate spindles, but a minority are β-fibers (α-motoneurons that innervate spindle intrafusal muscle fibers and skeletal muscle fibers). Intercostal muscles have a rich complement of muscle spindles and gamma motoneuron innervation (reviewed in [9]). Inspiratory activity of external intercostals is markedly reduced in the absence of feedback onto intercostal motoneurons from muscle spindle afferents. In contrast, the diaphragm and triangularis sterni muscle have very few muscle spindles and consequently a low number of gamma motoneurons in their motoneuron pools. Perhaps reflex activity mediated via muscle spindles would be functionally inappropriate for the diaphragm, the major muscle controlling inspiration. For instance, reflex activation of PMNs by spindle afferents could occur when the diaphragm is passively lengthened either due to trunk rotation of pressure applied by adjacent abdominal organs. Likewise, heightened fusimotor activity that can occur in association with certain states of alertness, would result in increased muscle spindle afferent discharge and reflex activation of PMNs. These occurrences could theoretically lead to disturbances in diaphragm function and breathing pattern.



Spinal Respiratory Neurons and Respiratory Control. Figure 5 Expiratory activity of lumbar motoneurons. Activity of the preinspiratory neuron located in the parafacial nucleus region projecting to the nucleus retroambiguus and traces of C4 and L1 root activity generated in an vitro neonatal rat brainstem-spinal cord preparation. The firing pattern of the preinspiratory neurons and L1 root in vitro consisted of two distinct bursts bracketing C4 root activity. Adapted from [8].

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Spinal Shock

Definition

Spinal shock results from a complete transaction of the spinal cord and denotes a state of reduced or absent spinal reflexes, which gradually recover within weeks and months and then often are enhanced.

Spinal Trigeminal Nucleus

Definition

The spinal trigeminal nucleus receives input from the pain and temperature (and some tactile) afferents in the trigeminal nerve (Vth cranial nerve). This nucleus is in the lateral brainstem and extends from the pons through the medulla to the spinal cord where it is continuous with the substantia gelatinosa region of the dorsal gray.

Spinal Trigeminal Tract

Definition

The spinal trigeminal tract is made of primary afferent fibers of the trigeminal nerve (Vth cranial nerve) that carry pain and temperature (and some tactile) information. The cell bodies of these fibers are in the trigeminal ganglion. The tract begins at the Vth nerve entry in the pons and courses lateral to the spinal Vth nucleus in its descent to the spinal cord where it is continuous with the tract of Lissauer.

Spinal Vertebrate

Definition

A vertebrate with a complete transection of the spinal cord.

Spine, Morphological Change

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Definition

Dendritic Spines and Filopodia

Spiny protrusions of dendrites that receive excitatory synaptic inputs. Dendritic spines possess a bulbous head, at which stable synaptic contact with a presynaptic terminal is formed. Dendritic ▶filopodia do not manifest a bulbous head and are often longer than spines as well as highly motile and unstable. Filopodia are numerous in neurons of young animals but are sparse in those of adults. It is often difficult to distinguish filopodia from thin spines. Filamentous (F) actin is highly enriched in spines

and filopodia, whereas microtubules are absent; in contrast, F-actin is less abundant and microtubules are present in the parental dendritic shaft.

Characteristics

Quantitative Description

Spines are present on a variety of neurons, but they are especially numerous (1–15 spines per micrometer) and prominent in the major projection neurons of the vertebrate brain, including cerebellar Purkinje cells, ►pyramidal neurons in the cerebral cortex, and medium spiny neurons in the basal ganglia. In pyramidal neurons, the morphology of spines is highly variable; spine–head volume varies from 0.005 μm^3 to 0.5 μm^3 (head diameter of 0.2–1 μm), spine–neck length from 0 μm to 1.1 μm, and spine–neck diameter from 0.04 μm to 0.26 μm. Spine structure is less variable in Purkinje neurons, with head volume ranging between only 0.06 μm^3 and 0.18 μm^3 [1]. The structure of spines, especially that of the neck, is difficult to study, even with serial reconstruction by electron microscopy, because the thickness of tissue sections (~0.06 μm) is similar to the diameter of spine necks. High-voltage electron microscopy allows examination of a large number of spines without serial sectioning (Fig. 1), and may prove useful for detailed quantitation.

Direct imaging of spines in living brain tissue is possible by ►two-photon excitation microscopy. With this fluorescence imaging technique, spine–head volume (V_H) can be determined by measurement of the total fluorescence intensity of the spine head. Spine–neck geometry can be similarly quantified from fluorescence images or can be determined by quantitative Ca^{2+} imaging [2], and expressed as a parameter, spine–neck Ca^{2+} conductance (g_N) (Fig. 2).

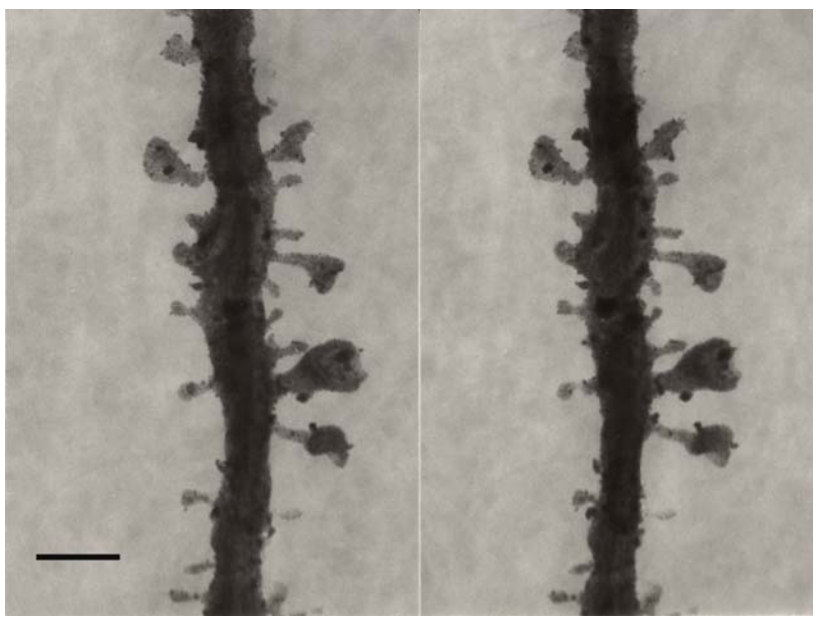
Spine–neck Ca^{2+} conductance varies by a factor of up to 1,000, and is approximately proportional to the second power of spine-head volume in hippocampal pyramidal neurons. This nonlinear relation may be essential for the plasticity of small spines and the stability of large spines [2]. Similar head-neck relations are also apparent by electron microscopy (Fig. 1). Three typical types of spine – thin, stubby, and mushroom – have been distinguished (Fig. 2), but these types reflect three extremes of one continuous population of spines.

Higher Level Structures

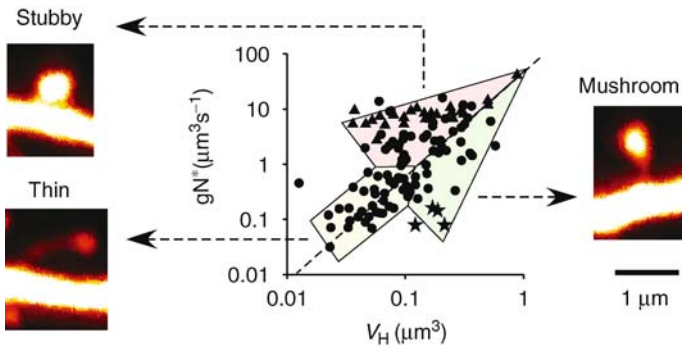
Spines are components of dendrites and of excitatory synapses. They are also one of the major constituents of the ►neuropile.

Lower Level Components

Synaptic contact is made at the region of a spine at which a ►postsynaptic density (PSD) is identifiable by electron microscopy, at the cytoplasmic face of the plasma membrane. Most spines also contain a ►spine apparatus, a structure thought both to function as a Ca^{2+} store and to house the machinery for protein synthesis. The spine apparatus is more prevalent in larger spines. Polyribosomes are also present in spine heads, where they are



Spine, Morphological Change. Figure 1 High-voltage electron microscopic stereo image of a dendrite of a rat hippocampal granule cell. Many partially hidden spines are apparent on the dendritic shaft. Golgi preparation with a thickness of 5 μm; scale bar, 1 μm. Courtesy of K. Hama. Methodology is described in Microscopy Research and Technique 29(1994) 357–367.



Spine, Morphological Change. Figure 2 Distribution of spine–head volume (V_H) and spine–neck Ca^{2+} conductance (g_N*) for 115 spines, in four dendrites, in slice-culture preparations of rat hippocampal CA1 pyramidal cells. Values of g_N were obtained from fluorescence images as described in [2]. The yellow, green, and red regions contain thin, mushroom, and stubby spines, respectively. Stars represent typical mushroom spines with long narrow necks and relatively large heads, and triangles typical stubby spines without a neck. Modified with permission from [2].

thought to participate in protein synthesis, and their prevalence is increased after tetanic stimulation.

Structural Regulation

Spines are either formed from dendritic filopodia after establishment of a stable synapse or emerge directly from a dendritic shaft. The dynamics of transitions among spines with different structures has been partly understood. Rapid enlargement of spines with a small head is induced by tetanic stimulation of presynaptic fibers, and gives rise to long-term potentiation (LTP) [3]. Spine enlargement and LTP can be induced at the level of a single spine by direct stimulation of the spine, indicating that individual spines are able to serve as memory elements at the cellular level. In addition, large spines (V_H of >0.1 μm^3) are resistant to long-lasting enlargement and LTP [3], and they can stably exist in living animals for months or more than a year [4,5], suggesting that large spines might represent physical traces of long-term memory.

Spines also change their shape sporadically with a time constant of minutes to hours, a process that can be detected as fluctuations in spine–head fluorescence and which possibly reflects treadmilling of actin. Indeed, many molecules that regulate the actin cytoskeleton affect spine structure [6]. Abnormal spine shape, or spine dysgenesis, is associated with various forms of mental retardation [7]. Spines are thus unusually numerous and tortuous in individuals with fragile X syndrome, the most frequent form of hereditary mental retardation. Many hormones, especially sex steroids, alter spine density.

Higher Level Processes

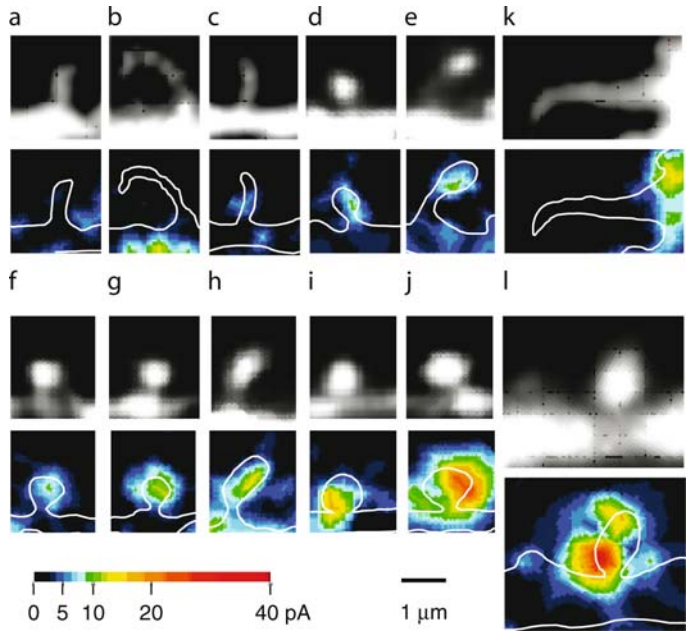
Spines are basic functional units of higher order brain activities, such as learning and memory as well as cognitive and executive processes. Spines are thus more prominent in higher animals and are absent from most invertebrate neurons. Spines are also present at extremely high density on the major projection neurons, which play a central role in mental functions, and are postsynaptic to most excitatory synaptic inputs. In addition, spine density and shape are affected by various environmental factors and are abnormal in individuals with various mental disorders. Spines also undergo extensive reorganization during the critical period of ocular dominance plasticity. Finally, spines detect coincidence of pre- and postsynaptic neuronal activities and respond with rapid structural and functional plasticity [3].

Lower Level Processes

Spine structure underlies the major spine function, the sensing of glutamate released from presynaptic terminals. It is now possible to measure the function of individual spines by two-photon uncaging of a caged-glutamate compound [2, 3, 8]. This approach has revealed that expression of glutamate receptors sensitive to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in spines is approximately proportional to spine–head volume [8] and that these receptors are absent from filopodia (Fig. 3).

The abundance of glutamate receptors sensitive to *N*-methyl-D-aspartate (NMDA) is also greater in larger spines than in smaller ones. Whereas expression of NMDA receptors is significant even in small spines, however, that of AMPA receptors is not, suggesting that small spines form silent synapses [2]. Small spines are also preferential sites for LTP [3]. The differential distribution of NMDA and AMPA receptors in small spines may reflect the abundance of binding partners for NMDA receptors in PSDs and the dependence of AMPA receptor function on F-actin [6].

The spine neck is a critical determinant of Ca^{2+} diffusion from the spine head into the dendritic shaft



Spine, Morphological Change. Figure 3 Spine geometry and expression of functional AMPA receptors. Fluorescence images (*upper panels*) and glutamate-sensitivity maps (*lower panels*) are shown for various dendritic spines of CA1 pyramidal neurons in fresh hippocampal slices prepared from adult (a–k) or 9-day-old (l) rats. The fluorescence profiles were obtained from stacked images containing the respective spine. The glutamate-sensitivity maps are based on AMPA receptor-mediated current, the amplitude of which is pseudocolor coded as indicated. The maps were smoothed by linear interpolation. White lines indicate the contours of dendritic structures. Representative data from thin spines (a–e), mushroom spines (f–j, l), and filopodia (k) are shown. Reproduced with permission from [8].

during NMDA receptor-mediated responses [2]. Furthermore, increases in the concentration of Ca^{2+} within spines are greater and more confined in those with a narrow neck. Given that the spine neck tends to be narrower in smaller spines (Fig. 2), increases in cytosolic Ca^{2+} concentration are larger and more confined in such spines, whereas they are smaller and spread into the parental dendritic shaft in large spines. The spine neck may also restrict the movement of large structures such as the spine apparatus and polyribosomes. In contrast, the diameter of even the smallest spine necks is not sufficiently small to substantially affect the propagation of excitatory postsynaptic currents.

NMDA receptor-dependent Ca^{2+} influx into the spine head induces enlargement of the head in a manner dependent on calmodulin and on actin polymerization [3]. The long-lasting phase of spine enlargement further requires the action of Ca^{2+}- and calmodulin-dependent protein kinase II. Spines also express metabotropic glutamate receptors and receptors for brain-derived neurotrophic factor (BDNF), which trigger the activation of various protein and lipid kinases (such as cyclic AMP-dependent protein kinase, protein kinase C, mitogen-activated protein kinase, phosphoinositide 3-kinase, and Src), protein phosphatases (such as calcineurin), and small GTPases (Ras, Rap, Rac, Rho) as well as stimulate protein synthesis. Such intracellular signaling is thought to alter spine morphology through regulation of the actin cytoskeleton as well as exo- and endocytosis. Spine molecules thus regulate spine structures and vice versa. The reciprocal relationships between spine molecules and structures may underlie the high stability of spines in the brain, and their characterization is important for an understanding of spine function at the molecular level.

Process Regulation

LTP and Dendritic Spines

LTP is induced at glutamatergic synapses on spines in an input-specific manner. In aspiny interneurons, however, LTP is either absent or spreads along dendrites [9]. Spines thus appear to support the induction and input specificity of LTP. Induction of LTP is input specific even at the level of the individual spine [3] as a result of the confined increase in cytosolic Ca^{2+} concentration within the spine head. LTP is associated with spine enlargement and actin polymerization, which results in accumulation of scaffold proteins and AMPA receptors through lateral diffusion and exocytotic insertion into the spine membrane.

Given that spine–head volume is correlated with AMPA receptor expression in the steady state [8], long-lasting plasticity would be expected to lead to an alteration of spine structure. The extent of immediate structural change, however, may be variable, depending on the specific synapse and experimental conditions. Structural plasticities of spines include phenomena other than LTP, since LTP is mainly associated with enlargement of small spines into medium-sized spines [3]. Such plasticities include the emergence of new filopodia or spines, reflecting the generation of new connections, and the maturation of large spines, reflecting the formation of highly stable connections.

Function

The reason why spines are necessary for the function and plasticity of synapses in the brain awaits further investigation. It has long been thought that the persistence of memory traces in a biological system requires their storage in a structural form [10]. If this is the case, then the structure and density of spines appear well suited for the rapid induction and maintenance of memory at the highest density, in a manner that satisfies Hebb's learning principle.

Pathology

Abnormalities in spine density or morphology, which are associated with various mental disorders, may partly reflect abnormal neuronal activities [7]. Dendritic spines, however, may be the primary sites of diseases, since mutations in proteins expressed in spines are identified in certain types of mental retardation [7]. Spine dysfunction likely underlies a broader range of mental disorders, given that glutamatergic synaptic transmission is impaired in many such conditions, including schizophrenia.

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Spines (Dendritic)

Definition

Small protrusions of the dendrite with which an axon terminal forms a synapse.

►Spine
►Morphological Change

Spinocerebellum

Definition

Several classifications are used to subdivide the cerebellum based on anatomical, phylogenetic and functional (i.e. termination of cerebellar afferents and efferents) findings. The anterior and posterior parts of the vermis and paravermal parts of the cerebellar hemispheres were called spinocerebellum because of their spinal afferents. The spinocerebellum corresponds to the paleocerebellum based on phylogenetic and embryological studies.

►Cerebellum
►Cerebellar Functions
►Posture Role of Cerebellum

Spinocervical Tract

Definition

An ascending pathway that arises from neurons of the spinal dorsal horn and projects via the ipsilateral

dorsolateral columns to the lateral cervical nucleus located at the C1-C3 level of the spinal cord.

►Asending Nociceptive Pathways
►Somatosensory Projections to the Central Nervous System

Spinoreticular Tract

Definition

Ascending somatosensory pathways that project and make synaptic connections within the reticular formation of the brainstem.

►Somatosensory Projections to the Central Nervous System

Spinothalamic Tract

Definition

The spinothalamic tract is a pathway that originates from neurons whose cell bodies are found in the dorsal horn, and their axons cross over within one or two segments and ascend within the ventrolateral white matter to the ventral posterior lateral nucleus of the thalamus. This is the classical pathway for transmission of nociceptive stimuli from visceral and somatic structures to areas of the brain via the thalamus that are involved with pain sensation.

►Ascending Nociceptive Pathways
►Thalamus

SPL – Superior Parietal Lobule

Definition

►Visual Space Representation for Reaching

Splanchnic Afferents

►Visceral Afferents

Spliceosome

Definition

A protein complex of proteins that mediate the splicing reaction.

►Alternative Splicing and Glial Maturation

Split Brain

Definition

Neurological state of separated left and right ►hemispheres effected surgically by sectioning the ►corpus callosum and ►anterior commissure, often in patients with otherwise untreatable epilepsy. Split-brain patients present with neurological pecularities yielding insights into the functional asymmetries between the two hemispheres.

►Corpus Callosum

Split Rhythms

Definition

A dissociation of circadian components induced by appropriate environmental conditions. In some species, exposure to constant light causes the usual 24 h activityrest cycle to dissociate into two components. These “morning” (M) and “evening” (E) components run at slightly different periods before coupling in a stable (antiphase) relationship. In hamsters induced to split, clock gene expression in the left and right Suprachiasmatic nucleus (SCN) assume an antiphase relationship as well. Related dissociations, which may not be mechanistically similar, may be induced by exposure to ultradian (much shorter than 24 h) light-dark cycles or to light-dark cycles with periods at the limits of entrainment for the organism. This latter type of dissociation may involve one oscillator that entrains to the light-dark cycle and another that is unable to entrain and therefore essentially free-runs.

►Circadian Rhythm
►Clock Genes
►Suprachiasmatic Nucleus

Spontaneous Activity

Barrages of action potential electrical discharges that do not bear any obvious relationship to brain activities such as sensory information processing or movement generation.

Spontaneous Internal Desynchronization

Definition

Loss of synchrony between two or more endogenous circadian rhythms, originally defined to describe dissociation between the sleep-wake cycle and the body temperature cycle in humans maintained in temporal isolation.

►Circadian Rhythm
►Internal Desynchrony
►Sleep-wake Cycle

Spontaneous Recovery

Definition

The re-emergence of conditioned responses after the passage of time following extinction training.

►Learning and Extinction

Spontaneous Saccades

Definition

Saccadic eye movements that are made with no apparent incentive and with no obvious external stimuli.

►Saccade, Saccadic Eye Movement

Sprouting

Definition

Growth of nerve fiber to form new synaptic connections. One trigger for sprouting at the neuromuscular junction is loss of synaptic activity.

►Neuromuscular Junction

SRBN Type II

Definition

Superior colliculus (SC) neurons characterized by activity which increases about 80–100 ms before the onset of the saccade, reaches a peak value that precedes saccade onset by 10–20 ms, and then wanes. They correspond to the more recently described build-up neurons (BUNs).

►Saccade, Saccadic Eye Movement
►Superior Colliculus
►SC – Tectal Long-Lead Burst Neurons

Src

Definition

A non-receptor tyrosine cytoplasmic kinase that can transfer a phosphate group from ATP to tyrosine residues of target proteins.

Src Homology Domain

Definition

A protein domain first identified as a conserved sequence in Src. This domain in a protein allows it to interact with phosphorylated tyrosine residues of other proteins.

SSDR

Definition

►Species-specific Defense Reaction

SSP

Definition

►Subacute Sclerosing Panencephalitis

Stability

Definition

A system is said to be stable if it returns to some equilibrium condition after it is perturbed.

►Control

Stabilography

►Stabilometry

Stabilometry

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Synonyms

Static posturography; Stabilography; Computerized stabilometry

Definition

Stabilometry is the objective study of body sway during quiet standing, i.e., stance in the absence of any voluntary movements or external perturbations. Conventionally, the study focuses on the properties of body sway during upright standing, thus far primarily measured by means of force plates. Sometimes, upper body sway is studied in sitting postures.

Purpose

Stabilometry aims at collecting information indicative of the steady-state functioning of the postural control system, and of its success in stabilizing the body against gravity, by examining the properties of measures, directly or indirectly related with ►postural sway.

Principles

Stabilometry is a valid, objective and functional evaluation of the postural control system in its steady-state behavior [1]. Quiet, upright stance is the basic, representative posture that is traditionally investigated in stabilometry although a few studies concentrate on sitting postures.

During the test, the subject is asked to stand upright in a stationary environment where, depending on the protocol, one or more sensory afferences can be made unavailable or manipulated. Upright stance is inherently unstable. Small deviations from an upright body position result in a gravity-induced torque acting on the body, causing it to accelerate further away from the upright position. Many muscles become tonically and phasically active, in a largely automatic way, to generate appropriate, corrective torques to oppose the destabilizing torque due to gravity. As a result of such an active process, even when visual, somatosensory, and vestibular systems are all active, a standing individual will sway slightly. This sway will increase, as sensory input is distorted or removed, as it may happen, e.g., (i) when vision is not available or is sway-referenced, (ii) when the support surface is compliant or sway-referenced, and (iii) when vestibular information is distorted. Similarly, this sway will decrease, when (i) sensory input is augmented or reinforced, (ii) by repetitive balance training, (iii) by an artificial biofeedback device, or (iv) by threat of a fall.

Postural sway during quiet standing reflects this interplay between gravity destabilizing the body and actions by the postural control system to prevent a loss of balance, and can be modeled with an inverted pendulum model of the body [2]. The regulatory mechanisms underlying postural sway are not fully understood yet, and controversy remains regarding the organization of sensory and motor systems contributing to spontaneous sway.

Balance impairments caused by altered sensory, motor, or central nervous function related to such factors such as older age and pathology (e.g., cerebellar ataxia, peripheral neuropathy, Parkinson's disease) will be reflected in characteristic, altered characteristics of postural sway [3–4]. The influence of different factors on postural sway

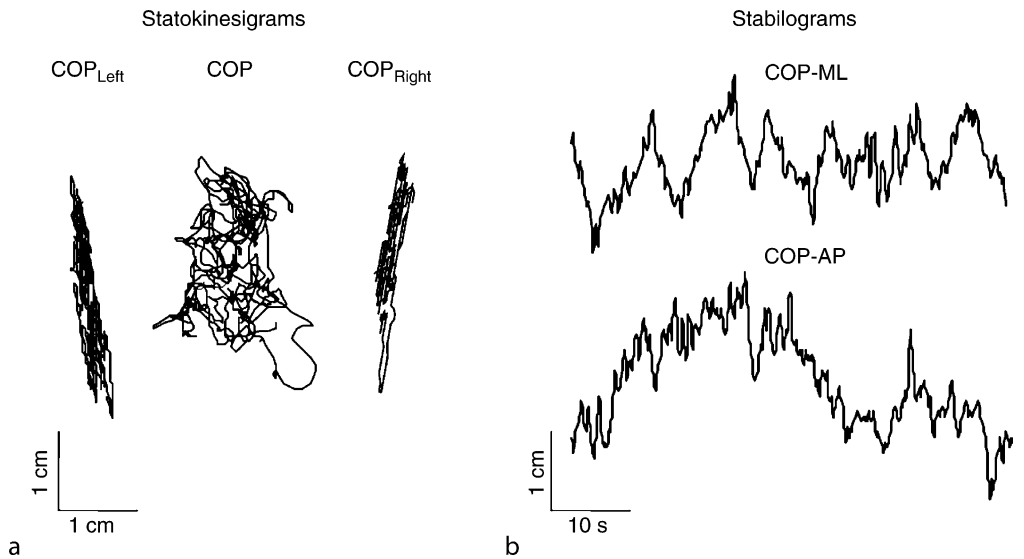
during quiet standing has been the focus of much clinical and basic scientific study.

Due to its complexity, the postural control system is challenging to measure with simple methods, although simple methods are needed, especially in clinical practice. Since a direct, multisegmental analysis of postural sway during stance may require complex kinematic trackers such as motion analysis systems, postural sway is most often described indirectly by the fluctuations of the ►center of pressure (COP) on the ground, measured with a force platform. By means of a set of mechano-electrical force transducers (strain gages or piezoelectric crystals), force platforms act as dynamometers and record the interaction between the feet and the ground, i.e., the ground-reaction, and the COP. Ground-reaction force and COP are related to postural sway, more precisely, to the motion of the body ►center of mass (COM), and consequently provide important insights into the process of controlling balance [2]. In the future, portable systems, based on miniaturized, inertial sensors (accelerometers, gyroscopes), may allow a direct, multisegmental analysis of body sway. Several studies are in progress to determine procedures to make measurement of sway with portable inertial sensors robust and valid [5].

The vast majority of studies in stabilometry have been limited to force plate studies using only one force platform. In that case, the COP reflects the net effect of the ankle muscles and the loading/unloading of each limb [2] as well as the movement of the COM of the entire body, and displays as a random-looking pattern when its antero-posterior (AP) coordinates are plotted against its medio-lateral (ML) coordinates. This plot is commonly referred to as statokinesigram (Fig. 1a). Alternatively, each COP coordinate can be represented as a function of time, to obtain the so-called stabilograms (Fig. 1b) [1].

If two force platforms are available, one for each foot, distinct left and right COP displacements can be measured (Fig. 1a) [2]. Since the ankle muscles are important controllers of the COP, the location of the COP under each foot is an outcome from concerted efforts of the ipsilateral, individual ankle muscles. Increasing plantarflexor activity (e.g., triceps surae, peroneii) moves the COP anteriorly; increasing dorsiflexor activity (e.g., tibialis anterior) moves the COP posteriorly. Increasing invertors' activity (e.g., triceps surae, tibialis anterior and posterior) moves the COP laterally; increasing evertors' activity (e.g., peroneii) moves the COP medially. Individual ankle muscle actions on the COP can be investigated through in-vitro studies [6] that demonstrated that the calf (plantarflexor group) is the most efficient COP controller in the anterior direction, while the tibialis anterior muscle and dorsiflexor group are the major COP controllers in the posterior direction. Two force platforms also disclose the lateral loading and unloading mechanism, and the consequent pressure modulation under each foot, controlled by the activity of the hip abductor/adductor muscles (e.g., tensor fascia latae, gluteus maximus, semimembranosus). In this case, the location of the total body COP either in the AP or ML directions can be computed by using Varignon's theorem that states that in equivalent force systems the sum of moments equals the moment of the resultant.

Several methods exist to describe postural sway using the COP statokinesigram and/or stabilograms. In general, measures that are most commonly used are



Stabilometry. Figure 1 Representative quiet stance recordings through a force platform. (a) AP vs ML coordinates of the COP in presence of a two force platform set-up (COPleft, COPright) and resultant, whole-body COP. (b) Time series of ML and AP coordinates of whole-body COP.

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those that describe statistical properties of the COP, treated as a stationary signal, in the time and frequency domain [7]. Time domain measures estimate a parameter associated with either the displacement (expressed in mm) or the velocity of the COP trace, and include parameters such as: mean distance from average COP position (mm), root mean square distance from average COP position (mm), total distance traveled by the COP (mm), peak-to-peak COP displacement (mm), mean velocity of the COP (mm/s), area of the 95% confidence circle or ellipse (mm^2), swept area (mm^2/s).

Frequency domain measures characterize the power spectral density of the COP, and include parameters as: total power (mm^2), power in selected bandwidths (mm^2), median frequency (Hz), 95% power frequency (Hz), centroidal frequency (Hz), frequency dispersion (dimensionless).

Many studies in force platform stabilometry characterized postural sway based on a single COP-based measure, but more recent studies usually include multiple measures [4,7]. Depending on the cause of the postural instability, velocity-related measures were often reported to separate stable postural control from reduced stability better than displacement-related measures [4,8]. No general rule of thumb is available, however, to select the best subset of measures needed in force platform stabilometry. Since many and varied sway measures exist, feature selection has to be preliminary performed to keep only independent measures and avoid redundancy, make statistical analyses stronger, and facilitate interpretation of the results.

The ideal set of measures to recommend for practical use should be minimally influenced by spurious sources of within- (e.g., non-stationarity, fatigue) and between-subject variability (e.g., anthropometry) that may peculiarly influence the characteristics of the COP. In addition, selected measures should be sufficiently sensitive to changes in hypothesized physiological determinants of postural sway and hence able to identify actual, significant changes in posture control across patients' or treatments' groups or across experimental conditions [9]. Several recent studies, using different methodologies, have recommended and justify different subsets of three to four COP-based measures, e.g., see [8].

Interestingly, COP displacements during quiet stance display a fractal behavior. This important property, common to many physiological processes, can be expressed in terms of statistical self-similarity. Such self-similarity implies that there is a scaling relationship describing how the measured value of a statistical property depends on the scale in which it is measured. The simplest scaling relationship determined by self-similarity has a power law form, leading to a straight line on log–log plots.

In the analysis of COP experimental data, the existence of scaling comes to light, for example, if the variance of the displacements (i.e., the distances between consecutive points of the statokinesigram) is examined over different time scales. One main implication of fractality is that scaling functions that describe how the values change with the resolution tells more about the data than the value of the measurement at any one resolution (in particular, at the higher resolution as it is commonly done by the summary statistic scores, working with the original sampled time series). For this reason, to obtain more significant parameters about the postural control system, techniques postulating the time-scale dependence of COP statistical properties have been proposed [10]. These techniques show that COP fluctuations have a structure that is dependent upon the time-scale of observation and not simply random. This result was interpreted by proposing different modes of postural control taking place over different periods of time and opened the way to more sophisticated tools in postural sway analysis.

Advantages and Disadvantages

Platform stabilometry is a simple and easy tool to objectively investigate the function of the postural control system in its steady-state behavior. To date, stabilometry undoubtedly suffers, however, from several limiting factors including (i) the absence of a definite "normal pattern"; (ii) the lack of standardization in the measurement protocols; (iii) the large number of highly coupled variables that are computed from the force platform recordings.

Most COP-based measures have in common a medium to large variability, both between- and within-subjects, and this may be a limiting factor when wishing to determine whether a postural performance is abnormal or whether it is sensitive to change from a treatment or a therapy [1,9]. The inherent variability of such measures in normal subjects has been the object of several studies. Within-subject variability has been partially explained by a learning effect that leads to an optimization of the energy expenditure by means of a progressive reduction in body sway over repeated trials. The large between-subject differences prevents defining normative values for stabilometric parameters [1]. This is a major restriction of stabilometry, which limits its routine use in clinical practice or as a first-level examination of postural control. For this reason, it is important to cope with all the potential sources of spurious variability that may mask or overwhelm control-related information. To this aim, first, a significant role can be ascribed to inconsistencies in the measurement procedure (between experimental sessions within the same lab and, more so, between different laboratories) including, e.g., reproducibility of the experimental protocol such as foot placement and duration of testing, environmental conditions, random errors, and signal processing. A second source of

variability is related to the intrinsic differences between subjects in terms of their biomechanics. Subject morphology, together with joints and muscle function, has been identified, in a systems approach, as the main biomechanical factors involved in balance control. Body size and foot placement are known to influence postural stability and their impact on COP-based measures can be at least partly removed through normalization [9].

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Stain

Definition

A stain is any number of chemical compounds which when applied to tissue appropriately will color cellular components. Thus details of particular cellular structure can be studied under a microscope. A variety of stains are used to study nerve tissue. Some, such as Nissl stains, mark cytoplasmic detail and show cell bodies. Others, such as the Weigert stains, mark the myelin and show myelinated axons. Still others, such as Nauta silver stains, show axons and their terminals, while Golgi stains show a few neurons in their entirety.

Staircase Method

Definition

A psychophysical procedure by which the stimulus intensity is changed according to an observer's response to bracket the threshold; an interactive variant of the method of limits.

►Psychophysics

Standing Wave

Definition

A periodic wave having a fixed distribution in space that is the result of interference. Such waves are characterized by the existence of nodes and antinodes that are fixed in space.

►Acoustics

Stapedius Muscle

Definition

One of two muscles in the middle ear of mammals that is involved in the middle ear muscle reflex. (The other middle ear muscle is the tensor tympani muscle.) The stapedius muscle arises from the auditory tube and inserts onto the stapes, or stirrup, which is the middle ear bone directly connected to the round window of the inner ear. The stapedius muscle is innervated by the facial nerve. Its contractions dampen sound-induced oscillations of middle ear bones and reduce sound amplitude, thus protecting the ear from intense sound signals.

►Auditory-Motor Interactions

Starburst Amacrine Cell

Definition

Retinal interneuron with a characteristic, radially symmetrical dendritic morphology that functionally participates in the propagation of Ca^{2+} waves in the developing retina and in the generation of direction selectivity in the adult.

►Retinal Direction Selectivity: Role of Starburst Amacrine Cells

Start Codon

Definition

A trinucleotide sequence within the mRNA that initiates RNA translation. The usual start codon is ATG in DNA.

Starting Phase

Definition

The point in time at which a sound wave starts relative to the period of the sound wave, expressed in degrees or radians.

►Acoustics

Startle Response

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Synonyms

Escape behavior

Definition

Startle responses are rapid movements that occur very quickly following an abrupt, unexpected, strong sensory stimulus, such as a loud sound produced by a slamming door. Startle or escape responses are shared by almost all animals, including both invertebrates and vertebrates [1]. In many cases, they are thought to serve protective functions such as avoiding the attack of predators. The form of the response varies across species. In humans, it usually consists of closing of the eyes and a hunching of the head and body. Extension of the legs in some mammals can lead to a jumping movement that might serve to move the animal away from an attacking predator. In fish, the startle (escape) response involves a rapid bend of the body that turns the fish away from the stimulus. This is usually followed by rapid swimming to avoid capture by a potential predator. In invertebrates, startle might consist of a rapid jump followed by flight in a fly, or a tail flip in a crayfish.

Characteristics

Quantitative Description

Perhaps the most characteristic feature of a startle response is the very short time between the stimulus and the start of the movement. This occurs in about 14 milliseconds (ms) in humans, 10 ms in rats and as little as 5 ms in larval fish [1]. Typically, the magnitude of the response is measured as the force or amplitude of the movement. In mammals, such as rats, this is accomplished by measuring the force generated by limb movements in specialized cages fitted with accelerometers. In fish, the angular velocity and magnitude of the bending of the body are measured using high-speed imaging because the movements are very fast. Startle responses can vary in magnitude depending upon the strength of the stimulus and its source, as well as the history of exposure to other stimuli. For example, responses are increased following induction of fearful states and are reduced in amplitude following prior exposure to a weak stimulus that does not elicit a startle response [2].

Higher Level Structures

Startle responses are typically produced by relatively large, fast conducting neurons. These are the giant neurons in invertebrate systems such as flies, crayfish, and squid. In vertebrates, the cell bodies of the giant neurons are in the hindbrain ►reticular formation and their axons have outputs in the brain and spinal cord. There are relatively few of these neurons in fishes and amphibians, where they include the well- studied giant ►Mauthner cells [3]. A larger number of neurons located in the ►caudal pontine reticular nucleus in the hindbrain mediates the startle response in mammals [4]. Among vertebrates, the pathways for sound elicited startle responses are strikingly similar, with very short pathways from the ear to giant neurons in the hindbrain,

and direct pathways from hindbrain to motoneurons and interneurons in the spinal cord.

Lower Level Components

Startle or escape responses typically engage local circuits controlling a variety of muscle groups, including muscles in the head responsible for eye blinks and jaw clenching, as well as axial (trunk) and limb muscles. Some of the networks for these circuits have been well described in fishes and invertebrates where the giant neurons connect directly to motoneurons, as well as to excitatory interneurons that drive motoneurons and inhibitory interneurons that control antagonistic muscle groups [5,6]. Evidence from mammals indicates similar patterns of output to local motor circuits in the head and spinal cord [4].

Structural Regulation

The patterns of recruitment of the giant hindbrain neurons vary in conjunction with variation of the behavior. This is best documented in fishes, where the form of the escape response varies depending upon the source of the sensory stimulus that elicits it [7]. This variation is associated with different patterns of activation of the giant neurons in the hindbrain [8]. The gradations of the magnitude of escape responses in mammals are also likely to be a consequence of changing patterns of recruitment of hindbrain neurons, because reductions of the number of neurons in lesioning experiments is associated with a reduction in response amplitude [9].

Higher Level Processes

The rapid nature of the startle response is reflected in a circuit designed for speed. There are only a few neurons in the path from sensory input to initial motor output – four in the pathway for auditory startle in fish and five in mammals. These pathways generally contain ►electrical synapses, which are associated with speed and synchronous activation of circuits. The giant neurons in the hindbrain of vertebrates also have some of the largest and fastest conducting axons in the central nervous system, designed to quickly relay the sensory signals to the spinal cord to produce a motor response.

Lower Level Processes

The rapid, powerful drive to the spinal cord is associated with a large pulse of activation in muscles that results from a synchronous activation of motoneurons. This may be important for overwhelming any ongoing muscle activity that might interfere with initiation of the startle or escape response.

Process Regulation

The magnitude of the startle/escape responses changes in conjunction with prior experience. Most notably, the response shows simple forms of learning such as ►habituation and ►sensitization [2]. Cellular data indicate that there is plasticity of synaptic connections onto the giant neurons in the form of ►long term potentiation and ►long term depression, which might underlie the simple forms of learning associated with the response [3]. Innervation of giant neurons by ►serotonergic and dopaminergic systems is consistent with evidence that changing levels of serotonin and dopamine can alter the startle response, with serotonin usually attenuating responses and dopamine elevating them [2]. Importantly, the startle response shows ►prepulse inhibition, with a reduced startle response to a strong stimulus when it follows a stimulus too weak to elicit a startle. Prepulse inhibition occurs broadly among species. In invertebrates, a neuron that produces it by ►presynaptic inhibition of sensory neurons has recently been identified [10]. As many neuropsychiatric diseases are associated with disruption of serotonergic and dopaminergic modulatory systems or with changes in prepulse inhibition, the startle system is becoming a model for identifying genes that might underlie diseases of the brain [11].

Function

Startle or escape responses appear to serve a protective function that is most obvious in invertebrate animals and aquatic vertebrates, where the circuits are recruited in response to predatory attacks. A similar anti-predatory role might occur in quadupedal mammals. In humans, the function is less obvious, although the tensing of the body and the closing of the eyes in response to a loud sound might serve to protect the body from possible injury, as these sounds might naturally occur in hazardous situations produced by breaking or falling objects such as rocks and branches.

Pathology

Abnormal prepulse inhibition of the startle response is associated with neurological disorders including ►schizophrenia, obsessive-compulsive disorder, and ►Huntingtons disease [11]. Some of these deficits are thought to result from problems in the control of the flow of sensory information through central circuits to motor output – a process called sensorimotor gating. This has led to studies of deficits in prepulse inhibition of startle in genetic models such as mice, as a tool to identify the genetic basis of neuropsychiatric diseases [11]. Mutations in receptors and transporters involved in serotonergic and dopaminergic transmission alter prepulse inhibition of the startle response and also contribute to psychiatric disorders. Exaggerated startle responses and a lack of habituation are associated with a disorder called hyperekplexia, or familial startle disease, which occurs as a consequence of a mutation

in the alpha subunit of the glycine receptor [12]. This is consistent with the known important role of inhibitory pathways in controlling startle responses and in sensorimotor gating more generally.

Therapy

Drugs that are known to alter serotonergic and dopaminergic transmission also have effects on startle behavior. The known circuitry and reproducible responses of the startle behavior, make it a good system for testing the effects of drugs that might serve to alleviate the neuropsychiatric disorders associated with changes in startle pathways [13]. Drugs that improve deficits in startle responses in animals or humans might also alleviate the more severe neuropsychiatric symptoms associated with these deficits.

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State

Definition

Particulars can be in different states. "State" can mean a state token, e.g. a concrete occurrence of molecular motion in a body or of a neural activity in a person's brain. Alternatively, "state" can mean a state type. This is either a property that can be shared by several things or persons, such as being hot or being in pain, or a kind of state tokens, such as a certain kind of molecular motion or neural activity. In control theory, a state is defined by a collection of variables that describes system behavior. Present state, together with the future inputs to the system, uniquely determines future states.

►Argument
►Control
►Logic

State, Functional

Definition

A functional state is a higher-order property of a particular system: the property of being in some inner state or other that plays a certain functional role, i.e. that bears certain (causal) relations to outer affections of the system (inputs), its outer behavior (outputs), and to other inner states. Different systems can be in the same functional state, although the inner states that play the functional role in question radically differ in nature.

►Argument
►Logic

State, Mental

Definition

A mental state is a state of the kind that is typically attributed by mental predicates such as "is in pain" or "believes that it is raining." In a narrow sense, only

long-term mental attitudes like beliefs (Belief) or desires are states. But mental events (sensations, feelings, thoughts) (Consciousness) are called states, too. Mental states may be physical states (identity theory), functional states (ontological functionalism), or sui generis (dualism).

►Argument
►Logic

State, Physical

Definition

States that can be attributed by a detailed description in the language of the physical sciences are physical states. If a state is of the same kind as these, it counts as physical even if that particular state cannot be described by current science. In a very narrow sense, only states describable by physics are physical. When contrasted with mental states, "physical state" often means "a state that is either physical or functional or a mixture thereof.

►Argument
►Logic
►State, Functional

State, Representational

Definition

Postulating representational states in order to account for a certain psychological achievement carries two main commitments: different representational states can occur independently of each other, and only their contents and functional roles, but not their intrinsic natures are of mental significance. It is often further assumed that such states form sentencelike or image-like complexes and that they are related to their contents one by one rather than holistically.

►Argument
►Logic
►State, Functional

State Estimation

Definition

The process of estimating the plant state from sensory feedback and knowledge of the plant dynamics and effector activations.

►Neural Networks for Control

State of Activation

Definition

Theory that states that the modulation of GABAergic synaptic connections between nucleus tractus solitarii (NTS) and dorsal motor nucleus of the vagus (DMV) is controlled by the levels of cAMP (cyclic AMP) in the NTS terminals. In "resting" conditions, the GABAergic synapse is unresponsive to neuromodulators, when the levels of cAMP are increased by hormones released following a meal, the synaptic connection is "primed" and available to modulation.

►Cyclic AMP
►Nucleus Tractus Solitarii
►Dorsal Motor Nucleus of the Vagus (DMV)
►GABA

State of Affairs

Definition

A situation, something that might be the case, if a state of affairs obtains it becomes a fact.

►Possible World

State Space

Definition

The space, which contains all the possible states of a system, e.g. all the possible values of its variables.

►Signals and Systems

State Variables (SVs)

Definition

Express relationships inherent in natural laws (e.g., forces and kinematic variables in Newton's laws of motion); any variables that cannot be changed independently of SVs (e.g., in the intact neuromuscular system, stiffness, damping, and the magnitude of muscle activation since they are coupled to changes in muscle force, a SV); constrained by natural laws, can only be changed indirectly by neural control levels, by regulating control variables.

►Equilibrium Point Control

Static

Definition

Static implies that there are no changes over time (*i.e.*, a steady-state has been reached). For skeletal muscle, static refers to the state when no length or force changes are occurring.

Static Air Pressure

Definition

The air pressure at a point in space that would exist in the absence of sound waves.

►Acoustics

Static and Dynamic Sensitivity of Sensory Receptors

Definition

Static and dynamic sensitivity are qualitative terms aimed to characterize the sensory receptor response to external stimuli. Static sensitivity describes the capacity for the receptor to signal the persistence of a (constant) stimulus, for some time after stimulus onset. Dynamic sensitivity describes the capacity for the receptor to signal when the stimulus intensity changes over time.

►Autonomic Control of Sensory Receptors
►Sensory Systems

Static Posturography

►Stabilometry

Static (Steady-State) Stiffness

Definition

The proportionality constant that relates the change in force (or torque), produced by displacement from an initial stationary position to a final stationary position, to the displacement.

►Impedance Control

Statics

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Definition

Statics is the science of equilibrium.

Description of the Theory

The fundamental equations of ►mechanics (q.v.) are differential equations, whose solution determines the motion of a mechanical system. A mechanical system is said to be in *equilibrium* if there exists an inertial frame for which the motion vanishes identically. In all other inertial frames, therefore, the motion can at most consist of a uniform translation, namely, each and every particle of the system moves with a constant ►velocity, equal

for all particles. A useful subdivision of classical mechanics from this point of view is into *statics* (the science of equilibrium) and *dynamics* (the science of motion). Although the first is clearly a particular case of the second, it is useful sometimes to regard it as an independent discipline. This point of view not only facilitates the treatment for those many applications in which motion is not of interest, but it also provides an intuitive basis to regard, somewhat paradoxically, dynamics as a particular case of statics, whereby the so-called *forces of inertia* are brought to bear.

The concept of equilibrium applies equally well to classical mechanics (q.v.) and to continuum mechanics (q.v.). This article will however, concentrate on the statics of a rigid body, leaving for the article on the ▶principle of virtual work (q.v.) a re-consideration of statics from a more general point of view. The first task is to obtain a set of necessary conditions for the equilibrium of a rigid body. Since, by definition, equilibrium can be regarded as the absence of motion (in an inertial frame), a direct application of Eqs. 6 and 7 of ▶Newtonian mechanics (q.v.) yields the following two vectorial *equilibrium equations*:

$$\mathbf{F}^{ext} = \mathbf{0}, \tag{1}$$

and

$$\mathbf{M}_0^{ext} = \mathbf{0}. \tag{2}$$

In words, a necessary condition for the equilibrium of a rigid body is that the sum of all the external forces and the sum of all the moments of the external forces with respect to a fixed point be equal to zero. Notice that, while Eq. 1 guarantees that the center of mass of the system will move at a constant velocity, the satisfaction of Eq. 2 is not sufficient to guarantee that the rigid body will be at rest from the rotational point of view. It is only for this reason that these equations are not also sufficient for equilibrium. To guarantee equilibrium, at some instant of time the angular velocity vector must vanish. From the point of view of statics as an independent discipline, however, these two vectorial equations are considered as the very definition of equilibrium.

Considering a system of rigid bodies interconnected perhaps by means of joints (such as the skeletal system), it is possible to mentally split this system into its component members (each bone, say) and to draw a *free-body diagram* of each member. This diagram must include not only the external forces directly applied to the member (such as weight, ground reaction, etc.), but also the forces transmitted by the other members from which it has been detached (joint forces and muscle forces transmitted through tendons and ligaments, for example). It is to the totality of these forces that Eqs. 1 and 2 are to be applied, resulting in a system of six *algebraic* equations for each member, involving just the forces and the geometry of the system. A system is called *statically determinate* if the number of equations obtained in this way is exactly equal to the number of the statical unknown quantities of the problem. These statical unknowns usually represent the forces of interaction (such as muscle and joint forces and ground reaction forces). If the number of statical unknown quantities is larger than the number of equations of statics, the system is said to be *statically indeterminate* and its solution will in general fall into the domain of continuum mechanics (q.v.) or require the incorporation of extra information (conveying, for example, the assumed *force sharing* conditions of agonistic muscles). Cases in which the number of equations of statics is larger than the number of statical unknown quantities (*statical* under-determinacy) may also occur, indicating that there are extra conditions to be satisfied between the geometry and the applied forces. To illustrate the various situations just described, the simple example of a two-bone planar system may suffice (e.g., the femur and the tibia). The planarity of the system manifests itself in the assumption that all forces involved belong to the plane in which the system is assumed to be constrained to move. Assume that the bones are rigid and that they are connected by an ideal frictionless hinge (the knee, say). Assume, moreover, that one of the bones is hinged at the other end to a fixed joint (e.g., a fixed hip). Assuming the plane of the system to be identified with an x-y coordinate plane, Eq. 1 reduces, for each bone, to two scalar equations (the sum of the x- and y- components of the external forces, respectively, equal to zero), while Eq. 2 becomes a single scalar equation (the sum of the z-components of the moments equal to zero), the other component equations vanishing trivially by the assumed planarity of the system. There is thus a total of six equations of statics, three for each member. Considering first the case in which there are no muscles involved and the system is subjected just to its own weight (hanging, as it were, as a skeleton in the closet), the unknown quantities are: the angular deviations of each bone from the vertical position (two quantities), the reaction force at the hip (two quantities) and the interaction force at the knee (two quantities). When drawing the free-body diagrams, the interaction force at the knee will appear in each of the diagrams, with opposite senses, as required by Newton's third law, the so-called principle of action and reaction (see the article on Newtonian mechanics). The system is, therefore, statically under-determinate, indicating that the geometry of the system is to be determined as part of the solution. It has, in fact, two solutions, only one of which (the one corresponding to the bones lying vertically directly *under* the hip) is stable. Assume now that the bones are connected by a single muscle, which is assumed to be perfectly articulated at the points of insertion. For simplicity, also assume that the muscle is of a known length (say, when fully activated). There is now a situation in which the bone-muscle system forms roughly the shape of the letter *A*, hanging from the hip. Again, the

system is statically under-determined, although less so than before. The number of statical unknowns has increased by one (the internal force in the muscle), while the number of geometrical unknowns has decreased by one. Suppose now that the free end of the tibia rests, in a frictionless manner, on the ground, thus eliciting a vertical reaction (assuming the ground to be below the hip at a distance strictly smaller than the sum of the lengths of the bones). The system becomes statically determined, its geometry being completely prescribed by the data. (There are actually four geometric ►configurations compatible with the given data). Suppose now that the free end of the tibia is anchored to the ground, by means of an ideal hinge, thus requiring both a horizontal and a vertical component of the ground reaction. The system becomes statically indeterminate. The statical indeterminacy can be exacerbated by adding more muscles in parallel with the one already in place.

As mentioned above, the idea of free-body diagram can be also applied beyond the domain of statics to derive the equations of motion of a system by incorporating the forces of inertia. This point of view, sometimes called ►*D'Alembert's principle*, requires that the right-hand sides of Eqs. 6 and 7 of Newtonian mechanics (q.v.) be regarded as some kind of negative external forces and moments. Defining, therefore, $\mathbf{F}^{ext}_{inertia} = -\dot{\mathbf{P}}$ and $\mathbf{M}^{ext}_{0,inertia} = -\dot{\mathbf{H}}_{\mathbf{0}}$, and incorporating these new "external" forces into our free-body diagrams, statics Eqs. 1 and 2 may be applied to the formulation of the dynamical problem.

In the case of continuum mechanics (q.v.), the problem of continuum statics consists of solving the system of partial differential equations obtained from the ►balance laws (q.v.) when all the time-derivatives are regarded as zero. In a more restricted sense, however, continuum statics applies mainly to the purely mechanical aspects, leaving thermodynamic considerations aside. Thus, a problem of continuum statics will usually involve only the balances of momentum and of ►angular momentum and a constitutive equation for the ►stress in terms of kinematical quantities only (see the articles ►Kinematics of Deformation and ►Constitutive Theory), while temperature, ►heat flux and ►internal energy are not taken into consideration.

An alternative formulation of statics can be obtained by means of the principle of virtual work (q.v.).

Statistical Inference

►Bayesian Statistics (with Particular Focus on the Motor System)

Statistical Mechanics

Definition

An extension of Newtonian mechanics in the later years of the nineteenth century, which explained the behavior of aggregates of molecules (gases) statistically; it resulted in a definitive formulation of the second law of thermodynamics by Boltzmann.

Statocyst

Definition

The balance organ of an invertebrate.

►Evolution of the Vestibular System

Status Epilepticus (SE)

Definition

Serious condition of prolonged and repetitive ►seizures that tend to be self-sustaining. The definition of prolonged has varied from 5 to 30 min. There are various clinical forms: subtle SE, impending SE, established SE, non-convulsive SE, and generalized convulsive SE. The transition from isolated seizures to SE probably involves changes in ►$GABA_A$ (►γ-aminobutyric acid) receptors, ►AMPA (►α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and ►NMDA (N-methyl-D-aspartic acid) receptors, as well as changes in neuropeptides. These changes may explain the hyperexcitability of cortical neurons, the tendency of seizures to become self-sustaining, and the development of resistance to antiepileptic drugs.

►Anticonvulsants

Steady (also Equilibrium) State

Definition

State of the system comprised of the organism and the environment, when neurons influencing the motor

outcome generate stationary (tonic) activity or remain silent, all torques and forces including those resulting from the interaction of the organism with the environment are balanced and do not change, and the body and its segments cease to move; may be changed by external forces or control variables causing motor actions.

►Equilibrium Point Control

Stellate Cell

Definition

Multipolar neuron whose dendrites project in all directions. Also used to describe multipolar neurons with less uniform dendritic fields.

Stellate Cell in Cochlear Nucleus

Definition

Neurons that occupy all parts the ventral cochlear nucleus, receive auditory nerve terminals in their dendrites, and project to the inferior colliculus or to the cochlear nucleus on the other side. They may have different functional roles depending on their targets.

►Cochlear Nucleus

Stem Cell

Definition

Immature undifferentiated cell endowed with endless capacities of self-renewal, i.e., to reproduce itself identically, and the ability to generate multiple mature cell types. It can be produced both during the embryonic development and in the adult age. Whereas embryonic stem cells can give rise to virtually all the cell types in the body, adult stem cells only generate a limited number of cell types depending on the tissue from which they are originated.

For instance, stem cells residing in the subventricular zone of the mammalian brain can be isolated and cultured. One single stem cell can proliferate to form a spherical aggregate of cells called a neurosphere containing both stem and progenitor cells. Plated onto an adherent support, cells differentiate into neurons, astrocytes and oligodendrocytes. Stem cells are, therein, multipotent cells as they produce a wide range of cell type.

Moreover, the stock of multipotent stem cells is maintained during the lifespan of the organism. According to their capacities, stem cell therapies are under investigation as they could replace dead cells and may provide successful cures for neurodegenerative and demyelinating diseases, heart failure, spinal cord injuries, among others.

►Adult Neurogenesis
►Neural Development
►Neurogenesis and Inflammation

Stem Cell Transplantation

Definition

Medical procedure in the field of hematology, oncology or regenerative medicine that involves transplantation of stem cells of different origins (e.g., neural stem cells, hematopoietic stem cells, mesenchymal stem cells, cord blood stem cells, etc.). It is most often performed on people with diseases of the blood or bone marrow, certain types of cancer or diseases of the central nervous system [e.g., multiple sclerosis (MS), Parkinson disease (PD), Huntington's disease (HD), etc.]. Transplanted stem cells are usually administered either locally (e.g., intraparenchymally), intravenously or intrathecally (e.g., trough the cerebrospinal fluid circulation). The main aims of the procedure are either the repopulation of the host bone marrow and the production of new blood cells (e.g., in the case of hematopoietic vs. cord blood stem cell transplantation), the replacement of lost vs. injured neural cells (e.g., in the case of neural stem cell transplantation) or the induction of peripheral immune tolerance (e.g., in the case of mesenchymal and neural stem cell transplantation).

►Autoimmune Demyelinating Disorders: Stem Cell Therapy
►Huntington's Disease
►Multiple Sclerosis
►Parkinson Disease

Stem Taxon

Definition
A stem taxon is one that shares some but not all derived characters with a well-defined clade.

►The Phylogeny and Evolution of Amniotes

Stepping Strategy

Definition
A change in support reaction to postural perturbation in which one or more rapid stepping movements are used to restore equilibrium.

►Postural Strategies

Step Response

Definition
The output of a system when a Heaviside (step) function is input into it.

►Signals and Systems

Stereocilia of Vestibular Hair Cell

Definition
Cilia projecting from the apical surface of the receptor hair cell. The cilia are connected to each other by small actin filaments and vary in stiffness. Stereocilia deflection leads to mechanoelectrical transduction in the kinocilium.

►Peripheral Vestibular Apparatus

Stereognosis

Definition
The ability to perceive the properties of an object by touch.

►Active Touch
►Haptics
►Processing of Tactile Stimuli

Stereogram

Definition
A set of objects seen by both eyes such that their fusion results in binocular disparity detection and stereoscopic vision.

►Binocular Vision

Stereopsis

Definition
The combination of image information from left and right eyes via binocular disparity provides the basis for stereoscopic depth perception.

►Binocular Vision

Stereoscopic Acuity

Definition
►Binocular Vision

Stereotaxy

Definition

Stereotaxy is a method for locating deep brain structures that can be reached from the surface with the use of electrodes or other probes. The probes can them lesion or electrically stimulate the target region or inject a drug or tracer. Usually a stereotaxic instrument is attached to the skull and deep structures are reached with the use of stereotaxic brain atlases prepared with standard coordinates based on skull landmarks and deep midline structures seen in scans of different types (e.g., X-ray or Magnetic Resonance Images).

Steroid Hormones

►Neuroendocrinological Drugs

STG

►Stomatogastric Ganglion

Stiff-man Syndrome

Definition

Uncommon disease consisting of several forms, with the severity of evolution differing in each individual case. It is characterized by symmetrical muscle ►rigidity and painful ►spasms of the lumbar paraspinal, abdominal, and occasionally proximal leg muscles, which often lead to skeletal deformity (e.g., lumbar hyperlordosis). There is continuous motor unit activity with abnormal exteroceptive reflexes. Variants may involve one limb only (stiff leg syndrome), and other symptoms and signs such as eye movement disturbances, ►ataxia, or ►Babinski sign, or concur with malignant disease. Antineuronal autoimmunity (against glutamic acid decarboxylase, GAD) and accompanying autoimmune diseases are characteristic features. Patients remain ambulant.

►Babinski Sign

Stiffness

Definition

The strict definition in physics is: change of force per unit change of length, or the slope of the force-length curve of a structure (df/dl). In motor control, the term characterizes the ability of the neuromuscular system to resist deviations from an equilibrium or current position elicited by external perturbations; required, together with damping, for stability of posture and movement; the ratio of the change in the static values of forces (torques) to a small ("infinitesimal") change in position elicited by an external load provided that control variables remain the same; measurements are comparatively easy for steady states of the system but are unreliable for transitional states (e.g. during movements) because of the necessity to extrapolate dynamic muscle forces and torques to static values, delays in the position-dependent muscle force regulation, and changes in control variables underlying active movements.

►Equilibrium Point Control

Stimulant Drugs

►Stimulants

Stimulants

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Synonyms

Psychostimulants; Stimulant drugs; Analeptics; Excitants; Activators; Energizers; Awakening agents; Tonics

Definition

Stimulants are chemical substances that temporarily activate the nervous system. In common usage, stimulants are generally understood as chemicals that increase activity of the ►central nervous system (i.e. psychostimulants) although such substances may also activate the ►sympathetic nervous system. The temporary effects of stimulants can include increased ►alertness, wakefulness, a feeling of well-being, euphoria, and increased ►heart rate and ►blood pressure. The substances may be derived from natural products (e.g. caffeine from the coffee plant) or can be synthesized (►methamphetamine). Stimulants are used both for therapeutic and recreational purposes.

Characteristics

Examples of Stimulants

The Table 1 provides representative examples of common stimulants used by humans.

Overview: What We Know and Do Not Know About Stimulants

This essay focuses to the extent possible on stimulant actions in the human, as it is the human stimulant user, rather than the experimental animal, that can best report on many of the key effects of the drugs. Good information is available on the acute (temporary) behavioural effects of stimulants in humans. However, there is much uncertainty regarding mechanisms that explain their behavioural effects.

Stimulants. Table 1 Examples of stimulant drugs used by humans

Classical stimulant drugs	"Atypical" stimulant drugs
Amphetamine and structurally related compounds	Caffeine
	Modafinil
D-amphetamine	
methamphetamine	
methylenedioxymethamphetamine (mdma, ecstasy)	
methylenedioxyamphetamine (mda, "love drug")	
phentermine	
ephedrine	
cathionine	
Fenfluramine	
Nicotine	
Cocaine	
Methylphenidate (Ritalin)	

Stimulant drugs known or suspected to have a major action as monoamine neurotransmitter releasers are **boldened**. Stimulants having a major action as monoamine neurotransmitter transporter inhibitors are *italicized*. Caffeine and modafinil are listed as "atypical" stimulants as the primary mechanism of action of some of the key acute effects of the drugs is probably different from that of the classical stimulants (caffeine: adenosine receptor antagonism) or is unknown (modafinil).

Acute Behavioural Effects

The typical acute (minutes to hours) effects of a low to moderate dose of a stimulant drug in a normal human include feelings of ►alertness, wakefulness, energy, well-being (euphoria at higher doses), and suppression of appetite. As a consequence, stimulants have been used to improve concentration and attention, counteract fatigue and excessive sleepiness (e.g. in ►narcolepsy), cause feelings of pleasure, and induce weight loss. Many stimulants also activate the cardiovascular system (cause increased ►heart rate and ►blood pressure).

The ►central and ►sympathetic nervous system effects are typically observed to some degree with all of the classical stimulant drugs with the differences in drug intensity and duration explained by drug pharmacokinetic properties, route of administration characteristic of the drug (e.g. oral vs. inhalation), and probably, drug maximal response. Unlike the classical stimulants (e.g. ►methamphetamine), the atypical stimulant modafinil can induce wakefulness with no or little accompanying activation of the cardiovascular system (►Nootropic Drugs).

In addition to the acute stimulant effects described above, one of the amphetamine derivatives, mdma (►ecstasy), is claimed by many stimulant users to promote feelings of openness, sociability, and talkativeness (and possibly empathy) to a greater extent than that caused by the parent drug ►methamphetamine, although this has yet to be verified.

Chronic Behavioural Effects Following Repeated Exposure

It is generally assumed from animal findings that partial ►tolerance will develop in the human to some or perhaps all of the acute behavioural effects of stimulant drugs following repeated exposure – but this has been somewhat difficult to prove in humans (►Tolerance and Dependence). The question of ►tolerance is best addressed by prospective studies of chronic drug exposure in previously drug-naïve humans. However, for many of the representative stimulants (e.g. ►methamphetamine, ►cocaine), data from such prospective studies are still too limited [1] because of the ethical problem of exposing humans repeatedly to drugs that might cause harm.

Findings from chronic stimulant users suggest that partial ►tolerance to some of the effects of stimulant drugs (e.g. drug liking, cardiovascular activation) most likely develops following repeated exposure to moderate to heavy stimulant doses, especially during a drug "binge" characterized by rapid dose escalation.

However, the extent to which such ►tolerance carries over to the next drug use that might occur a week or two later is still unclear. In the case of ►ecstasy, many users report some persistent (weeks to months or longer after last use) tolerance to the pleasurable effects of the drug with repeated drug use. This probably represents a combination of a true ►tolerance and some decrease in novelty of the drug experience.

Animal findings indicate convincingly that repeated intermittent doses of stimulant drugs can induce an *increase* in ►locomotion as compared with that produced by the first exposure to the drug. However, it is still quite uncertain [2] whether ►sensitization (reverse ►tolerance) to any of the behavioural effects of stimulant drugs reliably occurs in the human (possible examples being emerging ►psychosis and stereotyped movements in ►methamphetamine users) and the specific counterpart in humans to the motor sensitization reported in experimental animals is unknown.

A ►withdrawal syndrome, which can include ►depression, ►anhedonia, and ►anxiety, can develop within hours or days following drug cessation after repeated exposure to moderate to heavy doses of stimulant drugs, or to a single high dose of the drug. Typically, ►withdrawal features are the opposite of some of the acute effects of the drug (e.g. unpleasant vs. pleasant feelings; increased vs. decreased appetite) and can last a few hours to days or even weeks (see ►Tolerance and Dependence).

In some individuals, chronic exposure to stimulants leads to a state of drug ►addiction characterized by a ►compulsive wanting or ►craving for the stimulant drug and a loss of control. ►Addiction is not an obligatory component of a ►withdrawal syndrome.

Mechanism of Action of Some of the Acute Behavioural Effects of Classical Stimulants

Stimulant drug targets. Brain neuronal systems have been identified that are acted upon by stimulant drugs. However, not yet established is the extent to which these drug targets are critically involved in stimulant actions.

In brain, stimulant drugs act *inter alia* on neurones that utilize ►dopamine, ►noradrenaline, and ►serotonin as ►neurotransmitters. Studies of patients with the dopamine deficiency condition ►Parkinson's disease show that ►dopamine in the ►putamen and ►caudate subdivisions of the ►striatum is involved in ►motor control and probably in aspects of ►cognition [3] (►Drug Treatment for Motor Disorders and Antipsychotics). Dopamine, localized to the ►ventral striatum/►nucleus accumbens portion of the ►striatum has often been considered to mediate feelings of pleasure. However, this is likely an oversimplification and debate continues on re-defining this aspect of the role of ►dopamine from such possibilities (all related) as "liking," "wanting," and "►incentive salience" [4].

The precise roles of brain noradrenaline and ►serotonin are less certain as there does not exist any human conditions characterized by selective loss of either of the ►neurotransmitters. However, the ►antidepressant actions of fairly selective serotonin and noradrenaline ►transporter inhibitors suggest involvement of both ►neurotransmitters in ►mood and an extensive animal literature suggests an involvement of noradrenaline in arousal and ►attention [5] (►Antidepressants).

►Classical stimulants activate monoamine neurotransmitter systems. A primary action of the "►amphetamine-like" stimulants (see Table 1) is to elevate brain extracellular ►monoamine neurotransmitter (►dopamine, ►serotonin, noradrenaline) levels by enhancing ►neurotransmitter release from the nerve endings [6]. Although the mechanism by which ►amphetamine stimulants cause release is still under investigation, it likely involves (i) redistribution of the neurotransmitters from the synaptic vesicle (via the ►vesicular monoamine transporter [VMAT2]) to the neuronal cytoplasm and (ii) reverse transport of the ►neurotransmitter through the plasma membrane transporter into the extracellular space [7]. A primary action of "cocaine-like" stimulants is to increase extracellular ►monoamine neurotransmitter concentrations by binding to plasma membrane ►transporter proteins (►dopamine transporter, ►serotonin transporter, ►noradrenaline transporter) and thereby blocking reuptake of the ►neurotransmitter from the ►synapse into the nerve ending [6]. Some (but not all) data in the human suggest that cigarette smoking can cause a slight increase in release of ►dopamine in the ►striatum – an action attributed to ►nicotine. The ►dopamine-releasing action of ►nicotine is considered to be mediated, at least in part, by activation of ►nicotinic receptors of the α_4 and β_2 subtypes [8].

Since the stimulant drugs act, to a varying degree, depending on the stimulant, on all three ►monoamine neurotransmitter systems [6], it is difficult to ascribe specific behavioural effects of the drug to involvement of a single ►neurotransmitter. Speculations, mentioned below, on mechanism are primarily based on animal findings.

►Cardiovascular activation. Activation of ►heart rate and blood pressure caused by some stimulants (e.g. ►methamphetamine) has been commonly explained by a drug-induced release of noradrenaline from ►sympathetic nerve endings and subsequent activation of ►adrenergic receptors. However, the situation is probably much more complicated with some data suggesting involvement of ►monoamine neurotransmitters (►dopamine and/or noradrenaline) in brain as well as in the ►sympathetic nervous system.

►Alerting and attention. Animal data suggest that the ►alerting and improved ►attentional effects of

the prototype ►monoamine neurotransmitter releaser (►amphetamine) and uptake blocker (►methylphenidate) could be explained in large part by enhancement of brain noradrenergic function. This is also suggested by the efficacy of ►atomoxetine, reputedly a selective ►noradrenaline transporter blocker, in treatment of patients with ►attention deficit/hyperactivity disorder (►ADHD) (explained as a disorder of ►attentional control). Comparison of the maximal clinical response of ►amphetamine and methylphenidate (activate both ►dopamine and noradrenaline systems) vs. atomoxetine in treatment of ►ADHD may help to establish extent of involvement of ►dopamine.

►Liking. It is commonly assumed that "all roads lead to ►dopamine" when explaining the feelings of well-being and euphoria associated with a moderate stimulant dose.

This is supported by brain imaging findings in the human strongly suggesting that administration of a variety of stimulants (►amphetamine, ►nicotine, cocaine, methylphenidate) cause increased synaptic levels of ►striatal dopamine and that, in some studies, the extent of increase in ►dopamine correlates with subjective measures of ►mood [9].

At odds with the ►dopamine hypothesis, however, is the simple observation that the positive effects of stimulants in humans are not antagonized by dopamine receptor blocking agents. In contrast, preliminary data (requiring confirmation) indicate that the "positive" effects of at least three stimulant drugs (amphetamine, cocaine, ►nicotine [cigarette smoking]) are partially antagonized by non-selective ►opioid receptor antagonists (naloxone or naltrexone). This suggests that the "liking" effect of some stimulants might be mediated through a process involving activation of an endogenous ►opioid.

►Increased sociability with ecstasy vs. amphetamine The mechanism explaining this reputed drug effect is unknown but likely involves the ability of ►ecstasy to preferentially release the ►neurotransmitter serotonin as compared to ►dopamine, whereas ►dopamine (vs. ►serotonin) is preferentially released by ►amphetamine.

Mechanism of Acute Effects of Some Atypical Stimulants

►Adenosine is considered to be an inhibitory neuromodulator involved in regulation of the ►sleep-wake cycle. The mechanism of the modest stimulant action in humans of caffeine, an "atypical" stimulant found in coffee, tea, and cola, is likely related to its ability to block the action of ►adenosine at its adenosine A_{2A} receptor as suggested by the lack of stimulant effect of caffeine in mice lacking this receptor.

Modafinil is an atypical stimulant, structurally unrelated to the ►amphetamines, currently used clinically for the treatment of excessive ►sleepiness. This is an example of a stimulant in which animal data implicate many different drug targets, but insufficient information is presently available to identify those targets likely to be critically involved in its stimulant action.

Mechanism of Action of Some Chronic Behavioural Effects

►Withdrawal. Some of the unpleasant behavioural features of ►withdrawal to repeated exposure to stimulants are likely related to a "deficiency state" for those ►monoamine neurotransmitter systems that are activated acutely by the stimulants [6]. In the case of ►ecstasy, for example, the ►depression-like features during drug ►withdrawal are most likely due in part to an actual deficiency of brain ►serotonin. Similarly, the postmortem ►brain finding of low ►striatal dopamine in chronic ►methamphetamine users suggests that some features of ►methamphetamine withdrawal, including ►anhedonia and problems with ►cognition, can be explained by loss of this ►neurotransmitter [10]. It is also highly likely that diverse ►adaptations downstream from the ►monoamine neurotransmitter receptors underlie the ►withdrawal syndrome associated with stimulant drug taking.

►Addiction. Speculations on possible mechanisms explaining stimulant-induced ►addiction can be found in the Chapter on Tolerance and Dependence. This reviewer finds attractive the model proposing that ►addiction is a form of "pathological ►learning" for which ►dopamine (perhaps critically) helps facilitate the ►learning process and in which ►memories, once formed, are rather resistant to change [2].

No single neuronal system in brain has yet been identified which is critical in explaining the transition from stimulant "liking" to "wanting" or "►craving" in the human, including ►dopamine. Certainly, ►dopamine is somehow involved, at least initially, as stimulants that (rapidly) elevate extracellular levels of this ►neurotransmitter in human ►brain can be abused. However, the evidence for ►dopamine receptor blocking drugs influencing drug ►craving and ►relapse in humans is not compelling. Those stimulants that have a preferential action on the ►serotonin (vs. dopamine) system (►fenfluramine, ecstasy) appear to have a lower risk of ►addiction.

Clinical pharmacological studies testing potential anti-addiction medications in humans are key to identification of neuronal targets likely involved in stimulant addiction. Although such data are still preliminary, not always consistent, and no "magic bullet" has yet been discovered, some interesting findings have emerged:

In the case of ►nicotine addiction (as an example), emerging pharmacological data show that drugs blocking ►opioid and CB1 ►cannabinoid receptors help some tobacco smokers quit the drug, suggesting possible involvement of ►endogenous opioids and

►cannabinoids in ►craving and ►relapse in humans. Using also the example of ►nicotine, a rational approach in development of a drug to block relapse incorporates a "drug substitution" strategy in which the drug therapeutic is a "dual action" ►partial agonist drug that acts as an agonist at the ►nicotine $\alpha_4\beta_2$ ►receptor, but has lower (e.g. 30–70%) maximal response than ►nicotine (but still sufficient to reduce ►craving during drug ►withdrawal) and also acts as an antagonist in the presence of ►nicotine. Preliminary data suggest that such a ►nicotine partial agonist drug improve smoking quit rates in humans [8].

Do Stimulants Cause Persistent Brain Damage?

A variety of structural brain abnormalities have been reported in some chronic users of ►methamphetamine, ►ecstasy, and cocaine; however, to date the findings are too inconsistent and anecdotal to provide a definitive conclusion.

Good evidence exists in the animal literature that neurochemical markers of brain ►dopamine nerve terminals (►dopamine, ►dopamine transporter, ►VMAT2) are persistently decreased in experimental animals given high doses of ►methamphetamine (see [10]) whereas markers for ►serotonin neurones (►serotonin, ►serotonin transporter) are decreased in nerve terminal regions following high dose exposure to ►ecstasy. Oxidative damage due to formation of oxy-radicals derived from ►dopamine and ►serotonin is a plausible mechanism for the toxicity.

In the human literature decreased ►striatal concentration of the ►dopamine transporter in some abstinent (months to years) ►methamphetamine users has been reported (see [10]). Although low ►dopamine transporter does not necessarily equal actual loss of ►dopamine nerve terminals, the human data do suggest that some (likely dose-dependent) "damage" could occur to dopamine neurones in ►methamphetamine users that persists some months or longer after the last exposure to the drug. Similarly, emerging, though still preliminary, data describe a brain serotonin transporter decrease in the cerebral cortex of abstinent ►ecstasy users. The question whether these changes are associated with any functional impairment is still debated.

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Stimulus

Definition

The pattern of physical energy change set up by an object or event in the environment (distal stimulus) which excites the receptors of a sense organ (proximal stimulus).

►Psychophysics

Stimulus Translation

►Transduction

Stochastic Process

Definition

A process in which the characteristic variables undergo random fluctuations.

►Brownian Motions

Stochastic Resonance

Definition

Stochastic resonance refers to a nonlinear dynamical interaction of a periodic signal and noise appearing in multistable systems (e.g. a neuron) near a bifurcation. The noise can be either random or fractal and exist internal to the system or be externally applied. Information flow (the periodic signal) through the system is optimized by a particular noise intensity, thereby actually increasing the signal-to-noise ratio. Stochastic resonance is a strictly nonlinear effect, not accessible within the framework of linear signal processing theories.

Stomatogastric Ganglion

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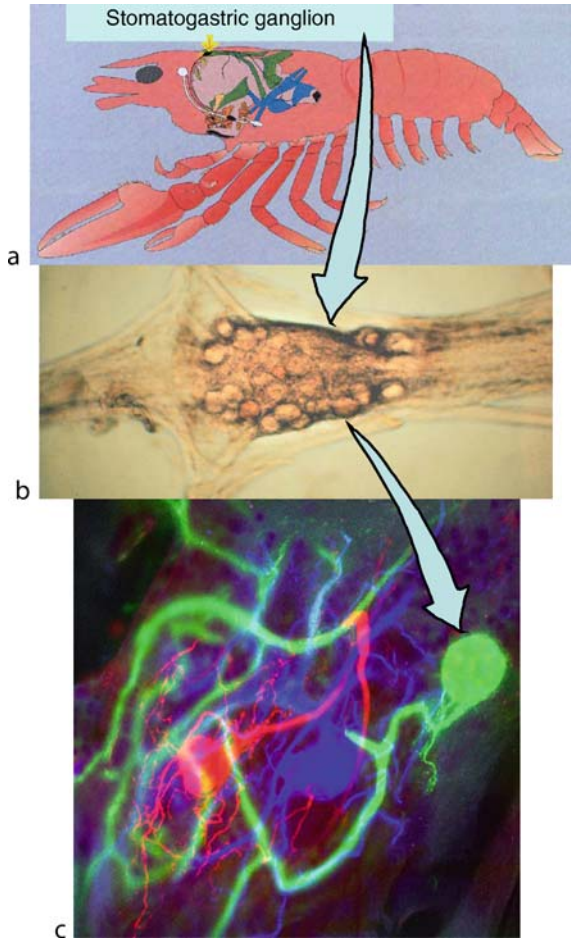
Synonyms

STG

Definition

The stomatogastric ►ganglion (STG) in lobsters, crabs and other crustaceans is one of the premier systems for studying how neural networks generate rhythmic motor patterns [1]. It is an important model system for more complex behaviors such as respiration, locomotion, rhythmic scratching, and mastication, and has given insights into the mechanisms underlying behavioral flexibility. The STG is part of the stomatogastric nervous system (STNS), which controls movements of the crustacean foregut (Fig. 1a). The STNS includes the STG, the oesophageal ganglion, and the paired commissural ganglia.

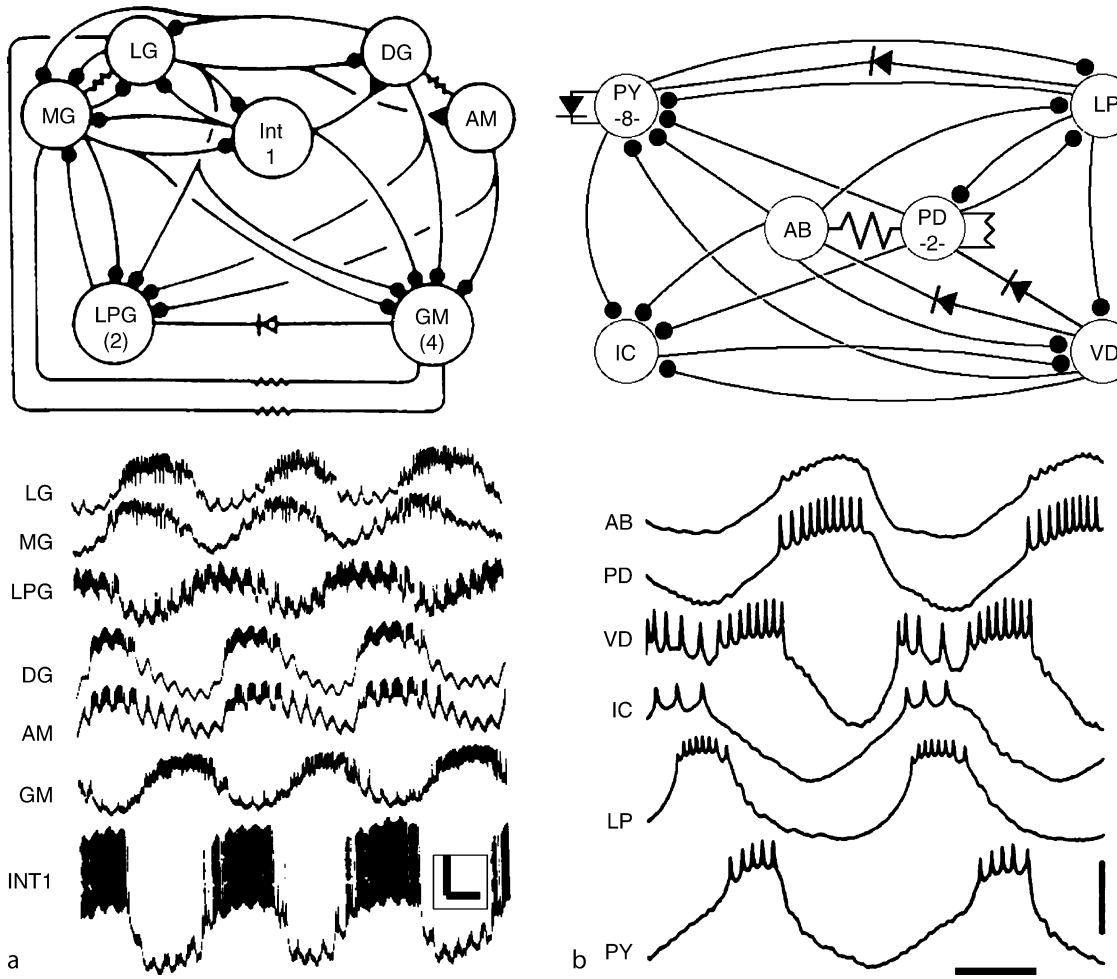


Stomatogastric Ganglion. Figure 1 The stomatogastric ganglion (STG) of crustaceans, its neurons and gastric and pyloric networks. (a) Schematic of the lobster digestive system highlighting the position of the stomatogastric ganglion and the muscles the gastric (green) and pyloric (blue) networks control (from Simmers et al. (1995) Am Sci 83:262–268). (b) Photomicrograph of the STG showing individual neuron cell bodies. The largest cell bodies are approximately 100 μM in diameter. (c) Individual STG neurons stained with fluorescent dextran amines: Pyloric dilator (*PD*, red), Lateral Pyloric (*LP*, green) and Pyloric Constrictor (*PY*, blue). Photograph taken by Peter Kloppenburg.

Characteristics

The STG is a small ganglion of about 30 neurons (Fig. 1b), all individually identifiable (Fig. 1c). It contains two complete ►Central Pattern Generator (CPG) networks that drive rhythmic movements of the foregut: the gastric mill and the pyloric networks. In the spiny lobster, *Panulirus interruptus*, the gastric mill network contains eleven identified neurons: one interneuron and ten neurons that act both as CPG neurons and as motoneurons. The gastric mill network generates slow rhythmic movements of the three internal teeth that masticate food inside the foregut (Fig. 2a).

The pyloric network contains fourteen identifiable neurons in six major classes (Fig. 2b). One is an interneuron while thirteen are dual function CPG/motoneurons. This network organizes more rapid rhythmic pumping, mixing and filtering movement in the pylorus, or posterior region of the foregut. These



Stomatogastric Ganglion. Figure 2 Networks and activity of the gastric mill and pyloric motor patterns. (a) Top: connectivity diagram of the gastric mill network, and bottom: intracellular recordings of from the different cell types during gastric network activity. Calibrations: 1 s and 10 mV. Neurons: LG Lateral Gastric, MG Medical Gastric, LPG Lateral Posterior Gastric, DG Dorsal Gastric, AM Anterior Median, GM Gastric Mill, INT1 Interneuron 1. (b) Top: connectivity diagram of the pyloric network, and bottom: intracellular recordings from the different cell types during pyloric network activity. Calibrations: 300 ms and 20 mV. Neurons: *PD* Pyloric Dilator, *LP* Lateral Pyloric, *AB* Anterior Burster, *VD* Ventricular Dilator, *IC* Inferior Cardiac, *PY* Pyloric Constrictor. In (a) and (b), Top, the filled circles indicate chemical inhibitory synapses, resistor symbols indicate non-rectifying electrical synapses and diode symbols indicate rectifying electrical synapses. From ref. [1].

networks vary only slightly between different crustaceans, showing their evolutionary conservation.

Upstream Events/Conditions

When isolated from the rest of the nervous system, both of the CPGs in the STG cease to function. Descending modulatory inputs from the commissural, oesophageal and other ganglia are essential to activate the motor patterns. In the lobster, there are about 120 central neurons as well as a number of sensory/modulatory neurons that affect the ganglion [2]. The CPG motor patterns vary markedly, depending on which modulatory inputs are active. A number of these modulatory neurons have been identified; when selectively stimulated, each can elicit a distinct variant of the gastric and/or pyloric motor patterns. Most of these modulatory neurons release two or more co-transmitters; often one is a fast-acting neurotransmitter like glutamate, while the others are slower acting neuromodulators including peptides (such as proctolin) or amines (such as dopamine) [3]. In addition, a number of circulating ▶neurohormones (such as serotonin) act on the STG over longer times and at lower concentrations. More than 20 modulatory substances have been identified that affect the STG networks.

Modulatory inputs reconfigure the CPGs in several ways. First, they determine which cells are actively firing in the network. Second, they alter the cycle

frequency, intensity of firing and phasing of the component neurons. Third, they can shift the allegiance of neurons to fire with a different CPG for an entirely different behavior. Finally, they can fuse two or three networks into a new motor network for a novel behavior.

Downstream Events/Conditions

Much work has gone into understanding how the pyloric network, and to a lesser extent the gastric mill network, generates its rhythmic output. In brief, the motor pattern is shaped by the interaction between two complementary processes: the intrinsic firing properties of the different neurons, and the pattern and kinetics of their synaptic interactions. Due to space considerations, in this paper we discuss how these processes interact to generate the pyloric rhythm. The gastric mill rhythm is more complex and more integrated with other STNS networks than the relatively independent pyloric network.

Intrinsic Properties of Pyloric Neurons

The six classes of neurons in the pyloric network each have a unique firing pattern during the pyloric rhythm. Each neuron can be studied in isolation from all synaptic input by a combination of photoablation of synaptically connected neurons and pharmacological blockade of pre-synaptic inputs. A number of distinct intrinsic electrophysiological properties shape the neurons' firing patterns [1].

With intact modulatory inputs, all of the neurons are capable of rhythmic ►bursting of different kinds and at different rates. However, this is lost when modulatory inputs from other ganglia are blocked: all of the neurons fall silent or fire slowly. Thus, these neurons are ►conditional bursters which oscillate only in the appropriate modulatory environment. The Anterior Burster (AB) typically oscillates at the highest frequency and thus acts as the primary pyloric ►pacemaker (Fig. 2b). The AB neuron is electrically coupled to the two Pyloric Dilator (PD) neurons, which oscillate more slowly and constrain the AB oscillatory frequency. These three neurons form the pacemaker group and play the major role in setting the cycle frequency.

The remaining follower neurons are all inhibited by the pacemaker group. All the follower neurons possess ►post-inhibitory rebound, where after synaptic inhibition they rebound to fire a burst of action potentials. Some of the neurons also show ►delayed excitation, such that they rebound more slowly after inhibition, and begin firing only after a delay. This delay is due to the activation of a subthreshold transient potassium current, I_A, which competes with a slow hyperpolarization-activated inward current, I_h, to set the rate of post-inhibitory rebound. Many of the neurons also express ►plateau potentials, where a short depolarizing input, or post-inhibitory rebound, can trigger prolonged action potential firing that lasts until synaptic inhibition or the slow development of outward currents repolarizes the neuron.

Synaptic Interactions

The pyloric network is highly interconnected (Fig. 2b) top. All the neurons make chemical inhibitory synapses, using either acetylcholine or glutamate which, unlike vertebrate systems, act as fast inhibitory transmitters. Release of transmitter is not only spike-evoked but also graded, with continuous release as a function of membrane potential during the neurons' oscillations. These synapses are highly susceptible to depression during normal oscillations: the synapses weaken as the cycle frequency accelerates [4]. In addition, several of the neurons make rectifying or non-rectifying ►electrical synapses with partner neurons, which help to synchronize or initiate activity.

Generating the Pyloric Rhythm

With modulatory inputs intact, the 14 neurons in the pyloric network fire rhythmic bursts of action potentials in a characteristic triphasic pattern (Fig. 2b). The major pacemaker, AB, and the electrically coupled PD neurons, burst synchronously in the first ►phase. This pacemaker kernel inhibits all the follower neurons. As the endogenous burst terminates, the follower cells repolarize by ►post-inhibitory rebound to resume firing, but at different rates, due to different amounts of subthreshold outward currents that cause delayed excitation. The IC (Inferior Cardiac) and VD (Ventricular Dilator) neurons rebound most quickly. However, the LP (Lateral Pyloric) neuron is not far behind, and it silences the VD due to a very strong synaptic inhibition, and inhibits PD. The LP then fires tonically, while the PY (Pyloric Constrictor) neurons depolarize more slowly by post-inhibitory rebound from their pacemaker inhibition and begin firing. In turn the PY neurons inhibit the LP and IC neurons, disinhibiting the VD neurons, which fire a second burst. These neurons fire until they are inhibited by the next pacemaker kernel burst, and the cycle repeats. The rebound burst of action potentials in follower cells is supported by their plateau properties.

The pyloric rhythm shows ►phase constancy, a general feature of rhythmic behaviors: while the cycle frequency can vary over time, the neurons adjust their burst durations to retain a constant phase relationship with one another. The neural mechanisms underlying phase constancy remain unclear, but frequency-dependent synaptic depression as well as the kinetics of activation, inactivation and deinactivation of voltage-sensitive ion channels play important roles [4]. The phase relations do change when the modulatory milieu is altered.

Nonlinear Muscle Responses to the Neuronal Motor Pattern

The muscles driven by the pyloric network have different kinetics of contraction: many of them are very slow, and exhibit a large tonic contracture with only small superimposed oscillations in response to the rhythmic pyloric neural drive. Subtle changes in the numbers of spikes per burst, however, can alter this resting contracture. The pyloric network receives inputs from the slower gastric mill CPG and the cardiac sac CPG, another network that causes slow rhythmic contractions of the foregut sac. These minor inputs cause subtle changes in cycle frequency and spikes per burst in some of the pyloric neurons. These small changes are magnified at the muscle level, so when both gastric and cardiac sac rhythms are simultaneously active, the major pyloric muscle contractions are in time with the much slower gastric mill and cardiac sac rhythms, despite the fact that only pyloric motoneurons innervate these muscles [5]. In addition, some pyloric muscles are themselves conditional oscillators whose intrinsic contractions interact with the oscillatory neural input; the motoneuronal drive entrains the muscle's rhythmic oscillations but does not affect their amplitude.

Neuromodulation

A large number of modulatory neurons act to reconfigure the STG networks over the short term, and the actions of applied neuromodulators such as amines and peptides has been studied in detail [1,2,6] (Fig. 3a).

These modulators alter the pyloric motor pattern by three mechanisms:

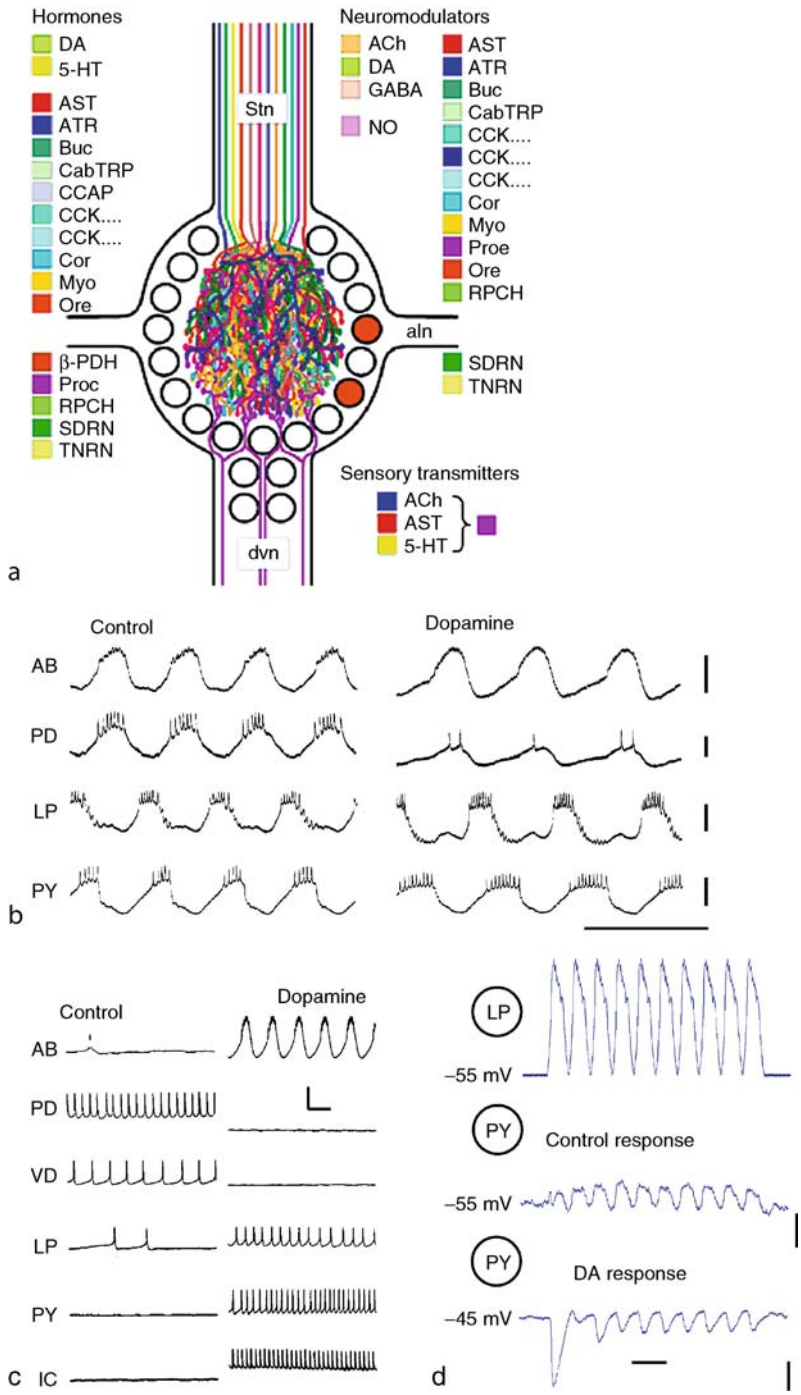
1. Alter the intrinsic firing properties of neurons. Modulators can shape the conditional oscillations, plateau properties, post-inhibitory rebound and delayed excitation of the different pyloric neurons. For example, DA enhances bursting in the AB neuron, enhances post-inhibitory rebound and plateau properties in the LP, IC and many of the PY neurons, and inhibits the PD and VD neurons [6]. As a result, the PD and VD neurons are phase-delayed or fall silent, while the other followers are phase-advanced and fire vigorous bursts of action potentials (Figs. 3b, c).
2. Change which neurons are active in the motor pattern. Modulators can excite some neurons while inhibiting others, changing the active components in the network (Fig. 3c). However, silent neurons can still affect the motor pattern when they are electrically coupled to active neurons, by exerting a functionally inhibitory electrotonic drag.
3. Alter the strengths of synapses in the network (Figs. 3d, 4) [6,7]. A single neuromodulator can strengthen some synapses while weakening others. These changes occur by both pre-synaptic increases or decreases in transmitter release, which is in part due to modulation of calcium currents in nerve terminals, and in part to post-synaptic alterations in transmitter responsiveness. Amines also modify electrical coupling, either directly or indirectly via changes in input resistance. At several synapses, which combine electrical and chemical inhibitory components, dopamine can invert the net sign of the synaptic interaction via opposite effects on the electrical and chemical components (Figs. 3d, 4). Not all of the observed synaptic modulation may have functional consequences for pyloric network function. The magnitude of synaptic strength changes that are sufficient to evoke changes in network activity is still not clear.

The complexity of these effects on the pyloric neurons' ionic currents and synaptic strength is illustrated for one neuromodulator, dopamine, in Fig. 4. In many cases, DA exerts conflicting effects on a target [6]. At several synapses it enhances pre-synaptic release while weakening post-synaptic responsiveness. In some neurons, DA alters complementary sets of ionic currents that by themselves would lead to either increases or decreases in a neuron's excitability. These opposing effects could act as brakes to constrain the neuronal activity within a certain window, and to prevent the neurons from being "over-modulated" and dysfunctional. Alternatively, opposing modulatory effects could themselves be subject to differential metamodulation by other transmitters, which could change the net sign of the DA effect.

DA is an example of a neuromodulator with widespread and divergent actions on the different synapses and neurons in a neural network. In contrast, a number of peptides act through independent receptors but converge on a single ionic current to activate multiple pyloric neurons by a common mechanism [2]. The different peptides target distinct populations of neurons (due to differential expression of their receptors), leading to different motor patterns despite their common ionic targets.

Involved Structures

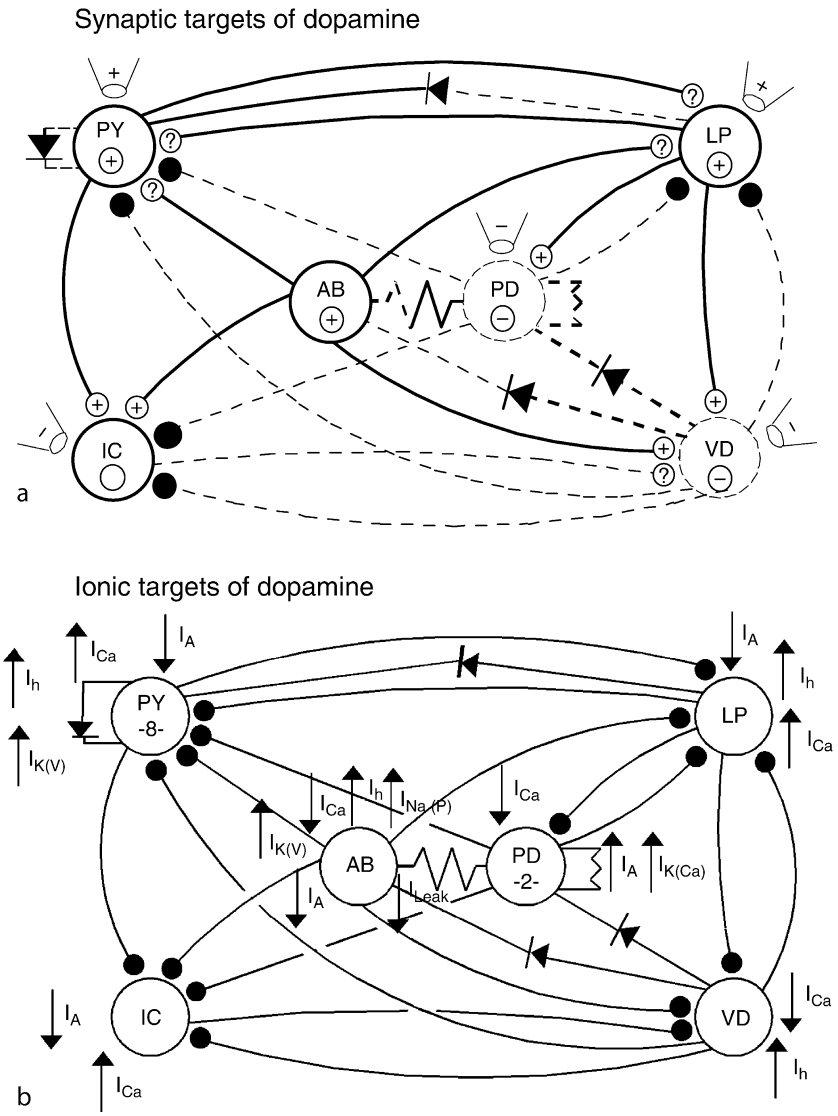
The variability in STG neuron firing properties arises from neuron-specific patterns of expression of genes that encode ion channels, receptors and enzymes. Currents that have been studied in detail include the typical inward currents such as the voltage-sensitive sodium ($I_{Na(V)}$), calcium (I_{Ca}), hyperpolarization-activated inward (I_h) and persistent sodium ($I_{Na(P)}$) currents, and the non-selective cation current (I_{CAN}). In addition, these neurons express outward currents including the transient potassium (I_A), delayed rectifier ($I_{K(V)}$), and calcium-activated ($I_{K(Ca)}$) currents. As described above,



Stomatogastric Ganglion. Figure 3 ►Neuromodulation of STG networks. (a) Diagrammatic summary of known neuromodulatory inputs into the STG (Figure from Eve Marder). (b) Pyloric activity recorded intracellularly from four pyloric neurons under control and dopamine conditions. Calibrations: 1 s and 10 mV (From Kloppenburg et al. (1999) J Neurophysiol. 81:29–38) (c) Dopamine effects on the excitability of synaptically isolated pyloric neurons. Calibrations: 1 s and 5 mV IC; 10 mV AB, PD, VD, LP, PY. (From Flamm and Harris-Warrick (1986) J Neurophysiol 55:866–881) (d) Dopamine reversal of synaptic sign at a mixed electrical/chemical inhibitory synapse. Realistic waveforms (30 mV) were used as voltage clamp stimuli in the presynaptic LP neuron while recording the responses in the post-synaptic PY neuron. Under control conditions, the PY neuron depolarizes in phase with the LP depolarizations. During application of dopamine, the PY neuron hyperpolarizes in phase with the LP depolarizations. Calibrations: 1 s and 1 mV Control, 10 mV DA response. (From Johnson et al. (2005) J Neurophysiol 94:3101–3111).

these currents are major targets of neuromodulators which alter the firing properties of neurons and the strengths of their synapses. Within a single neuron, modulators such as dopamine affect multiple ionic currents to alter its intrinsic firing properties (Fig. 4).

Interestingly, experimental and modeling studies have shown that many different combinations of ionic currents can generate the same basic firing pattern. For example, in different Inferior Cardiac neurons, the amounts of three outward currents varied over a wide range even though the neurons had very similar firing properties; modeling studies support this result, showing that many different combinations of ionic currents could generate the same bursting firing pattern. Similarly, when model pyloric



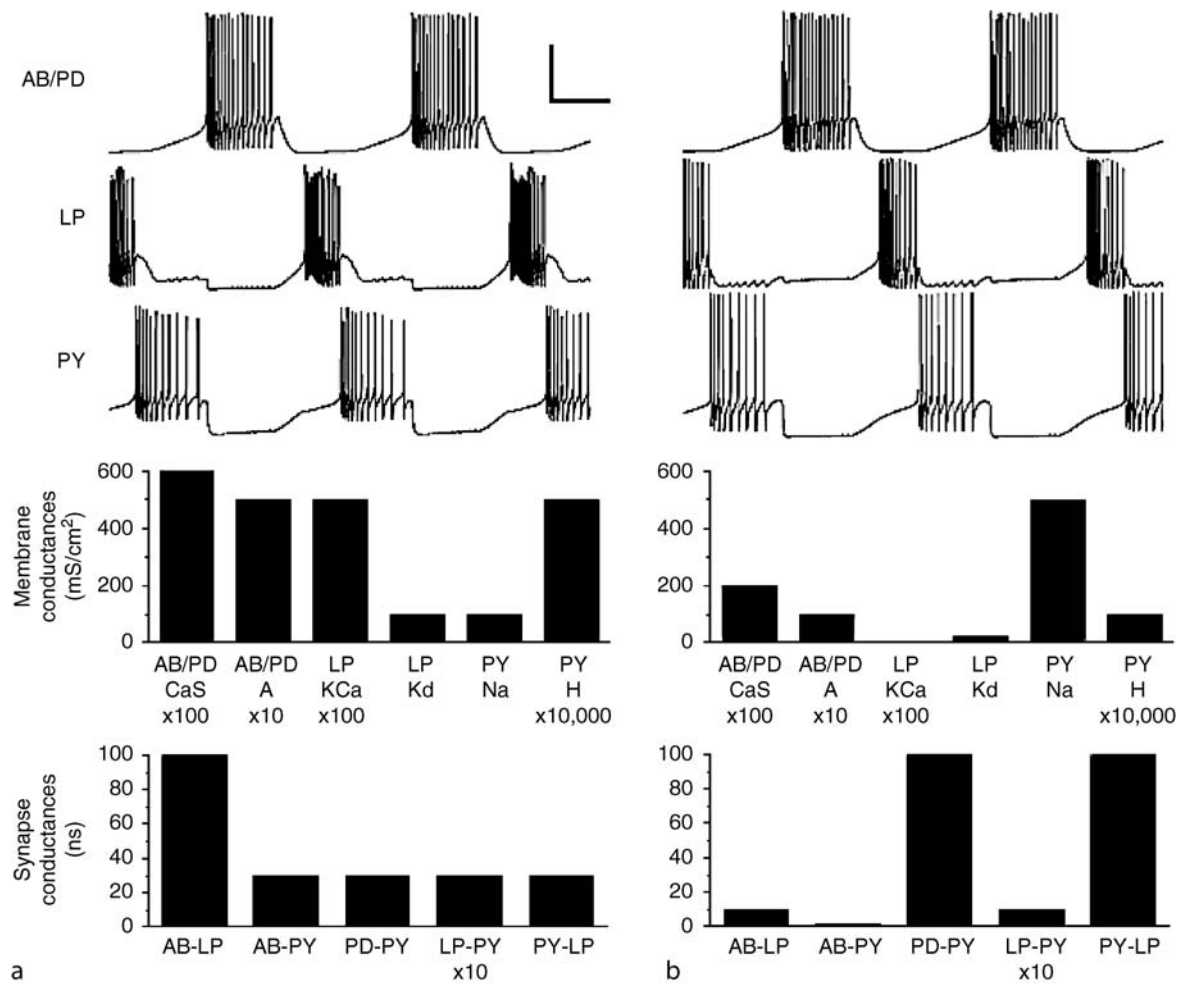
Stomatogastric Ganglion. Figure 4 Summary of dopamine (DA) effects on the intrinsic and synaptic properties of pyloric neurons in the STG. (a) Synaptic targets of DA. Dopamine alters the strength of every chemical and electrical synapse in the pyloric network. Bold lines indicate synapse strengthening and dashed lines indicate weakening. Electrode tips with (−) and (+) signs indicate reduced and enhanced responses to applied glutamate during dopamine application; (+) signs inside nerve terminals indicate DA enhancement of transmitter release; (+) and (−) signs inside neuron cell bodies indicate effects of DA on cell input resisyance. (b) Ionic targets of DA. Currents affected: $I_{Na(P)}$: Persistent sodium current; I_{Ca}: Voltage-sensitive calcium current; I_A: transient potassium current; $I_{K(V)}$: delayed rectifier potassium current; $I_{K(Ca)}$: calcium-activated potassium current; I_h: hyperpolarization-activated inward current; I_{Leak}: voltage-insensitive leak current. Upward and downward pointed arrows indicate DA's effects on different ionic current magnitudes in each neuron.

S

neurons were coupled via variable strength synapses to form more than 20 million versions of a simple three-neuron network, the same motor pattern could be generated by many different combinations of ionic and synaptic parameters [8] (Fig. 5).

Additional evidence for multiple ionic solutions to a neuron's firing properties comes from studies of ►homeostatic regulation, the slow compensatory changes the neurons make when their normal activity pattern is altered. The CPG motor patterns are normally completely dependent on modulatory inputs from other ganglia; when these are blocked the neurons lose their conditional bursting properties. However, if an isolated ►ganglion or neuron is maintained for several days in culture, the neurons restore their bursting properties which are now not dependent on modulatory inputs, and the pyloric rhythm is reactivated. The underlying mechanisms for this include a transcription-dependent increase in sodium and calcium currents and a decrease in potassium currents [9]. In other studies, artificial up-regulation of the transient potassium current, I_A, by RNA injection in single pyloric neurons leads to a proportional up-regulation of I_h [10]. Since the increased I_h counteracts the effects of the increased I_A, the firing properties of the neurons were essentially unchanged.

This work has led to the general conclusion that the firing properties of a neuron are not rigidly determined by the expression of a fixed ratio of ionic currents, but that there are multiple and redundant solutions for each neuron. It will be a challenge to identify the developmental mechanisms that allow this flexibility while reliably generating neurons with appropriate firing properties.



Stomatogastric Ganglion. Figure 5 Different synaptic and ionic current magnitudes can create similar pyloric activity patterns. (a) *Top*: Model network activity in three cells created by the specific model membrane and synaptic conductances shown in bottom. (b) *Top*: Similar model network activity created by very different ionic and synaptic conductances shown in bottom. Calibrations: 0.5 s, 50 mV. (From ref. [8]).

Methods to Measure This System

Studies of the STG have benefited from the convergence of a number of different but complementary experimental approaches:

1. Electrophysiology: Combined intracellular and extracellular recordings allow the complete pyloric or gastric mill motor pattern to be monitored simultaneously. The properties of single neurons can be studied in isolation after removing all synaptic input by fluorescent dye-induced killing of connected neurons and pharmacological blockade of synaptic inputs. Voltage clamp studies allow analysis of individual currents underlying neuronal firing properties.
2. Anatomy: Each identified neuron can be dye-injected, allowing its structure to be carefully mapped, and combined with immunocytochemical mapping of neuromodulator inputs.
3. Imaging studies: intracellular calcium levels can be monitored in single nerve terminals using calcium-sensitive dyes such as calcium green. Intracellular second messenger systems can also be monitored optically using fluorescence resonance energy transfer (FRET) signaling molecules.
4. Molecular biology: A number of ion channel genes have been cloned from lobster and their distribution in the STG mapped by immunocytochemistry. Some have been over-expressed in identified neurons and their effects on neuronal activity determined. Recently, a set of monoamine receptor genes has been identified, and a single cell microarray analysis of multiple genes is being developed.
5. Modeling: Models are a critical adjunct to all the work in the STG. These models have allowed a quantitative analysis of the roles of different synapses and ionic currents in shaping network function, and have demonstrated redundancy in ionic solutions to the firing properties of neurons.

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Stop Codon

Definition

A trinucleotide sequence within the mRNA that halts RNA translation. The three most common stop codons are UAG, UAA, and UGA.

Strain

Definition

A generic name for a variety of measures of the "change of shape and size" of a "small neighborhood" of a body point. In essence, all measures of strain are related to the positive-definite symmetric part in the polar decomposition of the deformation gradient.

►Mechanics
►Measurement Techniques

Strain-hardening

Definition

Most soft tissues become stiffer as the stretch or strain is increased – often associated with increasing recruitment

of previously slack collagen fibers. This material behavior is called "strain-hardening."

►Cardiovascular Mechanics

Streptavidin

Definition

Streptavidin is a 60 kDa tetrameric protein purified from the bacterium *Streptomyces avidini*. A recombinant 53 kDa form is also commercially available. Like the avidin protein found in eukaryotic sources, streptavidin has a very high affinity for biotin (K_d=10^{-13} to 10^{-15}) but lacks the extensive glycosylation found in avidin. The lack of extensive glycosylation means that strepavidin has the advantage of much lower non-specific binding than avidin and; is therefore, more useful in laboratory applications.

►Serial Analysis of Gene Expression

Stress

Definition

Is defined as a constellation of events, comprised of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), which subsequently activates physiological fight or fight systems in the body (stress response). The stress response results in the release of neurotransmitters and hormones that serve as the brain's messengers to the body. An important distinguishing characteristic of stress is its duration. Acute stress is defined as stress that lasts for a period of minutes to hours, and chronic stress as stress that persists for several hours a day or weeks or months. An important marker for deleterious amounts of chronic stress may be a breakdown in the rhythmicity of the circadian cortisol cycle. Stress has long been suspected to play a role in the etiology of many diseases, and numerous studies have shown that stress can be immunosuppressive and hence may be detrimental to health.

►Stress Response
►Measurement Techniques (Pressure)

Stress Effects During Intense Training on Cellular Immunity, Hormones and Respiratory Infections

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Synonyms

Heavy Exertion; Physical Exercise

Definition

In this essay on the influence of combined ►stress during intense training on ►cellular immunity, hormones and respiratory infections, we have argued that athletes and soldiers who engaged in intense and repeated ►exercise training programs and experienced combined stressors such as energy and/or sleep deprivation, and/or psychological restraint, are at risk of respiratory tract infections.

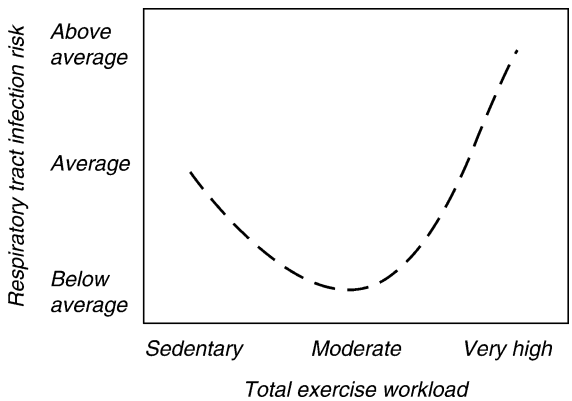
The two parts are distinguished as: (i) intense exercise and alteration of immune responses focusing on cellular immunity and the role played by cytokines. The relationship to the risk of ►upper respiratory tract infections (URTIs) is overviewed [1–4], and (ii) The ►Overtraining Syndrome (OTS) and ►neuroimmunomodulation [5,6]. OTS has been diagnosed in athletes and is characterized by a sports-specific decrease in performance despite periods of recovery together with disturbances in mood state. Signs/symptoms have been categorized according to physiological performance, psychological/information processing, immunological, and biochemical parameters. It is also probable that other signs/symptoms typically associated with overtraining, excluding organic diseases, are evident before deterioration in performance. These might include generalized fatigue, depression, loss of appetite, muscle and joint pain, and an increased incidence of illness. Thus, the relevance of implication of cytokines and the neurotransmitter serotonin in OTS are presented because they play a role in the regulation of immunity.

Characteristics

Hans Selye first popularized the concept of ►stress in the 1950s. Selye theorized that all individuals respond to all types of threatening situations in the same manner, and he called this the General Adaptation Syndrome (GAS). He claimed that, in addition to the sympathetic nervous system (SNS) arousal, other bodily systems such as the adrenal cortex and pituitary gland may be

involved in the response to threat. As the threat wanes, Selye suggested, body functions return to normal, thereby allowing the body to focus on healing and growth again. But if the threat is prolonged and sustained (chronic), the SNS arousal never gets "turned off," and health can be impaired. With a continuously suppressed immune system, for example, a person would be more vulnerable than usual to infection – which is one explanation of why some individuals get sick so often.

Soldiers or athletes are two populations that experience combined stressors during repeated military field operations or intense training such as intense physical exercise, sleep and energy deficiency, environmental conditions (cold, heat), and psychological pressure. The effects of these various stressors on the health are complex, but could be deleterious as it has been shown that chronic stress leads to immunosuppression. Several exercise researchers have elaborated on the "open window" model, proposing that the athlete who trains excessively, without sufficient recovery time, shows a cumulative effect of the vulnerable "open window" period lasting between 3 and 72 h, and thus may encounter the risk of developing transient immunosuppression and an increased risk of infections, particularly ►upper respiratory tract infections (URTIs) (Fig. 1) [3]. Other infections may occur via the eye, ear or skin. There have also been reports of intestinal upsets such as diarrhea, slow wound healing, and increased susceptibility to environmental and food allergens.



Stress Effects During Intense Training on Cellular Immunity, Hormones and Respiratory Infections.
Figure 1 Exercise and risk of upper respiratory tract infections (URTIs) (from Nieman 2000 [3], with permission of The American College of Sports Medicine). "J"-shaped model of relationship between varying amounts of exercise and risk of upper respiratory tract infections. This model suggests that moderate exercise may lower risk of URTI while excessive amounts may increase the risk.

Exercise, Alteration of Immune Responses and Risk of Upper Respiratory Tract Infections (URTIs): the Role of Cytokines

The notion has emerged that tissue damage associated with physical exercise, such as muscle and/or connective tissue and/or bone, may alter immune function [6]. Mild tissue damage, followed by recovery, is an integral part of adaptation associated with exercise, but if an athlete increases training loads with additional stress factors, it is possible that a more chronic form of tissue trauma appears. The inflammatory response to injury is characterized by an initial phase of acute neutrophil accumulation, and a later phase of mononuclear cell accumulation. Then, there is a cessation of inflammatory cell influx, and processes of injured tissue repair occur. An important aspect of an inflammation/immune response is the upregulation of cytokines produced by, and mediating communication between and within, immune and non-immune cells, organs and organ systems throughout the body including the central nervous system (CNS). ►Cytokines coordinate infiltration of white blood cells into injured tissue. During the course of inflammation, cells intrinsic to the injured tissue as well as immune cells recruited to the area release chemical attractants (chemokines) that cause leucocyte adhesion to vascular endothelium and migration into the tissue spaces. Chemokines are divided into two families, the CC and the CXC (conserved cysteine residues are separated by no other residue, CC, or by one other residue, CXC), and, like cytokines, display synergy, antagonism, redundancy and pleiotropy in chemotaxis.

When produced in large quantities, there is a spillover of cytokines into the circulation rendering possible the CNS assessment through several mechanisms. They represent a powerful mediator of the stress response in the CNS because they link the CNS, the neuroendocrine and the immune systems [7]. Cytokines are either pro-inflammatory (TNF-α, IFNγ, IL-2) and stimulate both the hypothalamo-pituitary adrenal axis (HPA) and neurotransmitters synthesis (serotonin and norepinephrine) or anti-inflammatory (IL-10, IL-4). Other cytokines such as IL-6 function as pro- and anti-inflammatory. Another anti-inflammatory mediator is the IL-1 receptor antagonist (IL-1ra) that blocks the IL-1 action. There is cytokine synthesis in the CNS, by the glia, microglia, astrocytes and neurons. Also, several tissues at the periphery are able to synthesize cytokines such as skeletal muscles, adipose tissue, epithelial tissue, and adrenals. Cytokine receptors are present in the CNS (to IL-1 in hypothalamus and hippocampus, to IL-6 in hippocampus) and in the periphery (to IL-6 in skeletal muscles, adipose tissue, and adrenals). They represent neuromodulators as they are involved in memory and sleep processes.

Numerous studies are related to the role of cytokines on immune response, particularly the specific and acquired immunity. This specific aspect is triggered by T and B lymphocytes that are respectively involved in the intracellular pathogens destruction (virus, bacteria) and production of specific antibodies to antigens. T lymphocytes are divided into two distinct subsets, named as Th1 and Th2 cells, which are respectively associated with cell-mediated immunity and humoral immunity. Although the two subsets play a role in homeostasis defense of the body, it appears that in response to trauma or infection the balance is in favor of one or the other. The Th1 response induces cell-mediated immunity (monocytes/macrophages) and is present in autoimmune diseases, while the Th2 response induces humoral immunity (differentiation of B cells in antibody-secreting plasma cells, synthesis of antibodies such as IgE, grow and activation of mast cells and eosinophils) and is present in allergy diseases. Regulation of the balance lies on their respective associated cytokines: Th1 includes IL-2, IL-12, IFNγ, while Th2 includes IL-4, IL-6, IL-10, IL-13, and TNF-α. It has been shown that acute and chronic stress can decrease the Th1 response and increase the Th2 response under influence of stress hormones, glucocorticoides (GC) and catecholamines [7]. Acting through their receptors, GCs decrease the cytokine production associated to Th1. Catecholamines triggered similar effects particularly via β-adrenergic receptors.

During strenuous exertion, the relationship between the defined parameters of immunosuppression in the "open window theory" and the incidence of URTIs is a matter of current debate. Many alterations have been noted on ►cellular and humoral immunity. These include suppressed neutrophil function, suppressed lymphocyte count and proliferation, suppressed natural killer (NK) cell count and activity, changes in polymorphonuclear cell priming potential, and decreased serum, nasal and salivary immunoglobulins (Igs) (Table 1) [2,3]. Several studies have explored the relationship between URTIs and two main immune parameters that are decreased during heavy exertion, salivary immunoglobulin A (sIgA) and blood NK cell counts and/or NK activity. At present it is mainly the fall in blood NK cell count and/or activity that have been shown to be associated with an increased risk of URTIs during intense training for soldiers or athletes [2]. Changes in other immune-related factors suggestive of immunosuppression have also been noted after heavy exertion. These include changes in hormones and cytokines favoring a shift from the Th1 to the Th2 cytokine pattern. During intense military training, a relationship between URTIs and NK cell counts concomitantly to hormonal and cytokine responses has been shown, suggesting induction of a Th2 immune response (i.e., decreases in immunostimulatory hormones such as leptin and prolactin and increase in IL-6) [2].

It is well documented that exercise affects local and systemic cytokine production, with similarities to the cytokine response to infection. In sepsis, the cytokine cascades are TNF-α, IL-1β, IL-6, IL-1ra, sTNF-R (soluble receptor to TNF), and IL-10. The cytokine response to prolonged endurance exercise differs from that of infection in the fact that TNF-α and IL-1β were not reportedly increased. Typically, IL-6 is the first cytokine present in the circulation after exercise followed by IL-1ra (IL-1 receptor antagonist), IL-10, and the chemokine IL-8 [4]. The Pedersen group has demonstrated that (i) the major source of circulating IL-6 during prolonged exercise is skeletal muscle, but there is also adipose tissue production, (ii) the muscle production is sensitive to muscle glycogen content, and (iii) during prolonged exercise IL-6 plays a role in glucose homeostasis and lipid metabolism [8].

Stress Effects During Intense Training on Cellular Immunity, Hormones and Respiratory Infections. Table 1 Changes in immune system components after prolonged heavy exertion (from [3])

• Neutrocytosis and lymphopenia, induced by high plasma cortisol
• Increase in blood granulocyte and monocyte phagocytosis, but a decrease in nasal neutrophil phagocytosis
• Decrease in granulocyte oxidative burst activity
• Decrease in nasal mucociliary clearance
• Decrease in natural killer cell cytotoxic activity
• Decrease in mitogen-induced lymphocyte proliferation (a measure of T cell function)
• Decrease in the delayed-type hypersensitivity response
• Increase in plasma levels of pro- and anti-inflammatory cytokines (e.g., interleukin-6 and interleukin-1 receptor antagonist)
• Decrease in ex vivo production of cytokines (interferon-g, interleukin-1 and interleukin-6) in response to mitogens and endotoxin
• Decrease in nasal and salivary IgA level
• Blunted major histocompatibility complex II expression in macrophages

The Overtraining Syndrome (OTS) and Neuroimmunomodulation

For the athlete, the increased susceptibility to infectious illness has been associated with the condition of overtraining syndrome (OTS), also referred to as "staleness" or burnout' syndrome. It is often suggested that OTS is the result of an accumulation of stressors that exceed an athlete's finite resistance capacity, similar to that which Selye observed. It is characterized by a sports-specific decrease in performance despite periods of recovery together with disturbances in mood state. Fry and colleagues [9] have categorized signs/symptoms of OTS according to physiological performance, psychological/information processing, immunological, and biochemical parameters. It is also probable that other signs/symptoms typically associated with overtraining, excluding organic diseases, are evident before deterioration in performance. These might include generalized fatigue, depression, muscle and joint pain, and loss of appetite (Table 2). At present, the definitive diagnostic criteria and the biochemical/metabolic mechanism for OTS are unknown. However, exercise scientists have suggested considering the endocrine, immune and nervous systems as a large system serving integrated functions. Thus, the "cytokine" and "IL-6" hypotheses of the OTS have been proposed.

Cytokines play a function as neuromodulators and immune mediators, and represent the systemic aspect of an immune/inflammatory response, which coordinates the whole body response by simultaneously acting on different organ systems including the central nervous system (CNS). Smith [6] hypothesizes that exercise-related immunosuppression is due to tissue trauma sustained during intense exercise, producing cytokines, which drive the development of a Th2 lymphocyte profile. A Th2 cell response results in simultaneous suppression of cell-mediated immunity, rendering the athlete susceptible to infection. Robson [5] explores the cytokine hypothesis of OTS with a direct focus on IL-6 and thus hypothesizes that the principal abnormal factors in OTS are an increased production of and/or intolerance to IL-6 during exercise.

The cytokine hypothesis of OTS relies on the fact that they can access the CNS and may induce brain-mediated signs of illness by acting at central, rather than peripheral, sites. They may directly access brain structures, either using a transport system to cross the blood brain-barrier (BBB), or acting at the level of circumventricular organs (CVO), where this barrier does not exist [6,7]. They may also inform the CNS indirectly via activation of afferent neurons of the vagus nerve; neural afferents may activate transcription and translation of cytokines within the CNS. In the brain, there are specific receptors for IL-1, IL-6, and TNF that have a discrete distribution. Blocking IL-1 receptors in the brain can prevent some of the sickness responses to peripheral administration of cytokines. Furthermore, administration of certain cytokines directly into the brain produces many or all of the sickness responses. IL-1 and IL-6 receptors in the brain are abundant in the area of the hypothalamus. The binding of cytokines in the hypothalamus results in activation of the hypothalamic-pituitary-adrenal axis (HPA-axis) and sympathetic nuclei, resulting in increased levels of circulating catecholamines, and cortisol, the traditional stress hormones. Robson [5] focuses on the IL-6 hypothesis of OTS because it has been shown that intracerebroventricular administration of IL-6 to rats stimulates the HPA axis, increases tryptophan and serotonin metabolism, induces fever, and decreases appetite and

Stress Effects During Intense Training on Cellular Immunity, Hormones and Respiratory Infections. Table 2 Signs and symptoms associated with overtraining syndrome (from [9])

A. Physiological performance
• Decreased performance
• Inability to meet previously attained performance
• Recovery prolonged
• Decreased muscular strength
• Decreased maximum work capacity
• Loss of coordination
• Reappearance of mistakes already corrected
• Chronic fatigue
• Insomnia with and without night sweats
• Muscle soreness or tenderness
• Loss of appetite
B. Psychological/information processing
• Feelings of depression
• General apathy
• Emotional instability
• Difficulty in concentrating at work and training
• Fear of competition
C. Immunological
• Increased susceptibility to and severity of illnesses, colds, and allergies
• Flu-like illness
• Minor scratches heal slowly
• Bacterial infection
D. Biochemical
• Negative nitrogen balance
• Depressed muscle glycogen concentration
• Mineral depletion (e.g., zinc, cobalt, aluminium, selenium, copper)
• Elevated cortisol
• Low free testosterone

locomotor activity. In addition, the exercise endurance is reduced in IL-6-deficient mice. For the athlete, several risk factors considered either individually or in combination but experienced chronically can weaken the BBB and permit the cytokine access to the CNS: the exercise workload, exposition to infectious agents, hyperthermia, hypoglycemia, and depression. The Nybo researcher group [10] has particularly evidenced the link between prolonged exercise-induced hyperthermia or hypoglycemia and central fatigue.

Examination of neuroendocrine and immune responses that exist during depression has offered insights into the mechanism and treatment of OTS. Similarly, the relevance of implication of neurotransmitters such as ►serotonin (5-HT: 5-hydroxytryptamine) and noradrenaline has been introduced. The 5-HT system is the largest brain system playing a role in the regulation of mood state, sleep, appetite, cognitive function, memory, circadian rhythms, motor function and sexual activity, neuroendocrine and immune responses. A recent study reports in one case of a severe OTS state a decrease in serotonin transmission in certain parts of the brain, using single-photon emission computed tomography (SPECT). Moreover, serotonergic neurotransmission is thought to be a neuromodulatory system exerting its activity in the CNS and in the periphery. Serotonin can affect immune functions and several findings suggest that modulation of the immune system by serotonin occurs at the lymphocytes level. Presence of 5-HT_{1B} receptors has been evidenced in rodent lymphocytes and splenocytes and a human T lymphoblastoid cell line. While there is no report on OTS and change in 5-HT in the immune system, it has been shown that 5-HT_{1B} receptors in lymphocytes are desensitized after intense military training [1].

Conclusion

In conclusion, populations such as soldiers or athletes submitted to combined stress exceeding stress tolerance [i.e., prolonged and repeated exercises, lack of sleep and energy intake, psychological stress, environmental conditions (heat, cold)] are at risk of immunosuppression and exposed to infections, particularly those of the upper respiratory tract.

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Stress in Mechanics

Definition

A generic name for a variety of measures of "the forces per unit area" at a point of a body. In essence, all measures of stress are related to the flux tensor associated with the flux of linear momentum. Specific examples are the first Piola-Kirchhoff stress and the Cauchy stress.

►Mechanics

Stress-induced Analgesia (SIA)

Definition

Pain reduction occurring in response to a physically taxing or stressful event, such as a forced cold-water swim. Presumed to involve both opioid and non-opioid systems.

►Descending Modulation of Nociception
►Gender/sex Differences in Pain

Stress/Pressure

Definition

The force per unit area exerted on a material. The SI unit for stress/pressure is newtons per meter squared (N/m2) which is given the name pascal (Pa).

►Measurement Techniques (Pressure)

Stress Response

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Definition

The stress response is a complex set of coordinated changes involving neuroendocrine, autonomic, and behavioral components. At the neuroendocrine level, a complex cascade of events is initiated in the brain and pituitary, culminating in the ACTH-induced synthesis and release of glucocorticoids from the adrenal glands. Autonomic activation is simultaneously induced, involving widespread and divergent outflow through the sympathetic nervous system and secretion of adrenal catecholamines, resulting in increases in heart rate, respiration, and blood pressure, as well as mobilization of energy resources. Behavioral changes are induced that promote increased attention and arousal, while inhibiting other non-essential activities (e.g. feeding, gastric motility, sexual behavior). The term *stress*, initially coined by in 1936 by Selye [1], described a pathophysiological state induced by physical or psychological stimuli, the persistence of which may lead to disease or death. Such challenges may be real or interpreted threats to homeostatic balance, and can result in an array of responses that may be adaptive or maladaptive.

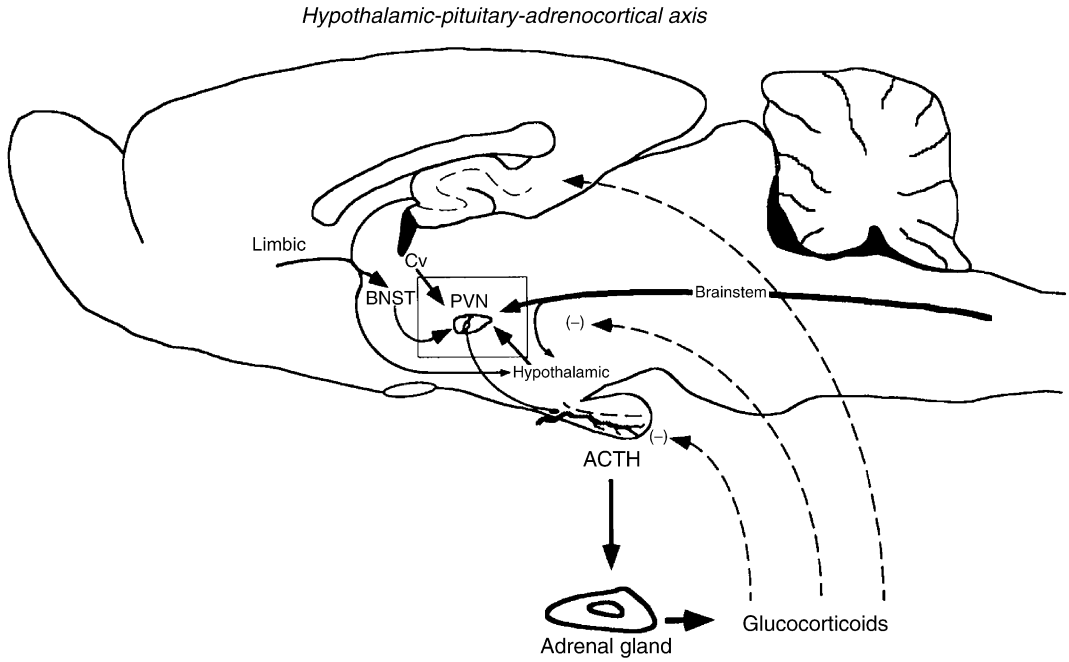
Characteristics

Stress Classes and Consequences

Numerous attempts have been made to subdivide stressors according to class. Most authors have delineated stressors of a psychological or psychogenic origin versus those of a physical nature. Stressors within the former category (e.g. novelty, social defeat) have more recently been termed *processive* or *anticipatory* to emphasize extensive neural processing occurring largely within limbic brain structures prior to transmission to the PVN. Stressors in the latter category (e.g. cardiovascular) have been termed "systemic" or "direct" to underscore a more immediate challenge to homeostasis, as well as an uninterrupted access to the PVN from key afferent sites, particularly in the brainstem. It is the case, however, that overlap exists among both stress classes and the neuronal circuits that mediate them. Remarkably, these circuitries are organized in a hierarchical fashion that enables an appropriate assessment or weighing of the significance of an internal or external threat, with subsequent translation into neuroendocrine, autonomic, and behavioral responses [2]. It also evident that exposure to stress can produce long-term changes in neuronal function through mechanisms at multiple levels, including synaptic neurotransmission, intracellular signaling, gene regulation, and even morphological changes within key structures. Many of these changes may be considered normal adaptations, even in cases of prolonged or chronic stress. However, when the capacity of the brain's stress circuitry to maintain normal responsiveness is exceeded in the face of ongoing challenge, stress may be considered maladaptive, and ultimately deleterious to health.

The Hypothalamic-Pituitary-Adrenocortical (HPA) Axis

The origin of the final common pathway of a major neuroendocrine response to stress is the hypothalamic paraventricular nucleus (PVN); neurons in the medial parvocellular division of this nucleus synthesize and release corticotropin–releasing hormone (CRH) and project to the median eminence, where CRH is released into the portal vasculature. CRH stimulates anterior pituitary cells to secrete adrenocorticotropic hormone (ACTH, and additional products cleaved from a common precursor, pro-opiomelanocortin; POMC). ACTH is (Fig. 1) carried through the systemic circulation to the adrenal cortex, where it induces the synthesis and release of glucocorticoids (primarily cortisol in humans, corticosterone in rodents) from the zona fasciculata of the adrenal glands. The hypophysiotropic CRH neurons of the PVN are therefore the primary integrators of the HPA axis, processing stress-related information carried over multiple afferent pathways that differ according to the nature or class of the stressor. The PVN also contains populations of neurons with projections to the brainstem and spinal cord. These neurons, together with cells from adjacent hypothalamic nuclei, regulate outflow to the preganglionic neurons of the autonomic nervous system, including those governing the sympatho-adrenal-medullary response. In addition, arginine vasopressin (AVP), a neuropeptide highly expressed in neurons of the adjacent magnocellular division of the PVN and principally involved in osmotic regulation, is



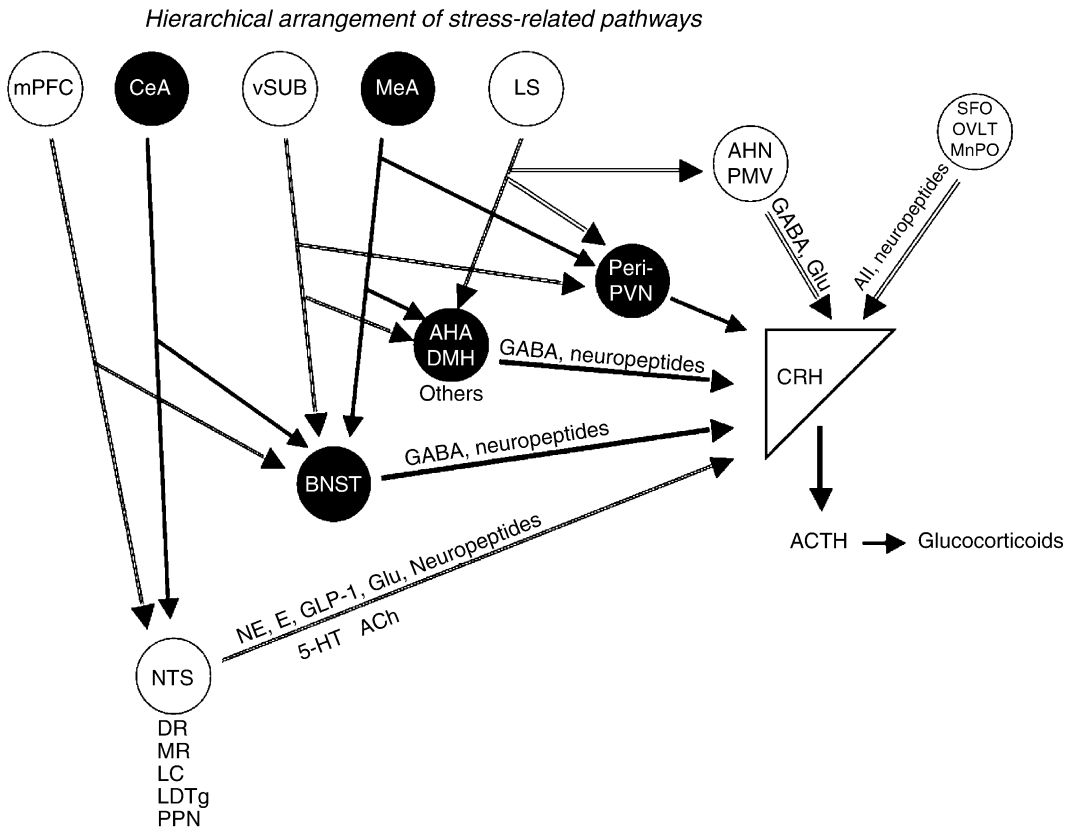
Stress Response. Figure 1 Diagram illustrating the major components of the Hypothalamic-Pituitary-Adrenocortical (HPA) Axis. Solid arrows indicate sources of regulatory afferents from the brainstem, limbic forebrain, hypothalamus, and circumventricular organs. Dashed lines denote major sites of glucocorticoid negative feedback. Abbreviations: *ACTH* adrenocorticotropic hormone; *BNST* bed nucleus of the stria terminalis; *Cv* circumventricular organs; *PVN* hypothalamic paraventricular nucleus.

co-expressed within hypophysiotropic CRH neurons. AVP is capable of potentiating the effects of CRH on pituitary ACTH release. While CRH is clearly the most potent ACTH secretagogue, hypophysiotropic CRH neurons are also capable of co-expressing a number of peptides in addition to AVP. Recruitment of these transmitters appears to be condition- dependent, affording a wide range of responsivity to the glucocorticoid stress response.

Glucocorticoids have powerful actions throughout the body, targeting a diverse array of tissues including muscle, fat, skin, bone, kidney and liver. These steroid hormones also have direct effects on immune cells, on the production of inflammatory cytokines, as well as within the CNS itself. Dysregulation of glucocorticoid secretion contributes to numerous disease states including cardiovascular, autoimmune, metabolic, and neuropsychiatric disorders. For example, oversecretion of glucocorticoids can suppress immune function, increasing susceptibility to infection [3], and HPA axis overactivity is a common feature in many patients with depressive illness [4]. Conversely, under-activity of the HPA axis increases susceptibility to autoimmune and inflammatory conditions. Regulation of glucocorticoid levels within a normal range is therefore critical to health. Glucocorticoids also play an important role in cognitive processes such as learning, memory and attention, all of which are affected by dysregulation of the glucocorticoid stress response as well as stress-induced changes in levels of circulating catecholamines.

Afferent Regulation of the PVN

CRH neurons of the PVN are under complex afferent regulation from numerous brain areas. These inputs can be divided into several major classes: brainstem nuclei, local hypothalamic regions, limbic-associated forebrain structures, and circumventricular organs [5] Major sources of stimulatory input to the PVN emanate from caudal brainstem regions containing the neurotransmitters norepinephrine and epinephrine. Most prominent among them are the A2 region of the nucleus of the tractus solitarus (NTS) and the A1/C1 area of the ventrolateral medulla, which have direct lines of input to the medial parvocellular PVN rich in CRH neurons. The noradrenergic input to CRH neurons is particularly dense, and pharmacological effects here are mediated via α-1 adrenergic receptors. These brainstem regions receive visceral afferent information carried (Fig. 2) via the ninth and tenth cranial nerves, and relay information to the HPA axis concerning the state of the internal milieu. They are also interconnected with brainstem cardiovascular and respiratory centers. More recent data have indicated that ascending projections from the NTS also include non-catecholaminergic elements. Moreover, numerous additional brainstem regions send projections to the PVN either directly, or via



Stress Response. Figure 2 Schematic diagram illustrating complex, hierarchically organized afferent regulation of hypophysiotropic CRH neurons of the HPA axis. White circles denote brain regions with excitatory outflow; black circles indicate areas thought to have inhibitory outflow. Abbreviations: *5-HT* 5-hydroxytryptamine (serotonin); *AII* angiotensin II; *ACTH* adrenocorticotropic hormone; *AHA* anterior hypothalamic area; *BNST* bed nucleus of stria terminalis; *CeA* central amygdaloid nucleus; *CRH* corticotropin-releasing hormone; *DMH* dorsomedial hypothalamic nucleus; *DR* dorsal raphe nucleus; *GLP-1* glucagon-like peptide I; *Glu* glutamate; *LC* locus coeruleus; *LDTg* laterodorsal tegmental nucleus; *LS* lateral septal nucleus; *MeA* medial amygdaloid nucleus; *MR* median raphe nucleus; *OVLT* organum vasculosum of lamina terminalis; *MnPO* medial preoptic nucleus; *NTS* nucleus tractus solitarius; *PPN* pedunculopontine nucleus; *SFO* subfornical organ; *vSUB*, ventral subiculum of hippocampus; *PMV* ventral premammillary nucleus.

forebrain relays. Included are serotoninergic fibers emanating from the dorsal and median raphe nuclei, cholinergic fibers from the pedunculopontine and lateral dorsal tegmental nuclei, noradrengeric projections from the locus coeruleus, as well as inputs from the lateral parabrachial nucleus and periaqueductal gray regions. The majority of these inputs are stimulatory in nature, and many transmit somatic and special sensory information to the PVN. In contrast, a series of local forebrain (including intrahypothalamic) regions are known to distribute GABA-mediated inhibitory projections to the PVN. These include the medial preoptic area, bed nucleus of the stria terminalis, dorsomedial hypothalamic nucleus, and anterior hypothalamic area immediately surrounding the PVN. Interestingly, limbic system associated inputs to the HPA axis (medial prefrontal cortex, hippocampus, amygdala) lack direct projections to the PVN, and influence CRH neurons via relays with neurons located within these local territories [6]. Beyond the aforementioned pathways, research over the past decade has focused on extrahypothalamic CRH and the urocortins-centrally expressed neuropeptides sharing a family resemblance to CRH and acting at its receptors [7]. In addition to these strictly neuronally mediated inputs, blood-borne chemosensory signals reach the PVN either directly via the intrinsic vasculature, or by circumventricular organs (subfornical organ, organum vasculosum of the lamina terminalis) that send neuronal relays to the PVN.

Glucocorticoid Regulation

Termination of glucocorticoid secretion following stressful episodes is accomplished by negative feedback occurring within different time domains and at multiple

levels of the HPA axis [8]. For example, glucocorticoids inhibit POMC expression and ACTH release at the level of the anterior pituitary, and inhibit hypophysiotropic CRH neurons at the level of the PVN through both genomic and non-genomic mechanisms. Glucocorticoids also act centrally at higher centers; glucocorticoid receptors are found at multiple central sites including the cerebral cortex, hippocampus, septum, amygdala, cerebellum, and brainstem. Two types of the receptor exist. The type II or GR (glucocorticoid receptor) has a widespread distribution in the CNS. The type I, or MR (mineralocorticoid receptor) receptor is more limited in expression, but has a 10-fold higher affinity for glucocorticoids than GR. Both are members of the steroid hormone superfamily, existing in an unbound state within the cytoplasm, but when bound by ligand are translocated to the nucleus where they bind to the promoter regions of responsive genes. Several lines of evidence have suggested that MR may be primarily important in maintaining basal expression of ACTH secretagogues (particularly at the circadian nadir), whereas GR may function principally at the circadian peak and following stressful stimuli. In addition, evidence suggests that glucocorticoid-independent neuronal inhibitory mechanisms are in operation during stressful conditions. For example, inhibition of ACTH release can occur in the absence of glucocorticoid negative feedback [9], implicating additional inhibitory mechanisms involved in restraining HPA-axis activation.

Limbic Control of Stress Responsiveness

A number of constituent elements of the limbic system have been heavily implicated in the responsiveness of the HPA axis. These regions share the common feature that they lack direct PVN projections. The hippocampus plays a prominent role in inhibition of the glucocorticoid stress response, consistent with its high levels of expression of glucocorticoid receptors (see above). Moreover, functional studies have demonstrated a deficit in negative feedback following lesions of this structure, as well as with receptor inactivation or with gene deletion. Anatomical data are consistent with this picture: the ventral subiculum, the major output structure of the hippocampus, sends an impressive excitatory (glutamatergic) projection to the basal forebrain, but does not contact PVN neurons directly. These signals are converted to an inhibitory signal at the PVN by way of relays among populations of GABAergic neurons in the hypothalamus and BNST.

The amygdala, in contrast to the hippocampus, appears to stimulate the PVN. A major distinction lies in the class of stressors in which these limbic nuclei play a vital role. The medial amygdaloid nucleus stimulates the HPA axis in response to anticipatory but not systemic stressors, whereas the reverse is the case for the central amygdaloid nucleus. Interestingly, projection neurons from both the medial and central amygdaloid nuclei are GABAergic, and like hippocampal projections, do not directly innervate the PVN. Rather, both medial and central amygdaloid regions are also thought to target local inhibitory relay neurons, and thereby function through a disinhibitory mechanism.

Numerous studies have implicated the medial prefrontal cortex in HPA axis regulation. An increasing body of literature has indicated that dorsal components of this region are inhibitory to the PVN, whereas more ventral territories appear to stimulate HPA output [10]. In both cases this limbic cortical output is mediated via multiple relays in forebrain (e.g. BNST), or in the case of ventral prefrontal areas (infralimbic cortex), brainstem regions such as the NTS.

Several additional forebrain regions considered part of the limbic system are known to affect HPA activity. These include the lateral septal nucleus, which inhibits the stress response, as well as limbic components of the thalamus (e.g. paraventricular nucleus of the thalamus) that mediate habituation of the stress response. Finally, several loci within the hypothalamus intersect with classical limbic circuitries, and relays through these regions permit limbic information to be processed with regard to ongoing physiological status. The net effect is that stressor salience is fine-tuned within these local circuits to account for caloric requirements, thermoregulatory status, osmotic balance, and diurnal rhythmicity prior to being translated to the PVN.

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Stress Response (Heat Shock) Protein

Definition

Protein that is synthesized in response to mechanical, chemical or thermal (heat shock) injury (stress), and which usually promotes survival of the cell.

Stretch-inactivated Cation Channel (SIC)

Definition

Stretch-inactivated cation channels underlie the hyperosmotic depolarization which is associated with an increase in membrane conductance. This response is due to the bi-directional, cell-volume-dependent modulation of a non-selective cation conductance. Cells shrinking in the presence of hypertonic solution disinhibit channel activity, which leads to depolarization.

Conversely, cell swelling induced by a hypoosmotic solution inhibits basal channel activity and leads to hyperpolarization.

►Blood Volume Regulation

Stretch Receptor

Definition

In many animals, muscles contain specialized sensory end organs that are activated when the muscle in which they are contained is lengthened or stretched. These sensory receptors signal the length of the muscle to the central nervous system (CNS) and can also signal the velocity of a change in length. In the lamprey, these receptors are located in the spinal cord itself and respond when the cord bends during body undulations.

►Intersegmental Coordination
►Sensory Systems

Stretch Reflex

Definition

The stretch reflex is a reflex that causes a muscle to contract and shorten after it is stretched. The elongation of a muscle, usually by an external perturbation is encoded by the firing of muscle spindle receptors within the muscle. The Ia muscle spindle afferents synapse on motoneurons of the same muscle, causing the muscle to contract in response to muscle stretch.

►Postural Synergies

Stretch Resistance

►Muscular Stiffness

Stretching Tensor

Definition

The symmetric part of the velocity gradient. Also called rate of deformation tensor.

►Mechanics

Stria Terminalis

Definition

The stria terminalis is the most important efferent of the amygdaloid body. It is a bundle of myelinated fibers

coursing in the lateral ventricle, in the groove between thalamus and caudate nucleus and dividing at the anterior commissure. Target areas are: preoptic area, anterior hypothalamic area, hypothalamic nuclei, interstitial nucleus of stria terminalis. It marks the border between diencephalon and telencephalon.

►Amygdala
►Evolution of the Amygdala: Tetrapods
►Diencephalon

Striate Cortex

Definition

The striate cortex (also called Brodmann's area 17, V1, and primary visual cortex) is the first cortical visual area. It lies in the calcarine sulcus of the occipital lobe and receives signals relayed from the retina via the lateral geniculate nucleus of the thalamus.

►Striate Cortex Functions
►Geniculo-striate Pathway

Striate Cortex Functions

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Synonyms

Area V1; Primary visual cortex; Brodmann area 17

Definition

Striate cortex is the primary sensory cortical area for vision. Damage to striate cortex causes blind regions, called scotomas, in the field of vision. Striate cortex derives its name from the stria of ►Gennari, a prominent band of ►myelin in layer 4, visible to the naked eye. In histological sections, striate cortex has a characteristic laminar cell structure (Fig. 1). Striate cortex is located within the calcarine sulcus on the medial face of each ►occipital lobe. It occupies about 10% of the whole cerebral cortex. Each neuron in striate cortex responds to visual stimuli presented within a small portion of the visual field, known as the ►receptive field (►Visual cortical and subcortical receptive fields). The properties of a visual cell can be ascertained by analyzing the response to different types of visual stimuli falling within the receptive field. Thus, the functions of striate cortex can be defined by identifying the cardinal properties of its constituent cells, such as selectivity for stimulus orientation, direction of motion and stereoscopic depth (►Binocular Vision). These properties must be synthesized within striate cortex, because they are not present in the cells that provide ascending input. Another way to define the functions of striate cortex is to examine how the properties of single cells are related to anatomical structures, commonly revealed by the presence of functional maps. Neurons with similar properties tend to be grouped together, and there is a continuous and gradual change in physiological characteristics across the cortical sheet. Numerous superimposed maps are present within area V1 that together provide full coverage of the visual field for multiple visual modalities.

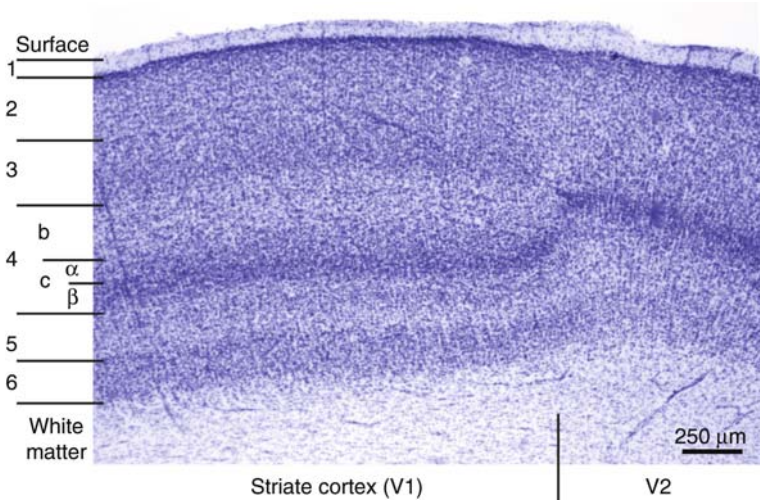
Characteristics

Overview

The neural processing of visual signals begins with the capture of light images by photoreceptor cells (►photoreceptors). After some internal retinal processing, visual information exits the eye in the form of action potentials propagated along the axons of ganglion cells (►retinal ganglion cells). These axons are grouped into bundles that form the ►optic nerves. The two optic nerves meet and decussate partially at the ►optic chiasm, to form the ►optic tracts. In the optic tracts, crossed fibers from the nasal half of each retina run alongside uncrossed fibers from the temporal half of each retina. The axons synapse on cells in the ►lateral geniculate nucleus (LGN) of the ►thalamus. The LGN provides the major ascending input to striate cortex, via the ►optic radiations, to layer 4. The main cortical output is derived from layers 2, 3, 5, and 6. Between the input and output layers, intracortical circuitry combines and elaborates visual signals to generate novel receptive field properties. The visual system includes a network of multiple cortical areas, each receiving input from and sending connections to other areas. Each area in the network acts as a specialized processing module, extracting specific types of visual information. Striate cortex can be thought of as the foundation of this network. It distributes and receives information from many different interconnected areas. Striate cortex also sends a major feedback projection to the LGN. The function of this pathway is contentious; it may modulate the flow of information into striate cortex.

Input

Cells within each layer of striate cortex have characteristic morphologies and patterns of connectivity (►Visual cortex – neurons and local circuits). The input from



Striate Cortex Functions. Figure 1 Cross section through striate cortex stained with cresyl violet to show neuronal cell bodies. The multi-layered structure of the cortical sheet is evident, as well as the transition between striate cortex and the second visual area, V2. Layer 4 is a conspicuous feature of striate cortex, containing two cell-dense input sublayers (4cβ and 4cα), as well as a cell sparse sublayer (4b) containing the stria of Gennari.

the LGN to striate cortex abides by a laminar organization, such that three categories of LGN cells project to three separate laminar divisions (Fig. 2), also see ►geniculo-striate pathways). Thus, the functional division in the LGN is maintained in the input layers of striate cortex. To generate more specialized functional properties, the signals from multiple LGN inputs converge onto single cortical cells. This convergent processing of visual information in striate cortex is achieved by complex circuits that operate between the input and the output cells.

Intracortical Circuitry

Intracortical circuitry forms the anatomical basis of neural processing of visual information (►Visual cortex – neurons and local circuits). Intracortical projections connect cells that are separated horizontally in the same layer or vertically in separate layers. These connections allow visual signals from many cells to combine and influence each other. In the case of striate cortex (Fig. 3). the dense internal circuitry provides ample opportunity for the integration of functional properties that remain segregated at the level of the LGN. The intracortical circuitry of striate cortex is responsible for the elaboration of the elementary properties of LGN cells into novel, more specialized attributes, such as orientation, direction and binocular disparity tuning.

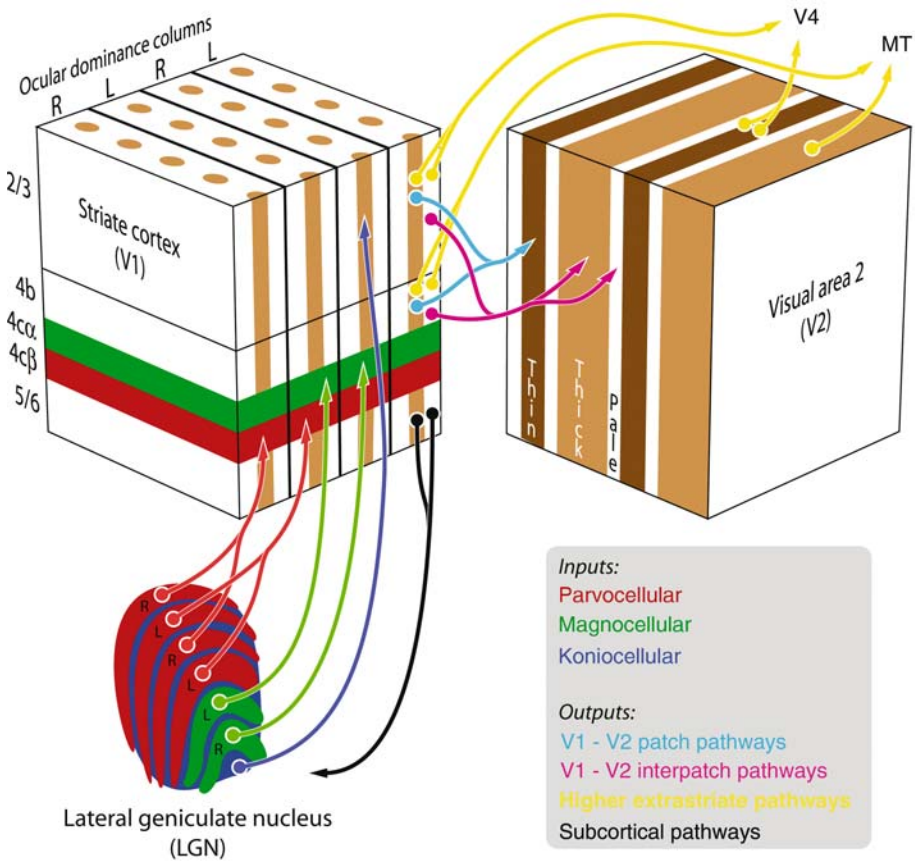
Retinotopy

Neighboring cells in striate cortex represent adjacent points in the visual field. This organizing principle is called ►retinotopy (Fig. 4). A consequence of retinotopic organization is the formation of a map of the visual scene on the cortex. The fovea in each retina corresponds to the ►fixation point. The fovea represented posteriorly near the occipital pole. A vertical line running through the fixation point divides the visual scene into left and right hemifields. Each hemifield is represented in striate cortex of the contralateral hemisphere. Thus if striate cortex on one side is destroyed, vision is lost from the visual field on the opposite (contralateral) side. In this case, the damage is said to have caused a ►homonymous hemianopia – loss of vision from both eyes resulting in complete blindness on one full side of the visual field.

When we examine something closely, like the printed words on a page, we move our eyes so that light reflected from the point of interest is focused onto the fovea of each retina. The ►eye movements (►Saccades) that control this behavior allow us to take full advantage of the fovea by placing it serially on regions of interest. Numerous specializations in the retina (including a high density of ones) endow the fovea with maximum resolution. As a result, more information emanates from the fovea than from the peripheral retina. To serve the fovea, a far greater amount of cortical tissue is allotted to central versus peripheral retina. In fact, the surface area of striate cortex devoted to 1° is about 10,000 times greater at the fovea than in the periphery. This results in distortion of the visual scene by the retinotopic map in striate cortex (Fig. 5).

Ocular Dominance

Cells in the LGN are monocular; they respond to stimuli presented to one eye but not to the other. Likewise, the

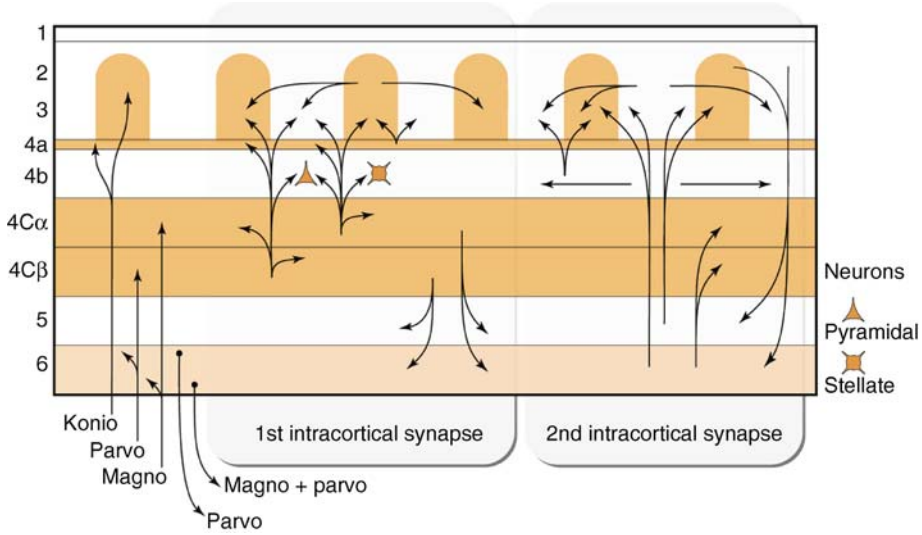


Striate Cortex Functions. Figure 2 Inputs and outputs of striate cortex. Cells in the LGN provide the major ascending input to striate cortex. Their axon terminals segregate both by eye (R, L) and by layer. Recipient cells in layer 4cβ (parvo), 4cα (magno) and 2,3 (konio) make extensive intracortical connections, partially merging inputs from the three functional LGN channels. The output from striate cortex to area V2 is organized by cytochrome oxidase compartment. The patches (vertical brown cylinders) project to thin stripes, and the interpatches project to thick and pale stripes. The output of V2 also respects cytochrome oxidase divisions: thick stripes project to the middle temporal area (MT), while thin and pale stripes supply area V4.

cells in layer 4c of striate cortex are monocular, because they are targeted selectively by LGN inputs. Layer 4c is segregated into regions dominated by the left eye or the right eye. These two domains interdigitate to form a labyrinthine pattern tangential to the cortical sheet-called "►ocular dominance columns". The pattern formed by ocular dominance columns is distinctive and robust [2]. It is best appreciated when the cortex has been removed from the rest of the brain, unfolded and flattened before histological sections are cut tangential to the surface [3] (Fig. 4b). Rather like a fingerprint, the ocular dominance pattern is unique and highly variable between individuals and species. Columns are found in most carnivores and primates, including humans. In animals that lack columns, monocular cells persist, but they are mixed homogenously in layer 4c. Ocular dominance columns are intriguing, but their function is unknown.

Disparity Selectivity

Most cortical cells in layer 4c are monocular, i.e. they respond to stimulation of only one eye. Binocular integration (►Binocular vision) occurs by the convergence of intrinsic projections from monocular cells in layer 4c onto single cells in the upper and lower layers of the cortex. Most binocular cells are sensitive to small differences in the spatial location of images falling on each retina. This endows them with the capacity to extract information about the depth of stimuli relative to the fixation point: a property known as ►disparity selectivity. Some binocular cells are tuned to respond maximally to stimuli placed on the fixation plane, whereas others prefer stimuli in front of or behind it. As a population, disparity-tuned neurons encode accurate information about depth, and therefore provide the cellular basis for the perceptual phenomenon of ►stereopsis. They also provide signals to the



Striate Cortex Functions. Figure 3 Intracortical circuitry within striate cortex. (*Left*) V1 is innervated by parvocellular, magnocellular, and koniocellular laminae of the LGN, which segregate in layers 4cβ, 4cα, and 4a 2/3 respectively. Even by the first intracortical synapse, these functional streams intermingle extensively. At the second intracortical synapse, increasing emphasis on horizontal projections further blends V1 signals. The relative strength of projections is not shown in this schematic diagram, nor is the diversity of cell types and classes comprising the intracortical wiring (Figure from [1]).

►brainstem for the ►oculomotor system to drive reflexive, ►disparity dependent► vergence movements that bring both foveas onto a common target in depth.

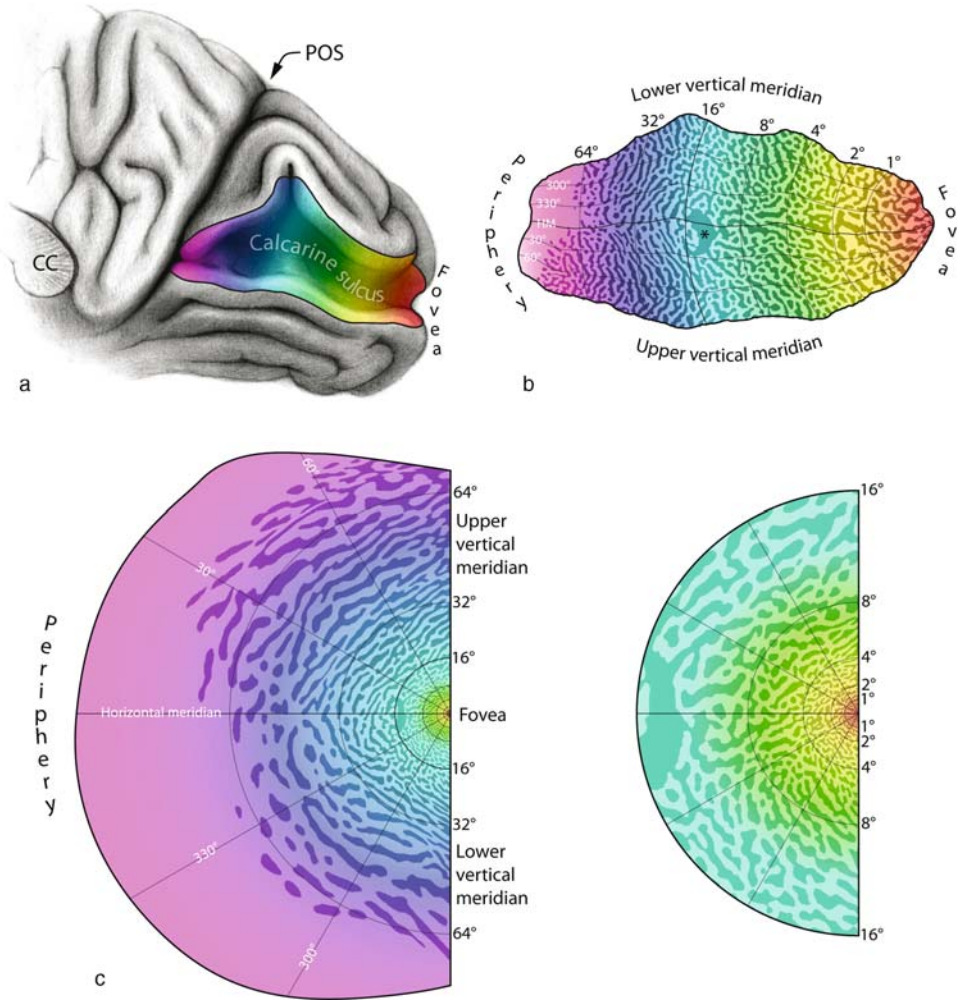
Specialized stimuli called random dot stereograms are often used to study stereopsis because they contain no depth cues except disparity. Random dot stereograms whose elements have opposite contrast in the two eyes (anticorrelated) do not give rise to a sensation of depth. However, cells in striate cortex are selective for the disparity in anticorrelated random dot stereograms. The difference between the responses of a striate cortex cell to correlated versus anticorrelated stereograms is an inversion of the disparity tuning curve. Thus, cells in striate cortex can exhibit disparity-tuned responses that do not lead to a perception of depth [4]. That the activity of cells in striate cortex does not necessarily correlate with perception is an interesting insight into striate cortex function. It is likely that networks of neurons from striate cortex to ►extrastriate areas (►extrastriate visual cortex) must also be activated to produce a conscious visual experience of depth.

Orientation Selectivity

Unlike cells in the LGN, which fire best to small spots of light, most cortical cells outside of layer 4cβ display ►orientation selectivity (Fig. 6). These cells respond optimally when the stimulus is presented at a specific orientation within the ►receptive field [5] (►Geniculostriate pathway; ►Visual cortical and subcortical receptive fields). Since they respond to ►contours, orientation-tuned cells comprise the elementary units necessary for form vision (►form perception). In striate cortex, orientation-tuned cells have a distinct functional organization: orientation tuning rotates gradually as the cortical sheet is traversed in a tangential direction. Optical imaging produces a strikingly ordered ►orientation map, containing singularities (as referred to as pin-wheeles) where neurons with different orientation preferences converge and saddle zones where transitions are more gradual (Fig. 7) [6]. Recent experiments have shown that neuronal maps can be described more accurately by invoking Fourier energy models, rather than simply orientation tuning [7].

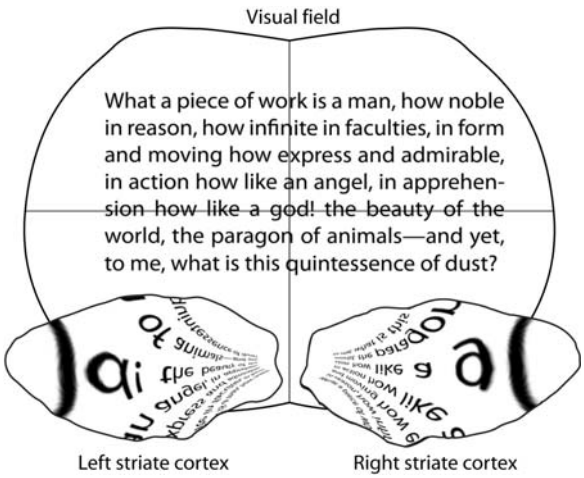
Direction selectivity

The detection of movement is a fundamental function of the visual system. Even animals with rudimentary vision are able to sense motion. In primates, motion vision is thought to be mediated by populations of cells whose responses are tuned to particular directions of stimulus movement. Such cells are less concerned with the orientation, form or color of the stimulus, but are often tuned to its speed. In some cases, the responses of direction selective cells are inhibited when the stimulus moves 180° opposite to the preferred direction. Since LGN cells do not exhibit direction selectivity, it must be generated within striate cortex by projections between multiple non-directional cells in specialized circuits. Direction selective cells are most prominent in layers 4b and 5/6 of striate cortex.

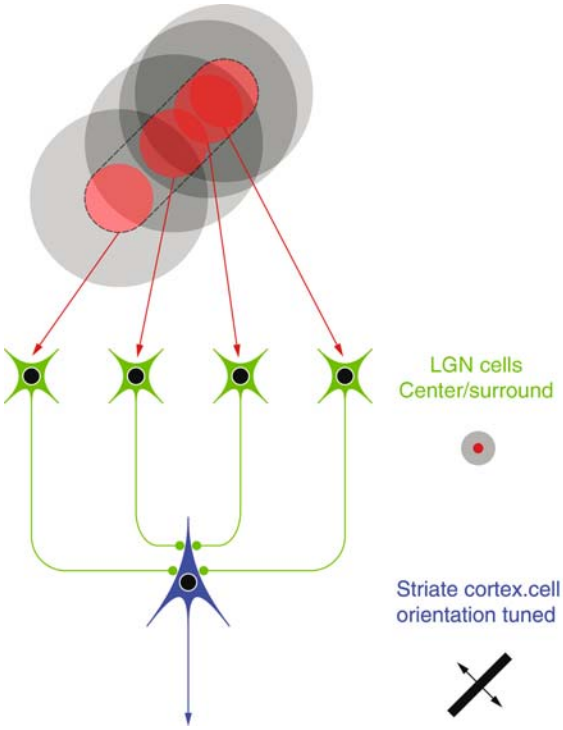


Striate Cortex Functions. Figure 4 The retinotopic map and ocular dominance column pattern in human striate cortex. (a) Medial face of the right hemisphere with the calcarine sulcus opened to expose striate cortex. Visual eccentricity is color-coded: the representation of the fovea is red and the far periphery is violet. cc = corpus callosum. (b) Unfolded striate cortex, showing retinotopic coordinates. The left eye's columns correspond to the pale regions. The blind spot appears as a solid oval (*). The representation of the monocular crescent also lacks columns, because the extreme temporal visual field is supplied by the contralateral eye alone. (c) Projection of striate cortex back onto the visual hemifield, demonstrating the magnification of central vision in the cortex. The central 16° are shown at higher magnification on the right. Since ocular dominance columns are relatively constant in size, their projection onto the visual field is greatly distorted by cortical magnification.

The direction-selective cells of striate cortex form the building blocks for motion vision (►Visual processing of motion). However, taken in isolation, their responses are not sufficient to describe completely the direction of motion of an object in the visual world. The receptive fields of direction-selective cells in striate cortex are small. Consequently, each cell can respond only to individual components of a moving object. Since the global direction of movement of an object is a sum of all of its component vectors, the responses of many striate cortex cells must be considered to gain an accurate measure of the object's direction; single cells in striate cortex are not equipped to provide this information. This is known as the ►aperture problem, because it arises when one observes the motion of an oriented contour through a small aperture that blocks the view of the ends of the line (Fig. 8). Direction-selective cells in layer 4b of striate cortex project directly to an extrastriate visual area, the medial temporal area (MT), also known as V5. MT cells are also direction-selective, but their receptive fields are larger than those of striate cortical neurons. Single MT cells receive input from multiple



Striate Cortex Functions. Figure 5 Projection of a visual image onto striate cortex. A greater amount of tissue is allocated to the representation of the central portion of the visual field in striate cortex, resulting in distertion of the text. The crosshair represents the center of gaze, which corresponds to the fovea in each eye. The left side of the visual field is reflected about a horizontal axis and projected onto the right hemisphere (and *visa-versa*). The increase in magnification from peripheral to central visual field in the cortical transformation of the image is logarithmic.



Striate Cortex Functions. Figure 6 The generation of orientation selectivity in striate cortex. The receptive fields of LGN cells have a center-surround structure. They each respond best to spots of light appearing at the center of the receptive field (*red*). Stimulation of the surround region (*grey*) inhibits the response of each cell. Here a population of center-surround cells (*green*) is shown, forming excitatory synapses onto a single cortical cell (*blue*). If a light impinges on the centers of the LGN cells simultaneously, the cortical cell will be activated maximally. The property of orientation selectivity may be derived from selective connections between such geniculate cells and cortical cells.

direction-selective cells in striate cortex, enabling them to be selective for the global direction of motion of an object in the visual world [8].

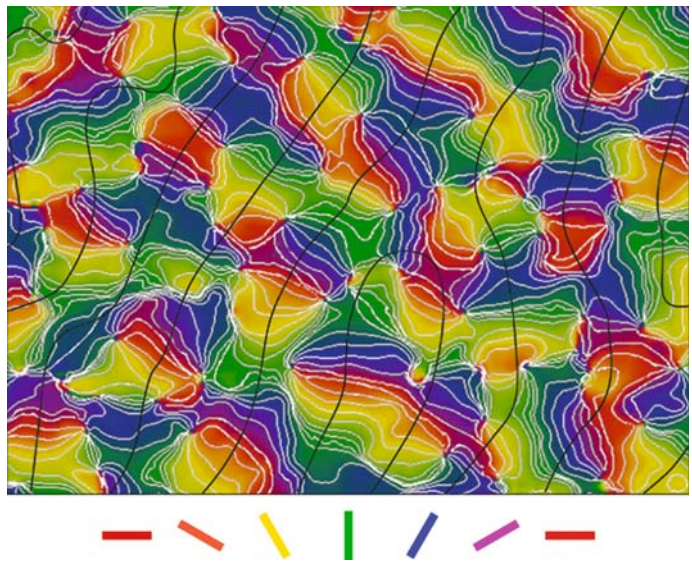
Color Selectivity

Cells influenced by the wavelength composition of stimuli are said to be color-selective, and provide information necessary for ►color perception (►Color processing). Many cells in striate cortex have a color-opponent, center-surround structure to their receptive fields. This organization reflects an imbalance in the spatial composition of inputs from different ►cone photoreceptors (►Photoreceptors) in the retina. Other cells display the property of double ►color opponency, i.e. their center and surround are maximally inhibited or excited by pairs of different wavelengths. Such cells are ideal for detecting chromatic borders. Some cortical cells are tuned to both the color and the orientation of stimuli.

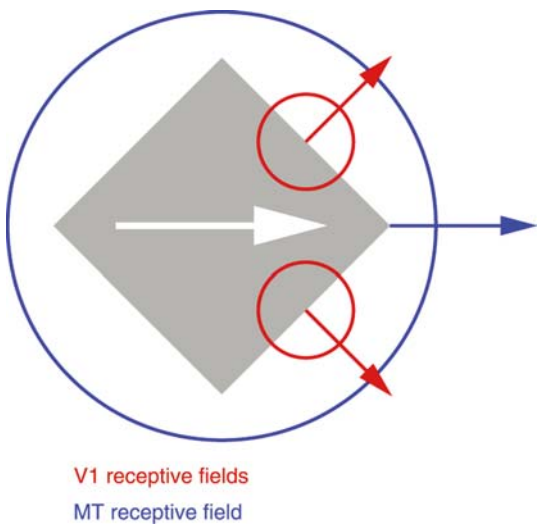
There is a diverse range of wavelength combinations present in natural illumination. The visual system must take into account the wavelength composition of the illuminating light to perceive accurately the color of objects. The process of discounting the influence of the illuminant is called ►color constancy. Cells in striate cortex respond only to the wavelength composition of reflected light rather than the perceived color of the surface [9], i.e. they do not exhibit color constancy. Consequently, "color" cells in striate cortex are more accurately referred to as wavelength-selective. The calculations necessary to provide color constancy must therefore be made in a higher visual area, such as V4. Just as for disparity and direction selective cells in striate cortex, wavelength selective cells encode a physical property of the world that does not necessarily correlate with perception.

Cytochrome Oxidase Architecture

Cytochrome oxidase is a metabolic enzyme present in mitochondria. The level of cytochrome oxidase is regulated by cell activity over a time scale of hours. In cortical tissue, the density of cytochrome oxidase is heterogeneous. In striate cortex, the input layers stain most richly, indicating that they have the highest rate of



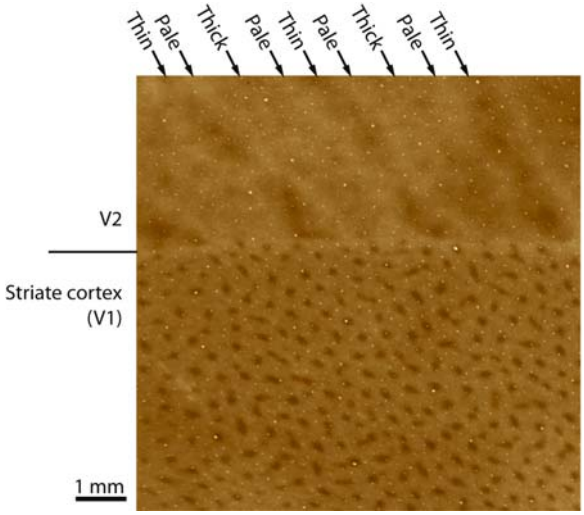
Striate Cortex Functions. Figure 7 Map of orientation preference in macaque striate cortex. Orientation selectivity is measured by optically imaging the cortical surface in the presence of a voltage-sensitive dye. Physiological response is color coded according to the orientation of the bar stimulus that generates the strongest signal. White lines are iso-orientation contours. Black lines represent the borders of ocular dominance columns. The iso-orientation lines converge at pinwheel centers which tend to be centered within ocular dominance columns (Data from [5]).



Striate Cortex Functions. Figure 8 The aperture problem. The direction of motion of an object (*the gray square*) cannot be determined by observing the direction of motion of individual local components. The global direction of motion of the object can be determined only from the sum of all the component vectors. Cells in striate cortex are able to signal the direction only of local contours because their receptive fields (*red*) are too small to sum vectors from the whole object. Cells in MT, however, have large receptive fields (*blue*) that are formed by combining the output from many cells in striate cortex. They are better equipped to solve the aperture problem and to encode the true direction of motion (*white arrow*) of the object.

physiological activity. In the tangential plane, cytochrome oxidase histochemistry reveals a regular array of patches, most prominently in layers 2 and 3 (Fig. 9). Also known as puffs or ►blobs, these patches span the full thickness of the cortex, except for layers 1, 4a and 4c. Patches are thought to constitute functional units within striate cortex, because their anatomical connections are distinct. In layers 2 and 3 they receive a direct projection from konio cells in the LGN (Fig. 2) (►Geniculo-striate pathway). Because this projection is monocular, and patches are located within the middle of ocular dominance columns, their cells usually show a strong response bias for one eye. Other physiological properties may correlate with cytochrome oxidase patches in striate cortex. For example, there is weak evidence that unoriented, color-selective cells are clustered within patches. Patches may also be aligned with pinwheel centers in the orientation map [6].

Visual area 2 (►area V2) also has a characteristic cytochrome oxidase architecture (Fig. 9), consisting of parallel stripes (see also ►Extrastriate visual cortex). Three distinct types of cytochrome oxidase stripes are present in the monkey, forming an alternating pattern orthogonal to the area V2 border. There are two classes of dark stripes – thick and thin – separated by pale stripes. The stripes in area V2 extend through the full thickness of the cortex. Each stripe class in area V2 has distinct functional properties, as shown by physiological recording. Moreover, the input and output connections of area V2 are organized by stripe type (Fig. 2).



Striate Cortex Functions. Figure 9 Functional compartments in V1 and V2 are interconnected. This tangential section was stained for cytochrome oxidase, revealing a regular array of patches in striate cortex and repeating cycles of thick-pale-thin-pale stripes in V2. Patches connect to thin stripes; interpatches supply thick and pale stripes.

Output

The main cortical projection target of striate cortex is V2. V1 cells in patches project to V2 cells in thin stripes (Fig. 2). This projection may be specialized for ►color processing, through a pathway that combines LGN ►parvocellular and ►koniocellular inputs in patches, and then proceeds via area V2 thin stripes to area V4. Cells located in the area V1 interpatch regions project to thick or pale stripes. A substantial proportion of interpatch cells have axons that bifurcate to terminate in both a thick and a pale stripe [1].

Cells in striate cortex also give rise to axons that project to extrastriate areas beyond area V2. Some ►direction-selective cells in layer 4b project directly to MT. Patch and interpatch cells in layers 2 and 3 project directly to area V4, an area thought to process color and form information that also receives input from V2's thin stripes and pale stripes. Thus, the outputs of striate cortex provide the origin for multiple cortical ►visual processing streams, each dividing further to become more specialized for specific visual modalities. Ultimately, these pathways result in a division of labor among multiple, functionally specialized regions of the brain.

Summary

Striate cortex contains cells that encode basic information about many visual modalities. However, the responses of these cells do not correlate directly with perception. Information must be passed from striate cortex to higher visual areas, where the activity of single cells provides a precise readout of sensory experience. Because signals pass through striate cortex *en-route* to these higher areas, lesions of striate cortex block the flow of information to the whole cortical visual system. Thus, while it may not signal perception *per se*, an intact striate cortex is necessary for conscious vision. Humans with lesions of striate cortex are capable of making only coarse visual discriminations in their blind fields. This preserved visual ability sometimes goes unnoticed by the subject until explicitly tested under laboratory conditions, prompting some investigators to call it "blindsight" (►Blindsight). The existence of such residual vision means that there must be an alternate route to higher cortical visual areas that bypasses striate cortex. Recently a neural pathway that could fulfill such a role was found in the macaque [10]. Small numbers of cells in the LGN were found to project directly to the extrastriate motion processing area MT. This pathway may be responsible for the rudimentary visual capacity to sense motion that persists in the absence of striate cortex.

Compared to more specialized extrastriate visual areas like MT, the functions of striate cortex are manifold. Perhaps it is best thought of as a refinery and distribution station, first extracting and purifying components of visual information, then routing them to appropriate specialized areas of the extrastriate visual system for more detailed analysis.

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Striatopallidum

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Synonyms

Basal ganglia; Cortico-subcortical reentrant circuit; Cortico-basal ganglia-thalamocortical circuit; Forebrain functional-anatomical system; Forebrain macrosystem

Definition

Striatopallidum refers to a general pattern of neural connectivity, originally limited to the basal ganglia (see essay on ►Basal Ganglia), relating the cerebral cortex to certain ►deep telencephalic nuclei, such as the ►caudate nucleus and ►putamen, which receive massive cortical ►projections and the ►globus pallidus, to which the caudate nucleus and putamen project. The globus pallidus in turn gives rise to outputs that (1) return to motor planning related parts of the cortex via relays traversing the thalamus (see essay on ►Thalamus) or (2) descend into the brainstem to terminate largely in the vicinity of motor related structures associated with the reticular formation of the brain (see essay on ►Reticular Formation). During the past 30 years the meaning of the term striatopallidum has broadened, as cortico-subcortical relationships resembling those of basal ganglia have been described in association with a number of structures classically grouped with the ►limbic system (see also ►Limbic System), including the ►nucleus accumbens, ►olfactory tubercle, ►amygdala and ►bed nucleus of the stria terminalis and some additional territories in the ►basal forebrain.

Characteristics

The prototypic pattern of neural connections in the striatopallidum, as alluded to in the definition given above, is classically associated with the ►corpus striatum, as in e.g., Nauta and Mehler's classic description of the connections of the ►lentiform nucleus in the monkey [1]. The term striatum refers to visible striations caused by axon fascicles fanning through the corpus striatum, which comprises the caudate and lentiform nuclei. The lentiform nucleus in turn consists of the putamen and globus pallidus. The cerebral cortex of projects massively to the caudate nucleus and putamen, which both comprise mostly medium size, densely spiny, inhibitory neurons, are structurally and physiologically similar and project massively to the globus pallidus. The globus pallidus differs from the caudate nucleus and putamen structurally and functionally and gives rise to the trans-thalamic and descending outputs from the complex. For unknown reasons, the term striatum came to be reserved for the caudate and putamen, distinguishing them from the globus pallidus, or pallidum. Although the deep telencephalic nuclei or basal ganglia, correctly also include the amygdala (also called the amygdaloid complex) and septal nuclei, common usage of the term basal ganglia became limited to the corpus striatum. Hence, the meaning of the term striatopallidum came to approximate that of the term basal ganglia.

A number of more or less epic conceptual developments during the past 30 years have served to broaden the definition of the basal ganglia, resulting in a gradually increasing usage of the term striatopallidum and generalization of its meaning. The first of these occurred during the early 1970's with the discovery that the olfactory tubercle in the rodent is occupied by neural tissue that, in terms of intrinsic character and extrinsic connections, is striatal [2]. The striatum in the olfactory tubercle, which came to be called ►ventral striatum, was observed to interdigitate with another distinct district in the tubercle containing neural tissue of pallidal character representing a rostroventral extension of the globus pallidus protruding into the basal forebrain and deep parts of the tubercle. Cortical inputs to the striatal district of the tubercle, which occupies its superficial and intermediate parts, arise in the primary olfactory (piriform) cortex. The striatal district of the tubercle projects to the overlying so-called ►ventral pallidum, which in turn projects to the ►mediodorsal nucleus of the thalamus [3]. These relationships, combined with the observation that the nucleus accumbens gives rise to a striatopallidal projection to an adjacent part of the ventral pallidum [4], served to confirm the longstanding, tentative characterization of the nucleus accumbens as part of basal ganglia [5].

These findings broadened the concept of basal ganglia. Now the entire cerebral cortex, including the olfactory cortex and hippocampus would be regarded as utilizing mechanisms provided by basal ganglia circuitry. The previously held concept that the cortico-subcortical relationships in brain can be split into distinct limbic (see also synopsis on ►Limbic System) and ►extrapyramidal (basal ganglia) sectors was no longer tenable. On the contrary, the parallel disposition of the newly discovered cortico-basal ganglia-thalamocortical circuit traversing ventral striatum, ventral pallidum and the ►thalamic mediodorsal nucleus and the "classical" basal ganglia circuit involving, e.g., the caudate nucleus and putamen, globus pallidus and anterior ►ventral tier thalamic nuclei (VA-VL), eventually led to a more refined appreciation of parallel, segregated basal ganglia-thalamocortical circuits ([6], see also essays on ►Basal Ganglia and ►Cortico-Subcortical Reentrant Circuits), an appreciation laden with implications for the

diagnosis and treatment of neuropsychiatric illness [7]. Furthermore, the continuity across dorsal and ventral striatopallidum of the massive terminations of the ventral mesencephalic dopaminergic projections energized fields of inquiry concerned with dopamine and its receptors, including neuropsychiatry (in particular as related to schizophrenia) and drug abuse research.

A second major conceptual "advance" was described in a paper that became quite influential essentially by reasserting the validity of some neglected concepts from the classical literature ([8] and references therein). These authors recapitulated the venerable, but largely forgotten, concept that the amygdaloid complex comprises two distinct sectors (see essay on Amygdala). One is a cortical-laterobasal part of the amygdala that is cortex-like in terms of its intrinsic cellular and neurochemical composition and extrinsic connections. The second is a centromedial part that includes the ►central (CeA) and ►medial nuclei (MeA) of the amygdala. Some additional structures exhibiting strikingly similar tissue composition and continuity with the CeA and MeA include the bed nucleus of the stria terminalis (BST), similarly differentiated and organized neuronal groups dispersed within the ►stria terminalis and certain basal forebrain territories extending between the centromedial amygdala and BST, all of which together came to be called ►extended amygdala. A central division of the extended amygdala gets its major descending inputs largely from the cortical-like laterobasal complex of the amygdala and gives rise to outputs to the ►lateral hypothalamus and brainstem somatic and autonomic motor effectors. A medial division of the extended amygdala gets descending inputs largely from the cortical nucleus of the amygdala and projects mostly to neuroendocrine effectors in the medial hypothalamus (see essay on ►Hypothalamus). While acknowledging that the extended amygdala exhibits features that strikingly resemble the intrinsic organization and extrinsic connections of striatopallidum, Alheid and Heimer [8] opted to emphasize those aspects of tissue composition and function that distinguish extended amygdala from striatopallidum and conceived of the two as distinct ►basal forebrain functional-anatomical systems. They also mentioned that additional evaluation would probably reveal the ►lateral septum to be an input (striatal) structure of yet another distinct striatopallidal-like basal forebrain functional-anatomical system receiving massive hippocampal inputs.

A couple of investigators subsequently adopted the fundamental tenets articulated by Heimer and Alheid so completely as to vigorously advocate that the cortico-subcortical relationships of the extended amygdala be regarded without qualification as striatopallidal [9,10]. One effect of these papers has been to further increase the currency of the term striatopallidum in contemporary neuroscience intercourse.

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Striatum

S

Definition

The striatal components of the striatopallidal complexes. In mammalian terminology, the dorsal striatum is also known as the caudate nucleus and putamen. It receives glutamatergic cortical inputs and dopaminergic inputs from the substantia nigra, and it projects to the globus pallidus. The ventral striatum consists of the nucleus accumbens and the olfactory tubercle. It projects to the ventral pallidum. The striatopallidal complexes are involved in circuits that control the suppression and/or initiation of movements.

►Evolution of the Diencephalon
►Evolution of the Dorsal Thalamus
►Striatopallidum

Striatum, Dorsal

Definition

Caudate nucleus and putamen as part of the basal ganglia.

►Basal Ganglia
►Striatopallidum

Striatum, Ventral

Definition

Part of the striatal complex comprising the ventral parts of the caudate nucleus and putamen, the accumbens and striatal districts in the olfactory tubercle, i.e. containing a dense accumulation of medium-sized, densely spiny GABAergic neurons.

►Basal Ganglia
►Striatopallidum

Striola

Definition

A central specialized region of otoconia and receptor cells that lies centrally in the otolith maculae.Within the striola lies the imaginary reversal line, where hair cells of opposing polarity reside.

►Peripheral Vestibular Apparatus

Stroke

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Synonyms

Cerebrovascular disease; Cerebrovascular accident; CVA, Brain attack

Definition

Stroke is defined as rapidly developed clinical signs of focal (or global[1]) disturbance of cerebral function lasting more than 24 h (unless interrupted by surgery or death), with no apparent cause other than a vascular origin: it includes patients presenting with clinical signs and symptoms suggestive of subarachnoid haemorrhage, intracerebral haemorrhage or cerebral ischaemic necrosis [1].

Characteristics

Epidemiology

Stroke is the second leading cause of lost disability-adjusted life years in high-income countries and of death worldwide, after ischemic heart disease; in 2001, an estimated 5.4 million people died from stroke worldwide [2]. In the USA, there are approximately 700,000 strokes each year, killing over 150,000 people; almost a third of stroke victims are younger than 65 years of age [3]. In Western societies, 80% of strokes are ischemic, and the remaining 20% are caused by hemorrhages. One-month case fatality rate for stroke ranges between 8 and 40%, with mortality highest for hemorrhagic strokes and in developing countries [3].

Etiology/Subtypes

A stroke is caused by disruption of blood supply to a part of the brain. Brain tissue that no longer receives its blood supply can die within a few hours unless something is done to stop the damage. Blockage of an artery leads to *ischemic stroke*. If this blockage lasts less than 24 h, with complete resolution of symptoms, it is called a transient ischemic attack (►TIA). Strokes due to bursting of an artery are called hemorrhagic strokes. In *intracerebral (or intraparenchymal) hemorrhages*, the blood clot forms in the brain itself, while *subarachnoid hemorrhages* are due to bleeding within the membranes surrounding the brain, usually around the base of the brain. Another, rarer form of stroke can occur when a vein (that drains blood out of the brain) is blocked. This is called a *venous stroke*. ►Hypertension is probably the most important modifiable risk factor for stroke: continuous high pressure in vessels results in atherosclerotic plaque formation and endothelial damage.

- *Ischemic Stroke (IS)* represents about 80% of all strokes and is caused by occlusion of an artery supplying the brain. This can be one of the large arteries in the neck or the base of the brain or in small arteries inside the brain itself. The artery occludes either locally or by a blood clot that formed elsewhere in the body and traveled to the brain

[1] Global: this applies to patients with subarachnoid haemmorrhage or deep coma but excluding coma of systemic vascular origin such as shock, Stokes-dams syndrome or hypertensive encephalopathy.

through the artery (►embolic infarct, see ►ischemic stroke). The main modifiable risk factors for ischemic stroke include arterial hypertension, ►atrial fibrillation, cigarette smoking, ►hyperlipidemia, ►diabetes mellitus, and a previous stroke or transient ischemic attack (TIA).

- *Intracerebral hemorrhage (ICH)* is caused by bleeding of a blood vessel inside the brain parenchyma and accounts for approximately 15% of strokes. Damage is caused both by the impaired blood supply and by the pressure on the brain from the hematoma. The most common cause of intracerebral hemorrhage is high blood pressure. Abnormally formed blood vessels in the brain can be another cause, especially in younger people.
- *Subarachnoid hemorrhage (SAH)* results from bleeding of an artery into the membranes surrounding the brain, usually around the base of the brain. Less than 5% of all strokes are SAH. The most frequent cause of subarachnoid hemorrhage is bleeding from an aneurysm. An aneurysm is a bulge of an artery caused by weakening and ballooning of a short portion of the vessel wall. High blood pressure, smoking, excessive alcohol-intake and a family history of burst aneurysms can increase a person's risk of subarachnoid hemorrhage [4].
- *Venous stroke* is caused by a blockage of the veins that allow blood to drain out of the brain (cerebral vein or venous sinus thrombosis). This causes a backpressure that can result in either ►ischemia or hemorrhage. Venous stroke most commonly occurs in the setting of a medical or genetic condition that increases a person's tendency to form blood clots (►hypercoagulable state). Severe dehydration or infection of the sinuses of the head can also predispose to venous stroke. Less than 1% of strokes are venous.

Signs and Symptoms

The symptoms of stroke depend on the type of stroke and the area of the brain affected. They are usually unilateral, occurring on the side of the body opposite to the affected side of the brain. As is implied in the word "stroke," symptoms typically develop suddenly and rapidly.

Common symptoms include weakness or numbness; confusion, trouble speaking or understanding; loss of vision in all or part of the visual field; loss of balance or coordination, trouble walking or dizziness. Loss of consciousness, headache, and vomiting at the onset occur more often in hemorrhagic stroke and venous stroke because of increased intracranial pressure (ICP).

Seizures may occur in up to 20% of ischemic, 30% of hemorrhagic, and in 40% of patients with venous stroke [5,6,7].

A combination of symptoms caused by impairment of one arterial territory is termed *vascular syndrome*, for example a posterior cerebral artery (PCA) syndrome includes visual problems, as the PCA supplies the visual ►cortex (see "ischemic stroke, vascular syndromes").

Differential Diagnosis

See: Table 1

Diagnosis

- Deficits are identified by a careful ►neurological examination, and the severity assessed using one of the standardized stroke scales, i.e., the National Institute of Health Stroke Scale (http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf).
- ►Laboratory workup should include basic metabolic panel with glucose, complete blood count, coagulation parameters and an EKG to identify arrhythmias and/or signs of acute or previous myocardial infarction. If this is abnormal, markers of cardiac ischemia should be checked. In the appropriate setting, hypercoagulable workup and vasculitis testing may be indicated, as well as hepatic function tests, toxicology screen, blood alcohol level, pregnancy test, arterial blood gas. If subarachnoid hemorrhage is suspected and CT scan shows no blood, a lumbar puncture is required.

Stroke. Table 1 Differential diagnosis of acute stroke presentation

• TIA	• CNS Infection
• Ischemic Stroke	• Tumor (with sz)
• Intracerebral Hemorrhage	• Peripheral nerve lesions
• Subdural Hematoma (small)	• Metabolic abnormalities
• Focal seizure	• Hyper/hypoglycemia
• Post-ictal Todd's paralysis	• Anamnestic deficit
• Syncope/Presyncope	• Esp. infected elderly
• Complicated migraine	• Toxic States
• Transient confusion in the elderly and/or demented	• Hypertensive Encephalopathy
• Vertigo of peripheral origin	• Conversion disorder

- ►Imaging: Non-contrast head CT remains the most commonly used imaging modality in the acute setting, because it is fast, easy, widely available and less expensive than MRI. MRI is more sensitive for detection of acute ischemic stroke and is better at identifying acute, small cortical, small deep, and posterior fossa infarcts, and at distinguishing acute from chronic stroke [5]. CT- or MR-Angiography is a helpful noninvasive method to identify any cervical or intracranial stenoses and can detect aneurysms in 95% of the cases [4]. Venous sinus thrombosis can usually be detected on MRI, but if there is clinical suspicion for it, CT- or MR-Venogram should be obtained.
- ►Ancillary tests
  - Cardiac monitoring for at least 24h after the event, to identify arrhythmias.
  - Echocardiogram is an ultrasound study of the heart that can look for any source of cardioembolism, for example wall motion, valvular abnormalities, or a clot inside the heart. "Bubble studies" can identify a ►cardiac shunt as a cause of ►paradoxical embolism.
  - Ultrasound of the arteries in the neck and brain (carotid ultrasound, transcranial ultrasound) evaluates the presence and degree of vessel narrowing and may identify clots traveling through that vessel.
  - With conventional angiography, the arteries and veins of the brain are best visualized and most vascular abnormalities can be detected. At the same time, it can be used for interventions such as closure of an aneurysm or opening of a blocked artery. Being an interventional procedure, it does have it's own risks, which should be weighed against the potential benefit.

Acute Management

The sooner a stroke is treated, the better the chance of recovery. Patients treated in hospitals with a dedicated Stroke Team or Stroke Unit and a specialized care program for stroke patients have improved odds of recovery. Thus, if a stroke is suspected, emergency medical services should be activated immediately [5]. The treatment of stroke is a rapidly evolving discipline and there are a number of modalities both proven and experimental that are effective in minimizing the damage and improving the outcome from stroke. The details of the treatment of stroke are outside of the intended scope of this encyclopedia.

Stroke Prevention

Almost a third of all strokes are recurrent attacks [3]. Thus, careful attention needs to be paid to all vascular risk factors. The ways to reduce the risk of a recurrent stroke are very similar to those that can prevent a stroke in the first place.

- Life style/diet: people with any vascular risk factors or a history of a stroke or a heart attack should limit their daily alcohol use, try to maintain their ideal body weight, exercise daily and stop smoking [8].
- Blood pressure (BP): hypertension, defined as a BP of 140/90mmHg or higher for an extended period of time, is the most important modifiable risk factor for stroke, and reduction of BP reduces this risk. Choice of BP-lowering agent is still uncertain but diuretics and/or ACE-inhibitors are recommended [8].
- ►Diabetes mellitus: The risk for stroke (especially ischemic stroke) in people with diabetes can be substantially reduced with tight control of blood glucose. People with diabetes should also be particularly weary of other risk factors, such as hypertension and hyperlipidemia.
- ►Hyperlipidemia: In patients with vascular disease or a history of an ischemic stroke, life style modification, diet and medications are recommended to lower cholesterol levels. Statins have been shown to reduce the risk of ischemic stroke but slightly increase that for hemorrhagic stroke [9].
- Antiplatelet therapy: Patients, who have had a non-►cardioembolic ischemic stroke, should take ASA to prevent stroke recurrence or any other vascular event. The use of other antiplatelet agents (dipyridamole, clopidogrel) may be considered as additional or alternative therapy.
- Anticoagulation is indicated in patients with atrial fibrillation (usually indefinitely), in those where a clear tendency for forming blood clots was found (indefinitely), and in patients with venous thrombosis (for six months, or longer if a presdisposing factor has been identified) [7]. Anticoagulation is relatively contra-indicated after intracerebral hemorrhage.
- After a hemorrhagic stroke, the use of blood thinning medication of any kind (antiplatelet or anticoagulation agents) is associated with a risk of another hemorrhage, but needs to be weighed against the risk of a thrombotic event on an individual basis.

Prognosis

Prognosis depends on the patient's age, type of stroke and how severe the stroke is at the onset. 20% of victims die within one month of having an ischemic stroke, 40% after an intracerebral hemorrhage and 30% after subarachnoid hemorrhage. The majority of survivors have some long-term disability; 50–70% of stroke survivors do become independent, 15–30% are permanently disabled and 20% live in a nursing home at three months after onset [3].

Stroke Rehabilitation

Early stroke rehabilitation services are very effective in reducing long-term disability and improving quality of life as well as reducing overall health care costs [10].

Rehabilitation doctors, Speech and Language therapists, Physical and Occupational therapists should be involved early on in the care of a stroke patient.

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Stroma

Definition

The connective tissue network (of endomysium, perimysium and epimysium) within a muscle. The word of Greek origin actually refers to a supporting function.

►Intramuscular Myofascial Force Transmission

Structure-from-Motion

Definition

The perception of three-dimensional structure from motion occurs when, for example, a two-dimensional pattern of dots moves in such a way that the dot trajectories are consistent with the retinal image projected by rotation of a three-dimensional object.

►Visual Motion Processing

Stumbling-corrective Reaction

Definition

A reflex initiated in walking mammals to lift the leg over an obstacle when the leg contacts the obstacle.

►Locomotor Reflexes

Stupor

Definition

Stupor denotes a state, from which the patient can be aroused by very strong stimuli, but he/she tries to avoid uncomfortable stimuli, and the verbal responses are absent or slow.

Subacute Sclerosing Panencephalitis (SSP)

Definition

SSP is a progressive, debilitating, and fatal brain disorder caused by infection with a mutant measles (rubeola) virus. A mutant virus is one that has undergone genetic changes (mutations).

Subcortical Infarction

Definition

Subcortical infarcts are located in the basal ganglia, internal capsule, or corona radiata and are thought more commonly to be caused by hypertension and diabetes and less commonly by cardiac or artery-to-artery embolism.

►Ischemic Stroke
►Stroke

Subcortical Visual Shell

Definition

Twelve contiguous retinorecipient nuclei of the thalamus and midbrain, not including the terminal nuclei of the accessory optic system. In order from ventrolateral to dorsomedial they are the ventral lateral geniculate n., intergeniculate leaflet, dorsal lateral geniculate n., lateral posterior n., posterior limitans n., nucleus of the optic tract, anterior pretectal n., posterior pretectal n., medial pretectal n., commissural pretectal n. and, positioned dorsocaudally, the superior colliculus.

►Intergeniculate Leaflet

Subgranular Layer of Hippocampus

Definition

The subgranular layer of the hippocampus is the region of the dentate gyrus between the granular cell layer and the hilus. Neural stem or progenitor cells (NSPCs) reside in this region. Neuronal progeny of these NSPCs migrate varying distances into the granular cell layer, extending their dendrites and axons into the molecular layer and CA3, respectively.

Subiculum

Definition

The subiculum is a band of cells that deep in the hippocampal sulcus continues the CA1 cell layer of Ammon 's horn and, for its part, joins the cell band of the presubkulum. It thus marks the transition from hippocampus to the area surrounding hippocampus. In the subiculum most efferents arise from the hippocampus (-> fornix), afferents come from the entorhinal area primarily.

►Telencephalon

Subjective Contour

Definition

►Illusory Contour

►Perceptual Filling-In

Subjective Day/Night

Definition

Used in circadian biology when a test subject is housed in constant conditions where circadian rhythms adopt their endogenous, free-running period. Subjective day defines the portion of the endogenous circadian rhythm that would normally be associated with the light phase (daytime). Subjective night defines the portion of the endogenous circadian rhythm normally associated with the dark phase (nighttime). The behaviorally active phase of diurnal organisms occurs during the subjective day whereas it occurs during the subjective night for nocturnal organisms.

►Chronobiology
►Circadian Rhythm

Subjectivity

Definition

Subjectivity may be attributed to (i) a particular mental event, because it is experienced by just one person, who has a priviledged access to it; (ii) types of [→] phenomenal consciousness (qualia), because only if one has had such experiences does one know what it is

like to have them; (iii) the entity (subject) that is in mental states, esp. if one takes it to differ in kind from physical objects; (iv) [→] self-consciousness because it is the awareness a person has of herself as herself.

►Argument
►Logic

Sub-Modality (also Quality)

Definition

Sub-modalities (qualities) refer to subclasses of modalities, such as, in the visual system, perception of shades of grey from black to white and of different colors, or in the tactile domain, differentiation of pressure, touch and vibration sensations.

►Sensory Systems

Submusosal Plexus

Definition

The submucosal plexus is a division of the enteric nervous system, a plexus of small ganglia and connecting nerve fiber bundles that lies within the submucosal layer, between the external musculature and the mucosa of the small and large intestines, forming a continuous network from the duodenum to the internal anal sphincter.

►Autonomic/Enteric Reflexes
►Enteric Nervous System

Subpallial Amygdala

Definition

Part of the amygdala that derives from the subpallium, i.e, the ventral part of the telencephalon. It is composed by nuclei of striatal and pallidal origin in all tetrapods.

►Evolution of the Amygdala: Tetrapods

Subparaventricular Zone

Definition

A loosely defined population of neurons that resides directly ventral to the paraventricular nucleus (PVN) in the anterior hypothalamus. Neurons in this region receive dense projections from the suprachiasmatic nucleus, the brain's circadian pacemaker, as well as projections from other hypothalamic nuclei. It is hypothesized that these neurons integrate circadian and metabolic information.

►Circadian Pacemaker
►Paraventricular Nucleus (PVN)
►Suprachiasmatic Nucleus
►Ventrolateral Preoptic Nucleus (VLPO)

Substance P

Definition

Substance P is a member of a group of polypeptides known as neurokinins or tachykinins. Substance P as well as neurokinin NK1 receptors have been detected in vagal afferent neurons in the area postrema, nucleus tractus solitarii and dorsal motor nucleus of the vagus. Substance P has been shown to increase the firing rate of neurons in the area postrema and nucleus tractus solitarii and to produce retching when applied directly to these areas in animal studies. Substance P is also a co-transmitter in nociceptive group C afferent fibers and is crucially involved in central sensitization.

►Area Postrema (AP)
►Hyperalgesia and Allodynia
►Nucleus of the Solitary Tract

Substantia Gelatinosa (of Roland)

Synonyms

►Gelatinous substance

Definition

A small-celled area in the posterior horn of the spinal cord. Pain fibers synapse here.

►Medulla Spinalis

Substantia Gelatinosa of the Spinal Nucleus of the Trigeminal Nerve, Caudal Part

Definition

Substantia gelatinosa (of Roland) at the level of the spinal nucleus of the trigeminal nerve, caudal part. Pain fibers synapse here.

►Medulla Spinalis

Substantia Innominata

Definition

The broad expanse of ventral forebrain territory situated beneath the globus pallidus (sublenticular substantia innominata) and anterior commissure (sublenticular substantia innominata) lateral to the lateral preoptic and lateral hypothalamic areas. Rostrally, it tapers into the deep layers of the olfactory tubercle and caudally it merges into the anterior amygdaloid area, ending where the internal capsule reaches the ventral surface of the brain to form the cerebral peduncle. The term, which implies an indeterminate neural organization, has lost some currency with the descriptions of the ventral striatopallidum, extended amygdala and magnocellular basal forebrain system, which occupy territory within the so-called substantia innominata.

►Striatopallidum
►Ventral

Substantia Nigra

Definition

The substantia nigra is the largest nucleus of the ►Mesencephalon. A distinction is made between:

- Substantia nigra, pars compacta
- Substantia nigra, pars reticulata

There is a very close, possibly even reciprocal point-to-point, connection between corpus striatum and substantia nigra. The substantia nigra, pars compacta, plays an important role in Parkinson's disease.

►Mesencephalon

Substantia Nigra, Pars Compacta

Definition

The dorsal, large-celled segments of the substantia nigra are globally known as pars compacta. The large, polygonal and dopamine-producing cells lie close together. Their very fine dopaminergic efferents form direct synaptic contacts with striatonigral projection neurons. This projection plays an important role in the initiation of voluntary, motor programs.

Parkinson's disease is characterized by progressive loss of neurons in the substantia nigra, pars compacta, degeneration of their ascending projections and reduction of the dopamine content in the corpus striatum. Symptoms include rigor, tremor, akinesia.

►Mesencephalon

Substantia Nigra, Pars Reticulata

Definition

The ventral, small-celled sections of the substantia nigra are called the pars reticulata. The cells (cell group A9) are less densely packed, and have a structure similar to that of the inner segment of the globus pallidus. They receive topically organized afferents from the caudate nucleus and globus pallidus (GABA, substance P, dynorphin, enkephalin). Efferents pass to the substantia nigra, globus pallidus, caudate nucleus, and putamen.

►Mesencephalon

Substantia Nigra: Role in Eye Movements

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Definition

The substantia nigra (SN), which is located in the ventral part of the midbrain, is either a part of the basal ganglia or closely associated with the basal ganglia.

Its contribution to eye movements is mentioned in the section "►Basal ganglia – Role in eye movements".

Characteristics

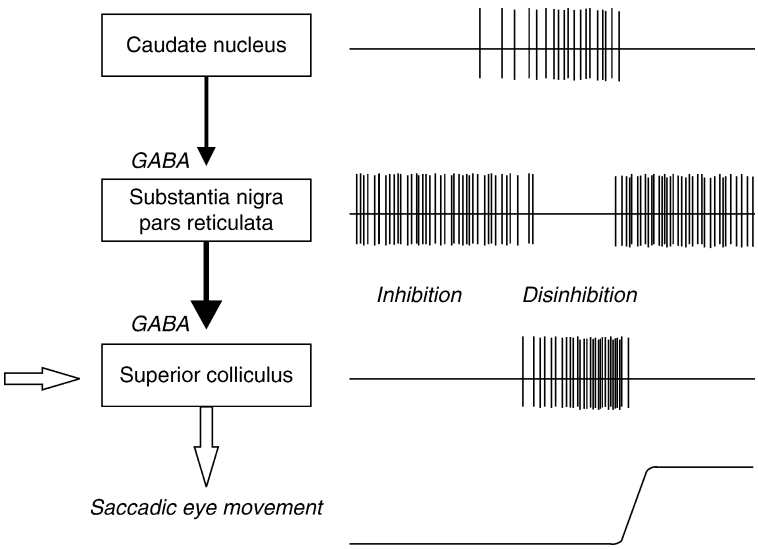
Lower Level Components

The substantia nigra (SN) is composed of two parts: pars reticulata (SNr), which contains GABAergic neurons, and pars compacta (SNc), which contains dopaminergic (DA) neurons. The relation of the SN to eye movements was first suggested by anatomical studies showing that some neurons in the SNr project to the ►intermediate layer of the superior colliculus (SC) [1] (Fig. 1). The SC in mammals is known to be crucial for orienting of the eyes and head toward an object of interest. An equivalent structure, which is called the optic tectum, is universally present in other vertebrates and is under the control of the homologue of the basal ganglia [2]. Thus, the role of the SN (or the basal ganglia) in eye movements should be considered in a larger framework of animal behavior in which orienting is crucial for survival.

Higher Level Processes

Neurons in the SNr are characterized by their rapid and tonic firing. Their firing frequency is usually between 40 and 100 spikes/sec in monkeys [3]. Neurons in the internal segment of the ►globus pallidus, many of which are related to skeletal movements, also fire rapidly and tonically. Thus, the high background activity is common to virtually all output neurons of the basal ganglia. Furthermore, virtually all of them are GABAergic. These facts indicate that neurons that receive outputs of the basal ganglia should be kept inhibited by them. The functional importance of the basal ganglia-induced inhibition can be demonstrated experimentally [3]. The inhibition can be reduced or eliminated by injecting a small amount of a GABA agonist (muscimol) into the SNr, because SNr neurons have a high density of GABA receptors and therefore muscimol would inhibit their firing. After muscimol injection in the SNr, animals can no longer maintain stable eye position and make saccades continually and probably involuntarily. This happens to all animals tested: monkeys, cats, and rats. Rats, compared with monkeys, exhibit a wider range of involuntary movements in addition to eye movements. A similar phenomenon occurs for skeletal movements when muscimol is injected in the globus pallidus internal segment. These findings may be relevant to the fact that patients with basal ganglia dysfunction usually exhibit some type of involuntary movements, such as tremor, dyskinesia, dystonia, ballism, and chorea. These involuntary movements may be caused by a reduction of the basal ganglia-induced inhibition. The reduction of inhibition could be sustained or phasic (possibly with rhythms).

However, the sustained inhibition alone can hardly be a motor control mechanism. Neurons in the SNr actually change (usually decrease) their firing rates in preparation for ►saccadic eye movement [3]. Many SNr neurons stop firing in response to a visual stimulus



Substantia Nigra: Role in Eye Movements. Figure 1 Tonic inhibition and disinhibition of superior colliculus neurons by the basal ganglia. The tonic inhibition of the superior colliculus (SC) by the substantia nigra pars reticulata (SNr) can be reduced by another inhibition from the caudate nucleus (CD) to the SNr. Both CD-SNr and SNr-SC connections are GABAergic. The level of the SNr-SC inhibition determines the likelihood of the occurrence of saccade which is triggered by excitatory inputs from saccade-related areas in the cerebral cortex (not shown).

if the animal is ready to make a saccade to it (Fig. 1). Other neurons do so just before the saccade. Many of these SNr neurons project to the intermediate layer of the SC [3] and have inhibitory synaptic contacts with saccadic burst neurons [4]. This means that the SNr-induced tonic inhibition on SC neurons is removed or reduced before saccade. Note that saccadic neurons in the SC receive excitatory inputs from many brain areas, especially saccade-related cortical areas: the ►frontal eye field (FEF), ►supplementary eye field (SEF), and ►lateral intra-parietal area (LIP). These excitatory cortical inputs, together with the SNr-induced disinhibition, would make SC neurons fire in a burst and the signal is sent to the ►brainstem saccade generators. Note, however, SNr neurons may increase their activity before saccade. In such a case, the SC would be less likely to generate a signal to induce saccades.

In short, the SNr-induced inhibition on SC neurons acts as a gate for saccade generation (Fig. 1). SC neurons are constantly bombarded by excitatory inputs from many brain areas because there are so many objects that can attract our attention and gaze. However, these inputs are often incapable of inducing a burst of spikes in SC neurons due to the SNr-induced tonic inhibition. Only when the SNr-induced inhibition is reduced, SC neurons would exhibit a burst of spikes reliably. This is probably a very efficient mechanism to select an appropriate action in a particular context.

Selection of action is meaningful only if the criteria of selection are identified. There are at least three criteria for the selection of information by the SNr. First, SNr neurons select the spatial vector of saccade by reducing their activity only before saccades that have a certain range of direction and amplitude. However, this selection is common to the excitatory inputs from cortical eye fields, and is unlikely to add a new feature to the signals carried by SC neurons. Second, SNr neurons may select saccades directed to the remembered location of a visual stimulus (►memory-guided saccades) rather than saccades directed to a visual stimulus (►visually guided saccades). This is based on the experimental observation, indicating that some SNr neurons reduce their activity selectively before memory-guided saccades [5]. Third, SNr neurons may select saccades that are directed to a spatial location where a larger ►reward is expected [6]. This is shown by the experiment in which the amount of reward is associated unequally among possible target positions. Many SNr neurons reduce their activity more strongly before a saccade to the location where a larger reward is associated. It is unknown how unique the second and third criteria are to the SNr, compared with other areas that provide the SC with inputs. This is a very important question on the function of the SNr and consequently the basal ganglia in general.

Lower Level Processes

How is the activity of SNr neurons generated? First, the rapid and tonic firing is thought to be caused by two factors: the intrinsic membrane properties of SNr neurons and the excitatory input from the ►subthalamic nucleus (STN). Second, the decrease in firing rate of SNr neurons is caused by GABAergic inhibitory inputs from the caudate nucleus (CD) [7] (Fig. 1). While the CD-SNr inhibitory connection is known anatomically, its function is confirmed physiologically by the presence of neurons in the CD that increase in firing rate before saccade, and the inhibition of SNr neurons in response to electrical stimulation of the saccade-related region in the CD (see section ►Caudate – Role in eye movements). Third, the cause of the increase in firing of SNr neurons is less certain. Two likely causes, based on anatomy, are the excitatory input from the STN and the reduction of the inhibition from the external segment of the globus pallidus.

As mentioned at the beginning, another part of the substantia nigra (SN) is pars compacta (SNc). While neurons in the SNr are GABAergic, neurons in the SNc are dopaminergic [8]. Neurons in the SNc are a significant constituent of midbrain dopaminergic neurons; others include the ventral tegmental area and the area dorsal to the SNc. A majority of SNc neurons project to the striatum, CD and putamen, and make synapses on projection neurons and interneurons. The importance of midbrain dopaminergic neurons in motor control is highlighted by Parkinson's disease, in which most of these dopaminergic neurons degenerate. Eye movements are also impaired in human Parkinson's disease and its animal models [3]. This seems largely due to a lack of dopaminergic effects on CD projection neurons because local degeneration of dopaminergic axons in the CD leads to severe deficits in saccadic eye movements.

Process Regulation

How then do dopaminergic neurons in the SNc contribute to saccadic motor control? Unlike SNr or CD neurons, SNc dopaminergic neurons neither fire before or after saccades, nor respond to a visual stimulus that guides saccades. Instead, they respond to reward if it is given unexpectedly [9]. Further, if different visual stimuli are presented to induce different saccades, and if one of the visual stimuli is consistently followed by a larger reward, then SNc dopaminergic neurons respond to it with a short burst of spikes and respond to the other stimuli with suppression of firing [10]. This dependency on expected reward value is common to SNr neurons, although the polarity of response is opposite (i.e., stronger inhibition in SNr neurons). It has been hypothesized that SNr neurons acquire the reward dependency from SNc dopaminergic neurons through

their connections to CD projection neurons. However, unlike SNr neurons, SNc neurons have no spatial selectivity: the reward value associated with the stimulus, but not its spatial location, matters. SNr neurons should then acquire spatial selectivity from non-dopaminergic mechanism, which presumably originates from cerebral cortical areas (including FEF, SEF, and LIP) and is mediated by the CD. To summarize, the CD is an important area where spatial information originates from the cerebral cortex and reward-related information originated from SNc dopaminergic neurons are integrated.

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Substantia Reticularis

►Reticular Formation

Substrate Adhesion Molecules

Definition

SAMs Molecules of the extracellular matrix with which cells can interact through membrane receptors. Collagen, laminin and fibronectin are examples of such molecules.

Subtetanic Contraction

Definition

Subtetanic contraction is the most common working mode of skeletal muscles: the muscle fibers are activated at a "sufficiently high" frequency such that the single twitch responses merge together, i.e. giving rise to temporal summation. The developed muscle force increases with increasing frequency of activation, due to the increasing temporal summation of single twitches, up to a maximum. The maximal force is achieved with the tetanic contraction, i.e. the condition in which maximal summation (fusion) of twitch responses is reached. Increasing the frequency of stimulation of muscle fibers beyond the tetanic stimulation frequency will not produce further increase in force.

►Force-frequency Relation of Skeletal Muscle
►Tetanus in Muscle Contraction
►Twitch (Muscle)

Subthalamic Nucleus (Luys)

Synonyms

►Nucl. subthalamicus (Luys)

Definition

A well-circumscribed, large-celled nucleus in the caudalmost region of the diencephalon. It belongs with the globus pallidus, inter alia, to the subthalamus.

The lateral globus pallidus projects strictly topographically to the subthalamic nucleus, which in turn projects with inhibitory effects to all parts of the globus pallidus. Efferents also to the caudate nucleus, putamen and substantia nigra. GABA is the transmitter for both projections.

►Basal Ganglia
►Diencephalon

Subventricular Zone (SVZ)

Definition

The subventricular zone (SVZ) is the region adjacent to the ventricular zone (VZ), which constitutes the wall of the lateral ventricle. It is most prominent in the medial and lateral ganglionic eminences of the embryonic brain. It is one of the few germinal zones in the adult brain and new neurons are continuously generated in the SVZ. In this region, there are at least four types of cells with distinct functions: Ependymal cells (Type E cells) line the wall of the ventricle. Type B cells are a special form of astrocytes that act as neural stem cells, and are slowly dividing. Type B cells most rapidly generate proliferating Type C transit amplifying precursors. Type C cells then differentiate into Type A cells, migrating neuroblasts. Type A cells migrate anteriorly and then enter the rostral migratory stream (RMS) leading to the olfactory bulb, where they differentiate into interneurons.

Succinylcholine (Suxamethonium)

Definition

Depolarizing blocker of the neuromuscular junction; like acetylcholine, it binds to acetylcholine receptors but longer, thereby preventing acetylcholine from docking onto its receptors; since it has the intrinsic capacity of acetylcholine of opening the receptor-related ion channels, it depolarizes the muscle membrane over a prolonged period and causes a depolarization block.

►Neuromuscular Junction

Sudden Infant Death Syndrome (SIDS)

Definition

Sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history. Leading cause of postneonatal infant mortality in the United States, Canada and European Countries.

Affected children typically die during the night and early morning hours. One of the leading hypotheses is that SIDS is caused by defects in brainstem neuronal networks that control respiration and/or cardiac stability during sleep. These defects result in a failure of protective responses to life-threatening stressors (e.g. hypoxia) during a critical period in the postnatal development of the child.

►Laryngeal Chemoreflexes

Sufficiently Exciting

Definition

Sufficiently Exciting refers to actions taken on (inputs to) a physical system. It is used in conjunction with a model estimator – one would like to "excite" the physical system with the purpose of creating data that reflects the behavior of this system as much as possible.

►Adaptive Control

Sulcus Lateralis (Sylvii)

Definition

Major fissure on the lateral side of the hemisphere between temporal and parietal lobes.

Sulcus Limitans

Definition

The sulcus limitans appears in the developing neural tube. The central canal of the tube forms a small sulcus at its midlateral point on each side. This sulcus defines the boundary between the dorsally developing sensory and the ventrally developing motor regions.

Summation by Retinal Ganglion Cells

Definition

Although retinal ganglion cells are the retinal sampling element, each ganglion cell may sum input from numerous photoreceptors. More numerous ganglion cells (e.g. midget cells) summate from fewer receptors than sparser cell types such as P giant cells. Also, all ganglion cell types summate over larger groups of photoreceptors in peripheral than in central (foveal) retina.

►Photoreceptors
►Retinal Ganglion Cells
►Visual Processing Streams in Primates

Summation Tones

Definition

Tonal components at the output of a nonlinear system with frequencies equal to the sum of the frequencies of the input tonal components.

►Acoustics

Sumo

Definition

Small Ubiquitin-related Modifier (SUMO) proteins are a family of 4 proteins that are similar to ubiquitin in that they can be covalently attached (sumoylation) to other proteins though a process analogous to ubiquitination.

Unlike ubiquitination, sumoylation is a post-translational modification that is not used primarily to tag proteins for degradation but rather is utilized in other cellular processes, such as nuclear-cytosolic transport, transcriptional regulation, apoptosis, protein stability, response to stress, and progression through the cell cycle.

►Receptor Trafficking

Sumoylation

Definition

SUMO conjugation to its target is analogous to that of ubiquitination in that it involves an enzymatic cascade. In the first step, an ATP dependent protease (the SENP proteases) cleaves a C-terminal peptide (the last four amino acids). SUMO then becomes bound to an E1 enzyme (SUMO Activating Enzyme (SAE)) and then passed to an E2 conjugating enzyme (Ubc9). Sumoylation then occurs on a protein with a consensus SUMO attachment sequence, with the help of an E3 ligase. The SUMO attachment sequence is the B-K-x-D/E motif. In the absence of this consensus sequence, the E3 ligase facilitates attachment. Several Sumo-E3 ligases exist and themost common are the PIAS proteins, which belong to the zinc-RING finger superfamily of proteins. Sumoylation, like ubiquitination, is reversible and SUMO can be removed by a protease (e.g. Ulp2) in an ATP dependent manner. SUMO, like ubiquitin, can form chains, but unlike ubiquitin, SUMO chains are likely to be preassembled prior to conjugation onto the target protein.

►Receptor Trafficking

SUNA

Definition

Short-lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms.

►Trigeminal Autonomic Cephalalgias
►Headache

SUNCT

Definition

Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing.

►Trigeminal Autonomic Cephalalgias
►Headache

Superior Cerebellar Peduncle

Synonyms
►Pedunculus cerebellaris sup.

Definition
The major cerebellar efferents pass through this peduncle: cerebellothalamic tract and cerebellorubral tract. Since they cannot be easily distinguished from each other they are collectively known as the "superior cerebellar peduncle."

The only afferent tract is the anterior spinocerebellar tract, conducting proprioceptive information from the spinal cord to the spinocerebellum.

►Cerebellum

Superior Cervical Ganglion

Synonyms
►Ganglion cervicale sup.

Definition
Sympathetic ganglion. The associated neurons are situated in the upper thoracic cord (the cervical cord has no sympathetic neurons).

Superior Colliculus

Synonyms
►Colliculus sup.

Definition
Upper hill of the quadrigeminal lamina. Involved in fast eye movements, synaptic center for optokinetic reflexes (saccades). Afferents from the retina and visual cortex (opticofacial winking reflex), inferior colliculus and auditory cortex (reflex movement in direction of source of noise). Involved in accommodation reflex. Efferents to oculomotor cranial nerve nuclei and spinal cord.

Damage to the superior colliculi results in interruption of reflex eye movements, but not in impairment of cognitive perceptivity (e.g. image recognition).

►Mesencephalon

Superior Colliculus and Hearing

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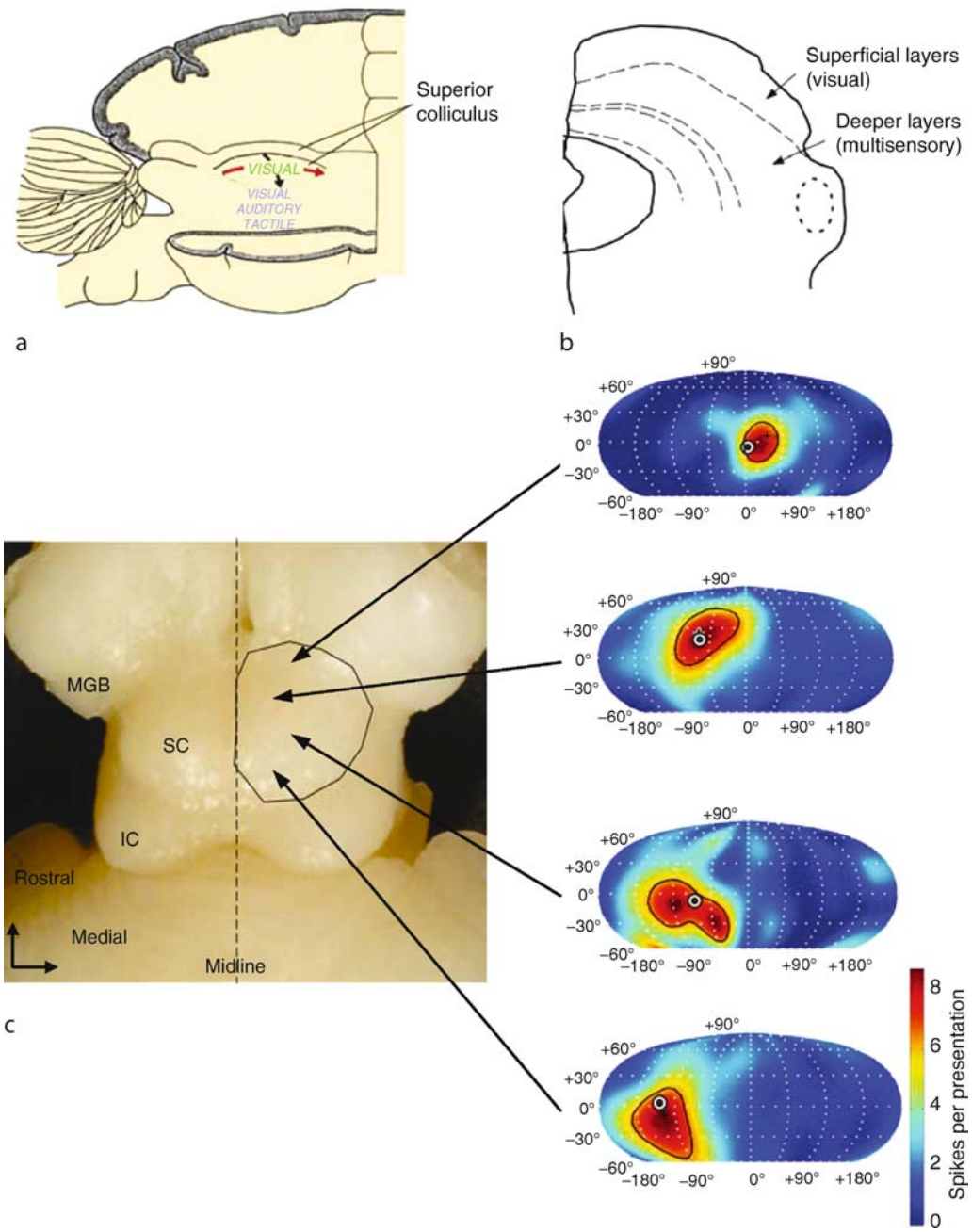
Synonyms
Auditory space map

Definition
The map of auditory space in the ►superior colliculus, which is superimposed upon and integrated with the representations of other sensory modalities, thereby allowing different sensory cues to guide orienting movements of the eyes, head and body.

Characteristics
One of the key functions of the central nervous system is to obtain information about the external environment and to control movement of the body within it. Critical to this is an ability to determine the whereabouts of specific events, such as potential prey or predators, so that they can be attended to, approached or avoided as the need arises. In order that they can trigger movement, sensory signals must be integrated with motor-related activity. This is actually a common feature of neurons in both cortical and subcortical areas that contribute to the control of movement. One brain region involved in sensorimotor processing that has received particular attention is the superior colliculus, which forms part of the roof of the ►midbrain (Fig. 1a).

This nucleus contains overlapping sensory and motor maps, which provides an efficient means by which activation by a stimulus from a particular location in space can be transformed into motor commands that specify the movements required to orient toward that stimulus [1].

Sensory Maps in the Superior Colliculus
While a role for the superior colliculus in the visual control of ►saccadic eye movements – rapid changes in eye position that redirect gaze toward objects of interest so that they can be seen with better resolution – has long been recognized, it is now known that this nucleus plays a more general function in mediating sensory-evoked orienting movements as well as certain other behaviors. The dorsally located superficial layers of the superior colliculus receive almost exclusively visual inputs that arise directly from the ►retina and indirectly from the visual cortex, whereas the more ventral intermediate and deep layers are innervated by auditory and somatosensory as well as visual structures. Consequently, these layers should be viewed as a



Superior Colliculus and Hearing. Figure 1 Representation of auditory space in the superior colliculus. (a) This schematic depicts the brain of a ferret, which is representative of other mammals, in which the posterior part of the cortex has been removed so that the left and right superior colliculi can be visualized. The sensory inputs to different regions of this midbrain nucleus are indicated. (b) Outline of a coronal section of the superior colliculus. The location of different layers is depicted by the dashed lines. The most dorsal superficial layers are exclusively visual, whereas the deeper layers contain neurons that are responsive to visual, auditory and/or somatosensory stimuli. Many neurons in the deeper collicular layers also discharge prior to eye and head movements toward these sensory targets. (c) Auditory spatial receptive fields of four deeper layer neurons recorded in the right superior colliculus at the positions shown on a dorsal view of the midbrain. Color scale indicates the mean number of action potentials evoked per stimulus presentation, with the maximum response indicated by the red regions. The black cross shows the direction of the centroid vector, which indicates the preferred sound direction for each neuron, while the white circle represents the location of a visual stimulus that evoked the strongest response from neurons recorded in the overlying superficial layers. Note that the visual and auditory receptive fields covary within the superior colliculus.

multisensory region, in which many of the neurons receive converging inputs from different sensory modalities (Fig. 1b).

Each of these sensory representations is organized into a map of space. This is based on individual neurons responding to the appropriate stimulus when it falls within a restricted region of space known as the ►receptive field. The locations of these receptive fields vary systematically with the locations of the neurons within the superior colliculus (Fig. 1c). Moreover, the visual, auditory and somatosensory maps are topographically aligned with each other. Thus, visual and auditory stimuli located in front of the animal or objects touching the face are represented in the most anterior or rostral part of the nucleus, whereas stimuli located behind the animal will activate the most posterior or caudal part. Similarly, neurons in the medial part of the superior colliculus respond most strongly to visual or auditory targets above the animal or to stimulation of the upper part of the body, while neurons on the lateral side respond best to stimuli coming from below.

The registration of the sensory maps across the different layers of the superior colliculus is also observed at the level of individual multisensory neurons, which have overlapping spatial receptive fields in each of the sensory modalities to which they respond. When different types of stimuli are presented together at approximately the same time and from the same region of space, these neurons typically respond more strongly than they do to each individual stimulus [2]. Indeed, the responses to multisensory stimulation sometimes exceed the sum of the responses to the individual stimuli. By contrast, if the different stimuli to which the neurons respond are widely separated in space or time, inhibitory interactions tend to be observed, resulting in weaker responses to multisensory stimulation.

In addition to having sensory responses, deeper layer superior colliculus neurons can exhibit premotor activity. In other words, they discharge prior to and during orienting movements of the eyes, head and, in species where they are mobile, the ears [3]. This motor-related activity is also organized into a map, which can be demonstrated by observing the amplitude and direction of the orienting movements produced by focal electrical stimulation of different regions of the colliculus. Because the sensory and motor maps are in register, neurons responsive to stimuli from a particular direction in space may also be active prior to movements that shift the direction of gaze to that location in space.

Direct evidence for a role for the individual sensory representations in the control of orienting movements has come from studies in which different regions of the superior colliculus have been inactivated. Cooling of the superficial layers of the colliculus on one side only degrades the accuracy of orienting responses to visual stimuli presented in the opposite hemifield, whereas additional inactivation of the intermediate layers results in auditory orienting deficits too [4]. Partial unilateral lesions of the deeper layers have also been shown to eliminate the improvement in the accuracy of localization responses that is normally observed when visual and auditory stimuli are paired at the same location in space [5], further establishing a link between the sensory response properties of superior colliculus neurons and orientation behavior.

Representing Auditory Space in the Brain

Maps of visual space and of the body surface in the brain have their origin in the way in which these sensory signals are represented at the receptor surface. The optical properties of the eye allow each part of the retina to sample a different region of the visual world, collectively giving rise to a neural map of visual space. Similarly, each region of the body surface is represented by the activity of ►mechanoreceptors in that part of the skin. The visual and somatosensory maps found in the superior colliculus and elsewhere in the brain therefore arise from spatially ordered projections that begin with the output from their respective sense organs.

The formation of a map of the auditory world in the brain presents a different challenge, however, as the auditory receptor cells in the ►cochlea are tuned to different sound frequencies rather than positions in space. The direction of a sound source is determined by comparing the amplitude level and timing of the sounds reaching the two ears. In addition to these "►binaural" cues, the external ear – the visible part of the ear – filters the incoming sound, changing its spectral composition in ways that depend on the direction of sound incidence. In humans and other mammals, binaural cues provide the principal basis by which sound sources in the horizontal plane are localized, whereas spectral cues are utilized for distinguishing between sounds in front of and behind the head and for localization in the vertical plane.

Neuronal sensitivity to each of these localization cues is first established in a different region of the ►brainstem. These pathways converge in the ►inferior colliculus, where a topographic representation of space first emerges, which is then transmitted to the deeper layers of the superior colliculus. The steps leading to the synthesis of the auditory space map have been studied in most detail in barn owls, a species with particularly good directional hearing [6]. Because of an unusual asymmetry in its ears, barn owls actually use one of the binaural cues – interaural level differences – to determine the vertical angle of their prey, such as a mouse on the ground, whereas interaural time differences are used for pinpointing its horizontal location. Although interaural time differences are the primary

cues for localizing low frequency sounds in mammals, they do not contribute to the spatial selectivity of superior colliculus neurons, which tend to be broadly tuned to high frequency sounds. Instead, the map of auditory space is based on a combination of interaural level differences and spectral cues [7].

Most studies have focused on how the direction of a sound source is represented in the superior colliculus. In echolocating bats, some neurons can specify target distance, as a result of being tuned to the delay between the animals' ultrasonic vocal signals and the returning echoes produced by reflections from objects in the flight path. The importance of the superior colliculus in acoustic orienting of echolocating bats in three-dimensional space is further highlighted by the finding that neurons in this nucleus discharge just before the animals produce biosonar pulses but not when they emit communication calls [8].

What Happens When the Eyes (or Ears) Move?

An important consequence of the differences in the way in which the visual, auditory and somatosensory maps in the superior colliculus are constructed is that independent movements of the sense organs – such as the eyes or the ears – should result in the sensory representations becoming misaligned. This is not a problem for the barn owl because its eyes and external ear structures are effectively immobile. But in mammals, changes in the direction of gaze are accompanied by shifts in the location of auditory and somatosensory receptive fields, indicating that these sensory signals are transformed into coordinates that take into account the current position of the eyes [3]. This presumably allows accurate orienting movements to be maintained irrespective of initial eye position.

Sensory Experience and the Development of the Auditory Space Map

In addition to being continually updated by eye-position signals, the auditory space map is shaped by sensory experience as it emerges during development [9]. This is necessary because the values of the auditory localization cues corresponding to a particular sound direction depend on the size and shape of the head and external ears, which can vary markedly between and within individuals. In particular, vision plays a key role in aligning the different sensory maps, as revealed by the dramatic changes produced in the auditory responses when visual inputs are altered. This has been demonstrated most clearly by mounting prisms in front of the eyes of young barn owls in order to shift their visual world to one side. The resulting misalignment between the visual and auditory maps is overcome by a corresponding shift in auditory spatial tuning. Similar findings have also been obtained in mammals [9], suggesting that establishing and maintaining the registration of the maps is critical for synthesizing the different sensory cues associated with targets that can be both seen and heard. As a result these cues can be used to specify the orienting movements that bring about a change in the direction of gaze.

The Superior Colliculus and Auditory Localization

Although a close relationship between the sensory representations in the superior colliculus and reflexive orienting behaviors has been established in a range of species, it is important to appreciate that a map of auditory space is not a prerequisite for localizing sound. In higher mammals (carnivores and primates), lesions of the auditory cortex result in deficits in sound localization, yet there is no evidence for a space map in the cortex. Instead, cortical neurons seem to carry information about sound source location in both the number and timing of their action potentials [10]. Nevertheless, it is likely that interactions between the cortex and midbrain, possibly mediated by descending ►corticofugal projections, contribute to behaviors that require sound localization.

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Superior Colliculus-Fixation Neurons

Definition

Neurons that have a steady discharge when a subject is attentively fixating a spot of light, even when the spot disappears and the subject fixates the same, though invisible, location in the dark. These cells are located in a restricted zone of the rostral superior colliculus encompassing the foveal representation of the visual field.

►Fixation System

Superior Colliculus – Quasi-Visual Neurons

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Definitions

Quasi-visual neurons – ►Superior colliculus neurons that exhibit a tonic discharge that begins ~70 ms after the onset of a visual target and continues until saccade onset, but that have response fields that are predictive of the vector of the saccade, rather than the retinotopic location of the visual target.

Characteristics

Higher Order Structures

Quasi-visual (QV) neurons are found in the intermediate gray layer of the superior colliculus (SC). The SC is a seven layered structure in the midbrain involved in ►sensorimotor integration and orienting behavior.

Parts of This Structure

Currently, very little is known about the morphological characteristics of QV neurons or their afferent and efferent projections. It seems likely, however, that these neurons receive direct projections from FEF. Neurons with similar properties have been described in frontal eye fields [1], and saccade related neurons in SC are known to receive direct projections from FEF. However, it should be pointed out that these authors believe that QV neurons in FEF are best thought of as visual neurons that would send signals to SC only indirectly.

Functions of This Structure

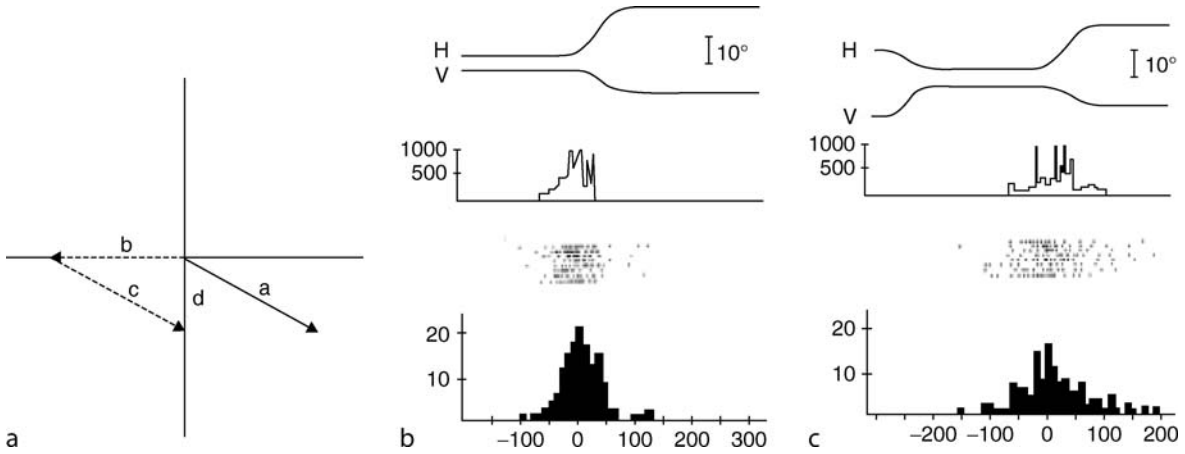
Quasi-visual neurons are one of several functional classes of neuron in primate superior colliculus originally described by Mays and Sparks [2]. On a simple, target-step saccade task, QV neurons resembled visual cells, with no alteration of firing rate associated with saccade onset. On these trials, they exhibited a sustained discharge that began ~70 ms after target onset and continued until the saccade occurred. Sustained responses occurred even if the target was flashed for only 20–80 ms.

The unique characteristics of these neurons could be seen using a ►double saccade task. On these trials, the vector of the saccade associated with the most vigorous discharge was found to be the same as that associated with the most vigorous discharge in the target step task (Fig. 1). This was true even though, for the double saccade task, no visual target ever appeared at the retinotopic location corresponding to the endpoint of the second saccade. That is, when a dissociation exists between the retinotopic location of the visual target and the saccade vector, the response fields of QV neurons appear to be associated with the latter. The timing of neuronal discharge was not tightly linked to either visual target onset or saccade onset.

On ►visual probe trials, a peripheral visual target was briefly flashed while the monkeys fixated a central fixation target. On these trials, QV cells exhibited a sustained discharge that persisted until ~200 ms after target offset. These authors also tried a variant of the double saccade task in which the second target was within the classical receptive field of the neuron. In this case, QV neurons discharged 110–120 ms after the onset of the second target, despite the fact that the first saccade was directed to a different location. Thus, these neurons are visually responsive, and can respond vigorously even when the saccade being planned is to a location outside their response fields. These results show that quasi-visual cells are neither completely visual nor completely motor, at least not in the usual sense. Instead, they seem to have elements of both visual and motor responses. These authors suggested that these cells might encode static eye position error (the difference between current and desired eye position).

Since Mays and Sparks first described QV neurons, several studies have suggested potential roles for these cells. Amador et al. [4] suggested that QV neurons might play an important role in the generation of anti-saccades. On ►anti-saccade tasks, these authors observed that monkeys occasionally made erroneous saccades to the target followed by extremely short latency "turnaround saccades" to the correct location. It was suggested that QV neurons may play a role in generating these very short latency turnaround saccades.

Very short ►intersaccadic intervals are sometimes observed when the task calls for a sequence of saccades [5]. These short intersaccadic intervals seem to require that the brain begin some of the computations



Superior Colliculus – Quasi-Visual Neurons. Figure 1 (a) The initial eye position is at the origin. The vector labeled *a* indicates a saccade in the ►target step saccade task, to the location marked with the arrow. In the double saccade task, the first saccade is labeled *b* and the second is labeled *c*. Note that the vector of the second saccade of the double saccade task matches the vector of the saccade in the target step task. (b) Response of a quasivisual neuron associated with the saccade labeled *a* in panel (a). (c) Response of the same neuron during the double saccade task. Note that the cell responds vigorously for saccade *c* even though no visual target ever appears at that retinotopic location. On visual probe trials, the cell would respond to the appearance of a visual target at the location indicated by *a,* even if the animal is not required to make a saccade to this location (data not shown) (Adapted from [3]).

necessary for the second saccade even before the first saccade is executed. Tian et al. [2] described neurons (also referred to as QV neurons) with very similar properties in monkey frontal eye fields. These authors reported evidence that these neurons form a map of the spatial locations of potential saccade targets. Such a map would allow sequences of saccades to be programmed, and spatially accurate saccades executed, even if the visual targets are all extinguished prior to the first saccade. Thus, it may be that QV neurons in SC play an important role in the generation of sequences of saccades by helping the brain to maintain a spatially invariant representation of possible saccade target locations, even though each saccade alters the retinotopic location of those potential targets.

However, it must be pointed out that, to date, no subsequent studies have used the double saccade task while recording from QV neurons in SC. Therefore, the original Mays and Sparks paper remains the only study to provide data regarding cells that can be confidently classified as QV neurons in SC.

Higher Order Function

QV neurons seem to be part of a spatial memory system that also encompasses the Frontal Eye Fields, and possibly the Lateral Intraparietal area and area 46.

Quantitative Measure for This Structure

Currently, the only quantitative measurements available for QV neurons are those related to the discharge properties of these neurons, discussed above.

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Superior Colliculus – Role in Eye Movements

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Definitions

►Gaze – The direction of the line of sight with respect to external space.

Oculocentric reference frame – A coordinate system specifying the location of a target with respect to the current direction of fixation.

►Superior colliculus – A seven layered structure in the midbrain, involved in ►sensorimotor integration and the control of orienting behaviors.

Characteristics

Higher Order Structures

The superior colliculus occupies an important central role in the circuitry controlling orienting movements (►Orienting responses) and sensorimotor integration. Consistent with these functions, this structure receives both sensory and motor inputs from a large number of cortical and subcortical areas.

Parts of this Structure

The superior colliculus is a seven-layered structure in the midbrain involved in orienting behavior and sensorimotor integration. The most dorsal of the three cellular layers and the surrounding two fibrous layers are generally referred to as the superficial layers [1]. The four ventralmost layers (two cellular and two fibrous) are typically referred to as the deep layers (or, alternatively, the intermediate and deep layers).

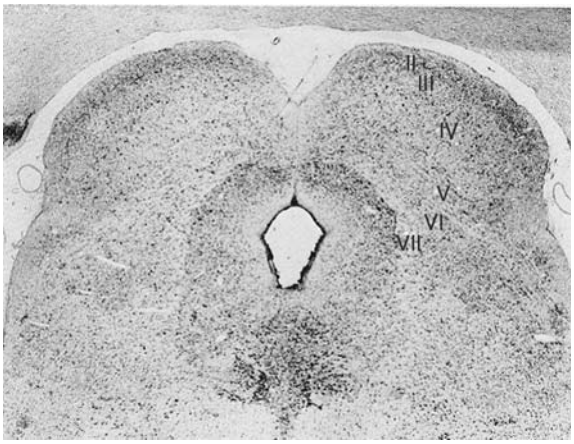
Functions of this Structure

The role of the superior colliculus in the control of eye movements is part of its more general role in the control of gaze, including combined movements of the eyes and head [1]. In the intermediate and deep layers, several classes of neuron modulate activity in association with saccades. Saccade related burst neurons (SRBN) are characterized by a high frequency burst of spikes, beginning ~20 ms before the onset of saccades of a particular vector [2]. The movement fields of these neurons are arranged in a topographic map that lies approximately in register with the receptive fields of visual neurons in the superficial layers. Thus, the vector of the saccade is encoded by the location of activity within the collicular map. Some burst neurons (referred to as visuomotor burst neurons) also exhibit a visually evoked burst of spikes that begins ~70 ms after target onset. These cells are sometimes regarded as a separate class, although a continuum exists between exclusively motor bursters and those with strong bursts for both target onset and saccade onset. Saccade-related activity is also, to varying degrees, often dependent on the presence of a visual target [3]. Some cells respond equally vigorously regardless of whether or not the visual target is extinguished before the saccade, while others do not respond at all if the saccade is directed to the remembered location of a target that has been extinguished. Again a continuum exists, with most cells responding more vigorously if the visual target is still present at the time of the saccade. On ►delayed saccade tasks, some neurons, usually referred to as prelude or buildup cells, display tonic activity during the interval, beginning roughly 70 ms after target onset and ending at saccade onset, often culminating in a burst of spikes that is time-locked to saccade onset. These cells have been described as having open movement fields, meaning that they respond to any saccade that is in the optimal direction and that is equal to, or larger than, a particular value [4]. Quasivisual neurons are another class of cell described by Mays and Sparks [2]. These cells appear to be encoding ►motor error, and are best thought of as being neither completely visual nor completely motor. Fixation neurons are found near the rostral end of SC. These cells fire tonically during periods of steady fixation and pause for most saccades in all directions. Injection of muscimol into the rostral SC interferes with the monkey's ability to suppress unwanted saccades to peripheral visual targets [5]. On the basis of these observations, it was proposed that fixation cells are involved in the maintenance of active fixation. As shown by Krauzlis et al. [6]; however, many of these cells also burst for small contraversive saccades. These authors concluded that these cells encode motor error. Thus, the exact role of fixation cells in the control of saccades remains controversial.

In most current models of the saccadic system, a corollary discharge of the premotor burst is fed back to a comparator, which compares actual eye displacement to desired eye displacement. When this value reaches zero, the saccade ends. According to one view, SC is kept up to date about the progress of the ongoing saccade through feedback signals from the brainstem saccade generator. Evidence to support this notion has come from studies in which saccades were interrupted mid-flight by stimulating the omnipause (OPN) region. Keller, Gandhi, and Vijay Sekaran [7], for example, reported that the saccade resumes after the end of the stimulation and reaches the target correctly. These authors found that the same region of SC that was active before the saccade becomes re-activated for the resumed movement, which seems to indicate that the SC must have received feedback regarding the interruption.

On the other hand, the SC might be upstream from the local feedback loop. According to this idea, the SC generates a saccadic command that is sent to the brainstem saccade generator, but receives no feedback related to the progress of the saccade. These models, however, have difficulty explaining results such as those described above [7].

Lefevre et al. [8] proposed a model of saccadic control in which the superior colliculus is seen as less important than the cerebellum. More specifically, these authors proposed that the superior colliculus determines the timing of saccade onset and provides a general drive



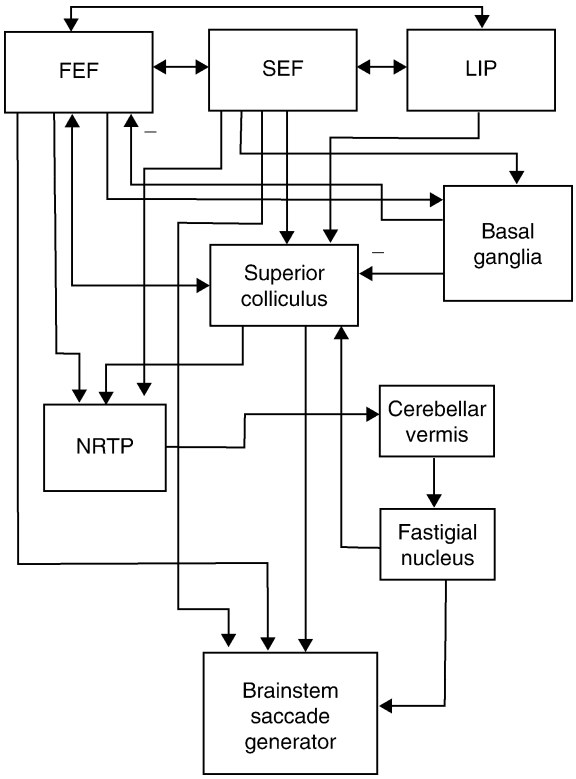
Superior Colliculus – Quasi-Visual Neurons.
Figure 1 Coronal section showing the superior colliculus. Layers are labeled with roman numerals (Adapted from [10]).

that moves the eyes approximately in the right direction. According to this view, activation of the superior colliculus is neither necessary nor sufficient for saccades to occur. In support of this idea, the authors pointed out that lesions of the cerebellum severely impair saccadic eye movements. In contrast, primates still make reasonably accurate saccades even when the superior colliculus is ablated. As post-lesion plastic changes in alternative saccadic pathways can potentially mitigate the effects of permanent lesions, several studies have examined saccade metrics and accuracy following reversible inactivation of SC (for example, see [9]). While these studies reported a noticeable tendency for the post-injection saccades to be slower, of longer duration, and hypometric, reversible inactivation of SC does not prevent monkeys from making saccades to visual targets.

Higher Order Function

As can be seen from the above discussion of cell types, there is good evidence that the SC is involved in the transformation of sensory signals into eye movement commands. The intermediate layers of SC receive visual, somatosensory, and auditory input from a large number of brain areas, as well as input from other saccade-related structures such as frontal eye fields, supplementary eye fields, and the lateral intraparietal area. As discussed above, a number of studies have described neurons in SC that are difficult to classify as clearly sensory or clearly motor [2].

In many species, the superior colliculus is involved in generating movements that orient the eyes and ears to visual and auditory stimuli of interest. In mammals, for example, the intermediate and deep layers carry signals related to movements of the eyes, head, and pinnae.



Superior Colliculus – Quasi-Visual Neurons.
Figure 2 Simplified wiring diagram of the saccadic system. The superior colliculus occupies a central role in the saccadic system circuitry.

Quantitative Measure for this Structure

Studies investigating the role of the SC in eye movement control typically attempt to quantify neuronal behavior by measuring the firing rate of individual neurons in the deeper layers. Most commonly, this involves measures such as firing rate, the number of spikes in the burst, and the timing of the burst with respect to visual target onset and/or saccade onset. For example, peak spike frequency is correlated with peak saccade velocity.

S

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Superior Frontal Gyrus

Synonyms

►Gyrus front. sup.

Definition

In the area of the frontal gyrus close to the precentral gyrus is situated the premotor cortex, which plays an important role in planning effector voluntary movements and has close interaction with the cerebellum, thalamic nuclei and basal ganglia.

At the level of the superior frontal gyrus is situated the frontal eye field, which is involved in planning voluntary eye movements. Hyperactivity of these neurons due to hemorrhage or tumors causes conjugate movements of both eyeballs (deviation conjugee). Conversely, destruction of tissue causes ipsilateral deviation conjugee, since now the activity of the contralateral eye field no longer has an antagonist.

►Telencephalon

Superior Longitudinal Fasciculus

Synonyms

►Fasciculus longitudinalis sup.

Definition

With its two branches (anterior brachium and posterior brachium), the superior longitudinal fasciculus establishes connections between virtually all cortical areas. The part of the fasciculus connecting the motor (Broca's) speech center with the sensory (Wernicke's) speech center is called the arcuate fasciclulus.

►Pathways

Superior Oblique Muscle

Definition

Superior oblique is one of the six eye muscles.

►Eye Orbital Mechanics

Superior Olivary Nuclei

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Synonyms

Nuclei of the superior olive; Superior olivary complex; SOC

Definition

The superior olivary nuclei are a group of nuclei located in the brainstem near the junction of the pons and medulla. It is the first auditory relay after the cochlear nucleus on the way to the auditory cortex and is the major point at which information from the two ears is integrated.

Characteristics

Introduction

The superior olivary nuclei or complex (SOC), as they are more commonly called, occupy an important and unique position in the ascending auditory pathway. The SOC lies at the ponto-medullary border. Acoustic information is conducted from the outer ear into the inner ear where the cochlea transduces the mechanical energy into neural impulses that are conveyed by the auditory nerve fibers, which compose one component of the VIII cranial nerve, into the central nervous system. The other component of cranial nerve VIII is the vestibular nerve which originates from the vestibular apparatus of the inner ear. All auditory nerve fibers

synapse in the cochlear nuclei where there is some initial processing of the afferent information. Cells in the cochlear nuclei then project to the SOC of both sides so that the SOC represents the first major point at which cells combine the inputs from the two ears. Therefore the SOC is a critical point for processing of binaural information which is essential for accurate sound localization. To understand the neural processing, we must first consider what cues are needed for sound localization.

Imagine walking down the street of a town late at night and suddenly hearing a strange sound. In this situation, there are two important tasks that our auditory system must do. It has to identify the sound (a cat meowing or the footsteps of a possible mugger) and it has to tell us where the sound comes from. We understand very little about how the auditory system can identify sounds but considerably more about the neural processes that underlie the ability to establish where a sound originates.

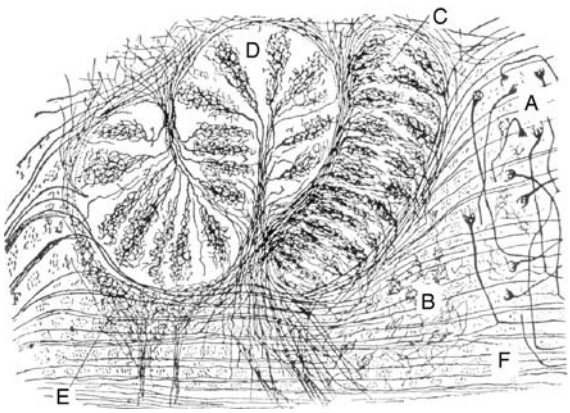
Note that the problem of localizing a stimulus is quite different for the auditory system than it is for the other two major sensory systems, vision and somatosensation. In both of the latter systems the location of a stimulus is naturally encoded in the location of the sensory receptor since there is a map of the space in the sensory epithelium, in the retina for the visual system and on the body surface for the somatosensory system. By contrast, the inner ear contains a map of the frequency, not location, of the sound. The location of the sound must then be computed by the nervous system by analyzing the small differences between the sounds at the two ears, ►interaural time differences (ITDs) and ►interaural level differences (ILDs, also called interaural intensity differences, IIDs). A remarkable feature of the auditory system is its sensitivity to these interaural disparities: the maximum ITD for the human head when a sound is opposite one ear is about 800 μs while human subjects can detect ITDs as small as 10 μs.

The maximum ILD is heavily dependent upon the frequency of the sound since the head acts as an effective acoustic shadow only for sounds with wavelengths that are shorter than the dimensions of the head, i.e. for high frequency sounds. Thus maximal ILDs are on the order of 20–30 dB at 15–20 kHz at the upper end of human hearing and only a few dB at the lower end of human hearing. Therefore, we would expect ILDs to be an effective cue only at high frequencies. The width of an average human head is around 15 cm which corresponds to the wavelength of a 2,000 Hz tone. Therefore ILDs should be effective for frequencies above 2 kHz and ineffective for lower frequencies. On the other hand the phase-locking that encodes temporal patterns in the cochlea is also frequency dependent: in mammals auditory nerve fibers will only phase-lock to tones below about 2–3 kHz. Therefore timing information about the fine structure of sounds is only preserved at low frequencies and ITDs would only be effective at those frequencies. The frequency dependence of ITDs and ILDs is the basis for the classical duplex theory of sound localization [1].

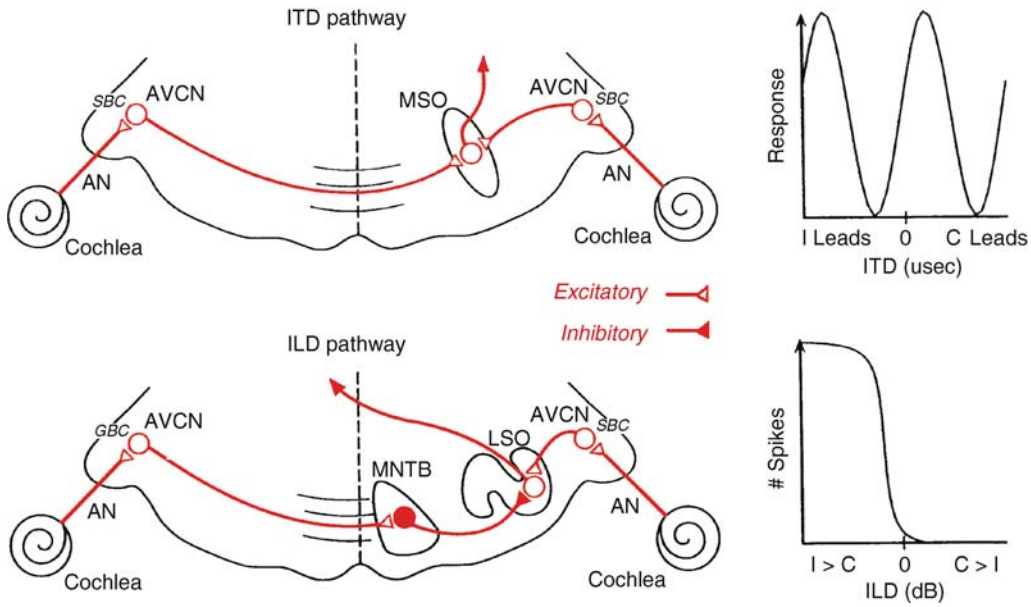
Where in the nervous system are these cues encoded? The most likely candidates are the nuclei in the superior olivary complex (SOC) which occupy a unique position in the ascending auditory pathway: they represent the first major point at which cells in the auditory system combine the inputs from the two ears. These inputs arrive from the anteroventral cochlear nucleus of both sides and they are shown in Fig 1 from a classical drawing of the left SOC [2] from Golgi stained sections of the neonatal cat. In Fig. 1 the midline is to the right and the three major nuclei can be discerned from lateral (left) to medial (right): ►lateral superior olive the (LSO), ►medial superior olive (MSO) and the ►medial nucleus of the trapezoid body (MNTB). In the cat in coronal sections the LSO takes the appearance of a prominent S-shape while the MSO is a narrow nucleus. The LSO and MSO are the key players in the encoding of the two interaural cues of ITDs and ILDs.

Processing of Interaural Time Differences

Fig. 2 shows simplified versions of the circuits that are believed to be important for encoding the interaural cues of ITDs and ILDs. ITDs are believed to be encoded by cells in the medial superior olive (MSO). Anatomically, cells in the MSO receive excitatory inputs from the spherical bushy cells of the anteroventral cochlear



Superior Olivary Nuclei. Figure 1 Drawings of the terminal arborizations from Golgi stains of afferents to the superior olivary nuclei of the neonatal cat. The three major nuclei are labeled: (A) medial nucleus of the trapezoid body, (C) medial superior olive, and (D) lateral superior olive. In addition two periolivary nuclei are also shown: (B) ventromedial periolivary nucleus and (E) lateral periolivary nucleus. The fibers of the trapezoid body (F) are also labeled.



Superior Olivary Nuclei. Figure 2 Schematic drawings of the two circuits in the superior olivary complex that encode interaural time differences (ITDs) (*above*) and interaural level differences (ILDs) (*below*). Abbreviations: *AN*, auditory nerve fibers; *AVCN*, anteroventral cochlear nucleus; *MSO*, medial superior olive; *LSO*, lateral superior olive; *MNTB*, medial nucleus of the trapezoid body; *SBC*, spherical bushy cell; *GBC* globular bushy cell. To the right are drawings of typical responses of a cell in the MSO (*top right*) to variations in ITDs of pure tones and responses of a cell in the LSO (*bottom right*) as a function of the ILD in dB. The response to ITDs is periodic at the period of the stimulus tone and reflects the fact that the cells in the MSO are sensitive to interaural phase differences.

nucleus of each side. MSO cells are unusual cytoarchitecturally in having prominent dendrites that extend to the lateral and medial side where they meet the afferents from the left and right side (Fig. 1). The afferents from the ipsilateral cochlear nucleus synapse on the lateral dendrites while those from the contralateral side synapse on the medial dendrites. Physiologically, the cells in the MSO have been shown to be binaurally excited and exquisitely sensitive to the time of arrival of sounds to the two ears [3,4]. MSO cells behave like coincidence detectors with very sharp temporal windows so that they respond only when the inputs from the two sides arrive coincidentally or nearly so. A widely accepted model of this circuit was first proposed by Jeffress [5] who hypothesized that the timing of the arrival of inputs from each side is governed by the delays associated with differences in axonal length and that there is a systematic change in axonal delays from one end of the MSO to the other, which would result in a map of ITDs across one axis of the MSO. Since the pathlength to the MSO is naturally longer from the contralateral ear, then a natural consequence of the coincidence mechanism is that MSO cells respond best when the sound source is in the contralateral sound field where the sound can reach the contralateral ear before the ipsilateral ear and thus compensate for the longer axonal path from the contralateral side.

Recent studies of the anatomy [6] and physiology [7] of the MSO have shown the existence of inhibitory inputs which originate from the medial nucleus of the ►trapezoid body (MNTB) and ►lateral nucleus of the trapezoid body (LNTB). The MNTB receives input from the spherical bushy cells of the anteroventral cochlear nucleus of the contralateral side while the LNTB receives input from the same cells on the ipsilateral side. The function of these inhibitory circuits is still controversial [8].

Processing of Interaural Level Differences

A parallel circuit in the superior olivary complex is believed to be responsible for encoding interaural level differences (ILDs) (Fig. 2, bottom). Cells in the ►lateral superior olive (LSO) receive excitatory input from the spherical bushy cells of the ipsilateral side and inhibitory input from the contralateral side that is relayed via an inhibitory interneuron in the medial nucleus of the trapezoid body (MNTB) [9]. The MNTB cells received input from the globular bushy cells of the contralateral side by way of a very specialized synaptic ending, the calyx of Held. In accordance with this circuit, cells in the LSO are excited by stimulation of the ipsilateral ear and inhibited by stimulation of the contralateral ear.

For binaural stimuli, LSO cells respond to the difference in intensity (ipsilateral intensity – contralateral

intensity) of the sounds to the two ears. Thus for free-field sounds, LSO cells respond well to stimuli presented in the ipsilateral sound field where the level of the sound is greater in the ipsilateral than the contralateral ear and poorly when the sound is in the contralateral sound field.

The large calyceal synapses between the globular bushy axons and the MNTB cells are very unusual one and can be seen prominently in Fig. 1. It is often said to be the largest synapse in the brain. The presynaptic element is so large that recordings can be made from both the pre- and post-synaptic neurons so that this synapse has become a model for biophysical studies of synaptic transmission.

It is well-known that there is a systematic crossed relationship between the representation in the cerebral cortex and body part or sensory field in all sensory and motor systems. The right motor cortex controls muscles on the left side of the body, cells in the left visual cortex have receptive fields in the right visual field, and cells in the left somatosensory cortex respond to touch or pain to the right side of the body. Note that cells in the MSO respond preferentially to sounds in the contralateral sound field whereas cells in the LSO respond to sounds in the ipsilateral sound field. This apparent paradox is resolved by having MSO project to the ipsilateral inferior colliculus while most LSO cells project to the contralateral inferior colliculus (Fig. 2). The subsequent projections of the inferior colliculus to the medial geniculate and then onto the cortex are all predominantly uncrossed which then makes cells in the auditory cortex respond to sounds in the contralateral sound field, as with the other sensory systems.

All of the nuclei in the superior olivary complex, like those of other ascending auditory nuclei are tonotopically organized, i.e. there is a systematic map of frequency along one axis of the nucleus. In accordance with the expectations of the classical duplex theory, both the MNTB and LSO have a disproportionate representation of high frequencies, which are associated with ILDs, while the MSO is biased toward low frequencies, which are useful for encoding ITDs. In animals with different head sizes, the ability to localize low frequency tones appears to be correlated to the size of the MSO. Interestingly, humans have a very prominent MSO, which is correlated with the importance of ITDs for sound localization but a very small LSO, even though we are clearly able to encode ILDs.

The Periolivary Nuclei

In addition to the major nuclei of the SOC, the MSO, LSO and MNTB, there are also some smaller nuclei that collectively are usually referred to as the periolivary nuclei. The size and prominence of the periolivary nuclei vary somewhat from one species to another and the identification of individual nuclei vary from one investigator to another. An interesting aspect of these nuclei is that in some animals they are the source of the olivo-cochlear efferents [10]. These efferent fibers project from to the cochlea and innervate primarily the outer hair cells, though there are also fibers that end on the inner hair cells. Since 90% of the auditory nerve fibers innervate a single inner hair cells, the action of the olivo-cochlear efferents must be indirect. Current theories center on the fact that the outer hair cells are motile and can contract which could affect the micromechanics of the basilar membrane motion and consequently modulate the inner hair cell response. In rodents the olivo-cochlear efferents originate from cells that are located within the lateral superior olive.

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Superior Olive

Synonyms

►Nucl. olivaris sup.; ►Superior olivary nucleus

Definition

The superior olivary complex comprises the nuclei:

- Nucleus of the trapezoid body
- Nucleus of the superior lateral olive

- Medial nucleus of the superior olive

and is thus a vital synaptic center in the auditory tract, playing an important role in acoustic reflexes (reflex eye movements towards the source of noise, fright movements).

►Mesencephalon

Superior Parietal Lobule

Synonyms

►Lobulus parietalis sup.

Definition

In the direction of the occipital pole, the inferior and superior lobules unite at the postcentral gyrus.

Analogous to the secondary motor cortex there is also a secondary sensory cortex for the somatosensory control; this is believed to stretch across both lobules and to be responsible for analysis, recognition and assessment of tactile information.

►Telencephalon
►Visual Space Representation for Reaching

Superior Prefrontal Gyrus

Definition

Part of the frontal lobe; involved in orchestrating executive function.

Superior Rectus Muscle

Definition

Superior rectus is one of the six eye muscles.

►Eye Orbital Mechanics

Superior Semicircular Canal Dehiscence Syndrome

Definition

Disorder of the labyrinth caused by a dehiscence (opening) in the bone that covers the superior canal. Patients can develop vestibular and/or auditory symptoms and signs. The effect of the dehiscence is to create a third mobile window into the inner ear.

►Disorders of the Vestibular Periphery

Superior Temporal Gyrus

Definition

The superior temporal gyrus is the cerebral cortical fold immediately ventral to the lateral fissure. Its posterior portion is part of the language cortex.

Superior Vestibular Nucleus

Synonyms

►Nucl vestibularis sup.

►Vestibular Nuclei
►Pons

Supernormal Stimulus

Definition

Stimulus with a releasing value that is higher than the releasing value of the natural key stimulus.

SuperSAGE

►Serial Analysis of Gene Expression

Supersensitivity of Blood Vessels

Definition

Increased response (constriction) of blood vessels to circulating or neurally released noradrenaline (and other vasoactive agents) following partial or complete denervation, decentralization or decrease of activity in postganglionic vasoconstrictor neurons. The increased response to noradrenaline is primary due to a decrease of neural uptake of noradrenaline by the postganglionic terminals.

►Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Supervenience

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Definition

Supervenience is a philosophical term of art that refers to the determination relation between lower and higher-level ontological phenomena. For example, physicalists believe that psychological facts supervene on neural facts.

Description of the Theory

In the 1970's and 1980's the concept of supervenience figured in philosophical debates as a promising way to shed light on the mind-body problem. According to the standard view in metaphysics and philosophy of mind, supervenience is a relation between two sets of properties such that:

1. They vary together in a regular way.
2. One set somehow determines the other.
3. That the two sets are different in kind.

For example, mental properties can be said to supervene on physical properties if they are covariant and if physical properties are more basic than mental properties. Likewise, baldness supervenes on the distribution of hair, computer operating systems supervene on computer hardware, ethical actions supervene on the movements of bodies, etc.

Supervenience is not an exotic or purely philosophical notion. The basic idea arises quite naturally out of our belief that some features of reality depend on others. In the philosophy of mind, the supervenience thesis rests on the belief that mental life depends on the activity of the brain (or on the brain plus some aspects of the environment). If one believes that any change at the psychological level can only happen by virtue of a change at the neural level then one holds a version of the supervenience thesis for mental life. While supervenience has some intuitively appealing features, the challenge is to get clear on the notions of fundamentality and determination that are central to the supervenience thesis.

The precise nature of the determination involved in the supervenience thesis depends, among other things on modal considerations; on what is meant by necessity and possibility. For instance, when one says that no higher-level change in the properties of an object is possible without a change in its lower-level properties, a variety of things can be meant depending on the force of "is possible." If one believes that the determination relation holds across all possible worlds then one is arguing for a stronger version of supervenience than if one contends that the determination relation holds only for our world, as it actually is, with its physical laws as they happen to be. Additionally, the supervenience thesis will have different implications depending on what one means by the object in question. Global, regional and local supervenience relations can be distinguished, depending on where one sets the parameters of the object in question. Global supervenience takes as its object, the entire universe, for regional and local supervenience the object is some subset of the universe.

Metaphysical Assumptions

Discussions of the notion of supervenience begin with some familiar and widely shared metaphysical assumptions. It is assumed, for example that facts about the natural world can be understood as falling into distinct levels. Chemical, biological, psychological and economic facts fall into distinct levels, hierarchically arranged from the more basic and general, or "lower," to the more specific and "higher." In this picture, physics is the most fundamental science and physical facts and laws have maximal generality, insofar as they apply to all of nature. With this stratified picture of nature comes the notion that each of the higher-levels depends on the lower levels in some sense. In this spirit, contemporary neuroscientists and philosophers of mind generally assume that psychological facts are determined by neuroscientific facts which are, in turn, determined by bio-chemical facts.

While supervenience is completely compatible with reductionism, supervenience theorists generally assume that the relationship between levels is non-reductive. Many philosophers who accepted non-reductive physicalism were drawn to supervenience as a way of embracing a respectable physicalist metaphysic while at

the same time maintaining a form of irreducibility for mental level facts.

Having a belief, a feeling or a desire is not simply a matter of possessing one or more of a defined set of physical properties. For instance, the dog, the octopus and the Martian might all be in pain while possessing differently structured brains, or even – at least in the case of the Martian – no brain at all. One can imagine different structures realizing precisely the kinds of behaviors or functions that we associate with any mental term. Considerations of this kind, so-called multiple realizability arguments, encouraged most contemporary philosophers of mind to abandon classical reductionism for some version of non-reductive physicalism. This means that they reject claims that the mind simply is the brain (the identity theory) as well as claims that the micro-physical description of reality is the only description we need (strong reductionism).

While multiple realizability arguments led many philosophers to reject straightforward reductionism, it seems unscientific to deny that mental life is dependent on the physical stuff in which mental life is realized. If one wishes to maintain a commitment to physicalism while rejecting reductionism one faces the problem of understanding the nature of the dependence between higher and lower-level facts about organisms. The mind-body problem in its contemporary form is the problem of reconciling physicalism and anti-reductionism. This is quite different from the mind-body problem we inherited from Descartes, which involved accounting for the interaction between spatial and non-spatial substances.

Philosophers noticed that this modern version of the mind-body problem could be understood in terms of the relationship between properties. For example, an object can have properties related to its shape, velocity, mass, position, color and the like without the problem of their compatibility or causal relations ever arising. Some of an object's properties clearly determine others. For instance, the characteristics of an object's surface will determine its colors. In other cases, properties may have no obvious connection or determinative relationship. Consider the relationship between the mass of a vase and its distance from Paris. The analysis of notions like mentality in terms of properties opened the possibility that an object can have both physical and psychological properties without encountering Cartesian-style problems about the relationship between spatial and non-spatial substances. Properties-based metaphysical analyses were attractive to non-reductive physicalists precisely because they permit us to talk about objects, events and states of affairs as having both physical and psychological properties.

Donald Davidson's anomalous monism is an example of this kind of properties- based metaphysics. Davidson accepted a physicalistic metaphysics while denying that science will generate a straightforward reduction of mental types to physical types. And yet, Davidson did not believe that mental life somehow floated free of the physical world. Rather, as a scientifically inclined philosopher, he was committed to the idea that there are no events that have only mental properties [1]. However, saying that an object that has mental properties must also have physical properties is not necessarily any comfort to the reductionist. After all, as Jaegwon Kim points out, while it is true that if an object has a color, it must have a shape, there is no necessary relationship between for example, the squareness of an object and its redness [2].

Anomolous monism, by itself, does not offer much of a theory of the relationship between mental and physical properties. And yet there seems to be more of a connection between minds and bodies than exists between shapes and colors. In his classic paper "Mental Events" Davidson attempts to reconcile his commitment to physicalism with his anti-reductionism using the concept of supervenience. Davidson is widely credited as introducing the term "supervenience" in its contemporary form in that paper. In a frequently cited passage he defines supervenience as meaning "that there cannot be two events alike in all physical respects but differing in some mental respect, or that an object cannot alter in some mental respect without altering in some physical respect" [1,3]. According to advocates of supervenience in the philosophy of mind, this definition has far more substance than something like the mere necessary dependence of color properties on shape properties. To say that minds supervene on brain states for example, is to suggest that one can only have a mental property by virtue of having some neural property, and that understanding this dependence relation will allow us to understand the nature of the relationship between mental life and embodiment. The implicit claim is that supervenience will give us more than the simple acknowledgement *that* there is some relationship between the two.

Kinds of Supervenience

In addition to assuming that facts about more fundamental levels of reality must determine facts at higher ontological levels, there are two additional assumptions that are related to the first:

1. Changes at the higher level depend on changes at the lower level.
2. Identical states of affairs at the lower level necessitate identical states of affairs at the higher level.

In the case of the relationship between mental and physical phenomena these two assumptions are exemplified in the following way:

1a. Changes at the psychological or mental level are only possible via changes at the neural level.

2a. It is impossible for organisms to be in identical brain states without also sharing the same psychological states.

For neuroscientists, these are fundamental assumptions. After all, neuroscience would of little general interest if psychological differences were not determined in some law-like way by neural differences. Of these two assumptions, 2 can be understood as the minimal requirement for a physicalist metaphysics. Of course 2a is debatable and might be made compatible with physicalism given some fancy philosophical footwork. We can rephrase 2 so as to bring out its modal character:

2m. It is not possible for two things to be identical at the lowest level and not identical at higher-levels.

In this form we can see that the strength of the modal component is very important to the meaning of the overall claim. If it is merely a claim about the way things happen to be in this world, then one is only committed to "weak supervenience." If it is a claim about the relationship between the two levels in all worlds that we can properly describe, then it is an example of a "strong supervenience" claim.

Debates over the nature of the determination relation itself have also distinguished between conceptual, metaphysical and nomological supervenience. To say that *m* nomologically supervenes on *p* is simply to say that there happens to be a lawlike connection between the two. For example *m* might supervene on *p* because of the ways that the laws of physics happen to stand in some world. This, of course, would be to claim that *m* weakly supervened on *p*.

Metaphysical supervenience involves the assertion that a determination relation holds across all possible worlds. If *m* metaphysically supervenes on *p* then in all possible worlds *m* will appear every time *p* appears. Finally, to claim that *m* conceptually supervenes on *p* is to suggest that anyone who understands the concepts *p* and *m* will recognize that they are related. Certain conceptual truths, for instance, that unmarried males are bachelors, or that 2 + 2 = 4 hold across all possible worlds. Conceptual truths of this kind sometimes entail supervenience relations. For example, as discussed previously, baldness, supervenes on hair distribution. Or, to put it another way, one's hair distribution properties determine whether one has the property of being bald. Since being bald, is, by definition connected to having an unacceptably meager distribution of hair, one can see hair distribution as determining baldness across all possible states of affairs. Both metaphysical and conceptual supervenience are cases of strong supervenience.

While it is illuminating to examine the consequences of altering the modal strength of claims about determination relations, such analyses do not provide significant insight into the nature of determination itself. Supervenience claims entail the existence of a determination relation, are governed in large part by one's modal commitments, however, bracketing the modal component of the claim, it seems that the supervenience claim itself does not do very much more than point to precisely the phenomenon we had hoped to understand, namely the covariation of mental and biological properties.

By saying that mental facts supervene on neuroscientific facts, philosophers promised some understanding of how higher-level facts about mental life are determined by lower-level facts about neuroscience. After three decades of debate, supervenience has not lived up to the hopes of its advocates. As Jaegwon Kim, one of the most important proponents of supervenience, puts it: "We must conclude then that mind-body supervenience is not an explanatory theory; it merely states a pattern of property covariation between the mental and the physical and points to the existence of a dependency relation between the two." (1998, 14) Property covariation is the problem to be explained, and can be accounted for in a variety of ways. Unfortunately, supervenience is not one of them. Perhaps one reason for increased interest in emergence and reduction in recent philosophy of mind may be the realization that these approaches hold out the possibility of the kind of explanatory account of the relationship between mind and body that supervenience failed to provide.

While even its most ardent advocates concede that supervenience did not live up to their expectations, it is nonetheless clear that analyses of the nature of supervenience have helped us to understand what counts as an acceptable explanation of the mind's place in nature given our basic commitments to physicalist metaphysics.

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S

Supervised Learning

Definition

Supervised learning is a form of learning in computational models such as artificial neural networks. The network is trained by computing the difference between its output and a teaching signal, which has to be

provided externally. This difference, the net error, is used in order to estimate by how much, and in which direction, to adjust connection weights in the network.

A disadvantage of supervised learning is that in many cases the existence of a teaching signal is not justified by the context of the application. It has been proposed that supervised learning occurs in the cerebellum.

►Cerebellum
►Connectionism
►Neural Networks

Supplementary Eye Field

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Definition

The supplementary eye field (SEF) is an area in the dorsal medial frontal lobe of the cerebral cortex that contributes indirectly to the control of movements of the eyes.

Characteristics

Higher Level Structures

SEF is located at the rostral end of the supplementary motor area, contiguous with the representation of orofacial, pinna and forelimb movements. SEF is located in Brodman's area 6 and corresponds to area F7 [1]. The human SEF is located on the medial surface of the superior frontal gyrus in the upper part of the paracentral sulcus (Fig. 1).

Lower Level Components

The connectivity of SEF is distinct from that of the skeletal motor cortex surrounding it, and SEF shares many but not all efferent targets and afferent sources with the frontal eye field (FEF) [2,3]. The major thalamic inputs to SEF arise mainly from the medial ventroanterior nucleus and the lateral segment of the mediodorsal nucleus as well as the intralaminar thalamic nuclei. These thalamic inputs convey signals mainly from the visuomotor zone of the substantia nigra pars reticulata, the intermediate layers of the superior colliculus and the face representation of the deep cerebellar nuclei. SEF projects to the caudate nucleus in a zone largely but not completely overlapping afferents from FEF, to the superior colliculus in a more diffuse pattern than the FEF counterpart, to specific brainstem oculomotor regions such as the nucleus raphe interpositus, the nucleus reticularis tegmenti pontis, the nucleus prepositus hypoglossi, the mesencephalic reticular formation, the interstitial nucleus of Cajal and the pontine reticular formation as well as the dorsomedial pontine nuclei.

SEF is reciprocally connected with several cortical areas, although fewer visual areas than is FEF. SEF interacts directly with area MST, the superior temporal polysensory area, area LIP, with anterior and posterior cingulate cortex and with the postarcuate premotor areas as well as the supplementary motor area and with prefrontal cortex in areas 12 and 46. SEF is also heavily connected with FEF in a spatial pattern that departs from the typical topography observed between other cortical areas.

Higher Level Processes and Lower Level Processes

Sensory Processes

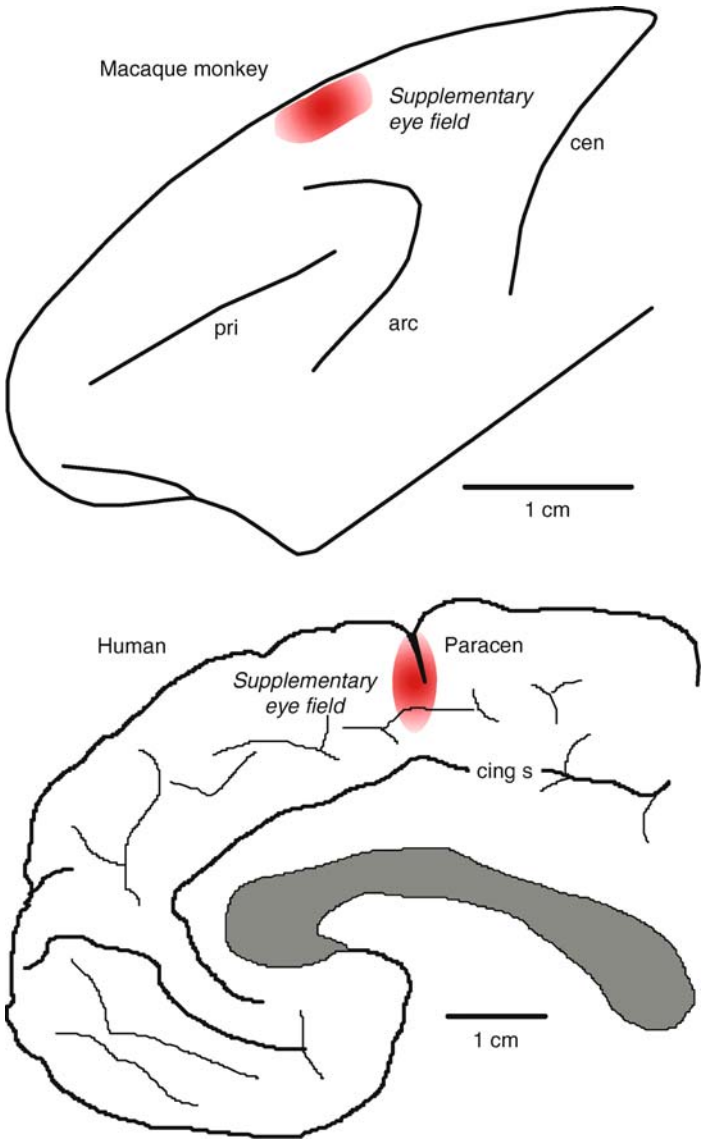
Neurons in SEF respond to visual and auditory stimuli [2,3]. However, visual responses are later and less vigorous than those observed in FEF. SEF neurons exhibit various kinds of extraretinal modulation including anticipatory activity and responses conditional on stimulus-response mapping rules [4]. Thus, SEF visual responses reflect less about the properties of the image and more about the stimulus in the context of the ongoing behavior.

Gaze Control

A great deal of evidence demonstrates that the SEF plays some role in the production of movements of the eyes [2,3]. In his pioneering electrical stimulation studies in humans, Penfield noted gaze shifts evoked by stimulation of the rostral part of the supplementary motor area (SMA). This finding has been confirmed using subdural electrode arrays to stimulate and record in humans. Schlag and Schlag-Rey first identified SEF as an area in which low intensity microstimulation evokes saccades and neurons discharge in relation to saccade production [5]. SEF neurons are also active in relation to the production of pursuit eye movements [6].

Numerous functional brain imaging studies using PET and fMRI have described activation in and around SEF of humans producing saccades [7]. Common findings include greater activation in SEF associated with antisaccades or memory-guided saccades relative to simple visually guided saccades.

Several other characteristics of SEF distinguish it from FEF. Electrical stimulation of many sites in SEF evokes saccades with dimension and direction dependent on the position of the eyes in the orbit, unlike what is observed in FEF or superior colliculus. Also, the saccade-related activity of many SEF neurons is contingent on the context in which the saccade is produced.

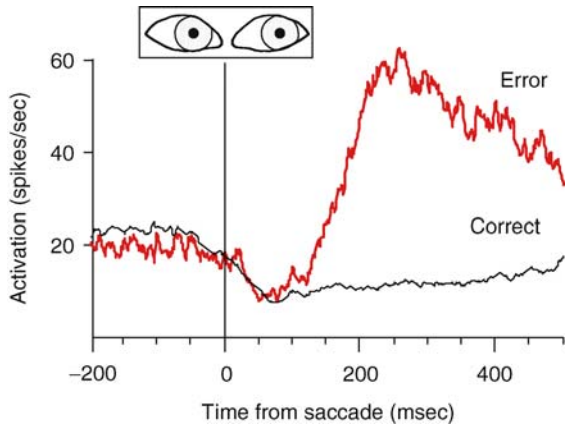


Supplementary Eye Field. Figure 1 Location of supplementary eye field in lateral view of frontal lobe of macaque monkey (*top*) and medial view of frontal lobe of human (*bottom*). In macaque monkeys, SEF is located on the dorsomedial convexity, medial to the upper limb of the arcuate sulcus. In humans, SEF is located dorsally on the medial surface around the paracentral sulcus. Abbreviations: *arc*, arcuate sulcus; *cen*, central sulcus; *cing s*, cingulate sulcus; *pri*, principal sulcus.

Finally, despite the apparent relation of SEF to saccade production, when tested in a task requiring control of saccade initiation, few neurons in SEF generate signals that are sufficient to control gaze. Thus, although anatomically and physiologically SEF seems to parallel FEF in many respects, SEF seems to play a less essential or potent role in saccade production.

Supervisory Control

Diverse more complex functional properties of SEF neurons have been described including conditional motor learning, object-centered representation, production of anti-saccades and sequences of saccades and eye-hand coordination. Theories of executive control cite five types of behavior that require supervisory control – planning or decision making, error correction, producing responses that are not well-learned, dealing with difficult or risky conditions and overcoming habitual responses. These categories include the conditions under which various investigators have reported neural activity in supplementary eye field. Therefore, these diverse findings can be organized under the hypothesis that SEF is part of a supervisory control network that is called into action when alternative



Supplementary Eye Field. Figure 2 Activity of a representative SEF neuron aligned on the initiation of a saccade that was correct (black) and an error (red). This neuron signaled the production of errors.

responses are difficult to distinguish, habitual responses must be overcome, consequences are uncertain, and deliberation is necessary [8,9]. The supervisory system exerts control over the processes that produce sensory-guided movements. Physiological evidence for a supervisory system in humans includes a scalp potential referred to as the error-related negativity that occurs when subjects produce errors. In macaque monkey SEF, certain neurons exhibit modulation specifically following a saccade that is an error (Fig. 2). Other neurons in SEF signal the anticipation and receipt of reinforcement. Still other neurons in SEF seem to signal the amount of mutually incompatible co-activation occurring. Error, reward and conflict signals form the basis of current models of executive control. Therefore, the most plausible current hypothesis about the function of SEF proposes that it provides executive control when saccades are produced under complex conditions.

Function

SEF contributes to the executive control of eye movements.

Pathology

Damage to SEF in humans or monkeys results in symptoms that are relatively mild and difficult to discern. Experimental ablation or inactivation of the SEF in macaque monkeys does not impair accurate fixation of eccentric visual targets or execution of saccadic eye movements to single visible or to remembered target locations. Modest impairment in production of sequences of saccades is observed. Transcranial magnetic stimulation that transiently inactivates SEF in humans also impairs production of a memorized sequence of eye movements. It should be noted that combined ablation of the FEF and the superior colliculus, leaving the SEF intact, produces effective gaze paralysis. These observations reinforce the conclusion that SEF plays an indirect role in gaze control. A recent report of one patient with a lesion restricted to SEF in one hemisphere described impaired self-control but intact error monitoring during a saccade task.

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Supplementary Motor Area (SMA, F3)

Definition

A secondary motor area located on the medial wall of the frontal lobe anterior to the hindlimb representation of primary motor cortex. This area has projections to primary motor cortex and is also contains large numbers of corticospinal neurons. SMA is important for producing bilateral movements and sequences of movements.

►Motor Cortex: Output Properties and Organization
►Primary Motor Cortex (M1)
►Visual Space Representation for Reaching

Suprachiasmatic Nucleus

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Synonyms

SCN

Definition

A hypothalamic nucleus lying above the optic chiasm and functioning as a master clock by setting the phase of activity of responses throughout the body.

Characteristics

There is a clock in the brain. If one were placed in an environment such as a cave, where there are no time cues at all, then cycles of sleep and wake would persist with a period of approximately 24 h. It was once considered possible that this ~24 h periodicity was the result of the earth's rotation around the sun. It is now well established however, that this rhythm is the achievement of a brain clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The experimental evidence that the SCN is the locus of a master clock in the brain that organizes the daily activities of the body is very robust, as it comes from many types of studies in many different labs, all of which converge on this conclusion. Thus, lesions of the SCN abolish all daily rhythms, transplants of the nucleus restore rhythmicity to an SCN-lesioned host animal, with the period of the donor, and ►rhythmicity of the SCN is sustained *in vitro and in vivo*, in the absence of input from the rest of the brain. In summary, the SCN is the locus of a brain clock that signals time of day to the body, findings that have been amply reviewed[1–4]. The SCN is necessary for these functions, and they can not be taken over by any other brain region.

The SCN is made up of individual cells that are themselves circadian clocks. The SCN contains ~10,000–20,000 neurons and about a third as many astroglia. For many years, it was unclear whether circadian rhythmicity was an emergent property of a network of ►oscillators working together, or a property of individual cells. The cellular basis of circadian rhythmicity was first seen in daily changes in spontaneous electrical activity of neurons. This discovery made it logical to seek the intracellular mechanism of rhythmicity. One of the most important discoveries of the past decade has been the identification of clock genes. These clock genes occur in a wide variety of organisms, ranging from prokaryotic bacteria, to plants, flies and mammals. Importantly, there is striking homology between clock genes among animals, enabling rapid discovery in research.

Within individual cells, the clock mechanism involves multiple core ►feedback loops consisting of positive and negative regulatory elements of transcription/translation which mediate the expression of a large number of genes at distinct circadian phases [4,5]. Briefly, the elements of the feedback loop include the transcriptional activators ►BMAL1 and ►CLOCK and the negative regulators PER and CRY which act on circadian ►E-box promoter elements. Post-translational modifications involving protein phosphorylation and ubiquitination temporally separate the turnover of the key positive and negative components of the clock, thereby producing a period length for the entire cycle of changes of approximately 24 h. Additional interlocking loops are produced by E-box–mediated regulation involving the ROR/►REV-ERB binding element (RORE) and the DBP/E4BP4 binding element (D-box). By assessing the expression level of key-clock genes and or their protein products, we can assess the time of day encoded in the cell.

Coordination of bodily rhythms and function of timing information. In orchestrating the timing of daily rhythms in physiology and behavior, the SCN prepares the body for the transitions between day and night. Daily rhythms can be seen not only in the salient behaviors of sleep and wake, but in virtually all behavioral and physiological responses that can be measured. For example, there are rhythmic oscillations in speed of responding in timed tasks, in the secretion of hormones, in concentrations of urinary metabolites, and in hunger and eating. Many of these responses enable the anticipation of changes that will soon occur. The optimal timing of each of these functions ensures their occurrence in the appropriate temporal niche: correct timing is a form of resource partitioning.

Light provides the most salient and reliable synchronizing or entraining signal from the environment, and functions to set the phase of SCN oscillators. The ►retina is the only light sensitive tissue in mammals, and the SCN receives direct input from the retina via the ►retinohypothalamic tract. (In contrast, non-mammalian vertebrates have a photosensitive ►pineal gland and/or ►photoreceptors within the brain itself and many organisms have light sensitive cells in various parts of the body). The SCN gets photic information from both rod/cone photoreceptors and from ►intrinsically photosensitive retinal ganglion cells (RCGs) [6]. The ►rods and ►cones, containing the photopigments rhodopsin

and iodopsin, are the classical photoreceptors in the outer retina of the eye. Rods and cones send their signals to neurons in the inner retina, the RGCs. Most RGCs project their axons via the optic nerve to brain areas involved in (conscious) vision. On the other hand, a small proportion (~1%) of RGCs expresses the photopigment ►melanopsin, is intrinsically photosensitive and project via the retinohypothalamic tract to the SCN among other brain regions. Projections of these intrinsically photosensitive RCG's make up about 80% of the retinal input to the SCN and regulate (not conscious) detection of light and dark, or nonvisual photoreception.

Intercellular communication in the SCN. One might imagine that SCN oscillators acts as a coherent unit, producing one synchronized rhythm throughout the nucleus. This is not at all the case. SCN neurons have a topographically and functionally structured arrangement, with distinct populations of neurons that are heterogeneous in morphology, physiology and neurotransmitter content [2]. Some neurons receive information about light via the retina, others mediate intercellular communication within the nucleus. Each of these functional cell types transfers photic or circadian signals to other brain regions. Synchronization of neurons within the SCN is achieved via multiple mechanisms including synaptic transmission, gap junctions, and possibly by diffusible signals, ensuring robust responses in the face of genetic or environmental perturbations. An orderly sequence of activation of cells occurs, and this has been studied by exploring the circuitry of the SCN.

The SCN has two main communicating compartments: ventral core and dorsal shell. Within the nucleus, the neurons located in a ventral "►core" subdivision receive light input from the retina and communicate that information to neurons of the dorsal "►shell." Core neurons express the neuropeptides, ►vasoactive intestinal peptide (VIP) and ►gastrin-releasing peptide (GRP). Core neurons are not detectably rhythmic or show very low levels of rhythmicity, measured by either electrical activity or clock gene expression. In a sense, core SCN neurons behave as "gates," sometimes open and sometimes closed to environmental input, and they function to narrow the phase dispersion of individual oscillating cells in the shell SCN [3]. Core cells express immediate early genes such as cfos and the core clock genes ►*Period1 (Per1)* and *Period2 (Per2)*, during the night or subjective night, but not during the day or subjective day. Furthermore, the expression of immediate early genes and proteins is highly correlated with the behavioral ►phase shifting effects of light. In contrast to the core, neurons of the dorsal shell contain ►vasopressin (►VP) and rhythmically express *Per1* and *Per2* [2] and have daily electrical activity rhythms, with higher firing rates during the day than at night. That rhythmic electrical activity is important in producing synchrony among SCN neurons has been shown in studies using tetrodotoxin, which prevents action potentials by blocking voltage-dependent Na+ channels. Application of tetrodotoxin to SCN slices, results in the loss of synchrony among SCN neurons.

The orderly expression of circadian rhythmicity dependent on networks of cells between core and shell and within shell networks has been confirmed by work both *in vivo* and *in vitro*. Lesions of the core SCN result in loss of behavioral and physiological rhythmicity, even when cells of the shell SCN survive ablation. If the dorsal and ventral SCN in a brain slice are separated by a cut, neurons in the dorsal shell become desynchronized, while those in the ventral core remain synchronized. In a slice preparation that lacks an ►SCN core, ►rhythmicity is unstable and of low amplitude, measured by bioluminescence of luciferase reporter for *Per2* [3]. In contrast, if a slice contains both core and shell neurons, a high amplitude, stereotyped spatiotemporal pattern of changes in gene expression occurs, with a complex wave of activation in a series of steps, beginning at the dorsomedial SCN, spreading ventrally in the outer shell and then centrally to the inner shell and a simpler pattern of deactivation involving a contraction of expression towards the central inner shell. A similar slow spread of signal is seen in SCN from animals sampled at different times. Taken together, these findings consistently indicate that core neurons are necessary for rhythmicity in SCN tissue and in the behavior and physiology of the animal, and that a temporally organized sequence of activation occurs on a daily basis in the SCN.

The major **neurotransmitters and chemical synapses in the SCN that comprise its circuits include** GABA, VIP and GRP. GABA and its receptors are expressed throughout the SCN. GABAergic transmission shows a circadian rhythm, and GABA treatment both phase shifts and synchronizes firing rate rhythms among SCN neurons [7]. In the SCN, both VIP and GRP occur in the core retinorecipient region and these peptides have daily rhythms, with GRP peaking in the day and VIP peaking in the night. VIP- and GRP-containing neurons have extensive intra- and extra-SCN projections and their respective targets, $VPAC_2$ receptor (encoded by the *Vipr2* gene) and the GRP receptor (BB_2) are both more heavily expressed in dorsal SCN. Mice lacking BB2 receptor expression maintain molecular and behavioral rhythmicity albeit with subtle alterations, indicating that GRP-BB2 signaling functions to amplify endogenous circadian rhythmicity. By contrast, mice deficient in VIP(*Vip*−/−) and mice lacking $VPAC_2$ expression ($Vipr^{2-/-}$) *are both incapable of sustaining normal circadian locomotor rhythms suggesting that this signaling system is necessary for sustaining circadian clock function. Indeed, molecular rhythms of clock genes and c-Fos are severely attenuated in the SCN of* $Vipr^{2-/-}$ *mice while the firing rate rhythms of* $VIP^{-/-}$ *and* $Vipr^{2-/-}$ *SCN cells are blunted or absent and show disrupted synchronization.*

GRP administration leads to induction of Per1 and Per2 mRNA as well as c-Fos protein in the dorsal SCN, and produces phase shifts in firing rate rhythms in SCN slices and in locomotor behavior. GRP administration restores neuronal rhythms in Vipr$^{2-/-}$ SCN slices.

Output signals of the SCN. Information from the SCN is transmitted directly, by neuronal projections to other brain regions and indirectly, via intermediate neurons to peripheral organs such as the pineal gland and liver via intermediate neurons [8]. Hypothalamic intermediate neurons in the ►subparaventricular zone and the paraventricular nucleus are important in this process. In addition, diffusible signals from the SCN are also sufficient to restore and sustain circadian behavioral rhythms in SCN-ablated animals. Consistent with this finding, transplanted fibroblasts assume the rhythmic phenotype of their host animal. Several prohormones and peptides are rhythmically produced in the SCN, and are candidate signaling molecules. Several diffusible signals have also been identified as output factors of the SCN, including ►transforming growth factor-alpha, ►prokineticin-2 and cardiotropin-like cytokine. Neural targets of SCN efferents such as the subparaventricular zone and ►paraventricular nucleus of the thalamus, express receptors for many of these molecules.

The brain clock is one part of the circadian system in the body. In regulating rhythmicity throughout the body, the SCN is part of a circadian system that involves a body-wide, hierarchically organized network of oscillators. The output from the SCN synchronizes the activity of ►peripheral oscillators, found in most tissues. These peripheral oscillators express autonomous rhythms, independent of the brain clock, but the SCN is required to synchronize the phase of peripheral oscillators within and between tissues.

The molecular oscillations of clock cells occur in virtually all tissues including the eyes, liver, kidneys, skin and muscles in mammals [9]. These oscillators in peripheral tissues can not maintain rhythmicity for a prolonged time, and dampen rapidly if they do not receive time cues from the SCN or the environment. The master clock in the SCN controls the peripheral oscillators by means of neuronal and/or humoral signals. When the SCN is lesioned, the circadian gene expression dampens in the peripheral tissues, probably because peripheral oscillators are desynchronized from each other. Understanding the actions of factors downstream of the SCN is will be a key to understanding how coordinated circadian rhythmicity is achieved in the brain and the rest of the body. Disruption of normal circadian patterns occurs in diverse disease symptoms including metabolism, cancer, and sleep [10], and the development of therapeutic interventions to treat circadian-related disorders depends on understanding the basic biology of rhythmicity and clocks.

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Suprachiasmatic Nucleus Core

Definition

One of two major anatomical and functional compartments of the suprachiasmatic nucleus (SCN). The core is more densely innervated by retina, visual thalamus, and brainstem than the other compartment , but contains fewer intrinsically rhythmic neurons or "clock" cells. Neurochemically, the core is typically demarcated by vasoactive intestinal polypeptide-containing neurons that densely innervate cells of the shell SCN. It is thought that the core SCN acts to integrate internal physiological and neural states with extrinsic environmental time cues and conveys these to the main oscillator in shell SCN. Reciprocally, circadian phase information from the shell SCN is relayed to the core SCN neurons via inhibitory synaptic transmission to ensure that core SCN neurons responses to extrinsic signals are appropriately phased.

►Suprachiasmatic Nucleus
►Suprachiasmatic Nucleus Shell

Suprachiasmatic Nucleus Gating

Definition

The notion of gating alludes to the function served by a "gate" in ordinary English usage. Thus, gating is the process in which a signal passes through when the gate is open, and fails to pass through when the gate is closed. The suprachiasmatic nucleus response to light is gated, in that a light pulse during the nocturnal animal's subjective night produces a change in gene expression in the nucleus along with a resetting of rhythmic behavior, while a light pulse during the animal's day produces no response. This is true even when the organism is housed in complete darkness, and the physical conditions at the time of exposure to light is identical at both times points.

►Clock Genes
►Suprachiasmatic Nucleus

Suprachiasmatic Nucleus Shell

Definition

One of two major anatomical and functional compartments of the suprachiasmatic nucleus (SCN). The shell is less densely innervated by retina, visual thalamus, and brainstem than the other compartment , but contains more intrinsically rhythmic neurons or "clock" cells. Neurochemically, the shell is typically demarcated by arginine vasopressin-containing and somatostatin-containing neurons. The precise distribution of these varies across the rostrocaudal axis of the SCN as well as between species. However, dense innervation of the shell SCN cells with fibers and terminals from neurons in core SCN is relatively invariant across most rodent species.

Currently, the shell is believed to function as the main oscillator of the SCN and regulates via inhibitory neurotransmission neural activity in the core SCN. Potential resetting information is in turn relayed to the shell SCN by core SCN neurons.

►Suprachiasmatic Nucleus
►Suprachiasmatic Nucleus Core

Supramarginal Gyrus

Definition

The supramarginal gyrus is the convolution of the inferior parietal lobule that arches around the terminal part of the ascending ramus of the lateral fissure. It is a part of the association cortex, which when damaged, can result in an agnosia, a failure to recognize. For example, in tactile agnosia there is a failure to recognize an object by tactile and kinesthetic sense (stereognosis) even though the sensory pathways and primary somatosensory cortex are intact.

Supramodal

►Multimodal Integration

Supraoptic Nucleus

Synonyms

►Nucl. Supraopticus; ►Supra-optic nucleus

Definition

Situated directly above the optic nerve, this nucleus together with the paraventricular nucleus forms the neuroendocrine system of the posterior lobe of the hypophysis. Efferents go to the neurohypophysis where they release into the blood ADH (vasopressin) and oxytocin. ADH (antidiuretic hormone) inhibits the permeability of renal epithelia to water. Oxytocin effects contraction of the uterus when giving birth and controls the release of milk during the lactation phase.

Dysfunction of this nuclear region induces the clinical manifestations of diabetes insipidus with severe polyuria (more than 20 l per day), since the lack of ADH results in a more or less unimpeded efflux of water from the renal epithelium.

►Diencephalon

Surface Perception

Definition
►Form Perception

Surface Processing

Definition
►Form Perception

Surface Traction

Definition
External force applied at the boundary per unit area. It represents the flux term associated with the linear momentum.

►Mechanics

Surrogate Outcome

Definition
A biomarker that is used as an outcome measure in, e.g. a clinical trial. Surrogate outcomes are powerful tools increasingly used in large, multi-center trials.

Surround Influence

►Contextual Influences in Visual Processing

Suture

Definition
The narrow, tight fibrous junction between two bony plates of the skull.

►Joints

Sweat Gland Control

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Definition
Thermal sweating plays an important role in keeping the body temperature constant. It appears over the whole body surface. In contrast, mental or emotional sweating is usually produced by emotion, mental stress and sensory stimulation. The active sweating appears on the palms and soles.

Characteristics
Quantitative Description
Human perspiration is classified into two types: insensible perspiration and active sweating. Insensible perspiration usually means the insensible loss of body weight. Water loss from the respiratory passages, the skin, and gaseous exchanges in the lungs contribute to the insensible loss of body weight. In the skin, the epidermis may be supplied with water originating from blood in the skin microcirculation and interstitial spaces so that water can evaporate from its dry surface. Thus, the evaporation of water from the skin seems to depend on several environmental factors such as ambient temperature and ambient humidity.

Heat, mental stimuli, muscular exercise and carbon dioxide are well known to induce active sweating in human beings. From the physiological point of view, such active sweating may be classified into two types: thermal and mental or emotional. Thermal sweating plays an important role in keeping the body temperature constant. It appears over the whole body surface. Emotion, mental stress and sensory stimulation are the other causal agents of active sweating. Mental or emotional sweating usually appears on the palms and soles. The physiological

features of mental sweating differ considerably from those of thermal sweating. Mental sweating has a shorter latent period for its onset. It immediately attains a certain rate of secretion that corresponds to the intensity of stimulation, remains as long as the stimulation lasts and subsides quickly after it ends.

Eccrine glands contribute to both types of sweating. The eccrine gland is tubular, the secretory part forming a closed coil. The duct begins in this coil and is partly embraced by it. It opens on the skin surface through a corkscrew-like channel that pierces the epidermis. The active sweat glands are present most densely on the sole, forehead and palm, somewhat less on the back of the hand, still less on the lumber region, and the lateral and extensor surfaces of the extremities, and least on the trunk and the flexor and medial surfaces of the extremities [1]. The secretory nerve fibers innervated in human sweat glands are sympathetic, which seem to be cholinergic in character as sweating is produced by pilocarpine and stopped by atropine [2]. Recently vasoactive intestinal peptide (VIP) coexisting in the cholinergic nerve fibers has been suggested as a candidate neurotransmitter that may control the blood circulation of the sweat glands [3]. The sudorific nervous system is also separated into parts for thermal and emotional sweating, each being controlled by its own regulatory centre in the brain that is associated with the sweat glands in its respective region of the skin.

Kuno (1956) [1] postulates that sweat glands of the general body surface are under the control of the center for thermal sweating which is a part of, or is closely associated with, the hypothalamic temperature regulation center. Whereas the center for mental sweating is located in the cerebral cortex and not only controls directly the sweat glands of the confined areas, such as palms and soles, but also affects sweating of the general body surface through exciting the center of thermal sweating. The presence of a cortical sweat-inhibitory center has also been suggested. Thus, sweat response to mental stimulation may appear body surface only when close to or above the threshold of thermal sweating. Even in a temperature environment, however, neural impulses for thermal sweating still reach the sweat glands and mental effects can be visualized on a focal area where local sweating has been provoked by a suforific agent [4]. Thus, the findings imply that the differences in nature between palmar and non-palmar sweating may possibly be relative ones, especially in the periphery, as suggested by Nakayama (1969) [5]. On the other hand, the other studies suggest that the palmar and non-palmar sweatings are under the control of essentially different central mechanisms as mentioned by Kuno (1956) [1]. It has been demonstrated that a single stimulus can cause inhibition of non-palmar sweating simultaneously with facilitation of palmar sweating [6]. Thus, various non-thermal stimuli appear to exert two ways of effects on non-palmar sweating, excitation and inhibition, while they equally bring about facilitation of palmar sweating. The stimuli that provoke emotional excitation or protopathic sensation are considered to produce facilitation of non-palmar sweating. Consequently, there appears to be a higher central mechanism that is closely associated with such mental functions and exerts an excitatory effect on the center for thermal sweating. The limbic cortex that is considered to be the structure closely related to emotion, protopathic sensation and also to autonomic functions may likely be involved in this mechanism. The sweat-suppressive response on the general body surface appears to be provoked by stimuli that act as mental stress involving thought and memory, and by efforts for physical tasks. It is assumed therefore that the activity of regions in the neocortex may be concerned with this sweat-suppressive mechanism, possibly by exerting an inhibitory effect on the center for thermal sweating. In contrast, palmar sweating responds to any non-thermal sweating [6].

Regarding central mechanisms of active palmar sweating responses, a very impressive paper by using the newly developed ratemeter [7] was reported that the average electroencephalographs (EEGs) contained slow wave fluctuations, which occurred 5 s prior to the onset of mental calculation-mediated palmar sweating response (MSR). The central source locations of the MSR-related potentials were analyzed by the EEG dipole tracing method. In conclusion, the mental stimulation activated the medial part of the amygdala 5 s prior to the MSR in one subject or the lateral part of the hippocampus 5 s prior to the MSR in another subject. Thus, it seems reliable to assume that the mental stimulation such as arithmetic calculations elicits electrical activity in the limbic system including the amygdala and hippocampus. This activation of limbic system was confirmed to increase the sympathetic sudomotor activity 3 s prior to the onset of MSR [7].

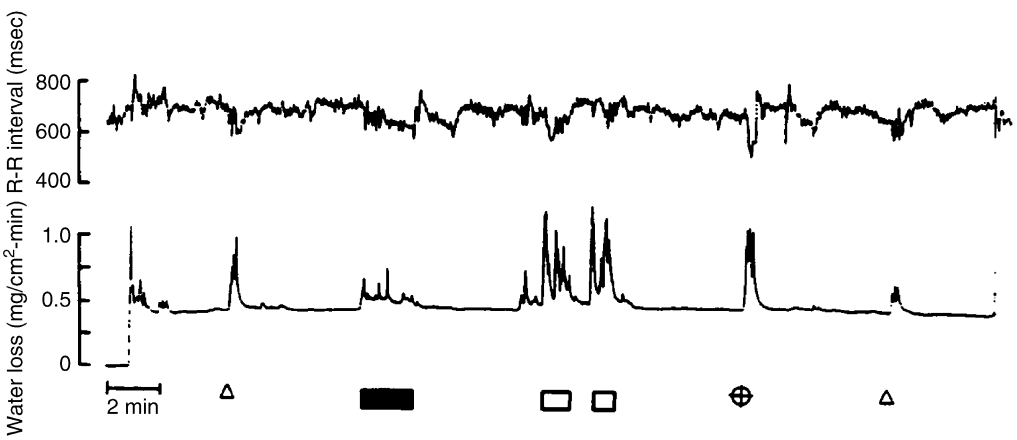
The amygdala has long been thought to be involved in emotional behavior, and its role in anxiety and conditioned fear has been highlighted [8]. Thus, emotional expression may be mediated by neural connections from the lateral to the central nucleus of the amygdala, which, through its projections to hypothalamus and brainstem areas, is thereby able to coordinate the behavioral, endocrine and autonomic responses that form an integrated emotional response [9]. In a clinical case, a complete reduction of active palmar sweating responses was reported in a young female patient with viral encephalitis that elicited inflammatory damage to the bilateral amygdala. The damage was confirmed through functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (Asahina M (2001) Personal communication). On the other hand, no functional change in noradrenergic sympathetic nerve fibers

innervated in microcirculation of the palmar skin was, however, observed in the same patient.

Measurements for Palmar Active Sweating

We measured the responses of active sweating by using the newly developed ratemeter (SKD-2000, Skinos, Nagoya, Japan) attached to the palmar side of the left thumb (attached area 1 cm^2). In brief, the ratemeter consists of three parts: (i) a specialized chamber equipped with a capacitance-typed humidity sensor and an electrical circuit to compensate changes in ambient temperature, (ii) a supply element for dehumidified air, and (iii) an electrical signal processing circuit. The ventilated chamber has two compartments. The first compartment is formed for mixing both the water perspired from skin and the dehumidified air supplied from the air supply unit. The second compartment is formed on top of the first one and connected with the first compartment through a communicating hole. The humidity sensor and a small thermistor are set on the roof of the second compartment. The dehumidified air passed through a tube filled with silica gel for drying was circulated through the two compartments (flow rate 300 ml/min). Thus, the ratemeter is handy and suitable to use clinically at the bed-side because of no usage of huge cylinder system. The absolute amount of palmar perspiration including active sweating responses is calculated electrically through three parameters: (i) relative humidity recorded with the capacitance-typed thin-film humidity sensor, (ii) temperature of air circulated through the ventilated chamber, and (iii) the saturated vapor pressure calculated theoretically with the air-temperature. These parameters are subjected to calculation in analogue of the absolute amount of the palmar perspiration, and then, after A/D conversion, to microcomputation. Ultimately, the absolute amount of the loss of water per a constant area of the palmar skin and a constant time is recorded on a chart recorder and stored into a personal computer. The data stored were analyzed with a commercial software program (Hyper Wave, Kissei Komtec, Matsumoto, Japan).

Figure 1 demonstrates representative recordings of mental and physical stimuli such as performance of mental arithmetic, talking with a friend, deep respiratory movement and hand grasping on palmar perspiration and on the R-R intervals determined by continuous recordings of a surface electrocardiogram. Palmar perspiration including active sweating was recorded by the home-made ratemeter with the capacitive humidity sensor. The insensible perspiration and active sweating were evaluated on the thumb of the left hand of a healthy man aged 48. Three cycles of deep inspiration with deep respiratory movement caused a marked decrease in the R-R interval followed by three spikes of the active sweating with a short time lag. Performance of mental arithmetic, such as repetitive subtraction of 7 from 1,000, also produced a significant increase in active sweating on the palm. The stimulation simultaneously produced a decrease in the R-R intervals with phasic oscillations, which returned to the control level with an overshoot after the stimulation. When a friend entered the examination room, a marked increase in the active sweating with many oscillations was observed without a significant change in the R-R intervals. When the subject started to talk with his friend a significant increase in the active sweating was found with a tentative decrease of the R-R intervals. Grasping of a 25 kg weight with the right hand for 20 s caused a cessation of respiratory movement followed by a marked increase in active sweating with oscillations and a sustained decrease in R-R intervals. These findings suggest that the new home-made ratemeter is



Sweat Gland Control. Figure 1 Representative recordings of palmar active sweating. The effects of mental and physical stimuli such as deep respiratory movement (Δ), performance of mental arithmetic (■), talking with a friend (□), and hand grasping (⊕) on palmar perspiration recorded by the ratemeter (lower panel) and on changes in the R-R intervals (upper panel) in a healthy male subject aged 48. [10].

suitable for detecting phasic changes in active sweating on the palmar skin and that the changes in sweating do not always agree with oscillatory changes in the R-R intervals in humans. In addition, grasping of the hand is confirmed to be one of best stimuli to selectively activate eccrine sweat glands in human palms.

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Sweating Disorders

Definition

The sweating disorders are classified into anhidrosis and hyperhidrosis. An anhidrosis disorder is defined as the inability of the body to produce and/or deliver sweat onto the skin surface. Hyperhidrosis over the whole body surface may be seen as a component of various diseases, e.g. night sweat, inphthisis. More marked hyperhidrosis appears restricted to certain parts of the body surface, and the following patterns seem to appear frequently, (i) Hyperhidrosis on the palms and soles, (ii) Hyperhidrosis of the axillae, (iii) Hyperhidrosis on the face, and (iv) other varied patterns of hyperhidrosis.

►Sweat Gland Control

Sweet Taste

Definition

►Taste – Sweet

Sydenham Chorea

Definition

Also known as Saint Vitus' dance. Sydenham chorea (SC) is the most common acquired ►chorea in children and presents as choreiform movements, obsessive-compulsive symptoms very similar to those in traditional obsessive-compulsive disorders, and behavioral and psychiatric changes. It occurs in association with rheumatic fever, which is an immunologically mediated disease following infection by group A beta-hemolytic Streptococcus (GABHS). Antibodies against GABHS cross-react autoaggressively with the heart, joints, skin, and brain tissues including the ►basal ganglia, which causes the motor and psychiatric changes.

►Basal Ganglia
►Basal Ganglia – Motor Function of

Sylvian Fissure

Definition

A deep sulcus found by F. Sylvius (1663), separating the temporal lobe from the frontal and parietal lobes. It is called also as the lateral sulcus.

►Somatosensory Cortex II (SII)

Sympathetic

►Central Integration of Cardiovascular and Respiratory Activity Studied In?Situ

Sympathetic Apraxia

Definition

Lesions of the ►premotor cortex in the dominant hemisphere may entail impairment of movements of the ipsilateral limbs.

►Limb Kinetic Apraxia

Sympathetic Block

Definition

Blockade of the activity in the sympathetic outflow to an extremity by a local anesthetic applied to the appropriate ganglion (ganglia) of the sympathetic chain. A measure of a complete block is an increase of skin temperature at a finger or toe tip to about 36°C.

►Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Sympathetic Ganglia

►Autonomic Ganglia

Sympathetic Ganglion Block

Definition

Normally in the paravertebral chain, the discharge of only one preganglionic axon is responsible for transmission to each postganglionic cell, as the only effective inputs are suprathreshold with a very high safety factor, as at the neuromuscular junction. Acetylcholine (ACh) released from preganglionic terminals activates subsynaptic nicotinic receptor-channels (nAChRs). Ganglionic nAChRs in sympathetic ganglia differ from nicotinic receptors elsewhere, with the α3/β4 subunit predominating.

The effects of specific antagonists depend on subunit composition, but will also depend on the size of the underlying synaptic current.

►Acetylcholine
►Autonomic Ganglia
►Sympathetic Pathways

Sympathetic Nervous System

Definition

Division of the autonomic nervous system that is concerned with catabolic activity by such actions as augmenting cardiac output, promoting blood supply to skeletal muscles and inhibiting the digestive system. This system arises from the thoracolumbar segments of the spinal cord in mammals. This system innervates the vasculature throughout the body as well as specific targets such as the dilator pupillae, the cardiac pacemaker, lymphoid tissues, the male internal reproductive organs, etc. It is excitatory to sphincters in the gastrointestinal tract and inhibitory to the rest of the gut.

►Ageing of Autonomic/Enteric Function
►Autonomic Ganglia
►Sympathetic Pathways

Sympathetic Pathways

Definition

The sympathetic pathways form one of the major subdivisions of the autonomic nervous system (there are also parasympathetic pathways and enteric pathways, and an afferent or sensory component). They extend from the thoraco-lumbar spinal cord to the peripheral organs, including the adrenal gland, heart and all the blood vessels of the body, and represent the autonomic thoraco-lumbar outflow.

The axons of the preganglionic neurons of the sympathetic pathways (preganglionic fibers) reach the corresponding ventral roots, they emerge as separate nerve (called white rami communicantes) which in turn reach the paravertebral sympathetic chain (or trunk).

The chain, a symmetrical structure on each side of the body, is made of ganglia and connecting nerve strands, and extends from the base of the skull to the sacral region; within the chain the preganglionic fibers spread out cranially and caudally and reach all ganglia. The

largest ganglia are the superior cervical ganglion, which provides sympathetic innervation to organs of the head, including cerebral blood vessels and skin, and the stellate ganglion, the main target of which is the heart.

Some preganglionic fibers reach the adrenal gland; others travel further away from the spinal cord, form the splanchnic nerves and reach sympathetic ganglia located in front of the abdominal aorta, the prevertebral ganglia. The preganglionic sympathetic neurons are cholinergic while the ganglion neurons and their postganglionic fibers are in the great majority adrenergic.

These secrete noradrenaline that stimulate the heart to beat faster and more strongly and blood vessels to constrict and to increase blood pressure (but to dilate pulmonary and coronary vessels).

Sympathetically Maintained Pain (SMP)

Definition

Sympathetically-Maintained Pain (SMP) is a pain that is maintained by sympathetic afferent innervation or by circulating catecholamines. It may occur in several conditions, such as Complex Regional Pain Syndromes (CRPS I and II), inflammatory pains, phantom pain, metabolic neuropathies, neuralgias. Blockade of the sympathetic outflow to the affected extremity by a local anesthetic injected close to the appropriate paravertebral ganglion/ganglia (stellate ganglion for forearm, lumbar ganglia L4/L5 for the hindlimb) significantly reduces the for ≥6 hours.

►Autonomic Control of Sensory Receptors
►Complex Regional Pain Syndromes – Pathophysiological Mechanisms

Sympatho-adrenal System

Definition

The sympatho-adrenal system is the adrenal medulla and its innervation by sympathetic preganglionic neurons. The adrenal medulla consists of cells that release either adrenaline or noradrenaline upon impulses in the preganglionic neurons. The sympatho-adrenal system is functionally distinct from the various types of sympathoneural systems.

►Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Sympathomimetics

Definition

Sympathomimetics are pharmacological agents mimicking the effects of stimulation of the sympathetic nervous system.

►Sympathetic Nervous System
►Sympathetic Pathways

Symporter

Definition

►Ion Transport

Synapomorphy

Definition

A shared derived trait. A trait present in all members of a phylogenetic group that are derived from a common ancestor, and not present in the sister group.

►Electric Fish
►Evolution and the Concept of Homology

Synapse

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Synapse

There are more than 100 billion neurons and many more glial cells in the human brain. Neurons extend long

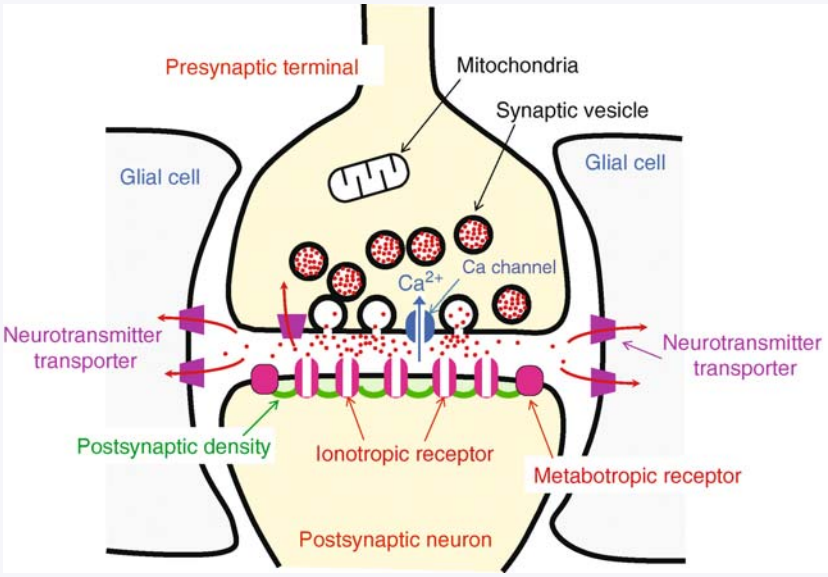
neurites and form neuronal networks whilst having functional contact through a specialized structure called the synapse, and various brain functions are conducted by this neuronal network. Neurons have two types of neurite, one is dendrite and another is axon. Neurons receive signals through many synapses formed on dendrite and cell soma. These signals are processed by summation or integration (►synaptic integration), and finally generate action potentials at the hillock of axon. Action potential propagates along the long axon and communicates a message to other neurons through synapses made along axons and/or axonal terminals.

There is a special gap between two neurons at the synapse, thus the electrical signal, the action potential, cannot propagate beyond the synapse. In many cases, synaptic transmission is mediated by a chemical substance called ►neurotransmitter. Since the electrical signal cannot spread over synapses without restriction, and signals propagate after conversion to chemical signals, it becomes possible for data processing to occur for the expression of higher brain functions. It may be possible to say that there are numerous numbers of biological switches, they are synapses, in the neuronal network, and multiple brain functions are achieved by controlling the neuronal network with these switches. More importantly, the properties of synapses are changing in the short-term as well as in the long-term in a neuronal activity-dependent manner, and sometimes, formation and disappearance of synapses occurs in some cases. This characteristic property of synapses called synaptic plasticity enables us to survive after a struggle for existence by acquiring and storing information from the environment, and using this information to properly modify the property of the neuronal network to make proper responses. More importantly, memories stored in the neuronal network are absolutely essential for human personality, and it has now become a very important problem to overcome memory disorders in an aging society.

Basic Structure and Functions of Chemical Synapse

Structure of Chemical Synapse

Usually, synaptic transmission is conducted unidirectionally from a presynaptic neuron to a postsynaptic neuron. As a consequence, a synaptic structure is composed of presynaptic and postsynaptic elements separated by a 20–50 nm space called the synaptic cleft (Fig. 1). In the presynaptic nerve terminal, many small clear vesicles called synaptic vesicles, which have a diameter of around 40–50 nm, are accumulated. There are also some large dense-cored synaptic vesicles that have a diameter of 70–200 nm. Presynaptic cytoplasm also contains mitochondria that are usually positioned some distance away from the synaptic vesicles. Mitochondria provide ATP, necessary for the accumulation of chemical neurotransmitters into the synaptic vesicles by active transport, and perhaps, are involved in the regulation of intracellular Ca^{2+} homeostasis. In the presynaptic plasma membrane face to postsynaptic membrane, there is a specialized region called the active zone, where neurotransmitter release occurs (►active



Synapse. Figure 1 Basic structure of chemical synapse. Neurotransmitters are stored in synaptic vesicles and are released from presynaptic nerve terminals by a Ca^{2+} -dependent exocytosis. Neurotransmitters activate both ionotropic and metabotropic receptors in the postsynaptic plasmamembrane. Neurotransmitters in the synaptic cleft are recovered for reuse to neurons and glial cells by membrane neurotransmitter transporters.

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zone). The synaptic cleft is filled with extracellular matrix, which contains a number of extracellular proteins thought to be important in synapse formation and stabilization, such as laminin and cell adhesion molecules (►synaptic adhesion molecule). Many ►ionotropic and (►G protein-coupled receptor (Metabotropic receptor)) metabotropic receptors are accumulated at the portion of postsynaptic membrane directly opposed to the presynaptic terminal. The region just beneath the receptor-laden postsynaptic membrane often has a characteristic protein-rich structure called postsynaptic density (PSD). In addition to the receptors, many proteins for signal transduction are functionally organized into a huge multi protein complex in PSD through bindings to several ►scaffold proteins. Some receptors also exist in the presynaptic plasma membrane, which are important for feedback regulation of neurotransmitter release. Except for the synaptic contact between the pre and post synaptic membrane, the synaptic structure is entirely covered with astroglial cells. Recent studies revealed that several neurotransmitter receptors are also expressed in glial membrane, and the glial cells may play active roles in the regulation of synaptic function.

Mechanisms of Chemical Synaptic Transmission

By an invasion of action potential into presynaptic nerve terminals, a voltage-dependent Ca channel is activated and Ca^{2+} ions are introduced into the nerve terminal, which triggers neurotransmitter release into the synaptic cleft by an ►exocytosis of synaptic vesicles involving docking and fusion of the synaptic vesicle membrane with the presynaptic plasma membrane. Neurotransmitters spread in the synaptic cleft by diffusion and bind to receptors in postsynaptic membranes for activation. ►Ionotropic receptors activation causes a rapid change in membrane potential and the probability of action potential generation. Activation of metabotropic receptors ►(G protein-coupled receptor (Metabotropic receptor)) slowly induces the generation of second messengers and/or a change in membrane potential through a modulation of ion channel function. All of these changes cause a change in responsibility to other synaptic input. After activation of these receptors, neurotransmitters in the synaptic cleft are removed by membrane transporters and/or neurotransmitter degradation enzymes in the neuronal and glial plasma membranes or the extracellular matrix to terminate synaptic transmission.

Presynaptic Mechanisms

Neurotransmitters

Two groups of substances are used as chemical ►neurotransmitters. One is a group of relatively small molecular size, which are some amino acids, monoamines, acetylcholine, and ATP, and another is a group of neuropeptides. Many nonpeptidic neurotransmitters are stored in small clear synaptic vesicles, whereas the peptidic neurotransmitters are stored in the large dense-core vesicles.

It is not so easy to classify a substance as a neurotransmitter, and even for glutamate, which is established as a major neurotransmitter in the vertebrate brain, it took a long time to be approved as a neurotransmitter. At least the following five conditions should be satisfied for classification as a neurotransmitter: (i) The substance is synthesized in neurons. (ii) The substance is stored in presynaptic terminals. (iii) The substance is released after stimulation of neurons. (iv) An equivalent effect is observed by the substance exogenously applied. (v) A removing mechanism exists.

Properties of Neurotransmitters

Dale's Low

Usually, every neuron has only one kind of small neurotransmitter (Dale's low). Thus, neurons can be characterized by the neurotransmitter that they have. For example, neurons having glutamate, γ-aminobutyric acid (GABA), adrenalin (epinephrine), and acetylcholine as neurotransmitters are called glutamatergic, GABAergic, adrenergic, and cholinergic neurons, respectively. However, ATP coexists with acetylcholine and catecholamine in some synaptic vesicles and in secretory vesicles. There is also a report showing that GABA and glycine are used as neurotransmitters in one neuron. Thus, it is not clear how Dale's low is strictly approvable. It is obvious that most of the neurons have both small clear synaptic vesicles and large dense-cored vesicles, and thus, most of the neurons have at least two types of neurotransmitter, one is nonpeptidic and another is peptidic.

Glutamate and Aspartate

In vertebrate brain, glutamatergic neurons are distributed throughout the central nervous system and glutamate is used as a major excitatory neurotransmitter in the brain. Glutamate is synthesized from 2-oxoglutarate, an intermediate product of tricarboxylic acid cycle, by transaminase. Glutamate binds and activates both ionotropic receptors such as NMDA receptors and non-NMDA receptors, as well as various metabotropic glutamate receptors. Glutamate is recovered from synaptic cleft by membrane glutamate transporters present in neuronal and glial plasma membranes. Aspartate is also used as a neurotransmitter in some kinds of neurons.

Gamma-Aminobutyric Acid (GABA) and Glycine

GABA and glycine are used as major inhibitory neurotransmitters in the mammalian central nervous system (CNS). GABA is synthesized from glutamic acid by glutamic acid decarboxylase (GAD). GABA activates ionotropic $GABA_A$ receptor and metabotropic

$GABA_B$ receptor. Glycine is mainly used in the spinal cord. Only the ionotropic receptor is known as a glycine receptor.

Monoamines

Non-amino acid compounds that have an amino residue such as catecholamine and indoleamine are generally known as monoamines. In the nervous system, dopamine, noradrenalin (norepinephrine), and adrenalin (epinephrine) are used as neurotransmitters, and are synthesized from tyrosine by tyrosine hydroxylase and following several other enzymes. As for indoleamine, serotonin is used as a neurotransmitter, which is synthesized from tryptophan by enzymes including tryptophan hydroxylase.

Most of the cell bodies of monoaminergic neurons are accumulated in the brain stem and their neurites are innervate to a broad range of brain regions. The axons of these neurons are highly branched and often have varicosities, and the monoamines are released from these structures diffusely around the releasing site. All of the receptors for monoamine neurotransmitters are metabotropic, and no ionotropic receptor is known so far. Thus, the major roles of monoamine neurotransmitters are not regular synaptic transmission conducted by glutamate and GABA, but are regulatory roles to alter the responsibility of postsynaptic neurons to other synaptic input.

Cell bodies of dopaminergic neurons are enriched in the substantia nigra and ventral tegmental areas in the mid brain, and participate in emotional control and complex motor activities. Seretonergic neurons are mainly located in the laphe nucleus in pons, and are related to mode and anxiety. Noradrenergic neurons are enriched in locus ceruleus in pons, and have responsibility for emotional excitement, judging for a decision, sleep and mood. In the mammalian peripheral nervous system noradrenalin is used as a neurotransmitter of postganglionic neurons.

Acetylcholine

Acetylcholine is a neurotransmitter of motor neurons in vertebrate neuromuscular junctions and induces very fast contraction of skeletal muscles. In mammalian CSN, cholinergic neurons are enriched in basal ganglia, such as nucleus basalis Meynert and septal nucleus, and pons, and these cholinergic neurons send their neurites to a broad range of brain areas. In the peripheral nervous system, acetylcholine is a neurotransmitter of preganglionic neurons and postganglionic neurons of the parasympathetic nervous system. Acetylcholine is synthesized in nerve terminals from acetyl-coenzyme A and choline by choline acetyltransferase. Acetylcholine activates the nicotinic acetylcholine receptor, an ionotropic receptor, and muscarinic acetylcholine receptor, a metabotropic receptor. Acetylcholine is released in the synaptic cleft and is hydrolyzed by acetylcholinesterase located in cell membranes as well as in the extracellular matrix. The resulting choline is used for acetylcholine synthesis after reuptake by membrane choline transporter.

ATP

ATP is a universal energy currency, but is also used as a neurotransmitter in neurons. ATP is shown to be stored in synaptic vesicles of *Torpedo* electric organs and secretory vesicles of adrenal chromaffin cells, however, the transport mechanism into synaptic vesicles is not yet known. ATP activates ionotropic P2X receptors and metabotropic P2Y receptors. ATP also activates metabotropic adenosine receptors after conversion to adenosine.

Peptidic Neurotransmitters

More than 50 neuropeptides are found in the mammalian brain and many of these peptides are likely to be used as neurotransmitters. After being synthesized in endoplasmic reticulum in neuronal cell soma, neuropepitdes are packed in vesicles and transported along long axons to presynaptic terminals. All of the neuropeptide receptors are metabotropic, and induce slowly activated and prolonged responses in their target neurons. Neuropeptides released into the synaptic cleft is degraded by extracellular peptidases without reuse. Conventional neuronal excitation does not induce exocytosis of large dense-cored vesicles, and neuropeptides are released only after high frequency stimulation. Thus, neurons change a property of synaptic transmission in a frequency-dependent manner.

Neurotrophins, such as nerve growth factor and brain-derived neurotrophic factor, are polypeptides essential for the survival and maturation of neurons in the developing stage. These neurotrophins are also expressed in adult brain and participate in the regulation of neuronal and synaptic activities [1]. At least some portion of neurotrophins are released from neurons by exocytosis in an activity-dependent manner. Neurotrophins exert their action through the activation of Trk receptors, which are members of the receptor tyrosine kinase super family.

Storage of Neurotransmitter into Synaptic Vesicles

Various ►vesicular neurotransmitter transporters for nonpeptidic neurotransmitters are expressed in small synaptic vesicles and specifically accumulate neurotransmitters in a type-dependent manner. H^+ -ATPase is also expressed in synaptic vesicle membranes, and creates a proton gradient across the membrane by the hydrolysis of ATP. All of the vesicular neurotransmitter transporters used this proton gradient to actively transport neurotransmitters into vesicles. Glutamate and glycine are very common amino acids, and thus the

expression of vesicular transporters of glutamate and glycine characterize glutamatergic and glycinergic neurons.

Exocytotic Release of Neurotransmitters

Exocytosis

Neurotransmitters stored in synaptic vesicles are released into the synaptic cleft by ►exocytosis, which involves the docking and fusion of the synaptic vesicle membrane with the presynaptic plasma membrane. The idea that neurotransmitters are released not by simple diffusion but by a package of elementary unit (►quantal transmission) was initially postulated by Kats and Miledi from a quantal analysis of synaptic transmission of frog neuromuscular junctions. This hypothesis is further supported by the discovery of synaptic vesicles using electron microscopy. Although it has been hypothesized that neurotransmitters are released by an exocytosis of synaptic vesicles, it is only recently that direct experimental evidence supporting this idea was obtained. Early experiments of freeze-fracture electron microscopic techniques revealed that small holes appeared along ►active zones and possible synaptic vesicle proteins appeared in the presynaptic membrane after electric stimulation of presynaptic fibers. The appearance of synaptic vesicle proteins in plasma membranes after stimulation was also observed in cultured neurons by immunocytochemistry, using antibodies that recognize epitopes located in the luminal site of synaptic vesicles. However, all of these results were obtained by using fixed preparations, and real-time process of exocytosis was not observed in these experiments.

The area of cell surface membrane is expected to be increased after the fusion of synaptic vesicle membrane, and cell surface area can be measured by observing membrane capacitance by an electrophysiological technique (►Capacitance measurement). Increment of cell surface area after stimulation is successfully observed in real time with good time resolution using adrenal chromaffin cells and Calyx of Held, a neuronal preparation having a giant presynaptic terminal. Furthermore, the process of exocytosis was visually observed in real-time in adrenal chromaffin cells and hair cells of the inner ear by using video-enhanced microscopy and total-reflection fluorescence microscopy (►evanescent field fluorescence microscopy). The exocytotic process was also monitored in various neuronal preparations, including neuromuscular junction, brain slice, and cultured neurons by using a fluorescence die, ►FM1-43, and pH-sensitive fluorescence proteins.

Merit of Exocytosis

Neurotransmitters released into the synaptic cleft bind reversibly to their receptors in the postsynaptic membrane, and the binding speed is dependent on their concentration. Thus, to achieve rapid activation of the receptor, it is necessary to increase neurotransmitter concentration very rapidly after action potential propagation to the nerve terminals. Various problems will arise for cellular metabolisms and function if any particular substance accumulates in the cytoplasm at a very high concentration. By using vesicles that have a lipid bilayer membrane, it becomes possible to accumulate neurotransmitters of very high concentration without any effect on cellular metabolism. The extracellular concentration can be increased very rapidly by releasing all of the content in a single process. It is also possible to regulate the efficiency of neurotransmitter release by changing the distribution and location of synaptic vesicles in presynaptic terminals.

SNARE Proteins

Both the plasma membrane and the synaptic vesicle membrane is composed of phospholipid bilayers, and it is necessary to fuse these two membranes for exocytosis. However, the hydrophilic head group of phospholipids are hydrated, and as two lipid membranes are difficult to bring close to each other within 2 nm, the assistance of proteins is necessary to promote membrane fusion. So called SNARE proteins play an essential role in bringing membranes close enough to induce membrane fusion (►Presynaptic proteins).

In neurons, three SNARE proteins, VAMP-2/synaptobrevin2 in synaptic vesicle membranes, and syntaxin and SNAP-25 in plasma membranes, are involved in the exocytosis of synaptic vesicles. It is now believed that membrane fusion is induced by a complex formation of these SNARE proteins. It is possible to regulate exocytosis and ►synaptic vesicle recycling by modifying the formation or dissociation of the SNARE complex. Many SNARE binding proteins are expressed in presynaptic terminals and are likely to be involved in the regulation of presynaptic functions.

Ca^{2+}-Sensitivity

Exocytotic secretion is a cellular function generally observed in eukaryotic cells. There are two pathways for secretion, one is an unregulated constitutive pathway and another is a regulated pathway. Neurotransmitter release is one of the regulated pathways and is triggered by Ca^{2+}. Various ►calcium binding proteins that have different affinities to Ca^{2+} are expressed in the brain, and it is widely accepted that the Ca^{2+}-binding protein which regulates neurotransmitter release is a synaptotagmin, a synaptic vesicle protein that has C2 domains. The affinity of Ca^{2+} to C2 domain is not very high, but this property is quite important for the Ca^{2+} binding of neurotransmitter release. Action potential invasion to presynaptic terminals activates a voltage-dependent Cachannel near the ►active zone, and Ca^{2+} influx into

the terminal triggers exocytosis. Intracellular Ca^{2+} will return to the basal level by Ca^{2+} excretion mechanisms, but it takes some time to return to the basal level. If the Ca^{2+} binding protein has a high Ca^{2+} sensitivity, neurotransmitter release will continue by this residual Ca^{2+}. Since neurons send different kinds of messages along axons by changing the pattern and frequency of action potentials, the resolution of signal will decrease if the neurotransmitter release is not terminated quickly after invasion of action potential. Many Ca^{2+} binding proteins of high Ca^{2+} affinity are also expressed, but their functional roles are not well defined.

Elementary Steps of Exocytosis

Prior to Ca^{2+}-induced membrane fusion, there are several elementary steps necessary for exocytosis, which are tethering, docking and ►priming of synaptic vesicles. Several ►presynaptic proteins are involved in each step, and neurotransmitter release is regulated by modifying the functions and properties of these regulatory proteins.

There are several different synaptic vesicle pools that have different exocytotic properties, such as readily releasable pools, releasable pools, and storage pools. In *Drosophila* neuro-muscular junction, these pools are specially refined by an imaging analysis (►synaptic vesicle recycling). Some synaptic vesicles are anchored to the actin cytoskeleton in presynaptic terminals through a phosphoprotein, synapsin, and their association is regulated by protein kinases. Some synaptic vesicles are believed to be preset in the vicinity of a Ca channel in the active zone to achieve very fast release of neurotransmitter within 0.2 ms after activation of Ca channel. The efficiency of neurotransmitter release could be regulated by changing the size of vesicle pools and location of the vesicles.

Synaptic Vesicle Recycling

After their synthesis in the cell body, synaptic proteins are transported to the presynaptic nerve terminals along axons by an axonal flow, and it takes time to reach the nerve terminals. Normal synaptic transmission is conducted by an exocytosis of small synaptic vesicles. If all of these vesicles are used only once without recycling, the synaptic vesicle is easily depleted after high frequency stimulation. To avoid such a situation, synaptic vesicles are locally recycled and reused (►synaptic vesicle recycling). After exocytosis, synaptic vesicle proteins are selectively recovered from the plasma membrane by clathrin-mediated endocytosis. The synaptic vesicles are reformed either directly or after being incorporated into an endosome-like structure. In some cases, neurotransmitters are released from synaptic vesicles by a kiss and run mechanism without full fusion. Neurotransmitters are released through a fusion pore, which is formed transiently by the docked vesicles and the plasma membrane. After detaching, the neurotransmitter is refilled and reused for the next stimulation.

Postsynaptic Mechanisms

Neurotransmitters bind to receptors in the postsynaptic membrane. Two types of receptors, the ►ionotropic receptor and the metabotropic receptor (►G protein-coupled receptor), are used for synaptic transmission and they induce postsynaptic responses in different mechanisms. Many different subtypes of receptors are usually expressed in the brain, and thus each neurotransmitter is able to induce different kinds of responses in different neurons and brain regions.

Ionotropic Receptors

Structure of Ionotropic Receptors

►Ionotropic receptors are ligand-gated ion channels, and their opening and closing is regulated by neurotransmitter binding. Ionotropic receptors are composed of several subunits, and an ion channel pore is formed in the center of the complex. The structure and numbers of subunits are varied among different receptors. Nicotinic acetylcholine receptor, $GABA_A$ receptor, glycine receptor and serotonin 5-HT_3 receptor have five subunits, and each subunit has four transmembrane segments with extracellular orientation of both amino- and carboxy-terminals. Glutamate receptors are composed of four subunits, and each subunit has two fully transmembrane segments and one loop structure arriving ion channel pore. The amino- and carboxy-terminal of each subunit are exposed to extracellular and cytoplasmic face, respectively. Glutamate receptors are further classified into NMDA receptor and nonNMDA receptor (AMPA-type and kainate-type) according to their pharmacological properties. The ATP receptor is composed of three subunits that have two transmembrane segments. Both amino- and carboxy-terminals are located in the cytoplasm.

Roles of Various Ionotropic Receptors

Ionotropic receptors can be classified into two types depending on the difference in ion permeabilities. Excitatory receptors permeate monovalent cations, such as Na^+ and K^+, and the activation of the excitatory receptor induced membrane depolarization called excitatory ►postsynaptic potential (epsp), which increases the probability to generate action potential in postsynaptic neurons. Some excitatory receptors, including NMDA receptors, also permeate Ca^{2+} that plays important roles for regulation of synaptic function and for synaptic plasticity. Glutamate, serotonin, acetylcholine, and ATP are neurotransmitters acting on excitatory receptors.

In contrast, inhibitory receptors have permeability to anions, typically chloride in many cells. Hyperpolarization of membrane potential called inhibitory

►postsynaptic potential (ipsp) is generated by the activation, which reduces the probability of action potential generation in postsynaptic neurons. The neurotransmitters of these receptors are GABA and glycine. It is noteworthy that GABA and glycine receptors do not always behave as inhibitory receptors. In immature neurons, the intracellular Cl^- concentration is higher than that in matured neurons, and thus activation of $GABA_A$ and glycine receptors induce an efflux of Cl^-, and depolarize membrane potential sometimes leading to action potentials.

Signal Processing by Ionotropic Receptors

In the neuromuscular junction, an action potential invaded in the endplate generates an action potential in skeletal muscles without failure, to assure rapid and smooth contraction of the skeletal muscle. In a marked contrast, the size of epsp in most of the central synapses is much smaller than that generate action potential, and single synaptic input will never generate action potentials. Every neuron has multiple innervations and an action potential is generated after the summation of individual epsps. There are two types of summation, special summation and temporal summation. Spatial summation is a way of achieving an action potential in a neuron which involves input from multiple cells. Because the potential produced by a brief synaptic current falls off relatively slowly, it is possible to get summation of the effects by repeated stimulation of a single ending if the frequency of firing of the presynaptic fiber is high enough. This type of summation is called temporal summation. Neurons receive both excitatory and inhibitory input, and a summation of epsps and ipsps, which is called integration (►synaptic integration), determines the probability of action potential firing.

Metabotropic Receptor

Roles of Metabotropic Receptors

Synaptic transmission mediated by ionotropic receptors induces a rapid change in membrane potential of postsynaptic neurons and is called an ordinary transmission. On the other hand, synaptic transmission mediated by metabotropic receptors (►G protein-coupled receptor (metabotropic receptor) is characterized as a slow and prolonged response to alter the responsibility to the following synaptic input, and is called a neuromodulatory transmission. Sometimes neurotransmitters for metabotropic receptors are called neuromodulators. Membrane potentials may change after activation of a metabotropic receptor, however, the change is small and slow compared to that caused by an ionotropic receptor.

The importance of neuromodulatory transmission is a long-lasting effect raging from several hundred milli seconds to several hours. These sustained effects are essential for various long-lasting brain functions such as learning, memory, and adaptation. Gene expression may be changed after activation of a metabotropic receptor, which induces very stable and sustained changes in neuronal properties.

Many more kinds of metabotropic receptors are expressed in brain compared to ionotropic receptors. Glycine is an exceptional neurotransmitter having no metabotropic receptor. All of the receptors for monoamines and neuropeptides are metabotropic, and only one type is ionotropic among six serotonin receptors.

Structure of Metabotropic Receptors

Metabotropic receptors are members of the ►G protein-coupled receptors (metabotropic receptors) (GPCR) and have seven transmembrane segments with an extracellular amino-terminal domain and an intracellular carboxy-terminal domain. The ligand binding site is varied among different types of receptors. Glutamate binds to the amino-terminal domain and catecholamine binds to a site in the transmembrane domain. Metabotropic receptors bind to tertrameric G proteins through the cytoplasmic region. The functional role of the metabotropic receptor is to activate G proteins. Tetrameric G protein is composed of three subunits, α, β, and γ, and 20, 5, and 7 different kinds of isoforms are expressed, respectively. The cellular response is varied depending on which type of G protein is coupled to the receptor. Activation of the receptors coupled to the Gs subfamily elevates intracellular cAMP concentration by activating adenylate cyclase, whereas that coupled to the Gi/o subfamily suppresses cAMP production. The receptors coupled to the Gq subfamily activate phospholipase Cβ and induce production of second messengers, diacylglycerol and IP_3. These second messengers can activate various protein kinases, and in turn phosphorylate various synaptic proteins to modulate synaptic functions. Gene expression is also induced by the receptor activation. Activated α and βγ subunits of G protein also bind to ion channels, and sometimes generate epsp and ipsp in postsynaptic neurons.

Receptor Ion Channel Complex Formation

►Scaffold proteins are proteins which have various protein binding domains in their structure, such as PDZ domain, SH3 domain GK domain. Many kinds of proteins including receptors, ion channels, and proteins for signal transduction, bind to the scaffold protein through specific binding motifs. Several scaffold proteins can be cross-linked with adaptor proteins. Thus, a fudge multiprotein complex is formed in the synaptic site. Presynaptic and postsynaptic protein complexes are cross-linked through cell ►adhesion proteins bound to the scaffold proteins, and these multi protein complexes play very important roles to properly arrange the many synaptic proteins at the synaptic site.

The binding of membrane proteins to the scaffold proteins could be regulated by protein phosphorylation, and these regulations may be important for the regulation of the synaptic function. Scaffold proteins are also important for the axonal transport of neurotransmitter receptors to the synaptic site. Cargo vesicles having a glutamate receptor are linked to microtubule-dependent motor proteins via scaffold protein complexes.

Removal of Neurotransmitter from Synaptic Site

Neurotransmitters must be removed quickly after activation of the neurotransmitter receptor. A prolonged exposure of neurotransmitters to their receptors results in various unfavorable phenomenon. Receptors will be desensitized, and the resolution of signals made by repetitive action potentials will be weakened. In addition to simple diffusion, membrane transporter and degradation enzymes mediate the removal of neurotransmitters from the synaptic cleft. The importance of the clearing system could dreadfully be visualized by a terrible criminal event by Japanese terrorists, who spread salin, an inhibitor of acetylcholine degradation enzyme, in the subway station and killed many people in Japan. It is also noteworthy, that huge numbers of people take a blocker of serotonin transporter to reduce anxiety.

Neurotransmitter Transporter

Most small neurotransmitters are recovered to presynaptic nerve terminals by membrane transporters (►neurotransmitter transporter) and further accumulated into synaptic vesicles by ►vesicular neurotransmitter transporters for reuse. So far, transporters specific for glutamate, GABA, glycine, dopamine, noradrenalin, serotonin, and choline have been identified. Membrane transporters actively transport neurotransmitters by using Na^+ gradients across plasma membranes, which are generated by Na^+/K^+-ATPase using hydrolyzing energy of ATP. Membrane transporters are also present in glial membranes. Glutamate incorporated into glial cells is converted into glutamine and sent to the neuron. Glutamine is again converted into glutamate in neurons and used again as a neurotransmitter.

Degradation Enzymes

Acetylcholine is hydrolyzed by acetylcholinesterase into choline and acetic acid. Acetylcholineesterase is localized in the plasma membranes of the CNS, but it also exists in the extracellular matrix in the neuromuscular junction. After hydrolysis, the resulting choline is reuptaken by membrane choline transporters and is used for acetylcholine synthesis. A part of the monoamines released into the synaptic cleft is metabolized by catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO). Peptidic neurotransmitters are degraded by peptidase.

Retrograde Messenger

Most neurotransmitters send information from presynaptic neurons to postsynaptic neurons, however, some information transmits in a retrograde manner. All ►retrograde messengers are labile and membrane permeable, and thus not stored in vesicles. They are generated by synaptic activation and act on presynaptic cells instantly by diffusion.

Nitric oxide (NO) is a messenger molecule of gas generated from arginine by nitric-oxide synthase (NOS). The life time of NO is only a few seconds. Ca^{2+} influx into postsynaptic cells via NMDA receptor and Ca channels activate Ca^{2+} -dependent NOS [2]. NO is diffused through plasma membranes and activates guanylate cyclase in the presynaptic terminal, resulting in a generation of cGMP, which in turn activates cGMP-dependent protein kinase. The presynaptic function could be regulated through the phosphorylation of some presynaptic proteins.

Cannabinoid is a chemical giving euphoria and found in hashish. It induces a neuronal action through the binding to cannabinoid receptors. Endogenous cannabinoid is generated in postsynaptic cells after synaptic activation, and the generated cannabinoid modulates presynaptic function through binding to a presynaptic cannabinoid receptor.

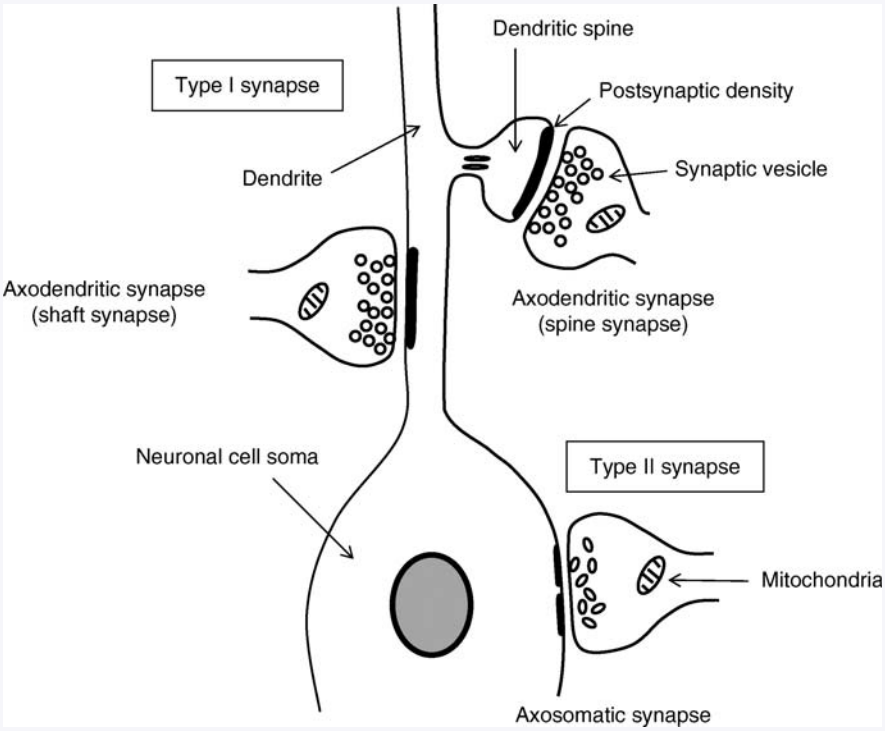
Variation of Synapse

Basic mechanisms of synaptic transmission are common among many chemical synapses, however, there are many variations in the structure of chemical synapses. In addition, there are also electrical synapses in the brain (Fig. 2).

Morphological Variations

There are two common morphological types of synaptic connections in the brain, Gray type I and type II. Type I synapses are often glutamatergic and therefore excitatory, whereas type II synapses are often GABAergic and therefore inhibitory. In type I synapses the synaptic cleft is slightly widened to approximately 30 nm, and the active zone is larger. The synaptic vesicles have a characteristic round shape in electronmicroscopy. The PSD is very thick, and amorphous dense basement-membrane material appears in the synaptic cleft. In type II synapses, the synaptic cleft is 20 nm across and the active zone is smaller. PSD is less obvious and there is little or no basement membrane in the synaptic cleft. The synaptic vesicles tend to be oval or flattened.

Ribbon synapses are found in certain primary sensory cells, such as photoreceptors and mechanoreceptors. These synapses are identified by the presence of proteinaceous ribbon within their presynaptic terminals. Spine synapses are a synapses formed on the dendritic spine. The spine is connected to the dendritic shaft by a thin neck which restricts the rise in



Synapse. Figure 2 Variations of chemical synapses in the central nervous system. Chemical synapses are classified by their mode of innervations and by the structure of postsynaptic density.

Ca^{2+} concentration in the spine. Thus, each spine represents a distinct biochemical component. The morphology and properties of spine synapses change dramatically in a synaptic activity-dependent manner, which is quite important for synaptic plasticity and possibly in memory storage.

Variation in Mode of Innervation

Neurons of the CNS have several thousand synaptic inputs on average, and synapses are formed in various regions of the neuron. The synapse made on dendrite and cell soma is called axodendritic synapse and axosomatic synapse, respectively. Many axodendritic synapses are excitatory, and axosomatic synapses are inhibitory. Dendrodendritic synapses are synapses formed between dendrites, and are characteristic for their bidirectional transmission. An axoaxonal synapse is a synapse formed at presynaptic terminals, and is responsible for presynaptic regulation.

Synapses in Peripheral Tissues

Synapses can also be found in peripheral tissues. The basic structure is the same as those of central synapses, however, there are marked variations in their structure to optimize their functional roles [3].

Neuromuscular Junction

The neuromuscular junction is a synapse formed between motor neurons and skeletal muscle cells. This synapse is specialized to provide transient, fail-safe excitation of the postsynaptic muscle cells, ensuring muscle contraction whenever the motor neuron is active. The speed of transmission is quite fast to induce rapid contraction of skeletal muscle. To achieve these characteristic properties, the neuromuscular synapse is optimized for releasing large quantities of acetylcholine very rapidly. The synaptic structure shows a characteristic structure called end plate. Thus, the epsp (►postsynaptic potential) of the neuromuscular junction is often referred to as endplate potential. A neuromuscular synapse consists of a highly branched presynaptic termination of the motor neuron that innervates long, cylindrical muscle cells. A single synapse has several hundred active zones, where a large cluster of synaptic vesicles is accumulated. The postsynaptic component apposed to the presynaptic active zone is characterized by a postjunctional fold, a tremendous number of nicotinic acetylcholine receptors are clustered at the peak of this fold. This arrangement allows the receptor to detect the release of acetylcholine quickly and efficiently. Acetylcholinesterase is found in the extracellular matrix of the synaptic cleft and postjunctional fold.

Autonomic Neuronal Synapse

Autonomic neurons regulate smooth muscle contraction and secretion from various endocrine and exocrine cells. The synapses of autonomic neurons act over a

slower time scale, and thus the synaptic structure is quite different from that of fast-acting synapses. Presynaptic terminals at these synapses are varicose in structure and filled with dense-core vesicles containing various neurotransmitters, including acetylcholine, catecholamines, ATP, and peptides. These vesicles are dispersed throughout the presynaptic cytoplasm, and there are no indications of the active zones. The synaptic cleft is larger than the one of other types of synapses and can be as great as 2 μm. The postsynaptic cell also lacks a postsynaptic density and receptor clustering.

Electrical Synapse

Although they are a distinct minority, electrical synapses are found in all nervous systems [4]. The extracellular space between pre- and postsynaptic neurons at an electrical synapse is 3–3.5 nm, which is much smaller than the synaptic cleft of general chemical synapses (about 20–50 nm). The narrow space between these neurons is bridged by a gap junction channel, and the intracellular current flow is through the gap junction. In the mammalian nervous system, most electrical synapses are bidirectional and the current can flow in either direction across the gap junction. These channels are formed by two hemichannels, one in the presynaptic neuron and the other in the postsynaptic neuron. Each hemichannel is called connexon, which is composed of six subunits of an identical protein called connexin, arranged in a hexagonal pattern with a 2 nm diameter central hole. At electrical synapses, the current generated by voltage-gated channels at the presynaptic neuron flows directly into the postsynaptic neuron, and thus, the transmission at such a synapse is very rapid (<0.1 msec) compared to a chemical synapse. Electrical synapses are present where the activity of neighboring neurons are to be highly synchronized. On the other hand, plastic regulation of transmission is difficult in electrical synapses.

Preparation for the Study of Synaptic Functions

Since a synapse is a very small fine structure containing a large number of proteins, it is not easy to study the synapse functions in the brain. Many unique preparations have been used for the study of synaptic functions.

Giant Synapse Preparation

In electrophysiological experiments, the synaptic current is recorded only from postsynaptic neurons, since the size of the presynaptic nerve terminal is too small to insert a microelectrode. To measure the membrane potential and capacitance, preparations having large presynaptic terminals, such as neuromuscular junctions and giant synapse of squid have been used. In the mammalian central nervous system, the Calyx of Held, a particularly large synapse in the auditory central nervous system, is used.

Slice Preparation

It is possible to keep brain thin slice (200–500 μm thickness) in artificial cerebro-spinal fluid saturated with 95% O_2/5% CO_2, pH 7.4 for several hours to several days, and the electric response can be monitored without disturbance of aspiratory and cardiac vibrations. Since neuronal networks are retained in the ►slice preparation, it is possible to study the properties of the neuronal network. It is also easy to change extracellular conditions, and many imaging techniques using various dyes sensitive to membrane potential, Ca^{2+}, and pH, as well as FM dye such as ►FM1-43 are applicable.

It is also possible to keep brain slices on membranes for longer periods in a cell culture media, preserving the neural network in these preparations. However, most of the synaptic contacts may be lost after preparation and are regenerated after cultivation. Proliferation of nonneuronal cells is also remarkable in this preparation, and the structural differences between the culture and the brain become larger with time.

Dissociation Culture of Neurons

Enzymatically dissociated neurons from embryonic and neonatal rodent brain are able to be kept in culture for long periods. Synaptic formation and neuronal maturation advances in culture. Many experimental techniques including electrophysiology, imaging, and biochemical measurement are easily applicable. Activity of the postsynaptic cell body could be monitored by electrophysiological methods as well as imaging techniques using voltage-sensitive dyes and Ca^{2+}-sensitive dyes. Presynaptic activity is monitored using FM dye (►FM1-43). Some caution should be kept in mind, that is, neuronal maturation may be advanced in culture, however, it is not certain how the maturation is completed. Except for cerebellar granule cells in culture, where >90% cells are glutamatergic neurons, it is also a problem that many kinds of neurons coexist in culture. Since many neurons extend many neurites and form numerous synapses randomly, it is difficult to get a record from pre- and postsynaptic neurons at the same time. To overcome this difficulty, an elegant method of culture called ►autapse has been developed. In this method, a single neuron is cultured on a small glial island of 200–700 μm diameter. The neuron makes synaptic contact on its cell body. It is possible to stimulate and record postsynaptic responses with the same single electrode. It is also possible to inject various substances and antibodies into the cell body to see the effect on both pre- and postsynaptic functions, since these substances easily diffuse to presynaptic terminals.

Adrenal Chromaffin Cell

Since the presynaptic terminal is a very small structure, it is difficult to quantically measure the process of neurotransmitter release in real time. Adrenal medullary chromaffin cells are derived from the same precursor cells as those of autonomic neurons and share many common properties with neurons. In fact, chromaffin cells from neonatal rat adrenal are still able to differentiate into neurons in the presence of nerve growth factor. It is easy to prepare a fairly homogeneous cell preparation, enough even for biochemical studies from bovine adrenal medulla. Chromaffin cells have about 30,000 dense-core vesicles containing either noradrenalin or adrenalin of around 280 nm in diameter, and release these catecholamines by a Ca^{2+} -dependent exocytosis. It is easy to keep in culture for a long period, enough to do multiple types of experiment including a transient gene expression using virus vector. The exocytotic process of the dense-cored vesicles is monitored by a membrane ►capacitance measurement, electrophysiological measurement with carbon fiber electrode, video-enhanced microscopy, and total reflection fluorescence microscopy (►evanescent field fluorescence microscopy). For biochemical analysis, membrane permeabilized model cells are used successfully. Clonal PC12 cells derived from rat adrenal tumor have also been used extensively.

Synaptosome

When brain is homogenized in an isotonic sucrose solution, nerve terminals are pinched-off and resealed to a round structure called a ►synaptosome of 0.5–1 μm in diameter. Synaptosomes are enriched in postmitochondrial P2 fraction of brain homogenate and further purified by a density gradient ultracentrifugation. Synaptosomes contain one to several mitochondria and regenerate membrane potential by the action of Na^{+}/K^{+}-ATPase when they are incubated in the presence of glucose and oxygen. They can be kept alive for several hours. PSD structures are tightly attached to most synaptosomes. Synaptosomes have been used for the biochemical assay of neurotransmitter synthesis, release and reuptake. By modifying the preparation, synaptoneurosomes and synaptodendrosomes in which both presynaptic terminal and dendritic spine are resealed, have been obtained.

A recent study revealed that glial cells release glutamate and various peptides by a Ca^{2+}-dependent exocytotic mechanism. A resealed cellular fragment of glial cells called gliosome is prepared from brain homogenate by a Percoll gradient ultracentrifugation. Gliosomes are different from synaptosomes in density and ultrastructural morphology. Glutamate is released from gliosomes in a Ca^{2+}-dependent manner.

Mutant Mouse

Many knock-out mice of synaptic proteins have been generated and successfully used for the study of these proteins in synaptic function.

Synapse Formation and Plasticity in Development

Synaptogenesis

During development, neurons extend neurites and make synaptic contacts after finding a proper target neuron. The tip of a growing neurite represents a characteristic structure called a growth cone, which is completely different from the presynaptic terminal in structure. A growth cone is enriched in actin and is a very active structure with extending and retracting filopodia to find a proper target cell. The extension of a neurite is controlled by various guidance molecules and growth factors.

The process of ►synaptogenesis was extensively studied in the neuromuscular junction [5]. On attaching to a target cell, the growth cone stops moving and shows morphological changes. The nerve terminal is bloated and synaptic vesicles appear inside. CAZ (cytomatrix assembled at active zone) becomes visible with maturation to form an active zone. In response to the presynaptic differentiation, postsynaptic differentiation also proceeds. Postsynaptic density and synaptic folding are formed beneath the active zone. Nicotinic acetylcholine receptor clusters are formed on the edge of synaptic folding, and acetylcholine esterase is enriched in the extracellular matrix in the synaptic folding. Several soluble factors including agrin play crucial roles in this coordinated differentiation. Morphological changes in synaptic structure during maturation are also observed in neurons of CSN.

Synaptic Plasticity in Development

A basic design of the neuronal network is genetically determined, however, activity-dependent fine tuning is necessary to complete the formation of the neural network. Most of the neurite extensions occur in an activity-independent manner, plasticity of the neuronal network is obvious in the stage of synaptogenesis. Synaptogenesis starts in the brain from late embryonic to early postnatal stages. In many brain regions, extra synapses are transiently formed during the early postnatal period, and are then decreased to adult level in an activity-dependent manner. In other words, multiple innervation occur first, followed by a selective ►synaptic elimination of extra synapses, with synaptic activity playing a crucial role in the selection.

Synaptic plasticity in development has been extensively studied in sensory systems. Retinal ganglion neurons send a projection to the visual cortex in the brain via monosynaptic transmission. In the adult brain, the projections from the left eye are spatially separated

from those from the right eye. In contrast, most neurons of the visual cortex have dual innervations from both the right and left eye at birth. In a particular period called the critical period during the early postnatal period, selective elimination of extra synapses occur to shift to a unitary innervation. Multiple innervated neurons compete with each other to occupy the synaptic site, and neuronal activity during the critical period has a definite effect on the competition. If one eye is closed during the critical period, synaptic connection from the closed eye fails in the competition and the modified innervation map is fixed through the whole of life. A similar phenomenon is also observed in the sensory cortex for face fungus in rat, and in the phenomena called ►imprinting in birds. Activity-dependent synaptic elimination (►synapse formation and elimination: competition and the role of activity) is also observed in climbing fiber synapse in cerebellum, and in neuromuscular junctions.

The critical period is different among different species. In the human cerebral cortex, the number of synapses increases markedly after birth and attains a maximal level around four months after birth. It declines thereafter to adult level in early childhood. The visual projection area is smaller and the auditory projection area is larger in a patient with a congenital visual defect than those of a normal person. If one eye is temporally closed with an eye bandage to cure cockeye during the critical period, the patient will have a visual defect throughout the whole of his life. On the other hand, if a person starts practicing the violin in the critical period, the person will have a more exhaustive movement of fingers since his motor area for fingers increased throughout life.

Synaptogenesis in Adult Brain

If new synaptic formation is an event in development, we can say that the brain continues to develop throughout the whole of life. Many synapses are forming, loosing and change their property to change the function of the neuronal network, and these characteristic features are an origin of many remarkable functions, including, learning, memory, thinking and creativity, those that are not determined by genetic information.

Neurogenesis still occurs in some regions of the adult brain including the dentate gyrous of hippocampal formation [6]. Newly formed neurites of granular cells forms many new synapses in the dendrite of CA3 pyramidal cells. There is good evidence to show that synaptogenesis also occurs in the adult bran. The number of dendrites, branching point of dendrites, and synapses increase in a rat brain cortex which is kept in a complex environment. A partial rearrangement of sensory cortex has been observed in some adult animals after inhibiting sensory neurons from the finger in prosimian and bat.

Synaptic Plasticity

Importance of Synaptic Plasticity

Signal processing by inonotropic receptor-mediated summation and integration (►synaptic integration) determine the output without changing the individual synaptic response. If a neuronal network only has such a system for signal processing, it is not possible to store information acquired by external inputs, or to use this information to change the property and function of the neuronal network in response to environmental change in the battle for survival.

A characteristic feature of synapses is to change the size of epsp dynamically in response to previous activity. In other words, the strength of synaptic transmission is continuously changing in an activity-dependent manner whilst retaining a history of prior activity. What kind of information is stored in the neuronal network as a memory is not determined by genetic information. Synaptic plasticity is believed to be a molecular and cellular basis of learning and memory. Identity is one of the most important properties for human beings, and is established on memories. Memorial defect by aging is now becoming a serious problem for the aged society, since the identity of the aged person disappears with the loss of their memory. It is also necessary to rearrange neuronal networks to change the response for adaptation to environmental change. These properties are also dependent on the characteristic property of the neuronal network. There are multiple mechanisms of variety of time scale in synaptic plasticity. In some cases, reconstruction of neuronal networks by loosing or forming synaptic contact occurs.

Plasticity of Various Time Constant

Facilitation

At most synapses, repetitive high-frequency stimulation (called a tetanus) is initially dominated by a growth in successive epsp amplitude, called synaptic facilitation. This process builds to a steady state within about 1 s and decays equally rapidly when stimulation stops. When a pair of stimuli is given to some synapses with several ten second intervals, the amplitude of the second response either increases, called paired-pulse facilitation, or decreases, called paired-pulse depression, compared to the first response. These properties are often used as a parameter of presynaptic activity.

Potentiation

Some synapses display a growth in epsp amplitude that lasts minutes and is called potentiation. The potentiation that appears after moderate (50–100 per sec) tetanic

stimulation is called posttetanic potentiation (PPT), which is observed in many synapses including the neuromuscular junction.

Long-Term Potentiation

In some synapses, a brief high-frequency titanic stimulation induces a long-lasting increase in the amplitude of epsp, called ►long-term potentiation (LTP). Whereas PTP decays within a few minutes, LTP decays over the course of several hours or, under certain conditions, up to a month or more. Low-frequency stimulation sometimes results in long-lasting depression of epsp, called long-term depression (LTD). It is also possible to cancel LTP and LTD by applying proper stimulation after a while, and these phenomenon are called depotentiation and dedepression, respectively. The expression and maintenance of LTP and LTD are not derived from a single mechanism, but are generated by multiple mechanisms, from short-time mechanisms without new gene expression to long-term mechanisms involving gene expression and protein synthesis.

Typical Studies of Synaptic Plasticity

Synaptic plasticity is quite an important phenomenon in brain functions, and extensive studies have been successfully conducted in invertebrate and vertebrate nervous system.

Aplysia Neuron

Aplysia is a marine mollusk and has a relatively simple nervous system. Eric Kandel and his colleagues found that *Aplysia* showed activities of primitive learning and memory, and extensively studied the mechanisms in cellular and molecular levels [7].

Some neurons have very large cell bodies and are easy to identify in ganglion. Major neurons are numbered and characterized. The identified neurons reconstruct a neuronal circuit in culture and show synaptic plasticity that is observed in the neuronal network of living animals. Thus, it is easy to study synaptic function for a long period (several hours to several days) with multiple techniques.

Aplysia uses gills for respiration that show a withdraw reflex when some stimuli is applied on their bodies to protect them. When animals were repeatedly stimulated with water puffing every three minutes for four hours, the withdrawal response decreased with time and finally showed no response. This phenomenon is called habituation, and is also popular in our life. This habituation originates from a change in synaptic property between the sensory neuron and the motor neuron. Inactivation of Ca channel responsible for neurotransmitter release, as well as a decrement of releasable synaptic vesicles is a major mechanism of this phenomenon.

When noxious stimuli are applied to a habituated *Aplysia*, the animal again shows a withdrawal response even to a weak stimulus that does not induce any response under normal conditions. This phenomenon, called sensitization, results from the stimulation of neurotransmitter release from the sensory neurons. A noxious stimulus activates interneuron innervated at the presynaptic nerve terminal of the sensory neuron. Serotonin released from the interneuron activates a presynaptic serotonin receptor of the sensory neuron. Activation of presynaptic serotonin receptor coupled with Gs results in an elevation of intracellular cAMP level, which in turn activates PKA. PKA suppresses K channel activity by phosphorylation, which in turn prolongs Ca^{2+} influx through Cachannels. The stimulation of neurotransmitter release from the sensory neuron is also induced by increasing the size of the releasable pool of synaptic vesicles in PKA- and PKC-dependent mechanisms.

Sensitization is usually retained for less than a day, however, when the noxious stimuli are repeatedly applied everyday for several days, the effect of sensitization sustains over one week. The important finding is that mechanisms are quite different between the short-term sensitization and the long-term sensitization, and new gene expression and protein synthesis are essential for the expression of the long-term sensitization. Prolonged and repeated activation of serotonin receptors results in continuous activation of PKA, and the catalytic subunit of PKA translocates to the nucleus and activates cAMP-dependent gene expression by activating CREB by phosphorylation.

LTP and LTD in Hippocampus

Memory formation and special learning are impaired when the hippocampus is injured in humans and rat, indicating that the hippocampus plays a critical role in memory. A lot of attention has focused on the hippocampus since LTP was found there. There are three synapses in the major neuronal circuit in the hippocampus, and LTP is observed in all of these synapses. The mechanisms of LTP induction are different among these three synapses, and the mechanism of the CA1 synapse has been most extensively studied. In brief, LTP is induced in a CA1 synapse according to the following mechanism. Synaptic transmission of the CA1 synapse is mediated by glutamate and two types of glutamate receptors, NMDA and AMPA, both being expressed at the post synaptic site. Under normal conditions, the NMDA receptor is blocked by Mg^{2+} ions, and the AMPA receptor plays a predominant role in synaptic transmission. High frequency stimulation activates many AMPA receptors and a resulting large depolarization of postsynaptic membrane cancels the Mg^{2+} block of NMDA receptors. In addition to Na^{+}, Ca^{2+} ions influxes into the

postsynaptic site, and induce a Ca^{2+} -dependent process that leads to LTP. CaMKII plays a critical role in the Ca^{2+} -dependent induction of LTP.

Several important ideas have been obtained from studies of hippocampal LTP, one of the most important ones being gene-expression-dependency. Just like short-term sensitization in *Aplysia*, expression of short-term LTP is not dependent on new gene expression and protein synthesis, and posttranslational modification including protein phosphorylation of preexisting proteins play major roles. On the other hand, gene expression and new protein synthesis are indispensable for the expression of LTP. Many genes changing expression patterns in the induction of LTP have been identified, however, the precise consequences of these gene expressions and LTP induction has not yet been clarified.

LTP in CA1 is associative (►associative long-term potentiation (LTP)) and both pre- and postsynaptic activities are necessary for their induction. In contrast, CA3 synapse shows no association, and it occurs by a presynaptic mechanisms. Cyclic AMP-dependent protein phosphorylation may play a critical role in the induction of CA3 LTP.

Cellular and Molecular Mechanisms of Synaptic Plasticity

There are many possible mechanisms for inducing a long-lasting change in synaptic properties and function.

Protein Phosphorylation

Gene expression is not required for the expression of short-term synaptic plasticity, and posttranslational modification of preexisting protein plays a crucial role in this mechanism. Activation of metabotropic receptors and Ca^{2+} mobilization activate various kinds of protein kinases and phosphatase, which in turn change the state of phosphorylation of many synaptic proteins. These mechanisms are present in both presynapse and postsynapse. In presynaptic terminals, protein phosphorylation modifies the presynaptic function by phospohorylating neurotransmitter synthesizing enzymes, such as cAMP-dependent phosphorylation of tyrosine hydroxylase, various proteins involved in neurotransmitter release (►regulation of neurotransmitter release by protein phosphorylation), and ►vesicular neurotransmitter transporter. In the postsynapse, phosphorylation of neurotransmitter receptors are predominant in its regulation [8].

Translocation of Receptors

In developing neurons, there appear many ►silent synapses in which are devoid of AMPA receptors and only NMDA receptors are expressed in the synaptic membrane. Since the NMDA receptor is blocked by Mg^{2+} at normal membrane potential, no synaptic current is induced by glutamate. With maturation of the brain, these silent synapses become activated, and the number of silent synapses decreases with maturation. However, some silent synapses are still present in the adult brain, and participate in the synaptic plasticity such as LTP.

In early studies, phosphorylation of the AMPA receptor was believed to be primarily important for the activation, however, recent studies revealed that translocation of the AMPA receptor from the intracellular store site to the plasma membrane is predominant in its activation. The expression of the AMPA receptor in the synaptic plasma membrane is likely to occur by an ►exocytosis of intracellular vesicles carrying AMPA receptors. Ca^{2+} is necessary to induce LTP in CA1 synapses. CaMKII is likely to be involved in triggering exocytosis.

Adhesion Molecules

Synaptic connection is retained by cell adhesion molecules in the presynaptic and postsynaptic membrane (►synaptic adhesion molecule). To alter the synaptic connection, the regulation of adhesion molecules is important. Cadherin-mediated regulation is important for the change in spine structure. Degradation of adhesion molecules is necessary for the rearrangement of synaptic connections. Many ►extracellular proteases are expressed in the synaptic area and play important roles in LTP formation.

Spine, Morphological Change

Actin cytoskeleton is abundant in the dendritic spine, and the spine changes their morphology dynamically in a synaptic activity-dependent manner (►spine, morphological change). There is a dramatic change in spine morphology several tens of minutes after induction of LTP. The dynamics of the actin cytoskeleton is regulated by Ca^{2+} and by multiple signal transduction mechanisms downstream of the metabotropic receptor and neurotrophin receptors. There are at least two types of spines. One is filopodia-like and has no AMPA receptor. Another is mushroom-like in shape and expresses AMPA receptor. After induction of LTP in the filopodia-like spine, it changes to the mushroom-like spine and acquires AMPA receptor.

In electronmicroscopic observations, two types of spine synapse are also observed, one is a nonperforated and another is a ►perforated synapse, in which PSD is discontinuous. The number of perforated synapses increases after LTP induction, and attains a maximal level 15–60 min after induction. Since some nonperforated synapses have no AMPA receptor, these morphological changes may be accompanied by the activation of ►silent synapses.

Many synaptic terminals are formed in the cell soma. Since the postsynaptic compartments are not separated

from each other, the effect of synaptic input spreads over the entire cell surface, no input specificity is achieved. On the contrary, the postsynaptic components of spine synapse are separated one by one, and the diffusion of various substances is restricted by the narrow spine neck. Thus, most changes in the postsynaptic site are restricted to the synapse, and input-specificity of plasticity appears.

In the memory circuit of an electrical computer, there are fudge numbers of condensers that are used for memory storage and calculation by changing the condenser into two states, charged and uncharged. In addition, each condenser is accompanied by a transistor switch to charge or discharge condensers. In the brain, there are numerous numbers of spines, which can change their state and shape reversibly. Each spine has an input of glutamatergic neurons, and the glutamate released from each presynaptic site can induce a change of spine structure and state. This analogy suggests a possibility that the spine might be an element for memory storage. There are fudge numbers of spines in the brain, enough to store fudge numbers of memories. Furthermore, since the structure of large spines is very stable, long-term storage of memory could be stored in the spine. In future, we might be able to read memory stored in the brain by analyzing spine structure.

Gene Expression and Protein Synthesis

New gene expression and protein synthesis is essential for the expression of long-term plasticity. Many genes whose expressions are changed in LTP have been identified and characterized. It is not so clear how these gene products participate in the changes of synaptic structure and functions in the brain.

Synaptic signals should be delivered to the nucleus where gene expression takes place. In CA1 synapses, synaptic activity is thought to be delivered by Ca^{2+} and/or Ca^{2+}-dependent protein kinases. In *Aplysia* neurons, it has been shown that MAP kinase and PKA translocate to the nucleus after stimulation and activate gene expression by phosphorylating CREB. The importance of CREB in long-term memory is also shown in the mammalian brain [9,10].

One of the characteristic features of synaptic plasticity is input specificity. Since proteins are usually synthesized in the cell body, the synthesized proteins should be transported selectively to synapses, where the synaptic activity for plasticity occurs. There are at least two possibilities to achieve this input specificity. One is a hypothetical idea of a synaptic tag [11,12]. Synaptic activity results a trace in synapse, and the newly synthesized protein accumulates at the specific synapse according to the tag.

The second idea is a local protein synthesis at the synaptic site [13,14]. It has now been established that some mRNAs are present in the dendrite, and a noncoding region of mRNA is essential for dendritic delivery of the mRNA. Several mRNA binding proteins have been identified. Many membrane proteins are glycosylated in the Golgi complex in the cell body, but the mechanisms of glycosylation of locally synthesized protein is not yet known.

Neuronal Defect Related to Synaptic Functions

Neuronal Defects in Development

Since synaptogenesis starts in the late stage of pregnancy, deficiency of synaptic function is not assumed to make severe effects on brain development during embryonic age. In fact, many knock-out mice of synaptic proteins died after birth. The severe effects are derived by disorders that occur during the critical period as described above.

Plasticity-Related Neuronal Defects

Plasticity of the dendritic spine structure and functions are quite important for the expression of various brain functions including learning and memory. Abnormal spine shape, or spine dysgenesis, is associated with various forms of mental retardation [15]. Reduction of hippocampal volume is observed in patients with major depression, possibly due to a retraction of dendrites and a reduction of neuronal connectivity. Antidepressant treatments appear to protect against hippocampal volume loss and also increases adult neurogenesis in hippocampus [16].

The secretion of glucocorticoids from the adrenal cortex is one of the major responses to stress. Strong and prolonged stress makes various severe effects on the structure and functions of the hippocampus, since its expression level of the glucocorticoid receptor is quite high. Repeated stress causes atrophy of dendrites in the CA3 region, and both acute and chronic stress suppresses neurogenesis of dentate gyrus granule neurons [17]. Maternal behavior in the rat permanently alters the development of stress response by altering glucocorticoid receptor expression in the hippocampus by an epigenetic mechanism. Pups which do not have enough maternal care during the first 10 days of life, showed stress vulnerability and increased anxiety throughout their whole life [18].

Psychoactive Drugs

Defects in synaptic function result in various problems in the brain, and many compounds that act on synaptic proteins are widely used for clinical use as physiological drugs. Tricyclic antidepressive agents like imipramine, and a selective serotonin reuptake inhibitor (SSRI) like fluoxetine, are widely used for the treatment of depression, bipolar disorder, and anxiety disorder by inhibiting serotonin transporter. Barbiturate and benzodiazepine are used as an antianxiety drug, which binds to the $GABA_A$ receptor and enhances GABA action by

increasing affinity of GABA to the receptor. Benzodiazepines are also used as a sedative and anticonvulsant drug. Positive and negative symptoms appeared in patient with schizophrenia, and antagonists of the dopamine receptor like haloperidol and that of the NMDA receptor are used for the treatment, respectively.

Drug Dependence

In many countries, street drugs are illegal since most of these compounds induce drug dependence. Many of these drugs exert their action by acting on synaptic proteins. Amphetamine and cocaine are stimulant drugs. They induce releases of dopamine and noradrenalin and suppress reuptakes of these neurotransmitters. On the other hand, morphine acts as an agonist of the opiate receptor. Marijuana is a psychoactive drug and an agonist of the metabotropic cannabinoid receptor.

Toxins

Many toxins exert their action by blocking the functions of synaptic proteins [19]. Tetanus toxin and botulinum neurotoxin are protein neurotoxins produced by an anaerobic bacterium, *Clostridium tetani* and *Clostridium botulinu*, respectively [20,21]. Several immunologically distinguishable forms of botulinum neurotoxin, designated as types A, B, C, D, E, F, and G, are produced by different strains of *Clostridium botulinum*. All of these neurotoxins act primarily on neurons and inhibit neurotransmitter release from presynaptic nerve terminals. These neurotoxins are composed of a heavy chain and a light chain held together by a disulfide bond. The heavy chain is responsible for the specific binding to their neuronal receptors in axonal terminals. As for type A and type B botulinum neurotoxins, neuronal receptors are identified as synaptic vesicle proteins SV2 and synaptotagmin, respectively. Following the attachment on the surface of axon terminals, the toxin can be taken into neurons by endocytosis, and then the light chain enters into the cytoplasm. The light chain is a Zn^{2+} -dependent protease and exclusively hydrolyzes peptide bonds within SNARE proteins in a type-specific manner, and inhibits neurotransmitter release by disturbing SNARE complex formation. Botulinum toxins are successfully used for the treatment of crossed eyes, migraine headaches, dystonia, and many other defects [22].

Tubocurarine chloride is a toxin obtained from the arrow poison curare. It binds to nicotinic acetylcholine receptor and blocks its function. Both α-bungarotoxin obtained in snake venom, and α-conotoxin obtained from the venom of the marine cone snail also inhibit the nicotinic acetylcholine receptor. Omega-conotoxins from the cone snail and ω-agatoxin isolated from the venom of spider inhibit neuronal Ca channels and suppress neurotransmitter release from presynaptic terminals.

Sarin (O-Isopropyl methylphosphonofluoridate) is an extremely toxic substance used as a chemical weapon. It is a very potent inhibitor of acetylcholinesterase. Acetylcholine is one of the most important neurotransmitters of the respiratory center in the brain stem, and disturbance of the cholinergic system in the center results in a blockage of the diaphragm. In the peripheral nervous system, the nicotinic acetylcholine receptor is desensitized, and thus sarin induces a paralysis of the muscles. Interestingly, donepezil, another inhibitor of acetylcholinesterase marketed under the trade name Aricept, is used in the treatment of Alzheimer's disease, where it is applied to increase cortical acetylcholine.

Autoimmundiseases

Some patients of autoimmune diseases have autoantibodies to synaptic proteins. ►Myasthenia gravis is a neuromuscular disease leading to fluctuating muscle weakness and fatiguability. The weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction. ►Lambert-Eaton myasthenic syndrome is also an autoimmune disease accompanied by progressed muscle weakness. The autoantibodies to Ca- channels and synaptotagmin, a synaptic vesicle protein, are generated in the blood of patients.

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Synapse Elimination

Definition

The removal of redundant connections formed during development or plasticity, also called pruning.

►Activity-Dependent Synaptic Plasticity
►Synapse Formation and Elimination: Competition and the Role of Activity
►Synaptic Elimination

Synapse Formation

Definition

Synapse formation is a multi-step process that occurs after the first contact of an axon and dendrite are made followed by recruitment of pre- and postsynaptic molecules important for synapse function.

►Synapse Formation and Elimination: Competition and the Role of Activity
►Synapse Formation: Neuromuscular Junction Versus Central Nervous System
►Synaptogenesis

Synapse Formation and Elimination: Competition and the Role of Activity

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Definition

Synaptic ►competition is a cellular process by which the presence of one synapse affects the stability or survival of other synapses on the same postsynaptic cell. Synapse elimination refers to synapse loss due to either a low "intrinsic merit" of the synapse for survival or to its failure in winning synaptic competition with other synapses on the same cell [1]. Such competition and elimination can be driven by either neuronal/synaptic activity or other activity-independent processes [2]. We here summarize the evidence of activity-dependent synaptic competition and elimination in various brain regions, together with potential underlying cellular mechanisms.

Characteristics

Introduction

Synaptic competition is a cellular process by which the presence of one synapse affects the stability or survival of other synapses on the same postsynaptic cell. Synapse elimination refers to synapse loss due to either a low "intrinsic merit" of the synapse for survival or to its failure in winning synaptic competition with other synapses on the same cell. Such competition and elimination can be driven by either neuronal/synaptic activity or other activity-independent processes. The idea that the strength of synaptic connections between neurons may be modified can be traced back to Ramon y Cajal, who proposed that such modification serves as a cellular mechanism for learning and memory. That memory formation involves making and breaking

existing synaptic connections has been a popular idea over the past century, but solid experimental evidence in support of this idea has been elusive. Recent morphological studies of synapse stability in the adult rodent brain have revealed rather limited synaptic remodeling under normal conditions. In contrast, initial synaptic connections established early in the developing nervous system undergo substantial remodeling, with some connections stabilized and others eliminated, as a result of experience. This developmental remodeling of connectivity often involves cooperative and competitive interactions between converging synapses on the postsynaptic cell and in many cases depends on the pattern of electrical activity. We here summarize the evidence of activity-dependent synaptic competition and elimination in various brain regions, together with potential underlying cellular mechanisms.

Visual System

Activity-dependent synaptic competition and elimination in the central nervous system was first indicated by work of Hubel and Wiesel on the development of ocular dominance columns (ODCs) in the visual cortex. Cortical neurons preferentially responding to one eye or the other are normally found to be segregated into alternating columns in the primary visual cortex, representing sorting of geniculocortical projections serving two eyes during postnatal development. The sorting process occurs prior to eye opening and is highly sensitive to visual experience. Depriving visual input to one eye of a newborn cat or monkey by suturing the eyelid during a critical period after birth leads to retraction of geniculocortical projections serving that eye. Interestingly, the consequences of visual deprivation during early postnatal period are much more severe in cats subjected to monocular deprivation than binocular deprivation, suggesting that competition driven by activity between two eyes, rather than the reduced activity in one eye, is responsible for sorting geniculocoritical projections. The ODCs develop by a progressive segregation of initially overlapping geniculocortical projections serving two eyes. While the initial alternating pattern of projections is established by mechanisms independent of the retina activity, pruning of extensive overlapping projections is likely to be driven by activity, including spontaneous or visually evoked retinal activity, because blocking the firing of retinal ganglion cells (RGCs) in both eyes prevents complete ODC formation.

Early in development there is also substantial overlap of retinogeniculate projections from the two eyes in the lateral geniculate nucleus (LGN). Segregation of these projections into eye-specific layers occurs before the onset of vision, but at a time when ►spontaneous activity waves are prominent in the retina. Blocking all activity in both eyes prevents segregation of retinogeniculate projections and can desegregate already existing eye-specific projections later in development, although it is unclear whether the specific pattern of the waves is required for eye-specific segregation. When the activity is altered in one eye, the more active eye acquires more synaptic territory than the less active eye, suggesting activity-mediated competition. Furthermore, even after eye-specific segregation is completed, activity in one eye can further prune retinogeniculate projections by reducing the convergence of RGC inputs onto a single LGN neuron from 12 to 20 to one. This within-eye pruning based on activity-dependent competition among RGCs facilitates sharpening of the receptive field of LGN neurons. Such activity-dependent competition may be attributed to the competition in the growth or stability of RGC axonal arbors. In the developing optic tectum of zebrafish, reducing neuronal and synaptic activity in a subset of RGCs leads to suppression of their axon growth and branching and this suppression is relieved by blocking the activity of nearby RGC axons as well [3].

The successive levels of the mammalian visual system are organized into retinotopic maps that preserve an orderly representation of visual inputs at the retina, through topographically precise retinogeniculate, retinocollicular and geniculocoritical projections. Formation of these maps requires specific patterns of spontaneous activity in the retina because disrupting these waves affects map formation at all levels. While the initial projections may establish a crude retinotopic map via axon guidance based on ►molecular cues, interfering with both axon guidance cues and spontaneous wave activity in the same animal results in a dramatic cumulative effect in disrupting the map in the superior colliculus. Finally, the development of retina circuitry itself also depends on activity. Depriving the retinal activity by blocking spontaneous activity or dark rearing blocks both the normal maturational loss of ON-OFF responsive RGCs and the pruning of dendrites at the stratified ON and OFF layers of the inner plexiform layer, although it is unclear whether dendritic pruning in this layer results from competitive interaction among bipolar inputs.

Somatosensory System

Somatosensory projections in the brain exhibit a ►somatotopic map, with axons of peripheral receptor sheets projecting in an orderly manner onto central brain structures. The most intensively studied system is the rodent trigeminal pathway where the patterned array of the whisker is replicated in the patchy distribution of afferents and the modular organization of their postsynaptic counterparts along the pathway from the periphery to the primary somatosensory cortex. The whisker-related patterns are first established in the brainstem nuclei, then in the ventro posteromedial

nucleus of the thalamus, and finally in the somatosensory cortex ("barrels"), where neurons respond best or exclusively to deflection of the corresponding facial whisker. These somatotopic maps emerge during early development in ascending order along the neuroaxis, with a sequence that includes afferent fibers segregation before rearrangement of their target neurons in discrete zones along the pathway. It is generally believed that the initial crude topographic projection of the afferent fibers is independent of sensory experience, but the presence of segregated afferent fibers and postsynaptic glutamate receptor activities are required for the subsequent parcellation of their postsynaptic targets [4].

That cortical map formation depends on a competitive process is suggested by the finding that damage of the branch of the trigeminal nerve supplying the whisker pad prior to birth results in a reduction of the cortical representation of the whiskers and a concomitant increase in the representation of other peripheral receptor surfaces. Whether and how such competition occurs through synaptic competition and elimination are unknown. ►Synapse elimination has been observed in the ventral posteromedial thalamic nucleus of young animals, where multiple afferents on each neuron are reduced to one or two afferents as the animal matures. However, this synapse elimination and remodeling occurs even in animals deprived of sensory experience from birth, indicating that the process is independent of sensory experience, although spontaneous neuronal activity may still be required.

Morphological organization of somatosensory cortical neurons into barrels during development depends on signals conveyed by invading thalamic axons and sensory activity. Indeed, primordial visual cortex transplanted into the neonatal somatosensory cortex form barrels when invaded by axons from somatosensory thalamic nuclei, and genetic manipulations that interfere with the appropriate segregation of these axons disrupt barrel formation. Moreover, that sensory peripheral sensory signals may be instructive in sculpting the somatosensory cortical map is also evidenced by lesion or genetic studies showing that altering the number of functioning whiskers leads to shrinkage, expansion or addition of barrels. However, such aberrant barrel formation may result from sprouting and retraction of afferents and dendrites due to neuronal degeneration and alteration in the number of afferents, involving competitive ►synapse formation, rather than activity-dependent synaptic competition. Notably, changes in whisker use drive functional changes in the barrel neurons without affect anatomical appearance of barrels, suggesting no gross reorganization of synaptic connections. Nevertheless, sensory deprivation results in a specific loss of GABAergic synapses and impairment of secondary dendritic branches in the barrel cortex. Thus, activity may lead to synapse elimination of at least a subset of synapses in the somatosensory cortex, presumably through a competitive process.

Auditory System

Sound entering the ear stimulates cochlea hair cells, which make synaptic connection with spiral ganglion cells that give rise to the primary auditory nerve for carrying auditory information into the brainstem. From there the signals converge in the inferior colliculus that sends projections to the thalamus, which further relays auditory signals to the auditory cortex. In these relay areas neurons are arranged in a topographic manner according to the sound frequencies to which they are most sensitive. Although the topography of these connections is apparent early in development, the precision of the map is refined later in development through an activity-dependent process [5]. Developmental pruning of both axonal arbors and dendritic branches has been widely observed in the auditory system. Cochlear nerve axons and their target neurons in nucleus magnocellularis (NM) undergo extensive parallel structural transformations involving pruning of cochlear axonal arbor, massive reduction of dendrites in NM neurons, and elimination of poly-neuronal innervation. Since otocyst removal has no effect on the extent, timing, and pattern of dendritic loss, this extensive synapse elimination is independent of the sensory activity. Interestingly, after this early massive remodeling, NM neurons undergo further dendritic growth before maturation in a sensory activity-dependent manner.

In contrast to that in the NM, developmental remodeling of axons and dendrites in the nucleus laminaris and superior olivary nucleus (SON) after the onset of hearing appears to be activity-dependent. Cochlea removal or blockade of glycinergic transmission impairs remodeling of axonal and dendritic morphology in SON. Since most of the remodeling occurs after the onset of hearing, acoustically evoked activity is likely to be involved, although spontaneous activity may also contribute. Indeed, correlated spontaneous activity is present in the embryonic brainstem and auditory nerve. The spatiotemporal pattern of spontaneous firing could provide developmental cues for the spatial ordering of auditory projections, as suggested by the presence of a systematic relationship between the rate of rhythmic bursting and the tonotopic location in the chick. Such activity-dependent remodeling of connectivity may contribute to the tonotopic map refinement at many different levels in the auditory system.

After the onset of hearing, the auditory cortex undergoes a transition from a tonotopic map dominated by broadly tuned, high frequency-selective neurons to the adult tonotopic map consisting of neurons that represent the full spectrum of acoustic inputs. ►Sensory-evoked activity is responsible for this transition. Early

acoustic environment is critical for the maturation of tonotopic maps, because exposing rat pups to pulsed white noise or rearing them in continuous moderate-level noise impairs the emergence of adult-like tonotopic map, whereas exposure to pulsed tones of specific frequencies results in accelerated emergence and expansion of auditory cortex representations of those frequencies. This activity-dependent remodeling of cortical maps are likely to involve synaptic competition and elimination, although whether functional refinement of the map directly reflects structural reorganization of synaptic connectivity remains to be determined.

Olfactory System

The olfactory sensory neurons in mammals express only one of about 1000 odorant receptor genes and neurons expressing a given receptor are randomly dispersed within one of four broad zones in the olfactory epithelium. The axons of these sensory neurons converge upon spatially conserved glomerulus within the olfactory bulb. The topographic mapping between sensory neurons and specific glomeruli may depend on the expression of specific molecules along their projection pathways or in themselves. There is evidence, however, that activity in these olfactory neurons may also play a role. Although the patterns of axon convergence in the bulb is largely intact in mice lacking functional olfactory cyclic nucleotide-gated channels, hence no odorant-evoked activity occurs in these neurons, non-correlated spontaneous activity may still be required for the correct mapping process. Indeed, sensory map is not affected when conditional expression of tetanus toxin light chain inhibits synaptic transmission in the majority of olfactory sensory neurons. However, inhibition of synaptic release in a small subpopulation of neurons expressing the P2 receptor results in correct targeting of the sensory axons initially, but the P2 glomerulus is not maintained and P2 neurons ultimately diminish. Preventing excitation of the neuron has a similar effect on the formation of the olfactory map. Thus, spontaneous neuronal activity may play a role in pruning or stabilization of axon terminals of olfactory neurons on their glomerular target cells, but there is little evidence that synaptic competition is involved in olfactory map formation.

Cerebellum

The two main afferent systems in the cerebellar cortex are the climbing fibers (CF) originated from the inferior olivary nucleus and the mossy fibers (MF) from various nuclei in the spinal cord, brain stem, and deep cerebellar nuclei. Each CF directly contacts the proximal dendritic compartment of a single Purkinje cell, whereas the MFs influence Purkinje cells indirectly through granule cells, whose axons form the parallel fibers (PFs) that synapse onto the dendrites of many PCs. There is evidence for a complex ►topographic map of these afferents fibers. For example, cutaneous inputs carried by CFs are topographically organized to form a map of peripheral body, with CF axonal arbors in register with cortical parasagittal bands of chemically heterogeneous PCs. The formation of these precise topographic maps involves both activity independent and dependent steps. First, positional information shared between CFs and PCs during embryonic development provides the molecular code for the formation of coarse-grained maps independent of neuronal activity. Activity-dependent mechanisms are later required for the transition to a fine-grained map, by pruning CF terminal arbors on each PC from multiple to single CF innervation [6]. This pruning involves strengthening one CF while weakening all other CFs during the first postnatal week, leading to the elimination of the latter. Moreover, alteration of the temporal pattern of CF activities specifically during development impairs such CF elimination in vivo, suggesting an activity pattern-dependent synaptic competition.

In addition to potential competition among homologous CFs, there is also heterologous competition between CFs and PFs that results in their segregation into different dendritic domains of each PC. Weakening of the CF input leads to the reduction of its dendritic territory and concomitant strengthening and expansion of the PF input, and vice versa. Furthermore, elimination of CFs depends on the activity of developing PF-PC synapses, because CF elimination is affected by reducing PF inputs, through granule cell degeneration, impairment of granule cell function, or genetic manipulation of PF-PC synapse formation or efficacy. The similarity in the consequence of reducing CF and PF activities in CF elimination suggests that similar mechanisms may underlie synaptic competition/elimination among homologous vs. heterologous inputs.

Autonomic Ganglia

Ganglionic cells in the autonomic nervous system are innervated by preganglionic neurons of the spinal cord or brainstem and send projections to target tissues via spinal nerves to control involuntary functions of the body. In mammals, characteristic patterns of sympathetic and organ responses elicited by the activity of individual spinal axons are due to mapping between specific spinal segments and peripheral targets. This mapping requires a stereotyped and selective innervation of ganglion cells by preganglionic axons, with each ganglion cell innervated by one or few axons from specific contiguous spinal cord segments. During development there is a transition from initially exuberant innervation of each ganglion cell by many preganglionic axons to innervation by only one or a few axons. Since the spinal segment responsible for activating the mature and neonatal ganglion cell is the

same, developmental synapse elimination involves reduction of preganglionic axons from the same spinal segment, suggesting competition occurs among axons of nearby spinal neurons. Furthermore, transection of a portion of preganglionic nerve innervating a developing ganglion leads to sprouting of residual preganglionic axons and partial restoration of original multiplicity of innervation. These results are all consistent with the idea that synaptic elimination is not simply due to the intrinsic merit of the input, but involves competition among inputs, presumably for a postsynaptic factor of limited supply, e.g., locally secreted trophic factor (see Mechanisms).

The competitive interaction that determines the final number of preganglionic axons converging upon a single ganglion cell depends on the proximity of competing synapses, with each surviving synaptic terminal claiming a certain territory on the dendritic or somatic surface and neurons with more extensive dendritic arbors receiving more axons. This distance-dependent synapse competition can be explained by a limited amount of available postsynaptic factors. This synapse competition appears to be activity-dependent, because among converging inputs to a single ganglion neuron, strong synapses become further strengthened and weak synapses further weakened during synapse elimination. Moreover, the synaptic strength for each synaptic input of a multiply innervated cell is, on average, weaker than that of a singly innervated cell, suggesting that the total synaptic strength of a postsynaptic ganglion cell is conserved, due to a limited amount of a synapse-related factor.

Neuromuscular Junction

Each muscle fiber in the neonatal animal is multiply-innervated by axon collaterals of several motoneurons, but becomes singly-innervated during early postnatal life [7]. This process depends on synapse elimination involving withdrawal of a subset of nerve terminals of each motoneuron innervating a given muscle (i.e., reduction of the size of motor units) rather than reduction in the number of motoneurons innervating a muscle. Partial denervation of the muscle at birth results in the retention of the large motor unit size without substantial collateral motor axon sprouting. Synapse elimination is competitive rather than a random process of withdrawal, since muscle fiber without a single axon is never observed. The elimination is also activity-dependent. Blocking motoneuronal activity prevents elimination, while elevating activity accelerates it. Importantly, when the relative synaptic efficacy of two competing axons at a single neuromuscular junction is impaired by genetic deletion of acetylcholine in one axon, the latter loses the competition, suggesting that the strength of the synapse is predictive of the outcome of the competition [8].

Mechanisms of Activity-Driven Synapse Competition

The Hebb's Rule for Synapse Competition

Hebb postulated that strengthening of a synapse might be achieved by repetitive presynaptic activation that leads to postsynaptic firing. This postulate was later transformed into a simple rule – coincident pre- and postsynaptic activity leads to synapse strengthening and stabilization. To account for the finding of Hubel and Wiesel on activity-dependent remodeling of connectivity in the developing visual system, Stent further extended the ►Hebb's rule by assuming that noncoincident pre- and postsynaptic activity leads to synapse weakening and elimination. Modeling studies showed that such correlation-based Hebb's rule could explain activity-dependent refinement of developing visual circuits. In the past decade, a temporally specific form of Hebb's rule has been proposed, based on findings of spike timing dependent synaptic plasticity in a variety of systems [9]. The temporal order in the spiking of pre- and postsynaptic neurons was shown to be critical for synaptic modification, in addition to the extent of coincidence in spiking: "Pre-before-post" results in strengthening and "post-before-pre" leads to weakening of the synapse. This spike-timing dependent plasticity offers an element of causality in the activity-induced synaptic competition: Inputs that contribute to (and cause) the postsynaptic spiking are advantageous in synaptic competition over those inputs arriving after postsynaptic spiking has just occurred. Importantly, experimental evidence for the validity of various forms of the Hebb's rule mainly came from studies of activity-induced functional changes of synaptic efficacy, e.g., long-term potentiation (LTP) or long-term depression (►LTD), rather than changes in the morphological connectivity.

Importance of Temporal Pattern of Activity

The importance of the pattern of activity in synapse competition has been demonstrated mainly in the development of ocular dominance and orientation selectivity of the primary visual cortex. Rearing kittens with induced squint (strabismus), which alters the pattern but not the absolute level of activity, results in striking changes in the binocular property of cortical cells, reflecting altered synapse competition of geniculocortical inputs. Artificially imposing synchronous activity on optic nerves from the two eyes prevents segregation of thalamocortical projections into ocular dominance columns, whereas asynchronous activity allows segregation. Similarly, synchronous activation of optic nerves blocks the development of topographic maps in the optic tectum and reduces orientation selectivity in the cortex. Spike-timing-dependent synaptic modification provides a natural basis for such pattern dependent competition. In the developing *Xenopus* visual system, spike timing-dependent induction of ►LTP and LTD has been demonstrated, but whether such persistent changes in

functional efficacy of synapse is causally related to structural changes in connectivity remains unknown.

Contribution by GABAergic Inhibition

Activity in the brain depends on a proper balance of excitation and inhibition. It is thus not surprising that GABAergic activity plays a regulatory role in the refinement of developing circuits. In mice lacking one form of the enzyme (GAD65) responsible for GABA synthesis, the ocular dominance plasticity resulting from monocular deprivation is absent, and increasing GABA inhibition in diazepam-treated mutant mice allows the appearance of ocular dominance plasticity. In the developing retinotectal system, a proper level of GABAergic inhibition is required for normal refinement of the retinotopic map in the tectum, both the \increase and decrease of inhibition impede ►map refinement. Interestingly, the role of GABAergic inhibition appears not only to reduce the overall neuronal excitation, but also to sharpen the temporal pattern of the neuronal activity by shortening stimulus-evoked discharges, potentially facilitating spike timing-dependent refinement of neural circuits. Shunting of specific excitatory inputs may also be achieved by selective distribution of inhibitory synapses on the dendrite. Finally, inhibitory synapses may also undergo competition and refinement as well, because they are integral part of the neural circuit. At present, it is unknown how nascent inhibitory connections, while playing important regulatory roles in refining excitatory connections, can themselves undergo activity-driven refinement and be properly consolidated into the mature circuit.

Causal Link Between LTP/LTD and Synapse Competition

At some synapses repetitive co-activation of the pre- and postsynaptic cell leads to not only homosynaptic LTP, but also heterosynaptic LTD of non-coactive converging synapses onto the postsynaptic cell, thus providing a potential competitive mechanism for synaptic elimination. The hypothesis that synapse stabilization and elimination are mechanistically linked to or even result from activity-induced LTP and LTD, respectively, remains to be fully tested. Many lines of correlative evidence support this hypothesis. Blocking NMDA receptor activation, which abolishes many forms of LTP/LTD, impedes refinement of developmental circuits. Repetitive visual stimuli that modify developing visual circuits can induce NMDA receptor-dependent LTP/LTD of retinotectal synapses. During the postnatal critical period, the composition of ►NMDA receptors undergoes experience-dependent developmental regulation in the visual system, and there is a correlation between the susceptibility for LTP/LTD induction and for circuit refinement. However, whether LTP/LTD is relevant or a prelude to structural refinement in the visual system remains unknown. Synapse elimination (structurally) will certainly eliminate the synaptic function, but whether LTD will lead to synapse elimination is unclear. Recent studies in hippocampal slices has provided evidence that LTP/LTD induction is followed by a swelling/shrinkage of dendritic spines, supporting the linkage between synaptic efficacy and synaptic structure.

The Trophic Factor Hypothesis

Purves and Lichtman have proposed that synaptic competition involves the competition between co-innervating presynaptic terminals for a limited amount of "trophic factors" derived from the postsynaptic cell. This hypothesis can be extended to factors in the postsynaptic cytoplasm or plasmalemma, together with a localized retrograde signaling to the presynaptic nerve terminal. Competition for the trophic factor can be regulated by activity. The activity can serve a permissive role for synapse competition by regulating the synthesis and release of trophic factors/retrograde signals, whereas other activity-independent mechanisms determine the competitive advantage of a synapse. For activity to serve an instructive role, the pattern of activity in the co-innervating nerve terminals may determine the outcome of competition by controlling the uptake or the efficacy of the trophic factor at the nerve terminal. The local release of trophic factors may also depend on local synaptic activation, which is in turn driven by the pattern of activity, including the timing of pre- and postsynaptic spiking. The ►neurotrophin family of proteins, which are known to regulate synaptic function and axon/dendrite morphology, are attractive candidates for the trophic factor in synapse competition [10]. The expression and secretion of neurotrophins, and their potentiating actions on the synapse, are all activity-dependent. Neurotrophins are required for the development of ocular dominance column and for the induction of activity-induce LTP in several systems. Furthermore, neurotrophin secretion is activity-pattern dependent, and the secreted neurotrophins are likely to act locally by its binding to cell surfaces at the synapse, allowing them to serve as local synaptic modulators. Activity-dependent depletion of available neurotrophins in the local environment of the synapse may lead to the functional and structural modification underlying synapse elimination.

Concluding Remarks

Studies of synapse competition and elimination in the near future are likely to be facilitated greatly by the availability of many new technologies for selective neuronal labeling and optical imaging in the living animal. Transgenic animals with selective populations of fluorescence-tagged neurons, together with in vivo multi-photon imaging, will allow us to directly monitor changes in the morphology of axons and dendrites during the process of synapse competition and refinement over

prolonged period in the intact brain. Fluorescent Ca^{2+} or membrane-voltage sensors will allow us to monitor neuronal activities, and photo-activated probes expressed in selective neuronal populations will allow us to directly manipulate neuronal activity and to examine how activity drives synapse competition and elimination.

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Synapse Formation: Neuromuscular Junction Versus Central Nervous System

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Synonyms

Synaptogenesis; Establishing stable neuronal contacts; Neuron-to-neuron communication

Definition

Synapses are the structural basis of communication between neurons in the ►central nervous system (CNS) and between neurons and muscle cells in the ►peripheral nervous system (PNS). Synapse development involves the formation of a contact between axon terminals and specific sites on the appropriate target. This is followed by contact stabilization and maturation which involves the recruitment of the appropriate protein machinery at pre- and postsynaptic sites.

Characteristics

Formation of the Vertebrate Neuromuscular Junction (NMJ)

Formation of a NMJ synapse involves the establishment of a connection between a presynaptic terminal of a ►motoneuron and a postsynaptic skeletal muscle cell. The NMJ is a large and accessible structure that develops in a stereotypical manner as each muscle fiber receives input from a single motoneuron axon. As a result, the molecular, cellular and physiological properties of this synapse have been well characterized. In the stereotypical NMJ, numerous presynaptic ►active zones are directly aligned with a postsynaptic specialization called a junctional fold.

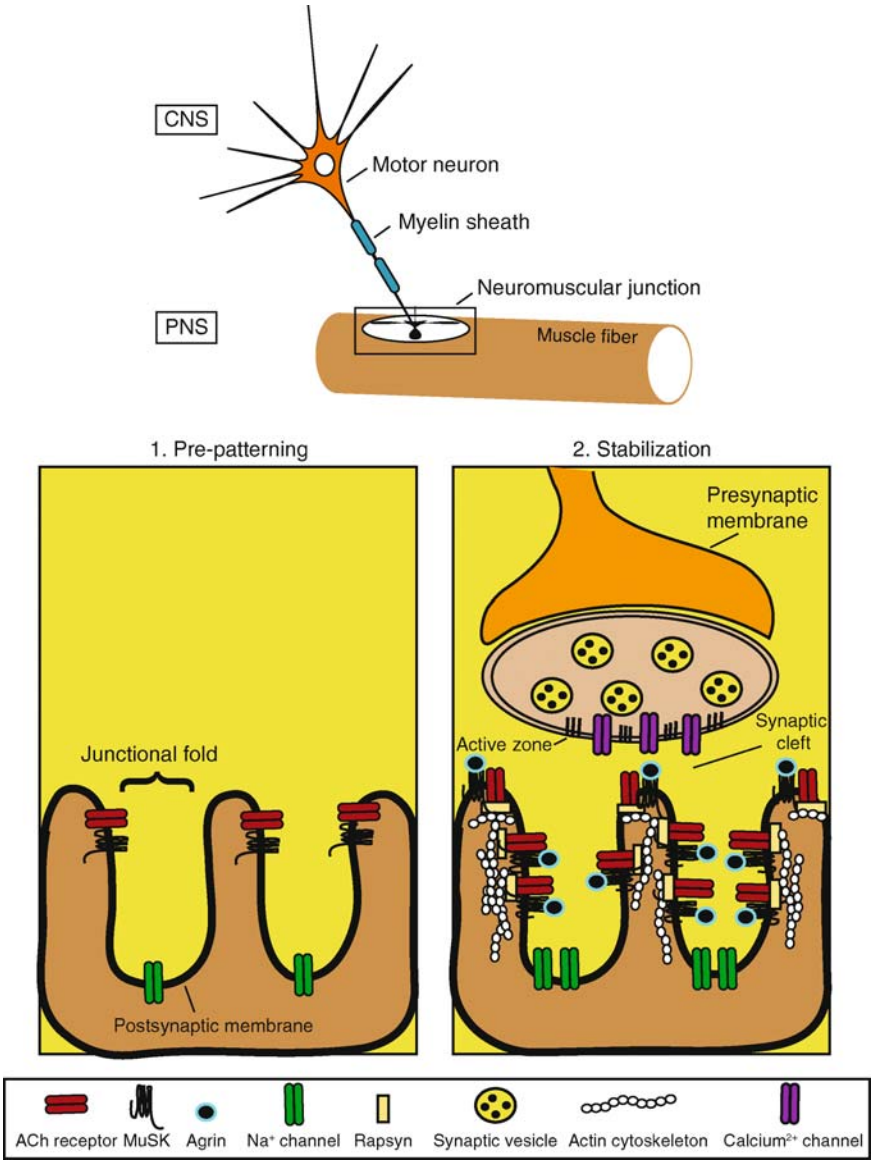
The folds are introversions into the muscle plasma membrane, with cationic ligand-gated ►acetylcholine receptors localized to the top and voltage gated sodium channels deeper within these folds [1]. In response to an action potential, the multiple release sites of the presynaptic terminal have a high probability of vesicular release and the amount of ►acetylcholine released saturates the ►postsynaptic receptors. To control the efficacy of transmission, an enzyme called acetylcholinesterase (AChE) present at the synaptic cleft, acts to degrade the released transmitter, terminating the signal. Another important structural component of the NMJ is the thick basal lamina of the ►extracellular matrix (ECM) that runs through the cleft. During formation and maturation of the synapse, components of the ECM at the NMJ serve critical signaling and structural roles as a diffusion barrier for AChE.

NMJ formation is directed by reciprocal interactions between motor neurons and muscle fibers. ►Laminins, a component of the NMJ basal lamina, have come forward as a muscle derived signal involved in the development of the presynaptic terminal [1]. Specifically, ►laminin β2 has been shown to act as a stop signal for incoming axons *in vitro*. Mice lacking laminin β2 form few active zones and fail to align vesicles apposed to receptors on the muscle fiber [1]. These results highlight the importance of muscle-derived signals in proper NMJ development.

At the postsynaptic side, high concentrations of acetylcholine receptors (AChRs) are clustered at central regions of the myofibers following muscle production. This occurs before the arrival of the motoneuron axonal ►growth cone, and is termed pre-patterning [2].

Recent in vivo studies demonstrate that AChRs are preferentially formed at the endplate band where

innervation occurs, suggesting that the site where the motoneuron contacts the muscle may not be the only factor determining synapse location. As the motoneuron axon approaches the muscle fiber, secreted factors such as ►agrin and ►neuregulin, are released from the axon that results in further clustering of AChR and maturation of postsynaptic specializations [1] (Fig. 1). Agrin is secreted by motor neurons and by muscle, which binds



Synapse Formation: Neuromuscular Junction Versus Central Nervous System. Figure 1 Sequence of events that underlie synapse formation at the neuromuscular junction. Motor neurons from the motor cortex located in the CNS send axons ensheathed in myelin to target muscle cells. A contact between a motoneuron axon and muscle fiber constitutes the neuromuscular junction (NMJ; left panel). At NMJ, acetylcholine receptors (AchRs) are positioned at the postsynaptic membrane opposite to the presynaptic nerve terminal ►active zone containing the neurotransmitter acetylcholine (Ach). An early step of NMJ synapse formation is pre-patterning of AChRs in the endplate region. This is thought to be a muscle-specific program as initial clustering of AChRs occurs in the absence of input from the motor neuron. It is thought that MuSK activation occurs independently of agrin to induce AChR clustering during pre-patterning. Synapse stabilization and maturation involves enhanced clustering of AChRs and this process is thought to require agrin and MuSK. Furthermore, rapsyn, a scaffolding molecule bound to the actin cytoskeleton, also modulates anchoring of AchRs. Based on findings reviewed in [1].

to ►muscle-specific receptor tyrosine kinase (MuSK). Activation of ►MuSK causes enhanced AChR clustering and the production of more AChRs [3] (Fig. 1).

In mice lacking agrin, AChRs are reduced in number with a wider distribution and show incomplete motoneuron terminal differentiation, suggesting that postsynaptic differentiation is necessary for additional presynaptic development [1]. AChR-inducing activity (ARIA) or ►neuregulin-1 increases AChR expression through activation of its receptor, membrane associated tyrosine kinases related to EGF receptors (►erbB receptors) [1]. Unlike agrin, neuregulin/erbB signaling is dispensable to NMJ function, and thus may play a modulatory role in NMJ development [1]. Another protein important for pre-patterning of AChR clustering is the scaffolding molecule ►rapsyn, which directly binds to and stabilizes AChRs on the surface of the developing muscle. Interestingly, since rapsyn-deficient mice lack receptor clusters [2] (Fig. 1). Studies on mice deficient in the enzyme required for neurotransmitter synthesis, ChAT [1] revealed that motoneuron activity is important for the refinement and maintenance of NMJs [1]. In summary, recent studies revealed several signals from both the pre- and postsynaptic sites are needed to establish stable contacts between ►motoneurons and muscle cells and to induce receptor clustering and maturation of the NMJ.

Formation of Central Nervous System (CNS) Synapses

Synapse Heterogeneity

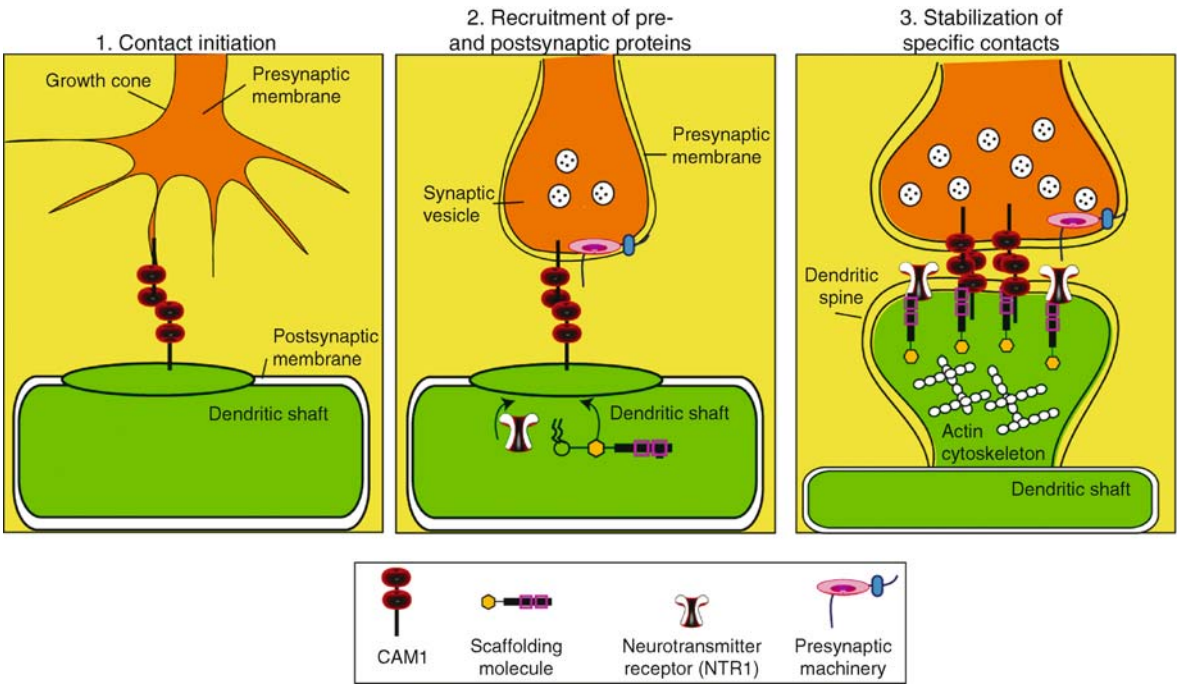
Mechanisms involved in central nervous system (►CNS) synapse development are far less understood due to multifarious neuronal types and the neurotransmitter they release. In addition, there are differences in their temporal development [2]. Neurotransmitter released from pre►synaptic vesicles bind to postsynaptic receptors eliciting a specific effect that depends on the (i) type and number of postsynaptic receptors, (ii) developmental stage of the neuron, (iii) type of neurotransmitter released, and (iv) neuronal activity [2]. Despite the complexity of CNS synapses, the basic principles of NMJ formation still hold true, such as the cooperation of axonal and target-derived signals and modulation by activity. Several classes of molecules including ►cell adhesion molecules, secreted factors, and scaffolding proteins have emerged as important proponents for the formation and maintenance of CNS synapses (Fig. 2).

Overview of Synaptogenesis: Carefully Choreographed Steps

The formation of a CNS synapse involves several key steps, which include: neuronal contact establishment, recruitment of pre- and postsynaptic proteins, contact stabilization and maturation [2] (Fig. 2). Each of the steps of ►synaptogenesis outlined above requires crosstalk between two neurons. Developmental regulation of protein expression, as well as mechanisms that govern localization of neurotransmitter receptors and associated proteins to particular contact sites, are key processes that control synaptic contact maturation and function.

Correct connectivity is essential for a functional neuronal network thus, target regulation must be specific [2]. To achieve this, axons often travel long paths before reaching the appropriate target cell (Fig. 2). This has been described in terms of axonal ►growth cones that extend ►filopodia searching for the proper target. Dendrites also extend growth cones and are decorated with filopodia which are thought to be important for contact initiation [2] (Fig. 2). Axon guidance is aided by cues in their environment that act as attractive and repulsive cues. Secreted factors, for example, Wnt and fibroblast growth factor (FGF) function as retrograde signals to regulate axon arborization and synaptic differentiation. Specifically, Wnt is released from postsynaptic neurons, resulting in a decrease in axon extension and an increase in growth cone size. This effectively "slows" down the axon once it reaches the appropriate target and enhances the possibility of contact initiation.

A successful contact formation requires cross-talk between the axon and target cell to recruit the appropriate neurotransmitter release machinery and their receptors at contact sites [3]. Cell adhesion complexes are also attractive candidates for the regulation of synaptogenesis as they can function to bi-directionally regulate molecular and morphological changes in ►synapse formation [3]. Due to the large number and diversity of neuronal contacts formed during synaptogenesis, multiple adhesion systems must exist to offer sufficient possible combinations to ensure formation and stabilization of proper contacts between neurons. A prime example includes ►cadherins, homomeric adhesion molecules, thought to regulate target recognition in the CNS. The cadherin superfamily is comprised of more than 100 members, including classical cadherins, cadherin-related proteins and ►protocadherins, many of which are expressed in the brain [3]. Thus, matching cadherins in axons and dendrites is believed to promote selective adhesion between appropriate partners in a "lock and key" fashion. Because of their adhesive properties, adhesion molecules are thought to serve four major functions: (i) Synaptic contact initiation, (ii) contact stabilization and recruitment of other molecules that regulate synapse maturation, specificity and function, (iii) maintenance of mature synapses, and (iv) trans-synaptic signaling which allows communication between the pre- and postsynaptic compartments to synchronize neurotransmitter release and postsynaptic neurotransmitter activity and signaling [3]. Importantly, recent studies revealed that many

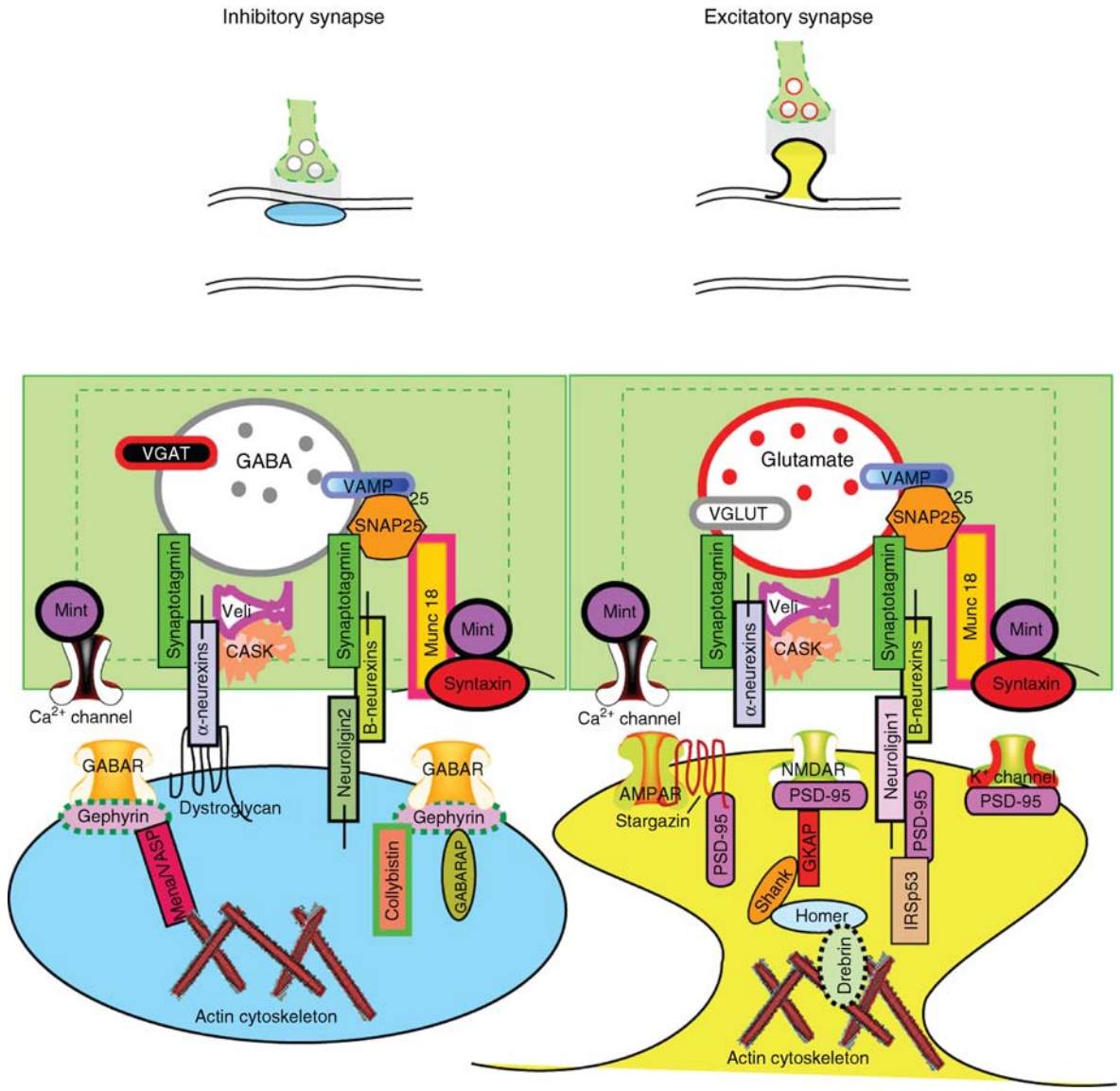


Synapse Formation: Neuromuscular Junction Versus Central Nervous System. Figure 2 Proposed role of cell adhesion and scaffolding molecules in the formation and stabilization of glutamatergic CNS synapses. (left panel) Specific cell adhesion molecules (CAMs) are thought to control contact specificity. At this early stage, axonal growth cones are thought to contact the dendritic shaft of postsynaptic cells to establish a contact. Dendritic filopodia are also thought to participate in initial contact initiation and formation of bulbous protrusions known as dendritic spines. Initial contact can also occur by axons contacting dendrites in passing. Another key step in synapse formation is contact maturation at which recruitment of pre- and postsynaptic proteins takes place. (middle panel) During synapse maturation, presynaptic neurotransmitter synthesis and release machinery are recruited to the presynaptic terminal (referred to as presynaptic machinery in legend). At the postsynaptic side, cell adhesion molecules, scaffolding proteins and neurotransmitter receptors are recruited. (right panel) Some of the key neurotransmitter receptors and associated adhesion and scaffolding proteins recruited to mature glutamatergic excitatory synapses are indicated. The recruitment of these proteins is thought to regulate both contact stabilization and neurotransmitter receptor clustering, as well as changes in synapse morphology such as spine formation. The dynamic addition and removal of these molecules at mature synapses controls synaptic strength and plasticity.

aspects of memory formation and animal behavior can be affected when adhesion molecules are disrupted or eliminated. Thus, delineating the role of the various adhesion systems in synapse formation will help not only understanding the intricate mechanisms involved in neuronal contact formation and maturation, but also in establishing the specific neuronal circuits that regulate neuronal communication and ultimately brain function. However, numerous adhesive complexes have been discovered and this makes them both interesting and difficult to study.

A family of cell adhesion molecules that are emerging as critical modulators of synapse induction and maturation are postsynaptic ►neuroligins and their presynaptic binding partners, ►neurexins [3,4] (Figs. 2 and 3).

One thousand isoforms of neurexins potentially can be generated by alternative splicing and this suggested a role for these molecules in controlling synapse type and specificity. The intracellular domains of both neuroligin and neurexin are short and terminate in PDZ (PSD-95, discs large and zona occludens1)-domain binding sites, which aid in connecting them to other synaptic proteins [3,4]. For instance, association of ►neuroligin-1 with scaffolding molecules such as PSD-95 can modulate synapse size and number (Fig. 2). Surprisingly, recent studies illustrate that neuroligins and neurexins can regulate formation of glutamatergic (excitatory) synapses and GABAergic (inhibitory) contacts, where neuroligin-1 is localized primarily to ►excitatory synapses and ►neuroligin-2 is localized to ►inhibitory synapses [3,4] (Fig. 3). Manipulation of the levels of these proteins can influence the excitatory/inhibitory synaptic ratio, leading to the proposal that neuroligins may play a role in maintaining the balance of synaptic input. Other adhesion molecules including SynCAMS, ephrins, and SALMs also play a role in synapse induction and maturation (Fig. 2). This highlights the



Synapse Formation: Neuromuscular Junction Versus Central Nervous System. Figure 3 Differential recruitment of adhesion and scaffolding molecules to excitatory and inhibitory synapses. Excitatory and inhibitory synapses are distinguished based on their morphology and molecular composition. (left panel) The majority of inhibitory transmission in the mammalian CNS is mediated by GABA and these inhibitory synapses are mainly formed on dendritic shafts. (right panel) In contrast, glutamatergic synapses are the major excitatory synapses in the CNS, which are mainly formed on dendritic protrusions known as spines. Inhibitory and excitatory synapses share the majority of proteins involved in presynaptic release however, their terminals contain specific enzymes that synthesize and transport neurotransmitters into presynaptic vesicles. At the postsynaptic membrane, distinct neurotransmitter receptors, adhesion and scaffolding proteins are localized. Excitatory synapses also contain an electron dense organelle called the postsynaptic density (PSD). The differential sorting of adhesion and scaffolding molecules to particular neuronal contacts is thought to modulate synaptic signaling. For instance, the adhesion molecule neuroligin1 is enriched at excitatory sites where it regulates recruitment of PSD-95, a major scaffolding molecule localized to excitatory synapses. In contrast neuroligin2, is enriched at inhibitory synapses and induces recruitment of gephyrin. This differential recruitment of proteins at particular synaptic sites is thought to gauge retrograde signaling at the synapse as well as clustering of neurotransmitter receptors and associated proteins. Coupling of adhesion and scaffolding molecules also provides an anchor to the cytoskeleton and controls synapse morphology. Based on findings reviewed in [4].

redundancy of signals present in the CNS for contact initiation and synapse maturation.

Morphological and Structural Changes Associated with Synapse Maturation

During the recruitment of pre- and postsynaptic proteins to initial sites of contact, the content and morphology of pre- and postsynaptic membranes develop in a coordinated manner. Maturation of glutamatergic synaptic contacts, the most characterized synapses in the brain, involves the formation of spines, ►actin rich dendritic protrusions with a bulbous head [4]. Spines are thought to emerge from dendritic filopodia, long and thin protrusions which have been proposed to initiate contacts by actively seeking nearby axons [5]. Mature spines contain an electron dense organelle called the ►postsynaptic density (PSD) which contains receptors and associated scaffolding and signaling molecules which are thought to regulate ►glutamate receptor clustering and function at the synapse [5]. Several adhesion and scaffolding molecules that regulate spine morphology have been identified (Fig. 2). Adhesion complexes affecting spine morphology include: neuroligins, cadherins, integrin ligands (laminin and reelin), Eph receptors and syndecans as well as members of the immunoglobulin superfamily [6]. Scaffolding proteins affecting spine morphology include PSD-95, shank/homer complex and IRSp53. Overexpression studies in cultured neurons of PSD-95, neuroligin and IRSp53, two proteins that bind to PSD-95, increases the density of ►dendritic spines [6]. Another key molecule involved in spine morphogenesis is drebrin A as it promotes actin assembly and the synaptic clustering of PSD-95 in the ►PSD [7]. Interestingly, overexpression of drebrin A, shank/homer complex or syndecan can accelerate the maturation of filopodia-like protrusions into mature spines [6]. Furthermore, blocking N-cadherin function results in loss of spines and appearance of filopodia-like protrusions. Finally, integrin ligands have been shown to affect dendritic spines: laminin increases spine density whereas reelin promotes spine stability [2].

Clustering of neurotransmitter receptors and associated proteins at newly formed contact sites is critical for synapse maturation. Most of our knowledge of the importance of molecules in the control of receptor clustering and function has emerged from the discovery of scaffolding proteins associated with ►glutamate receptors. These studies revealed that scaffold proteins function to bind and recruit other proteins that regulate actin cytoskeleton remodeling and signal transduction. This links neurotransmitter receptor activation to intracellular cytoskeletal and signaling modification. An important family of molecules that participates in this process is the scaffolding proteins that regulate clustering and assembly of neurotransmitter receptors as well as proteins that regulate actin cytoskeleton remodeling and signal transduction [6]. The membrane-associated guanylate kinase (MAGUK) family of scaffolding proteins is of central importance in regulation of protein clustering at the synapse. Many MAGUKS contain PDZ domains which function in protein-protein interactions. The prototypical MAGUK is PSD-95 which binds directly to N-methyl-D-aspartate-type (►NMDA) glutamate receptor subunits and voltage-gated potassium channels and indirectly to α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (►AMPA) type glutamate receptors [8] (Figs. 2 and 3). Overexpression of PSD-95 enhances maturation of presynaptic terminals and increases spine size. Consistent with this, knockdown of PSD-95 results in reduced clustering of AMPA receptors (AMPARs), GKAP and Shank and an overall decrease in the number of excitatory contacts [9]. Despite the striking effects of PSD-95 on synapse maturation of cultured neurons, the majority of excitatory synapses in PSD-95 knockout animals display normal synapse number and size [9]. This result could be explained by a redundancy in the function of the numerous PDZ proteins located at the synapse. AMPARs are directly linked to two other scaffolding proteins glutamate-receptor-interacting protein/AMPAR-binding protein (►GRIP/ABP) and protein interacting with C kinase 1 (PICK1) and these interactions may regulate synaptic targeting and trafficking of AMPARs [8] (Fig. 2). GRIP is localized to both axons and dendrites in neurons and functions to stabilize AMPARs and other interacting proteins at synaptic sites. PICK1 is present at synaptic and non-synaptic sites in neurons and may function to direct AMPARs to endocytic or exocytic buds through BAR domain binding, which is a sensor for lipid membrane curvature (Fig. 2). Phosphorylation of the C terminus of GluR2 alters its binding specificity for GRIP and PICK1, and contributes to synaptic plasticity by altering AMPAR trafficking [8].

In contrast, the majority of inhibitory transmission in the mammalian CNS is mediated by ►GABA, a neurotransmitter responsible for modulation of neuronal excitability and function [2]. GABAergic synapses are not associated with a clear PSD and are usually found on the dendritic shaft [4,5]. Thus, excitatory and inhibitory synapses can be distinguished based on morphology and molecular composition of the postsynaptic component [2] (Fig. 3).

The last step in synapse development involves fine-tuning of neuronal circuits such that the formed synapses may be stabilized or lost [2]. Recent studies suggest that neuronal activity plays a role in fine-tuning the number of contacts formed, ultimately leading to

stabilization of a particular subset of contacts which persists in the adult nervous system [3]. In the adult brain, changes in synaptic content, shape and their adhesive properties are thought to be the key mechanisms that control synaptic strength and plasticity, processes implicated in the regulation of information storage and transfer between neuronal cells. Thus, the continual formation and remodeling of synaptic contacts in early development and adulthood, respectively, play a key role in refining neuronal circuitry and communication between neuronal cells.

Abnormalities in Synapse Development Associated with Neurodevelopmental Disorders

Recent studies indicate that improper synapse formation may be a leading cause of neurodevelopmental disorders such as ►autism, mental retardation, and schizophrenia [10]. Autism is the most genetically determined disorder manifested at early stages of postnatal development [10]. Thus, the behavioral and cognitive deficits exhibited in autistic patients are thought to result from improper development of neuronal circuitry implicated in sensory, mnemonic, social and emotional information processing [10]. Interestingly, neuroimaging studies of aberrant circuitry in autistic patients has lead to a model whereby altered excitation (E)/inhibition (I) ratio involved in information processing may underlie the dysfunctions in patients with autism [3]. During brain development, alteration in the E/I ratio can lead to abnormal synaptic connectivity and function, resulting in severe neurological impairments. As mentioned earlier, neuroligins are important proteins for controlling the function of excitatory and inhibitory synapses, making them good candidate genes affected in autism. Indeed, rearrangement of chromosomal regions of neuroligins and PSD-95 genes and mutations in neuroligins and neurexins have been associated with autism [10]. In addition, mutations in the adhesion molecule NrCam and the scaffolding protein Shank3 have been linked to autism, however, the underlying biological mechanism(s) associated with altered expression of these proteins remains unclear [6]. Many forms of mental retardation and memory impairment also have been also linked to defects in spine maturation [5]. Thus, emerging evidence indicates that defects in synapse formation/maturation may be a common defect associated with several neurodevelopmental disorders.

Acknowledgments

The author, Pamela Arstikaitis, would like to dedicate this article to the memory of the supervisor, Dr. Alaa El-Husseini who recently passed away. Alaa was a brilliant scientist whose love and passion for science was contagious as he touched numerous people with his energy and aspirations.

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Synapse Loss

►Synaptic Elimination

Synapse Maturation

Definition

During the process of synaptogenesis, multiple molecular components are required for a fully functional synapse. The final assembly and activation of these components is referred to as synapse maturation.

►Synaptogenesis

Synapse Refinement

Definition

Similar to synapse elimination, refinement refers to the fine tuning of neuronal connections, often occurring after and in response to activity patterns.

►Activity-Dependent Synaptic Plasticity

Synapsida

Definition

A clade of amniotes incorporating mammals and those amniotes more closely related to mammals than to true reptiles. In the past, non-mammalian synapsids were often referred to as "mammal-like reptiles," but this term is inaccurate. These animals were not reptiles.

►The Phylogeny and Evolution of Amniotes

Synapsin

Definition

Synapsins are protein molecules that bind vesicles to the presynaptic membrane.

►Membrane Components
►Synaptic Transmission

Synaptic Adhesion Molecule

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Definition

Synaptic adhesion molecules are a diverse family of cell adhesion molecules involved in the development and maintenance of synapses [1–4].

Synaptic adhesion molecules are localized transiently or permanently at mature synapses and/or developing precursors, and in most cases, they are highly enriched in the synaptic membranes. They may directly participate in adhesion by connecting pre- and postsynaptic membranes together, or adhesion may not be their primary function, but the specific ligand-receptor recognitions transmit signals to the cytoplasm. They may be involved in one or multiple steps in synapse development and maintenance: specific target recognition, synaptic differentiation, and stabilization and modulation of synaptic structure (see Function). As brain function relies on specificity of synaptic connectivity among different classes of neurons as well as regulation of synaptic connections, these molecules must play pivotal roles in the development and maintenance of lower and higher brain functions. Impairment of synaptic adhesion molecules is likely to affect brain functions (see Pathology).

Characteristics

Higher Level Structures

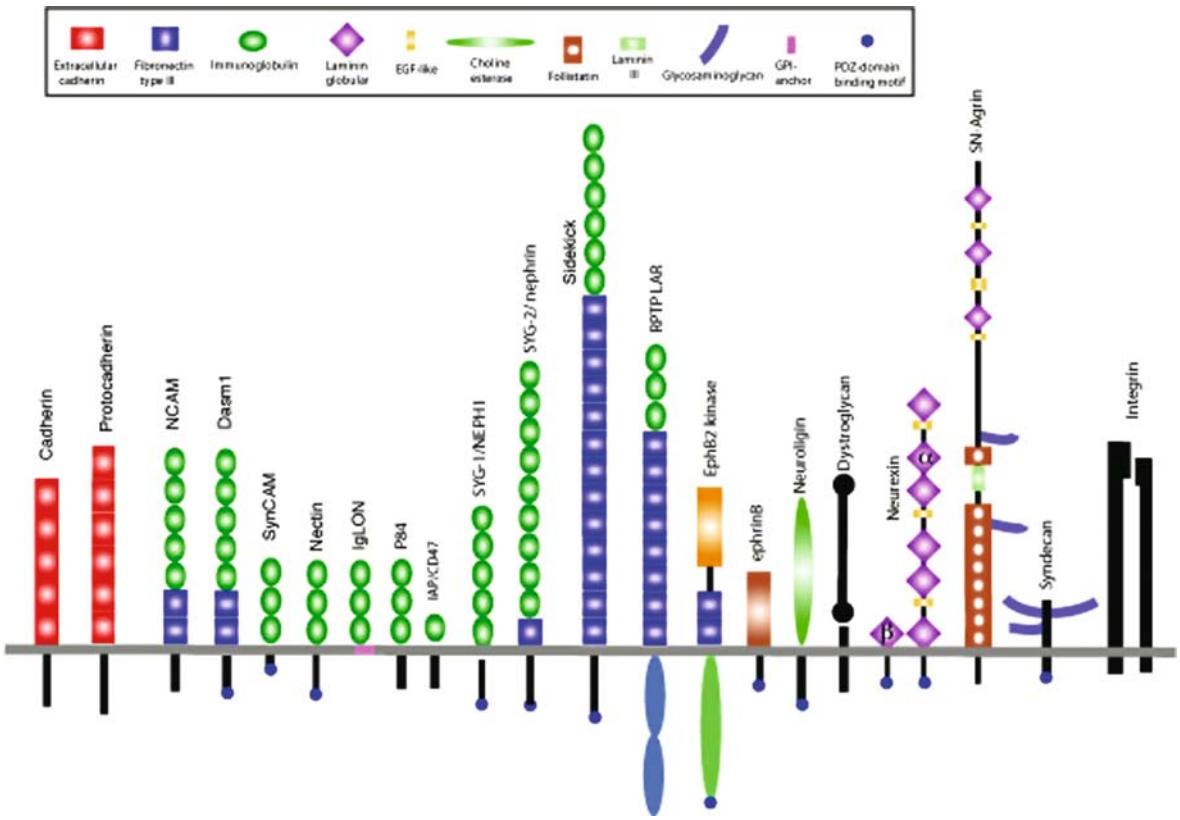
The term "synapse (synaptein)," first coined in 1897 by Charles Sherrington, comes from the Greek: "syn" meaning "together," and "haptein" meaning "to fasten or bind." As this etymology indicates, two neuronal membranes at synapses close together with a narrow space (~20 nm) between them: synapses are specialized forms of cell-cell junctions. A principal difference between synapses and other junctions is that synapses are asymmetric between presynaptic and postsynaptic structures. The presynaptic specialization, usually on the axon, has an apparatus for neurotransmitter storage and release (the synaptic vesicle and active zone). The postsynaptic specialization, usually on dendrites, has neurotransmitter receptors, and associated scaffolding and signaling proteins (the postsynaptic density).

There are two types of adhesive structures at synapses: puncta adherentia and synaptic junctions [5]. Synaptic junctions are the sites of neurotransmission, whereas puncta adherentia are formed at the surrounding area outside of the active zone. The puncta adherentia are a neuronal form of ►adherence junctions that are maintained by cadherins. The occurrence of these adhesive structures and synaptic adhesion molecules varies depending on which synapse or stage of development is observed.

Lower Level Components

Many of the synaptic adhesion molecules are members of the cadherin and immunoglobulin superfamilies [2,3] (Fig. 1).

Another major family of adhesion molecules, the integrins, is also present at synapses, together with members of families that are adhesive but are not generally considered as adhesion molecules- e.g. the Eph receptor



Synaptic Adhesion Molecule. Figure 1 Synaptic adhesion molecules.

kinases and their ephrin ligands, and neurexins and their partners, the neuroligins.

Classic cadherins are Ca^{2+}-dependent, single-pass transmembrane molecules with five extracellular cadherin (EC) repeats, which mediate primarily homophilic (more rarely heterophilic) adhesion. N-cadherin was one of the first adhesion molecules shown to be localized at the synaptic cleft. Cadherins directly couple to cytoskeletons via intracellular proteins called catenins, and generate puncta adherentia at synapses.

The protocadherins bear varying numbers of EC repeats in their ectodomains. The vertebrate protocadherin genes have a genomic organization that is similar to that of the immunoglobulin gene, and which consists of "variable" and "constant" exons orientated in a tandem array on a single chromosome. This striking genomic organization led to (as yet unproven) postulation that protocadherin diversity underlies synaptic specificity. Indeed, some members are concentrated at synapses, albeit not confined to them.

The immunoglobulin (Ig) superfamily represents a highly diversified group of cell surface molecules responsible for a wide range of molecular and cellular recognition functions. They contain varying numbers of extracellular cysteine-looped domains that are characteristic of antibody molecules. Many have one or more fibronectin type III (FNIII) repeats between the Ig domains and the membrane. This superfamily can be further classified according to occurrence of other domains. Synaptic adhesion molecules belonging to this superfamily are N-CAM, Dasm1, nectins, SynCAMs, IgLONs, Syg-1, Syg-2, sidekicks, and LAR. A striking feature of most, if not all, synaptic adhesion molecules of this family is that they possess a C-terminus motif for binding PDZ scaffolding proteins that likely contribute to their synaptic localization.

Integrins are heterodimers of α and β subunits, and mediate adhesion of cells to the extracellular matrix and to other cells. Integrins are present at the vertebrate neuromuscular junction, where they presumably interact with the basal lamina. Several integrins have also been observed at vertebrate central nervous system synapses.

Eph receptor tyrosine kinases and their ephrin ligands can be grouped into two families: ephrinA ligands are attached to the membrane by a glycosylphosphatidylinositol-anchor and bind to EphA receptors, while ephrinB ligands are transmembrane proteins that bind to EphB receptors. EphB receptors have been localized to the synapse.

Neuroligins constitute of a family of neuronal cell-surface proteins with a cholinesterase domain that lacks enzymatic activity. Neuroligins bind to β-neurexins,

another class of neuronal cell-surface proteins that contain laminin globular domains. There are three neurexins, which undergo extensive alternative splicing to potentially express a bewildering number of isoforms. Both neurexins and neuroligins have a motif for binding to PDZ scaffolding proteins, and are enriched at the synapse.

In addition to these adhesion molecules, several transmembrane molecules have been reported to be localized at synapses. These include syndecans, dystroglycan, and membrane-tethered agrin. Leucine-rich repeats-containing transmembrane molecules including the *capricious* protein were accumulated at some Drosophila neuromuscular junctions.

Function

Specific Target Recognition

Specific connectivity among a myriad of neurons is the hallmark of the nervous system. Following differentiation and migration, a developing neuron reaches its final destination in the nervous system. To establish neuronal connections with its target, a neuron must extend axonal and dendritic processes towards the proximity of targets located significant distances away, and finally select the choice of proper partner neurons with which to form specific synapses in a jungle of neuronal processes. Presynaptic inputs from defined neurons are not only connected to specific types of postsynaptic neurons, but are often synapsed to restricted subcellular compartments such as spines vs. shafts or dendrites vs. soma. To explain the mechanism that underlies synaptic specificity in neural circuit formation, Roger Sperry formulated the "chemoaffinity theory," in which adhesion molecules determine wiring specificity of the "lock and key" sort. Many examples of receptor-ligand partners are known that guide growth of axons towards their approximate target areas. However, there must also be molecular and cellular mechanisms that mediate the interaction between direct synaptic partners and initiate synapse formation.

Recent studies on an array of Ig superfamily molecules have shown that this group of adhesion molecules is important for the synaptic specificity. For example, SYG-1 and SYG-2 were isolated in a genetic screen for *C. elegans* mutants with altered synaptic positions. SYG-1 and SYG-2 belong to a subgroup of the Ig protein family that is conserved from *C. elegans* to human [6]. Sidekicks have been implicated in selective synapse formation in the chick retina. A shared feature of SYG-1, SYG-2, and sidekicks is a motif for binding to PDZ-scaffolding proteins, suggesting a model in which adhesion-triggered recruiting of key PDZ proteins is a first step in precise synaptic wiring. Neurofascin is an L1-related Ig superfamily molecule, and its ankyrin-dependent subcellular localization determines subcellular localization of GABAergic synapses in the cerebellum.

Synaptic Differentiation

Synapse formation involves stabilization of initial sites of weak adhesion between axons and targets, followed by recruitment of specific protein complexes to newly formed presynaptic and postsynaptic structures [4,7,8]. Axons can usually release small amounts of neurotransmitter even before they contact a postsynaptic partner, and many postsynaptic cells express neurotransmitter receptors before they are innervated. Once pre- and postsynaptic processes establish contact, the machineries for release of and response to neurotransmitter are concentrated at sites of contact, and placed in precise apposition to each other. Important features of presynaptic differentiation include aggregation of appropriate synaptic vesicles and association with active zones; critical features of postsynaptic differentiation include clustering of specific postsynaptic receptors and association with signaling and scaffolding proteins. There is also a high degree of variation in synaptic neurochemistry and morphology- e.g. excitatory, inhibitory, asymmetric, symmetric, ribbon, en passant, and terminal. The fact that these specializations develop specifically at contact sites, and that they develop in exact apposition, demonstrate that adhesion-mediated local signaling must provide the coordination between the target neuron and the innervating axon.

The synaptic adhesion molecule neuroligin-1 was the first target-derived signal shown to induce presynaptic differentiation of excitatory synapses in hippocampal axons [2]. This differentiation is mediated by neuroligin interaction with β-neurexin. More recently, it has been revealed that this interaction mediates both glutamatergic and GABAergic synapse formation in hippocampal neurons, and differences in neuroligin isoform and binding specificity may control the formation and functional balance of excitatory and inhibitory synapses. SynCAM1 is the other membrane protein shown to provide a target-derived signal during synaptic differentiation [8]. SynCAM1 belongs to a family of proteins characterized by three extracellular immunoglobulin-like domains and a cytosolic tail with a PDZ-binding motif. SynCAM and neuroligin-1-induced artificial synapses were essentially identical, but it appears that neuroligin-1 contributes to more morphological aspect of synapse induction.

A panoply of synaptic adhesion molecules were also shown to control localization and function of postsynaptic neurotransmitter receptors. The EphB receptor tyrosine kinases and their ligands, the ephrinsB regulate function of a NMDA type glutamate receptor. The receptor-type protein tyrosine phosphatase LAR is an Ig superfamily that is important for the surface expression and clustering of AMPA-type glutamate receptors at synaptic sites. In the developing brain, excitatory synapses initially contain only NMDA receptor and therefore are "silent" at the resting membrane potential.

However, later, synapses acquire AMPA receptors. Dendrite arborization and synapse maturation 1 (Dasm1), the Ig superfamily member, appears to control this excitatory synapse maturation [9].

Stabilization and Regulation of Synaptic Structure

At all the intracellular junctions, adhesion molecules connect two membranes, and stabilize the architecture of the junction. Likewise, synaptic adhesion molecules protect synapses by adhering pre- and postsynaptic membranes. Stability of interneuronal synaptic membranes from mechanical force is obvious from the ability to isolate intact synaptosomes. The fact that synaptic adhesion molecules stabilize synaptic structure indicates that strengthening and weakening of adhesion could regulate synaptic structure. Such a function would be of importance to synaptic plasticity, which is believed to involve changes in synaptic density and size, to synapse maturation, which requires the organized enlargement of presynaptic boutons and postsynaptic structures, and to synapse elimination, which is de-adhesion of two synaptic membranes. These synaptic remodeling events are likely to contribute to one of the mechanisms that underlie learning and memory.

The majority of excitatory synapses in the brain are made onto dendritic spines, knobby protrusions of the dendritic shaft. Dendritic spines are highly dynamic, and undergo a variety of actin cytoskeleton-based morphological changes both during synapse formation, and in response to activity changes. It is believed that changes in dendritic spine number and morphology reflect synaptic plasticity, particularly changes in synaptic connections between neurons. Several studies have shown that a cadherin-catenin adhesion system controls spine structure in cultured hippocampal neurons [10]. N-cadherin localization and adhesive strength change in response to neural activity. These observations suggest that synaptic activity dynamically regulates both the strength and the localization of cadherin-based adhesions, changes that may be important for regulating synaptic plasticity.

Pathology

As synaptic adhesion molecules regulate synaptic development and maintenance, their dysfunction may cause synaptic deficits that ultimately underlie disorders ranging from neurodevelopmental syndromes to neurodegenerative disorders. Autism is a neurodevelopmental syndrome that affects an estimated 2–6 per 1,000 individuals. It has been hypothesized that changes in neuronal circuitry and synaptic signaling are responsible for the behavioral and cognitive aberrations in autistic patients. Point mutations in neuroligins have been linked to a small subset of patients with autism-spectrum disorders. Cognitive decline characterizes mental retardation syndromes such as Cri-du-Chat and neurodegenerative disorders, such as Alzheimer's disease. Involvement of cadherin-mediated adhesion in cognitive decline has been suggested by cognitive dysfunction in δ-catenin-deficient mice, and cleavage of N-cadherin by presenilin 1-dependent γ-secretase protease. Mutations in the nectin-1 gene cause cleft lip/palate ectodermal dysplasia, frequently associated with mental retardation.

Impaired development and plasticity of synapses could also underlie the synaptic pathology of schizophrenia. However, more research is needed on which and how synaptic adhesion molecules contribute to etiology of this psychiatric disease.

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Synaptic Competition

Definition

A mechanism for synaptic refinement, in which less heavily used synapses are eliminated.

►Activity-Dependent Synaptic Plasticity

Synaptic Convergence

Definition

The projection of multiple neurons onto a single target neuron. Synaptic convergence makes it possible for the target neuron to integrate across many synaptic inputs.

Synaptic Depression

Definition

The reduction in postsynaptic response to presynaptic release of neurotransmitter that occurs during trains of stimuli. At the neuromuscular junction, the cause of synaptic depression is thought to be a reduction in release of acetylcholine following each stimulus. At other synapses, there may also be a postsynaptic contribution.

►Acetylcholine
►Neuromuscular Junction

Synaptic Elimination

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Synonyms

Synapse loss

Definition

Synaptic elimination is a process of brain development that reduces the number of synaptic contacts. The process is important for the formation of precise neural circuitry, which is necessary for proper brain functions. Synaptic contacts are generated in excess during the early phase of development. In subsequent stages, the redundant synapses are eliminated while the proper ones are strengthened to construct specific neural connections. Synapse elimination takes place in various neural tissues including cerebral cortex, cerebellum and ►neuromuscular junctions, and is supposed to be a general mechanism of the development of neural circuitry. The process of elimination is often regulated by neural activity so that active synapses are strengthened, whereas the inactive ones are weakened and ultimately eliminated.

Characteristics

Quantitative Description

The brain is not mature at birth and significant developmental events take place postnatally. During postnatal development, there is a period (►critical period) of exuberant synapse formation followed by a period of synaptic "pruning" in the brain. The developmental profile of synapse number and density (number of synapses per unit volume) has been examined in various mammalian species including human.

In the primary visual cortex of monkey, synapse density increases rapidly around birth [1]. This period of ►synaptogenesis begins two months before birth, and the synaptic density reaches approximately the same level as that in adults. The rapid synaptogenesis continues for another two to three months after birth when the synaptic density reaches its maximum (about 90 synapses/100 μm^3). The synapse density is maintained at this high level during the next two years. At puberty, however, synapse elimination begins and the synapse density rapidly decreases to the adult level (40–50 synapses/100 μm^3) by five postnatal years. The postnatal development of synapse density reveals a similar profile, high synapse density during adolescence and lower density in maturity, in other cortical areas such as somatosensory, motor and limbic areas [2]. While the rapid synaptogenesis takes place concurrently in different cortical areas, the synapse elimination appears to begin earlier in the visual and somatosensory cortex than in the prefrontal cortex. However, the period of synapse elimination largely overlap with each other among cortical areas, and reach the adult level at the time of sexual maturity.

The development of cortical synapses follows a similar time course in the human brain. In human visual cortex, the synapse density shows a rapid increase at around two months of age and reaches the maximum at 8–10 months [3]. The synapse density then declines to the adult level at around ten years of age. In the frontal cortex, however, the beginning of synapse formation is delayed, and the synapse density gets to the maximum value at around two years of age. The high synapse density remains until eight years of age, and then slowly declines to the adult level at around 16 years. Thus, the rapid synaptogenesis and the following synapse elimination might take place at different times in different cortical areas in human [4].

The synapse elimination is regulated by experience-dependent mechanisms. If monkeys are raised without visual inputs by removing both eyes in utero, the

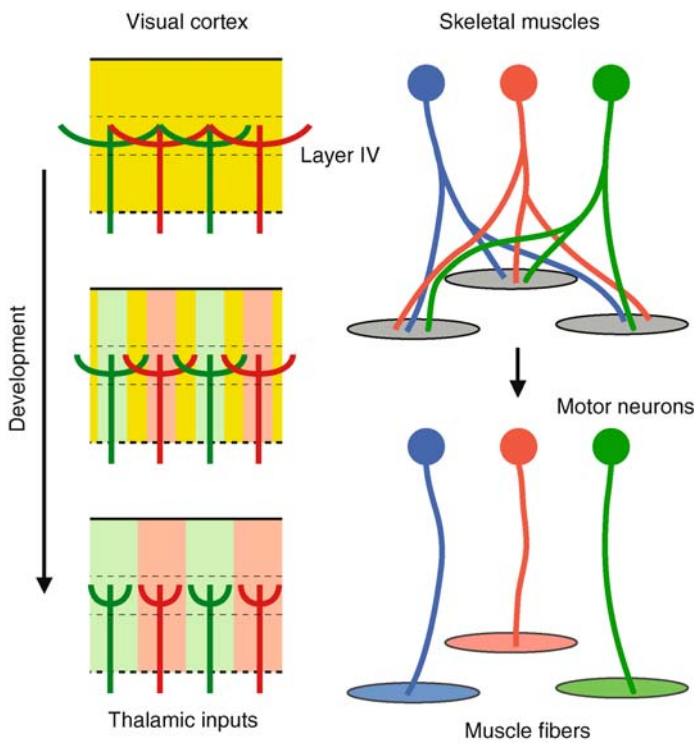
decrease of a class of synapses in the visual cortex does not take place [5]. Furthermore, visual deprivation in one eye of developing animals leads to a strong suppression of cortical response to the deprived eye, and ultimately to the selective pruning of the input axons carrying information from the deprived eye [6].

Higher Level Processes

The elimination of redundant synapses is an important step for the construction of specific neural circuitry in the mature brain. Early formed neural connections tend to include aberrant projections. During development, the synapses made by such aberrant axons should be eliminated and the axon should finally retract. For example, refinement of neural connections by elimination of redundant synapses is well documented in skeletal muscles and autonomic ganglia [7]. Early in development, each muscle fiber and ganglionic neuron is innervated by multiple input axons from motor neurons and preganglionic neurons, respectively (Fig. 1, right).

Thereafter, all but one input axon innervating the same target lose their synaptic contacts and retract, so that each muscle fiber and ganglionic neuron is innervated by a single axon in the adult. Although the synapses made with the inappropriate axons would disappear, the appropriate axons that will innervate the target in maturity grow in size and complexity to make more synaptic contacts. Thus, the development of neural networks is not a simple formation or elimination of synapses, but the redistribution of synapses so that each axon can focus its contacts to the appropriate targets.

A similar process also operates in the central nervous system. Input axons carrying information from each eye distribute separately in the primary visual cortex of higher mammals including cats, monkeys and humans [8] (Fig. 1, left). In young animals, however, the input axons from two eyes widely spread over the visual cortex and overlap with each other. The input axons gradually retract from inappropriate cortical territory and obtain the adult-like segregated distribution. In the cerebellum of newborn animals, the Purkinje cells are innervated by multiple climbing fibers that originate in the inferior olive [9]. During development, redundant climbing fibers are eliminated and single fibers innervate each Purkinje cell.



Synaptic Elimination. Figure 1 Schematic representation of the rearrangement of neural connections during postnatal development. In the primary visual cortex (*left*), the ascending axons from the lateral geniculate nucleus provide inputs to cortical layer IV. The axons from two eyes (red and green, respectively) initially overlap and gradually segregate to occupy different cortical regions. The muscle fibers are innervated by multiple motor neurons at birth (*right*). The input axons lose their synaptic contacts to the inappropriate targets and project to single muscle fibers in the adult.

Process Regulation

The synapse elimination is largely regulated by mechanisms depending on neural activity. The developmental refinements of neural circuitry in various brain areas show that the competition between inputs plays an important role in determining which synapse should be eliminated (►activity-dependent synaptic competition).

The direct observation of the process of synapse elimination in neuromuscular junctions offers a great deal of insight into the mechanisms of the process [7]. In the mouse neck, each muscle fiber receives axonal innervations from several motor neurons at birth. The number of innervations reduces in the following two weeks and each muscle fiber begins to receive single input. Before the withdrawal of redundant axon terminals, synapses on them reveal a functional weakening. Synaptic potentials recorded in the developing muscle fibers show that each of the multiple inputs has strong synaptic effects, enough to cause muscle contraction at birth, and the strength of each synaptic input is often indistinguishable from each other. Therefore, it is difficult to predict which input would subsequently monopolize the fiber. The input that is going to be eliminated ultimately becomes gradually weaker before any sign of retraction could be observed in the presynaptic terminals. The weakening of synaptic potentials is caused by a reduction in neurotransmitter release and by a reduction in postsynaptic receptor density. The physiological synapse elimination is followed by axonal withdrawal of weak inputs.

Synaptic interactions play a key role in determining which input should be eliminated. If neural activity of motor neuron axons is blocked pharmacologically, redundant axons do not retract and ►multiple innervations persist. Suppression of synaptic interactions at the neuromuscular junctions by blocking acetylcholine (ACh) receptors also prevents the input elimination. Thus, neural activity and the following synaptic interactions are necessary for the synapse rearrangements (►activity-dependent synaptic rearrangement). In addition, if a small part of a single neuromuscular junction, which is innervated by one axon, is functionally blocked by applying an irreversible blocker of the postsynaptic ACh receptors, the ACh receptors gradually disappear only in the blocked region. Subsequently, the axon terminals innervating the blocked region withdraw as observed in natural development. On the other hand, blocking ACh receptors in the entire area of a single neuromuscular junction does not induce synapse elimination. Thus, synapse inactivation can lead to elimination of the synapse only when the other synapses are active, suggesting that local imbalance of input strength is an important factor to initiate synapse elimination. The synaptic interactions at active synapses might generate suppressive signals in the postsynaptic cells that can destabilize inactive synapses in the surrounding region, together with supportive signals that maintain the activated synapse. Although the molecular machinery of such intercellular signaling is yet to be characterized, several protein kinases and phosphatases might be involved in the process. For example, in mutant mice in which protein kinase C (PKC)-gamma is genetically inactivated, the elimination of multiple innervations of cerebellar Purkinje cells by climbing fibers, as mentioned above, is markedly prevented [10]. Thus, the activity of PKC is essential for normal elimination of redundant climbing fibers.

The relative strength of inputs also guides the rearrangement of input axons in the visual system [8]. Blocking visual inputs from one eye induces a strong suppression of the cortical responses to the eye, followed by a significant retraction of input axons serving the eye. If the visual inputs from both eyes are blocked, however, the suppression of cortical responses is limited and the input axons are maintained.

Pathology

Abnormal synapse elimination prevents the construction of normal neural circuitry and is supposed to underlie various psychiatric disorders, such as fragile X syndrome and schizophrenia.

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Synaptic Excitability

Definition

Related to the responsiveness of a neuron to excitatory input.

Synaptic Inputs

Definition

The contacts between neurons are called synapses. Any given neuron can receive input from just a few to over 100,000 other neurons. The synaptic inputs can be excitatory, meaning that they are likely to make the cell produce action potentials, or they can be inhibitory, meaning that they are likely to stop the cell from producing action potentials. Synaptic inputs interact with the electrical excitability of neurons to process neural information and generate output action potentials.

Synaptic Integration

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Synonyms

Dendritic integration; Single neuron computation

Definition

Neurons in the central nervous system receive many thousands of synaptic inputs, integrate them, and give off outputs in the form of nerve impulses. The process of determining outputs from the inputs is called ►synaptic integration. Since most of the synaptic contacts are made on the dendritic arborization, and the nerve impulses are generated at the initial segment of the axon near the cell body, the most important part of the integration takes place at the dendrites, and hence is referred to as ►dendritic integration [1]. Some of the integration takes place at ►presynaptic terminals where transmitter release is regulated by inputs from other sources. In addition to synaptic interactions, neurons and glial cells interact with each other via non-synaptic mechanisms such as ►volume transmission [2] or ►ephaptic interaction. All of these processes and mechanisms are involved in the integration of information in the neural cell assembly. Further, the process of synaptic integration is not stereotypical but, over various lengths of time, undergoes plastic changes that are referred to as ►synaptic plasticity. Some forms of synaptic plasticity, the short-term plasticity, such as ►paired pulse facilitation, take place while incoming information is being processed, and thus can be regarded as part of the integration processes.

Characteristics

Dendritic Integration

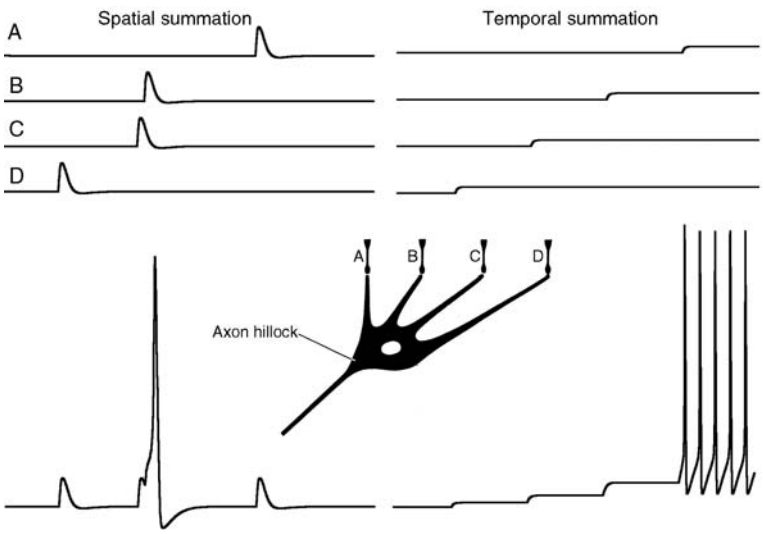
Most of the synaptic contacts are made on dendritic processes, where there are special structures called postsynaptic density apposing presynaptic terminals. Binding of transmitters released from the presynaptic terminals to the receptors located at the postsynaptic density generates postsynaptic potentials. The postsynaptic potentials spread along the dendrites to the cell body and to the initial segment of the axon. In the course of the spread, the potentials are distorted depending upon the electrical properties of the dendrites. If the ►summation of the distorted postsynaptic potentials provides sufficient depolarization, nerve impulses are generated at spike initiation zones somewhere along the dendrite-soma-axon axis, most probably near the initial segment, and will be sent out as outputs.

Synaptic Summation: Spatial and Temporal Summation

There are two basic modes of summation, ►temporal summation and ►spatial summation. Summation of postsynaptic potentials with a fast decay time can be significant only when the inputs coincide in time. This kind of summation happens when synaptic inputs arrive at spatially separate synaptic sites, and is called spatial summation. Neurons that summate inputs with this manner are called coincidence-detectors. Postsynaptic potentials with a slow decay time can summate over time, even when inputs arrive with some delay. This kind of summation is called temporal summation, and the neurons that show temporal summation are called integrate-and-fire units (Fig. 1).

Synaptic Summation: Non-linear Summation

Summation of postsynaptic potential is generally non-linear for several reasons. One reason is that a large change in membrane potential induced by one input can reduce the driving force for the synaptic current for the second input. Another reason is that an increase of membrane conductance induced by one input can shunt the postsynaptic current of the second input. For instance, GABA mediated transmissions usually result



Synaptic Integration. Figure 1 Spatial summation and temporal summation. Two modes of synaptic summation, when four synaptic inputs (A–D) arrive at four separate locations of a neuron with brief intervals. Spatial summation (left): Summation of postsynaptic potentials with a fast decay time can be significant only when they coincide in time. Temporal summation (right): Postsynaptic potentials with a slow decay time can be summated overtime.

in a small change in membrane potential, usually hyperpolarizing, but can inhibit the response for the second input because the postsynaptic current due to the second input flow through the GABA receptor channel without charging the membrane. This type of inhibition is called ►shunting inhibition.

Spread of Postsynaptic Potential in Passive Dendrites

One of the characteristic features of neurons is that they have rich dendritic arborizations. Due to this, the neurons are not isopotential, and postsynaptic potentials will be distorted as they spread from the input location to other locations along the dendrites. The conceptual basis of our understanding, concerning the manner by which postsynaptic potential spreads along the dendrite, was established by W. Rall and his colleagues through theoretical and modeling studies [3]. According to their pioneering works, in which cable theory was applied by assuming that the dendrites can be lumped to a simple cable, the important factors that determine the spread of potential are the passive properties of the dendrites, such as the diameter, membrane resistivity and cytoplasmic resistivity. They predicted that the amplitude of postsynaptic potentials decay significantly as they spread from the input site towards the cell body or the initial segment. The longer the dendrites, the greater the decay. They also predicted that the dendrites behave as frequency filters that curtail fast component. These predictions have been shown to be the case experimentally by performing multiple electrical recordings from single neurons [4] (Fig. 2).

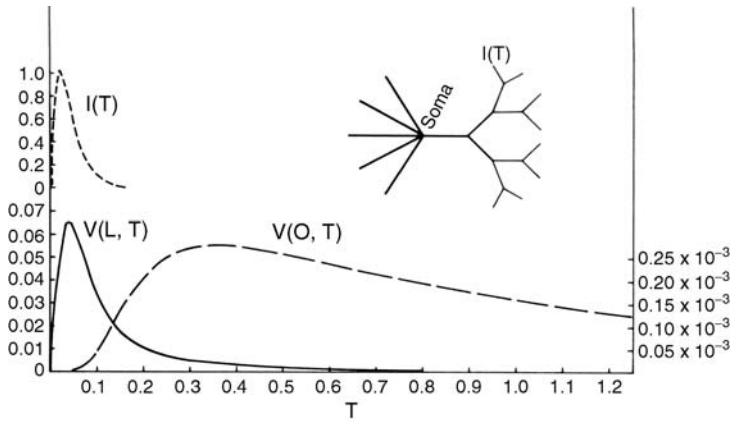
The extent of shunting inhibition depends on the locations of synaptic contacts. For instance, a GABA mediated inhibitory input made on the distal end of a dendrite would not strongly inhibit a glutamate mediated excitatory input made near the cell body, whereas a GABA mediated input made on the cell body or on the initial segment can prevent the cell from generating an outgoing impulse, no matter how many excitatory inputs the cell receives (Fig. 3).

Roles of Active Membrane Properties on Dendritic Integration

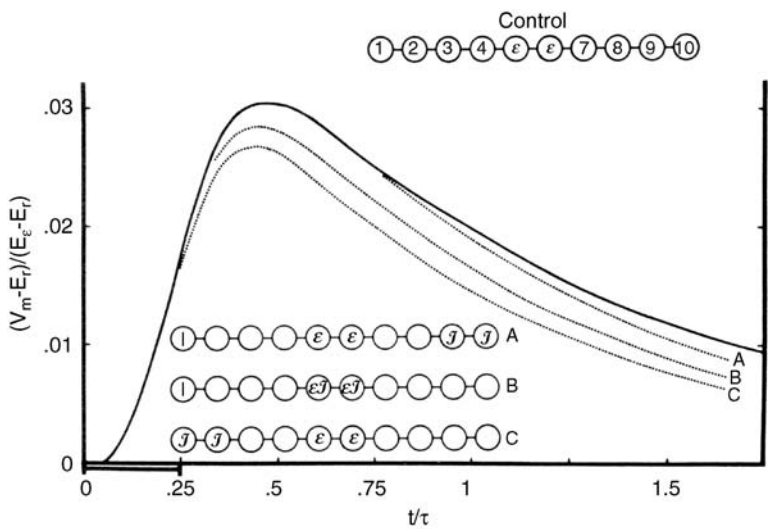
Despite early studies showing active properties of dendrites, it has long been the common understanding that the dendrites are electrically passive structures providing nothing but an area for synaptic contacts. Recently, however, it has become well recognized that various types of voltage-gated ion channels with different ion selectivities, voltage sensitivities, kinetics and density distributions are distributed along the dendritic membrane [5]. These channels endow the dendritic membrane with complex characteristic features that may have strong impacts on dendritic integration.

Low Voltage-Activated Ion Channels

Some types of ion channels distributed along the dendrites, such as A-type K channels and T-type Ca channels are low-voltage activated, show rapid inactivation, and can be activated or inactivated by small changes in membrane potential near the resting potential. There are some other types of ion channels, such as Ih channels, that can be activated by hyperpolarizing the membrane potential below resting potential. These low voltage activated channels may



Synaptic Integration. Figure 2 Distortion of postsynaptic potentials computed voltage time course at the input receiving branch terminal (solid curve) and at the soma (lower dashed curve) for an injected current $I(T)$ (upper dashed curve) are shown. The soma response $V(0,T)$ (scale at left) is much smaller and slower than the response at the input site $V(L,T)$ (scale at the right). The neuron model is shown on the upper right (adapted from Rall W, Rinzel J (1973) Biophys J 13:648–688).

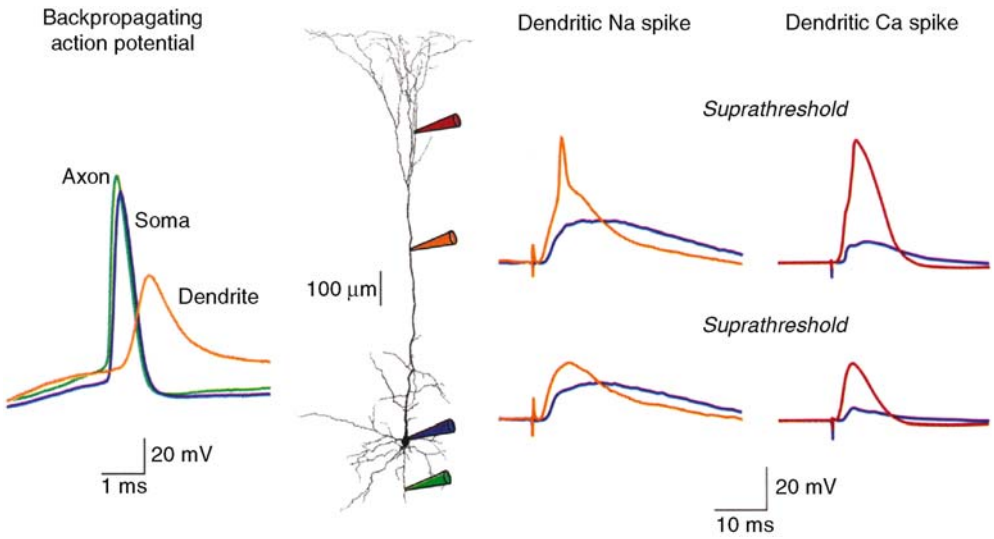


Synaptic Integration. Figure 3 Effect of inhibitory-conductance location upon transient soma-membrane depolarization. The continuous curve represents the uninhibited "control" transient in compartment 1 for an excitatory input ($\mathcal{E}$) at compartments 5 and 6. The dotted curves show the inhibitory effect of having $\mathcal{J}$ in compartments throughout the time (adapted from Rall W (1964) In: Reiss RF (ed) Neural theory and modeling. Stanford University Press, Stanford, CA).

distort postsynaptic potential by boosting or dampening membrane potential changes.

Dendritic Action Potentials

Dendritic membranes of many types of neurons in the central nervous system are excitable. Cortical and hippocampal pyramidal neurons generate Na dependent fast action potential, which can propagate along the dendrites. The direction could be either forward (from the dendrites toward the cell body) or backward (from the some toward dendrites) depending on the situations [6]. Pyramidal neurons and cerebellar Purkinje neurons generate Ca dependent slow action potential in their dendrites. Although it has been shown that these dendritic action potentials can be triggered by synaptic inputs, their functional roles are not yet well understood. One possible role is that these potentials may be important in determining the pattern of the output in the form of axonal impulses. Postsynaptic potentials generated by local synaptic inputs, which are not large enough to initiate action potentials at the initial segment, might trigger dendritic action potentials that



Synaptic Integration. Figure 4 Dendritic Excitability. Recordings are from neocortical layer 5 pyramidal neurons. Left: An action potential evoked by distal synaptic input recorded simultaneously from the axon, soma, and the apical dendrite 300 µm from the soma. Right: Generation of dendritic Na and Ca spikes. Recordings are made simultaneously from the soma and the dendrite (adapted from Hausser M, Spruston N, Stuart GJ (2000) Diversity and dynamics of dendritic signaling. Science 290:739–744).

convey information to the initial segment and initiate impulses that can travel down the axon. Another possibility is that the dendritic action potential may be important in inducing a transient increase of intracellular Ca concentration (Fig. 4).

Transient Increase of Intracellular Ca and Dendritic Integration

Transient increase of intracellular Ca accompanies various neuronal activities [7]. There are several sources for the Ca. Firstly, activation of Ca-permeating ligand gated channels, such as NMDA-type glutamate receptor or nicotinic acetylcholine receptors α7 subunits, allow Ca to enter from the extracellular space. Secondly, Ca enters through voltage gated Ca channels, activated during Ca-dependent action potentials or during depolarization due to any mechanism. Thirdly, activation of intracellular signaling pathways induces Ca release from intracellular stores.

Elevated Ca modulates synaptic integration by various mechanisms. Some of these mechanisms are by directly gating ion channels such as Ca-dependent K channels, by modulating ion channels through Ca-dependent phosphorylation, or by triggering synthesis of proteins involved in synaptic responses such as transmitter receptors.

Synaptic Integration at Presynaptic Sites

The presynaptic terminals are also postsynaptic sites at many synapses, in that various types of receptors on the membrane receive ligands from various sources. Firstly, axons of some neurons, such as GABAergic interneurons, make synaptic contacts on presynaptic terminals and inhibit transmitter release [8]. This type of inhibition is called ►presynaptic inhibition. Secondly, transmitters released from the terminal can diffuse in the synaptic cleft to bind to receptors on the synaptic terminals and inhibit transmitter release. This type of action is called ►autoreception. The transmitter can also diffuse at longer distances (►spill over), and act on the presynaptic terminals of nearby neurons as well as on the postsynaptic neurons. Interaction by these mechanisms is called volume transmission.

In addition, molecules that can diffuse across membrane, such as nitric oxide, carbon mono-oxide, arachidonic acids, and endocannabinoids that are generated in the postsynaptic neurons, diffuse back to the presynaptic terminals and modulate synaptic transmission. This type of mechanism provides additional pathway of volume transmission, and is called ►retrograde transmission [9].

At the presynaptic terminals, the probability of transmitter release can vary from time to time as nerve impulses arrive at the terminals. This phenomenon can be demonstrated by activating the presynaptic fibers at short intervals, typically few tens of milliseconds. The release probability for the second impulse may be either higher or lower compared to that for the first impulse. These types of short-term plasticities are called paired pulse facilitation or ►paired pulse depression, respectively.

The details of integration in presynaptic terminals are not well understood. Since transmitter release is a rather complex phenomenon involving large varieties of molecules and mechanisms, the mechanisms for the integration in the presynaptic terminals are likely to be diverse.

Higher Level Processes

Integration of information is the most important task the brain or nervous system performs. To execute this task, assembly of neurons and neuroglias form networks at local and global levels. Synaptic integration is an cellular-level elementary process for this task. At the local and global network level, information is integrated by processes that have principles of their own.

Lower Level Processes

The following is a list of the important lower level processes involved in synaptic integration:

1. Gating of ion channels
2. Synaptic activation of intracellular signaling pathways
3. Dynamics of Ca ion
4. Diffusion of molecules in and out of the cells
5. Release of transmitters

Process Regulation

Process of synaptic integration is regulated both extrinsically and intrinsically. Depending on mental or physical situations, various neuromodulators such as catecholamines or peptides, activate receptors on neurons, modulate functional proteins and lipids, control gene expressions, and regulate synaptic integration. Activities of neurons give rise to activation of similar intracellular mechanisms that can be activated by neuromodulators, and regulate synaptic integration.

Function

Synaptic integration is the basis for any kind of information processing taking place in the central nervous system.

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Synaptic Long-Term Potentiation in Pain Pathways

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Synonyms

LTP

Definition

►LTP is an intensively studied model of synaptic plasticity. LTP is defined as a long-lasting (but not necessarily irreversible) increase in synaptic strength. Early phase LTP is independent of *de-novo* protein synthesis and lasts for up to three hours. Late phase LTP involves protein synthesis and lasts longer than three hours. Synaptic strength is the magnitude of the post-synaptic response (i.e., the post-synaptic potential or the post-synaptic current, but not action potential firing, see below) in response to a pre-synaptic action potential. LTP can be expressed pre- and/or post-synaptically. Synaptic strength can increase if the release of neurotransmitter(s) is enhanced and/or if the postsynaptic effects of the neurotransmitter(s) become stronger. LTP at synapses in hippocampus is the prime model for learning and memory formation. Recent studies have shown that LTP can also be induced in pain pathways and likely contribute to hyperalgesia caused by inflammation, trauma or neuropathy.

Characteristics

How to (and how not to) Measure LTP

When studying LTP it is essential to measure the changes of mono-synaptically-evoked post-synaptic

currents or potentials in response to a single pre-synaptic action potential. Whole-cell patch-clamp recording is now the most often used technique. To evaluate LTP at the first synapses in nociceptive pathways, transverse slices from lumbar spinal cord of rats or mice with long dorsal roots attached can be prepared to study mono-synaptic, Aδ-fiber or C-fiber evoked excitatory postsynaptic potentials or currents in identified dorsal horn neurons [1].

Some aspects of LTP can only be studied in the entire animal. *In vivo* C-fiber -evoked field potentials can be measured in superficial spinal dorsal horn, for example in response to high intensity electrical stimulation of the sciatic nerve for up to 24 h [2]. These extracellulary recorded field potentials reflect summation of post-synaptic, mainly mono-synaptically-evoked currents but not action potential firing [2].

LTP can not be directly investigated by recording action potential discharges of post-synaptic neurons because action potential firing not only depends upon synaptic strength, but also on membrane excitability and the balance between excitatory and inhibitory input to the neuron. For the same reasons poly-synaptically-evoked responses can generally not be used to study synaptic strength and changes thereof.

Induction Protocols

High Frequency Electrical Nerve Stimulation

LTP at spinal synapses of small diameter primary afferents has most often been induced by high intensity, high frequency burst-like stimulation (typically 100 Hz bursts given several times for 1 s at C-fiber strength) both, *in vitro* and *in vivo*. In spinal cord slice preparations, both, Aδ-fiber and C-fiber [2,4]-evoked responses are potentiated by high frequency stimulation (HFS) when post-synaptic neurons are mildly depolarized to −70 to −50 mV. The same HFS induces, however, long-term depression (LTD) of Aδ-fiber-evoked responses if cells are hyperpolarized to −85 mV, suggesting that the polarity of synaptic plasticity is voltage-dependent.

The role of most spinal dorsal horn neurons in nociception is uncertain with one notable exception. Lamina I neurons that express the NK1 receptor play a pivotal role in development of hyperalgesia in behaving animals. Interestingly, HFS induces LTP selectively at C-fiber synapses with lamina I neurons that express the NK1 receptor and send a projection to the parabrachial area (Fig. 1). In contrast, HFS fails to induce LTP at synapses with neurons that express the NK1 receptor and send a projection to the periaqueductal grey or at synapses with neurons which do not express the NK1 receptor and have no identified supraspinal projection (Fig. 1) [1,3].

Conditioning HFS at C-fiber intensity of sciatic nerve afferents induces LTP of C-fiber, but not Aβ-fiber -evoked field potentials in superficial spinal dorsal horn of deeply anaesthetized rats [2,4]. In contrast, conditioning HFS at A-fiber intensity fails to induce LTP of either A- or C-fiber -evoked field potentials in intact animals. In spinalized animals, conditioning HFS at Aδ-fiber intensity induces, however, LTP of C-fiber-evoked field potentials.

Low Frequency Electrical Nerve Stimulation

Some C-fibers may discharge at rates as high as 100 imp s^{-1} for short periods of time (e.g., at the beginning of a noxious mechanical stimulus). Most C-fibers discharge, however, at considerably lower rates, around 1–10 imp. s^{-1} (e.g., in response to an inflammation or an injury). Conditioning stimulation within this lower frequency range is also successfully used to induce LTP at C-fiber synapses. In a spinal cord-dorsal root slice preparation, conditioning electrical low frequency stimulation (LFS 2 Hz for 2–3 min, C- fiber strength) of dorsal root afferents induces LTP selectively at C-fiber synapses with lamina I neurons that express the NK1 receptor and project to the periaqueductal grey (Fig. 1) [3]. C-fiber synapses with lamina I neurons that express the NK1 receptor and project to the parabrachial area or with no identified supraspinal projection are, in contrast, not potentiated by LFS (Fig. 1) [3]. Thus, the pattern and the frequency of discharges in C- fibers determine which synapses at the origin of different ascending pain pathways are potentiated.

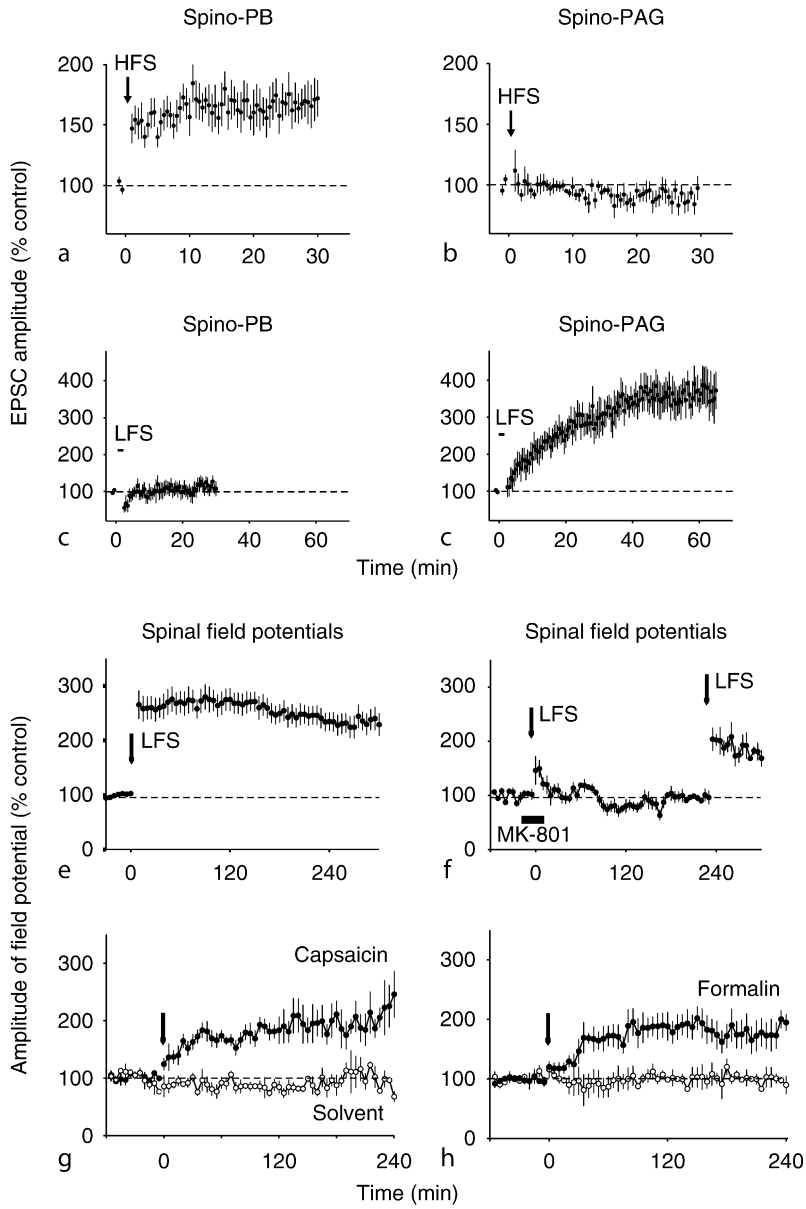
In spinal cord slices from neonatal rats, field potentials evoked by electrical stimulation in the tract of Lissauer are potentiated by repetitive burst-like stimulation at 10 Hz.

In deeply anaesthetized adult rats with their spinal cords intact, LFS (at 2 Hz for 2–3 min) of sciatic nerve at C-fiber intensity but not at Aδ-fiber intensity also triggers LTP of C-fiber-evoked potentials (Fig. 1) [3].

In conclusion, HFS and LFS have divergent effects on the strength of different C-fiber synapses. This finding is in line with previous reports illustrating that the frequency of the afferent barrage in C-fiber may have qualitatively different effects in spinal cord. For example, brain-derived neurotrophic factor is released from primary afferents in spinal cord slices in an activity-dependent manner by HFS at 100 Hz, but not by 1 Hz LFS of primary afferent nerve fibers. Furthermore, in spinal cord slices from mice, HFS (100 Hz) of primary afferent nerves at C-, fiber intensity, but not LFS (900 pulses at 1 Hz) selectively induces phosphorylation of extracellular receptor-activated MAP Kinases (ERK1/2) in spinal dorsal horn lamina I.

Natural Noxious Stimulation

In the brain, LTP induction requires synchronous, high-frequency pre-synaptic activity or pairing of low-level



Synaptic Long-Term Potentiation in Pain Pathways. Figure 1 A-D show contrasting forms of LTP expressed in distinct groups of spinal lamina I projection neurons *in vitro*. A, B Time courses of mean amplitudes (±SEM) of C-fiber-evoked EPSCs in lamina I neurons with a projection to the parabrachial area (PB, n = 8) or the periaqueductal grey (PAG, n = 7). Conditioning HFS induced LTP in all spino-PB neurons tested but was ineffective in spino-PAG neurons. C, D Conditioning LFS induced LTP in all 18 spino-PAG neurons tested but was never effective in seven spino-PB neurons. E–H LTP can be induced by natural, low frequency afferent barrage evoked by inflammation of peripheral tissue *in vivo*. Mean time courses of C-fiber-evoked field potentials recorded extracellulary in superficial spinal dorsal horn in response to electrical stimulation of left sciatic nerve of deeply anaesthetized adult rats with spinal cords and afferent nerves intact. Conditioning electrical LFS (2 Hz, 2 min at C-fiber intensity) of sciatic nerve at time zero (arrow) induced LTP (n = 28, E) which was prevented by NMDA receptor antagonist MK-801 (3 mg kg^{-1}, i.v.-infusion over 30 min: horizontal bar, n = 5, F). A second conditioning LFS four hours later (arrow) was partially effective in inducing LTP. Subcutaneous injections of transient receptor potential vanilloid 1 channel agonist capsaicin (1%, 100 µl, n = 5, G) or formalin (5%, 100 µl, n = 6, H) into the glabrous skin at the ipsilateral hind paw, within the innervation territory of the sciatic nerve at time zero (arrows) induced LTP (closed circles), while injections of the respective solvents (open circles) had no effects (n = 3 in each group). Modified from [4].

pre-synaptic activity with strong post-synaptic depolarization. At least some of the C-fiber synapses in superficial spinal dorsal horn are apparently unique in that LTP can be induced by LFS and by natural, low or high frequency, asynchronous and irregular discharge patterns in sensory nerve fibers. In animals with spinal cord and descending pathways intact, intraplantar subcutaneous injections of capsaicin (100 µl, 1%) or formalin (100 µl, 5%) induce slowly rising LTP (Fig. 1) [3].

Some forms of low level afferent input lead to LTP only if descending, presumably inhibitory pathways are interrupted or weakened. Noxious radiant heating of hindpaw skin induces LTP in spinalized animals but not in animals with spinal cord intact. Likewise, repetitive, noxious squeezing of the skin or the sciatic nerve induces LTP of C-fiber-evoked field potentials only in spinalized rats. These findings demonstrate that endogenous antinociceptive systems not only raise thresholds for nociception, but also those for the induction of LTP.

Pharmacological Induction

LTP can also be induced at C-fiber synapses in the absence of any pre-synaptic activity. Spinal application of a dopamine 1/dopamine 5 receptor agonist in *vivo* induces a slowly developing LTP of C-fiber-evoked field potentials that lasts for at least 10 h and which is blocked by a dopamine 1/dopamine 5 receptor antagonist. In spinalized, deeply anaesthetized, adult rats, superfusions of spinal cord segments with NMDA (10 µM), substance P (10 µM) or neurokinin A (1 µM) are all sufficient to induce LTP of C-fiber-evoked field potentials. With spinal cord and descending (inhibitory) pathways intact, spinal applications of NMDA (1–100 µM), substance P (1–100 µM) or neurokinin A (1 or 10 µM) fail, however, to induce LTP of C-fiber-evoked field potentials.

LTP of A-Fiber-Evoked Responses

Spinal field potentials evoked by excitation of primary afferent A-fibers are depressed by conditioning 50 Hz stimulation of the sciatic nerve. After systemic application of the $GABA_A$ receptor antagonist bicuculline, the same conditioning stimulus now produces LTP rather than LTD [5]. Similarly, 50 Hz conditioning stimulation produces short lasting potentiation followed by LTD in control animals, but LTP in animals with a chronic constriction injury (CCI) of the sciatic nerve. Topical application of muscimol (10 µg), a $GABA_A$ receptor agonist, to spinal cord prevents tetanus-induced LTP of A-fiber-evoked field potentials in animals with a CCI. This also suggests that the polarity of synaptic plasticity is context-sensitive and not solely dominated by the type of afferent input.

Signal Transduction Pathways of LTP Induction and Maintenance

LTP can, in principle, be induced and expressed by pre-synaptic or by post-synaptic mechanisms or by any combination thereof. At present, there is clear evidence for a post-synaptic, Ca^{2+}-dependent form of LTP induction in spinal cord lamina I neurons. Induction of LTP at C-fiber synapses requires co-activation of NK1 and NK2 receptors, opening of ionotropic glutamate receptors of the NMDA type, opening of T-type voltage-gated calcium channels, and activation of group I but not group II or III metabotropic glutamate receptors. Activation of NK1 receptors by substance P may directly enhance single NMDA channel opening and NMDA receptor-mediated currents in lamina I neurons. All this may lead to a substantial rise in post-synaptic $[Ca^{2+}]_i$.

A rise in post-synaptic $[Ca^{2+}]_i$ is essential for LTP induction, and the magnitude in $[Ca^{2+}]_i$ rise is linearly correlated with the magnitude of LTP *in vitro* [1]. Recent data demonstrate that LTP-inducing stimuli cause a substantial rise in $[Ca^{2+}]_i$ in lamina I neurons not only in slice preparations, but also in intact animals [3]. Not surprisingly therefore, signal transduction involves Ca^{2+}-dependent pathways including activation of protein kinase C, calcium-calmodulin-dependent protein kinase II (CaMKII), protein kinase A (PKA) phospholipase C (PLC), inositoltriphosphate-3 (IP_3) receptors, mitogen-activated protein kinase (MAPK) and nitric oxide synthase (NOS).

Inhibition of protein synthesis in spinal cord by either cycloheximide or anisomycin selectively inhibits the maintenance of the late-phase of spinal LTP, but does not affect either LTP induction or baseline responses of C-fiber-evoked field potentials [6].

Importantly, the very same signal transduction pathways are required for full expression of hyperalgesia in animal models of inflammatory and neuropathic pain.

LTP Induction can be Prevented

In mature rats, a deep (surgical) level of anesthesia with either urethane, isoflurane or sevoflurane is insufficient to pre-empt LTP induction of C-fiber-evoked field potentials [7]. LTP is, however, prevented by low dose intravenous infusion of the µ-opioid receptor agonist fentanyl [7]. Similarly, LTP of spinal field potentials elicited by stimulation in the tract of Lissauer in spinal cord slices is blocked by DAMGO, a more specific agonist at the µ-opioid receptor. Activation of spinal α_2-adrenoreceptors by clonidine or spinal application of the benzodiazepine diazepam also prevents LTP induction *in vivo*.

Functional blockade of glial cells by intrathecal administration of fluorocitrate changes the polarity of HFS-induced synaptic plasticity. When HFS is given

1 hr, but not 3 hr after fluorocitrate, LTD but not LTP of C-fiber-evoked field potentials is induced.

Reversal of LTP

After LTP induction of C-fiber-evoked field potentials, synaptic strength can be normalized by brief, high frequency conditioning electrical stimulation of sciatic nerve fibers at Aδ-fiber intensity. Reversal of LTP by Aδ-fiber stimulation is time-dependent and effective only when applied 15 or 60 min but not 3 h after LTP induction.

Spinal application of either NK1 or NK2 receptor antagonists one to three hours after HFS (i.e., after LTP is established) does not affect maintenance of LTP [2], suggesting that activation of these receptors, which are required for the induction of LTP, are not essential for its maintenance.

Functional Consequences of LTP in Pain Pathways

Changes of synaptic strength may have a powerful impact on signal flow in selected pathways. A typical consequence of LTP at excitatory synapses would be an increase in action potential firing of the same and perhaps also downstream neurons in response to a given stimulus. Indeed, LTP-inducing conditioning stimuli have been found to facilitate action potential firing of multireceptive neurons in deep dorsal horn [8]. This is likely due to LTP at the first synapse in the nociceptive pathway, but other mechanisms of facilitation should not be excluded. Action potential firing would also be enhanced if membrane excitability is increased (i.e., the threshold for action potential firing is lowered), if inhibition is less effective or if inhibition is even reversed and becomes excitatory (e.g., due to a reversal of the anion gradient in the post-synaptic neuron).

Conditioning HFS of the sciatic nerve fibers that induces LTP at synapses of C-fibers in spinal cord has behavioral consequences in rats and causes thermal hyperalgesia of the ipsilateral hind paw for six days. This suggests that LTP at C-fiber synapses has an impact on nociceptive behavior.

Perceptual Correlates of LTP in Pain Pathways

In human subjects, conditioning HFS of cutaneous peptidergic afferents causes increased pain perception in response to electrical test stimuli applied through the same stimulation electrode [9]. Noxious stimulation with punctate mechanical probes in skin adjacent to the site of HFS conditioning uncovers a marked (2–3 fold) increase in pain sensitivity (i.e., secondary hyperalgesia [9]). Touching the skin around the conditioning stimulation electrode with a soft cotton wisp evokes pain only after HFS. Thus, HFS also induces secondary mechanical allodynia. Hyperalgesia at the conditioning site but not secondary hyperalgesia or allodynia at adjacent skin areas is prevented by pre-treatment with ketamine, a clinically used drug which, among other effects, also blocks NMDA receptors.

All thermal modalities comprising cold and warm detection thresholds, cold and heat pain thresholds as well as pain summation (perceptual "wind-up") remain unaltered after conditioning HFS of peptidergic skin nerve fibers.

When verbal pain descriptors are used to evaluate pain in addition to its perceived intensity after HFS, a significant long-term increase in scores for sensory but not for affective descriptors of pain is detected [10]. Within the list of sensory descriptors, those describing superficial pain, those for heat pain and those for sharp mechanical pain are all potentiated. The authors conclude that brief painful stimuli rarely have a strong affective component and that perceived pain after HFS exhibits predominantly a potentiation of the C-fiber-mediated percepts hot and burning [10].

In humans subjects, conditioning LFS also causes increased pain sensitivity in the area around the LFS conditioning skin site, but a depression of pain evoked by stimulation through the same electrode [9].

Conclusions

LTP at synapses between primary afferent C-fibers and a group of nociceptive neurons in spinal cord lamina I that express the NK1 receptor for substance P is a potential mechanism underlying some forms of pain amplification in behaving animals and perhaps human subjects. Both LTP and hyperalgesia involve the same essential elements (i.e., primary afferent C-fibers and lamina I neurons that express the NK1 receptor). Further, the induction protocols, pharmacological profile and signal transduction pathways are virtually identical.

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Synaptic Modification

►Synaptic Plasticity

Synaptic Plasticity

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Synonyms

Synaptic modification; Long term potentiation; Hebb-like learning rules; Spatiotemporal learning rule LTP STLR

Definition

Long term Potentiation (LTP) and Hebb-like Learning Rules

Long term potentiation (LTP) is a long-lasting increase in the amplitude of a synaptic response following brief, high-frequency activity of a synapse and is loosely defined as an enduring, activity-dependent increase in synaptic efficacy.

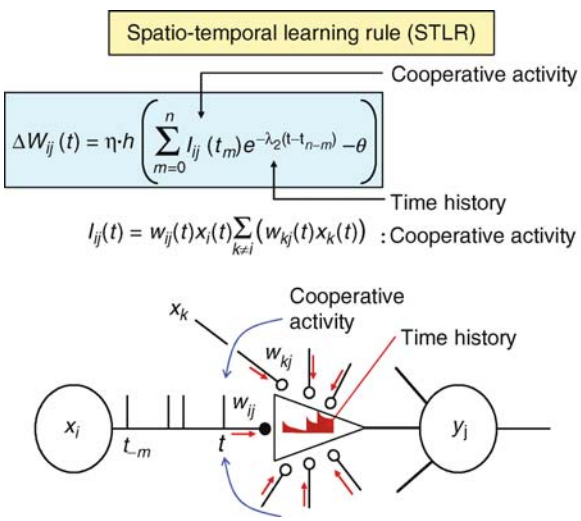
Hebb-like synaptic plasticity is the assumption that synaptic modification is strengthened only if the pre- and post-synaptic elements are activated simultaneously.

LTP that requires coincident pre- and post-synaptic activity is a plausibly biological correlate for the Hebbian synaptic modification.

Characteristics

Hebb and the Spatiotemporal Learning Rule (non-Hebb)

Synaptic plasticity is considered to be a fundamental mechanism of learning and memory. Hebb [1] proposed the idea that synaptic modification is strengthened only if the pre- and post-synaptic elements are activated simultaneously. Experimentally, long term potentiation (LTP) and long term depression (LTD) are generally considered to be the cellular basis of learning and memory. Recently, a series of experiments provided direct empirical evidence of Hebb's proposal. These reports indicated that synaptic modification can be induced by repetitive pairing of EPSP and back-propagating action potentials (BAPs) [2]. Pre-synaptic spiking within tens of milliseconds [ms] before post-synaptic spiking induced LTP whereas the reverse order resulted in LTD. This spike timing dependent LTP/LTD has been confirmed by using pyramidal cell pairs in hippocampal cultures, in which they found an asymmetric profile of LTP and LTD in relation to the relative timing between EPSPs and BAPs [3]. On the other hand, the spatiotemporal learning rule (STLR), proposed as a non-Hebb type by Tsukada et al. [4,5] (Fig. 1), consists of two distinctive factors; "cooperative plasticity without a cell spike," and "its temporal summation."



Synaptic Plasticity. Figure 1 The spatiotemporal learning rule (STLR).Where $w_{ij}(t)$; the value of a weight from neuron *j* to neuron *i* prior to adjustment, $\Delta w_{ij}(t) = w_{ij}(t+1) - w_{ij}(t)$, η; the learning rate coefficient, $x_j(t)$; the level of excitation of input to neuron *j*, $y_i(t)$; the output of neuron *I*, $I_{ij}(t)$; the value of cooperative activity from neuron *j* to neuron *i*, $h(u)$; a sigmoid function of the potentiation force, θ is the thresholds, and λ_2 is the decay constant of temporal summation which is a slow dynamic process (λ_2 = 223ms) (Aihara, et. al. 2000).

Experimental Support for STLR (non-Hebb)

The STLR consisted of two defining factors: (i) cooperative plasticity without a post-synaptic spike and (ii) temporal summation. We have obtained evidence for temporal summation from neurophysiological experiments by applying temporal stimuli to Schaffer collaterals of CA3 [4,6]. The coincidence of spike timing of Schaffer collateral paired stimuli of CA3 played a crucial role in inducing associative LTP [7]. The ►homosynaptic and ►heterosynaptic associative LTP could be induced under conditions which inhibited the activation of dendritic Na + channels. Our results show that LTP can indeed occur at dendritic synapses of hippocampal CA1 pyramidal neurons even in the absence of a post-synaptic somatic spike. These results suggest that if the two inputs synchronize at the dendritic synapse of CA1 pyramidal cells then the synapse is strengthened and the functional connection is organized on the dendrite. If the two inputs are asynchronous then the connection is weakened. The functional connection/disconnection depends on the input-input timing dependent LTP (Fig. 2).

This differs from the Hebbian learning rule that requires coactivity of pre-synaptic and post-synaptic neurons. The STLR incorporated two dynamic processes: fast (10–30 ms) and slow (150–250 ms) processes. The fast process works as a time window to detect a spatial coincidence among various inputs projected to a weight space of the dendrites of hippocampal CA1 pyramidal neurons, while the slow process works as a temporal integrator of a sequence of events. By fitting parameters to the physiological data of the LTP time scale, we determined the decay constant of fast dynamics to be 17 ms, which corresponds to the period of hippocampal ►gamma oscillations [8]. In contrast, the decay constant of the slow dynamics is 169 ms, which corresponds to a ►theta rhythm. In combination, these findings suggest that cell assemblies are synchronized at two time scales in the hippocampal-cortical memory system. This phenomenon appears to correlate with the memory formation in the spatio-temporal context.

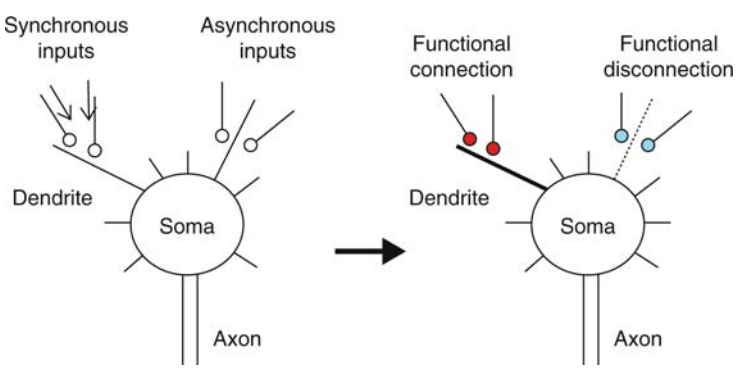
The Functional Differences Between STLR and Hebb

We applied two rules to a single-layered artificial neural network and compared its ability to separate spatiotemporal patterns with that of other rules, including the Hebbian learning rule and its extended rules. The simulation results [5] showed that the STLR rather than the Hebbian learning rule or its extensions had the highest efficiency in discriminating spatiotemporal pattern sequences. The novel features of this learning rule were induction of cooperative plasticity without a post-synaptic spike and the time history of its input sequences.

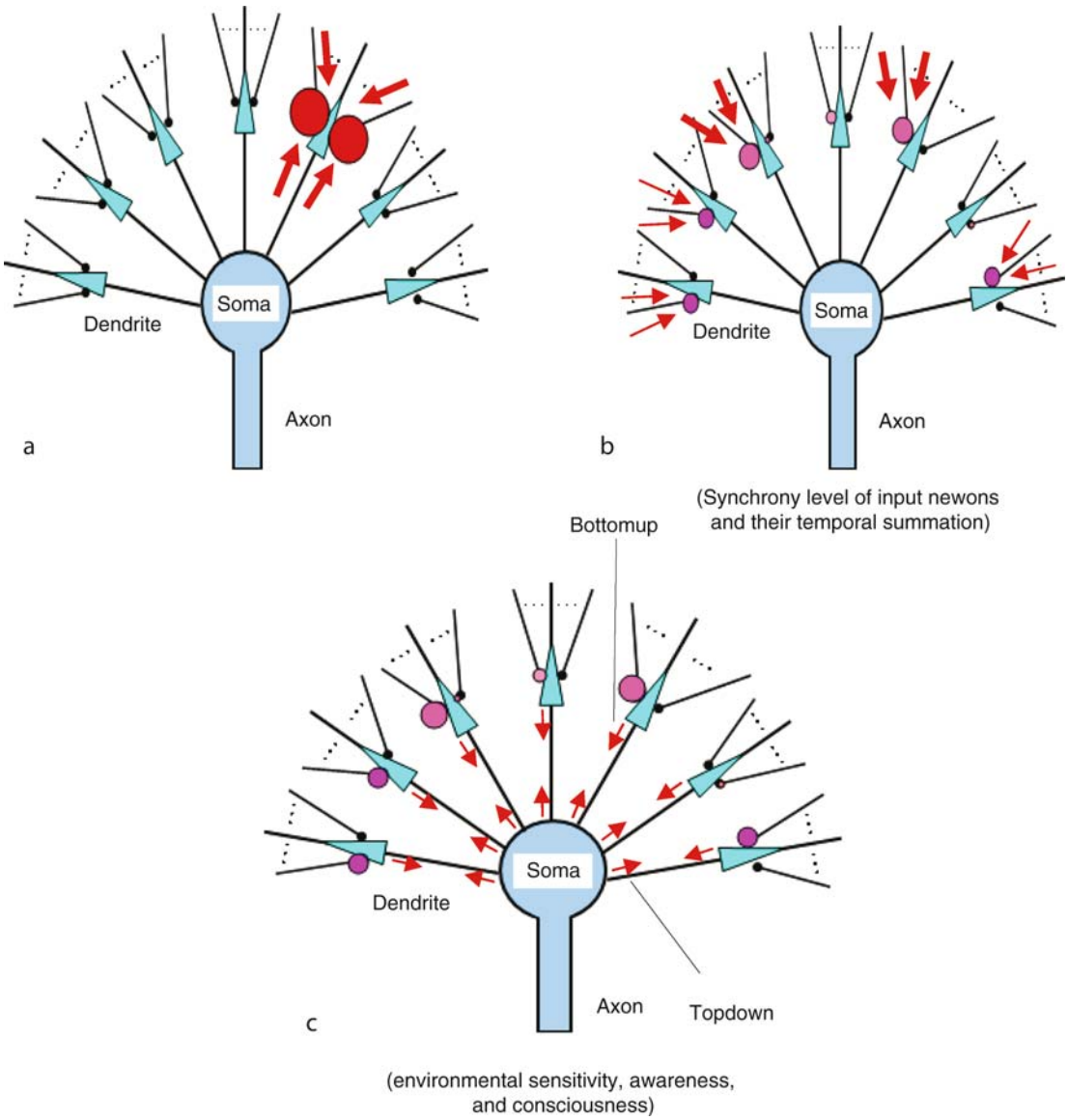
According to the Hebbian rule, connections strengthen only if the pre- and post-synaptic elements are activated simultaneously, and thus, the Hebbian rule tends to map all of the spatio-temporal input patterns with identical firing rates into one output pattern. Hebbian rule has a natural tendency to attract analogous firing patterns into a representative one, so called "pattern completion." In contrast, the STLR produces different output patterns depending on individual input patterns. Thus, the STLR has a high ability in pattern separation, while the Hebbian rule has a high ability in pattern completion.

The extension of the theoretical simulation results imply that this phenomenon occurs in a dendrites-soma system of a single pyramidal cell. This system includes a spine structure, ►NMDA receptors, and Na + and Ca + channels. The pyramidal cell integrates all of these local dendrite functions. Our previous research revealed that the STLR and the Hebbian rule coexist in single pyramidal neurons of the hippocampal CA1 area. The Hebbian rule leads to the pattern completion (Fig. 3a) and the STLR leads to the pattern separation (Fig. 3b).

In the STLR, synaptic weight changes are determined by the "synchrony" level of input neurons (bottom-up), whereas in the Hebbian rule, the soma



Synaptic Plasticity. Figure 2 A schematic representation of functional connection/disconnection by cooperative activity dependent LTP/LTD.



Synaptic Plasticity. Figure 3 Functional differences between Hebb (a), and STLR (b), and their interaction (c) in a dendrite(local)-soma(global) system of single pyramidal cells of the CA1.

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fires by integrating dendritic local potentials or by top-down information such as environmental sensitivity, awareness, and consciousness (top-down) (see Fig. 3c and its legend). The coexistence of the STLR (local information) and the Hebbian rule (global information) on the neuronal level may support this dynamic process that repeats itself until the internal model fits the external environment. The dendrite-soma interaction in pyramidal neurons of the hippocampal CA1 area can play an important role in the context formation of policy, reward, and value in ►reinforcement learning.

The role of soma spiking as top-down information raise a number of interesting computational predictions. Fist, hippocampal theta is one of candidates of top-down information which is driven by the medial septum [9]. The theta stimulation in the adult rat hippocampas can induce LTP [10]. Second, extrinsic modulators, such as acetylcholine, serotonin, norepinephrine and dopamine, can alter neuronal throughput and BAPs (so-called "meta-plasticity") in such way that these transmitters diffuse broadly.

When you are confronted by certain situations, you naturally compare it to your previous experiences and attempt to predict what may happen and plan your actions in respect to predicted outcomes that we found favorable. In this way, your past, present, and pre-future memory work together and determine your actions. If these actions do not fit, then a new hypothesis is

formulated, new data is reasoned, and the previous model is amended. The coexistence of the STLR and the Hebbian rule may support this dynamic process, which repeats itself until the internal model fits the outer environment. In reinforcement learning, the dendritic-soma interaction in single pyramidal neurons of the hippocampal CA1 area can play an important role in the context formation of policy, reward, and value.

►Hippocampus: Organization, Maturation, and Operation in Cognition and Pathological Conditions

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Synaptic Plasticity, Selectivity

Definition

When high-frequency stimulation is applied to one of the two independent pathways innervating the same postsynaptic cells, LTP is usually induced selectively in the tetanized pathway and is not induced in the other independent pathway. This characteristic of LTP is called "selectivity" or "specificity."

►Memory, ►Molecular Mechanisms
►Associative Long-Term Potentiation (LTP)
►Long-Term Potentiation (LTP)

Synaptic Properties

Definition

The strength of synaptic connections and whether they are inhibitory or excitatory are all properties which affect the network behavior. Synaptic transmission can be modulated in diverse ways both pre and postsynaptically. Also critical is temporal summation of postsynaptic potentials, which can lead to short term potentiation of synaptic properties.

Synaptic Proteins and Regulated Exocytosis

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Synonyms

Exocytotic cycle; Synaptic release mechanism; Machinery of the neuronal secretory pathway

Definition

As one of the most highly differentiated and thus specialized secretory cells, neuronal functions are in many ways directly or indirectly defined by the specificity, efficiency, and speed of the synaptic release process. From the instant that a depolarizing waveform invades the terminal of a chemical synapse to detection of a post-synaptic response can be as fast as ~150 μs; the lag between calcium influx and fusion is estimated to be as little as 60 μs. Despite hundreds of synaptic vesicles (SV) in a given neuron, the supply is not inexhaustible, necessitating that neurons also have fast

and efficient mechanisms to retrieve, refill and recycle SV, in particular to compensate for high frequency release under strong (e.g. highly repetitive) stimulus conditions. This dynamic cyclic pathway, coupling the release and retrieval processes, together with preceding steps that efficiently direct and move nascent SV from the trans-Golgi toward the synapse and then onto specialized sites on the plasma membrane (PM), is generally referred to as the regulated exocytotic pathway. Localized transient increases in cytoplasmic free calcium concentrations ($[Ca^{2+}]_{free}$) in the vicinity of open voltage-gated ►Ca^{2+} channels act as focal sources of $[Ca^{2+}]_{free}$ that may reach 10–100 μM (relative to ~200–300 nM resting $[Ca^{2+}]_{free}$). These transient ►Ca^{2+} microdomains are the primary trigger (e.g. "regulator") for the defining step of exocytosis: fusion of the SV and PM. This regulated membrane fusion (e.g. merger of the apposed bilayer membranes) results in an opening (the fusion pore) that enables release of the SV luminal content into the synaptic cleft; the released neurotransmitters then interact with receptors on the post-synaptic membrane, resulting in the depolarization of that cell and thus propagation of the original electrical signal to the next component(s) of the neural circuit.

The regulated exocytotic pathway thus consists of a series of concomitant and inter-connected stages that overlap temporally and also at the molecular level. Being highly conserved across eukaryotes, much has been learned over the last three decades using other secretory cell types and even cell fractions as model systems; despite access even to synaptosomes, the extremely small size and accessibility issues inherent to most synapses, and the fast kinetics of the release process, severely limited or obviated the coupled functional–molecular analyses necessary to effectively dissect underlying molecular mechanisms. The inability to "cleanly" separate certain functions still limits our understanding of specific molecular mechanisms. This is slowly changing, with many research groups bringing different combinations of refined and advanced techniques to bear on questions of the specific roles that particular proteins, or protein interactions, play at defined stages of the exocytotic pathway. The integrated work from a tremendous range of research teams – combining electrophysiological (e.g. patch clamp), imaging (e.g. ►Total internal reflection microscopy and confocal microscopy), ultrastructural (e.g. ►Electron microscopic tomography and rapid freeze), molecular biological, proteomic, and other research techniques, in a range of fast secretory cell types (albeit perhaps not all as fast as the "fastest" of neurons, e.g. neuroendocrine cells, oocytes, paramecium, and so forth) – makes this area one of the most fruitful inter- and multi-disciplinary junctions in modern Cell Physiology. In the last 15 years alone the field has gone from having virtually no known key proteins, to having identified dozens or more proteins critical to the exocytotic pathway, with some even known to function at reasonably well-defined stages and with certain partners. There is little doubt that the interdisciplinary and cooperative interactions that have fuelled this area of research will continue to drive a fuller and more thorough molecular understanding of the different stages in the exocytotic pathway, their transition points, and what specific adaptations and mechanisms may (or may not) be neuron-specific.

Characteristics

Based originally on the convergence of results from a range of different functional assays in a variety of different cellular model systems, the exocytotic pathway is now generally thought of as constituting a series of stages [1]. The actual proteins functioning at a specific stage, or indeed the specific molecular function of a given protein (or its interactions) in one or more stages, is often not yet so well understood. This is however rapidly changing with the continued growth and application of cutting-edge technologies in Neuroscience research. The exocytotic pathway (or more specifically the path of an SV in this cycle) is thus generally said to proceed via the following stages: trafficking, targeting, tethering, docking, priming, triggering, fusion, and retrieval. To specifically delineate it from the release portion of the exocytotic pathway, the retrieval stage is commonly referred to as endocytosis. Short descriptions of each stage follow and include mention of at least some of the proteins that are more commonly agreed to (likely) function in the associated molecular mechanisms. It is important to note that despite often being cartooned as specific steps, there are no clear-cut delineations between many of the stages, and indeed molecular mechanisms contributing to a given stage may already initiate their functions in preceding stages. For example, while some representations suggest that priming occurs after docking, considering the myriad of molecular alterations that may underlie this stage it is possible that some occur before, during, or after tethering and docking. Potential confusion is further compounded by the aforementioned speed of exocytosis in neurons, in many instances making the timing of specific molecular events difficult to clearly define.

Trafficking

Newly synthesized SV leave the soma and undergo anterograde transport to the synapses via well-characterized mechanisms. This energy-dependent axonal transport utilizes microtubules as cytoskeletal tracks and is mediated by the motor protein kinesin (an ATPase with a microtubule binding domain). At the synaptic terminal, other transport or translocation machinery appears to take over, not only for further SV trafficking

but, importantly, to aid in segregating SV into functionally-defined sub-populations or pools. Defined largely based on the results of secretion assays and time-resolved electrophysiological measurements (e.g. membrane capacitance changes assessed by patch clamp recording) these pools are defined not only physically but in most cases also molecularly, generally corresponding to the different stages of exocytosis [1]. Moving from the axon-terminal interface toward the release sites of the synaptic terminal, three sequentially arranged pools of SV are broadly described as:

1. Unprimed (UPP) – a large population of SV mostly located deeper within the terminal that, upon passing through preparatory steps, can refill the Reserve pool. Also known as the resting or depot pool, these SV can be recruited during periods of massive stimulation and/or disruption of SV retrieval and recycling.
2. Reserve (RP; a.k.a. slowly releasable) – a population of SV that are not fully release-ready but can be rapidly recruited to that terminal pool.
3. Readily releasable (the RRP) – those SV fully docked at the PM and competent for fast, Ca^{2+}-triggered release; a sub-population of only a few vesicles has been identified as an Immediately releasable pool (IRP).

In the terminals it appears that the myosin motor proteins mediate translocation between these pools, utilizing actin clusters as tracks; myosin is known to interact with the SV proteins synaptobrevin (a.k.a. VAMP) and synaptophysin. Actin clusters also likely serve in some capacity to delimit SV movement between pools.

Targeting

The next stage or process is intimately linked with trafficking and tethering (see below) as there must be a control mechanism to ensure that SV are targeted to appropriate synapses and subsequently, within the terminal, to proper/effective release sites. Concerning the latter, there is little direct evidence for specific protein functions although small G-proteins of the rab family have been suggested to have a role, as has the ►exocyst complex.

Tethering

Those SV destined to fuse with the PM must of course be positioned at it. The localization near and initial loose or reversible attachment of SV to the PM is termed tethering and may in part involve cytoskeletal elements and rab proteins. At the ultrastructural level, tethering generally refers to those SV-PM attachments at distances that are greater than half an SV diameter (e.g., >25 nm). Due to their roles in linking the SV and cytoskeletal elements, and in promoting SV clustering at active zones (see below), the synapsins have also been implicated as tethering elements.

Docking

Proceeding from the tethered state, a more stable and intimate contact of the SV and PM is required to ensure the efficiency of triggered fusion and reduce the associated energy barriers. This likely represents a continuum of molecular states, from tethering through to the loose formation of inter-membrane SNARE complexes. Physically, a fully docked SV is generally regarded as being held within ~5–10 nm of the PM.

In nerve terminals, tethering, docking, and in particular fusion, are restricted to a specialized area of the presynaptic PM known as the active zone (AZ). This is a region of clustering of voltage-gated calcium channels that are close to, or constitute part of, SV docking sites. In electron micrographs, the AZ appears as an electron dense region of the PM, with an associated cytomatrix complex, and these are located directly across the synaptic cleft from the postsynaptic density; his tight alignment ensures the speed and fidelity of synaptic transmission [2]. Thus, proteins enriched in the AZ and its cytomatrix have been implicated in tethering and docking [1–3]. These include the rab-interacting RIM, as well as Piccolo, Bassoon, Munc13, ►Liprin-α, and ►ELKS that have been shown to interact with each other as well as with other accessory proteins including synaptotagmin, ►spectrin, calmodulin, ►DOC2, ►14-3-3, Munc18, and elements of the cytoskeleton, as well as with the voltage-gated calcium channels (that bind syntaxin, SNAP-25, synaptotagmin, and ►CSP via a specific protein interaction, or ►synprint, domain). Scaffold/►adaptor proteins including ►CASK, ►Mint, and ►Velis have also be identified as binding partners of some of these potential docking elements. In addition, syntaxin, that binds Munc13, is recognized to be required in docking. It seems likely that this is due to its role in the so-called inter-membrane SNARE complex that bridges the SV and PM. Specifically, syntaxin and SNAP-25 form dimers at the AZ, and these then bind with synaptobrevin on the vesicle membrane; together, these form extended coil-coil structures that are said to "zipper-up" from their N-terminal ends toward the C-terminal ends (containing the membrane anchoring regions) and thus bring the membranes into close apposition. This complex (likely in multiple copies at a docking site) is also thought to ensure the specificity of SV targeting. As the initial complex is in only a loose interaction, this and intermediate states (preceding the final tightly coiled complex), may represent increasingly stabilized interactions involved in tethering and docking.

Priming

At the different stages described, and upon docking to the membrane, SV also undergo a series of molecular alterations that imbue them with full Ca^{2+} sensitivity and fusion competence. Simply, the SV become part of the RRP (or even IRP) and are capable of fast, Ca^{2+}-triggered release. Priming is thus another broad term, describing all functional molecular modifications, specifically including any ATP-dependent processes that facilitate and enable subsequent fast SV fusion. A number of proteins have been identified as critical to priming, including phosphatidylinositol kinases and the phosphatidylinositol transfer protein. As priming is sensitive to the levels of $[Ca^{2+}]_{free}$, and requires ATP, protein kinase activities have also been found to be critical. Specifically, the activities of the cAMP-dependent protein kinase and of protein kinase C have been linked to the replenishment or maintenance of the RRP; this could in part be due to stabilization of the inter-membrane SNARE complex [1]. Although it may occur rapidly and exist only transiently, many now consider the fully zippered SNARE complex to be the final step of priming; at this point the SV and PM are in close apposition as required to efficient fusion, the tight coiling of the SNARE complex likely having reduced part of the high energy barrier to subsequent membrane merger [4 and references therein].

Triggering

After priming, the ensuing molecular steps, up to and including fusion, do not require ATP. This has been interpreted to indicate that the localized fusion site has been set-up (e.g. much like a "loaded-spring") to respond with virtually unfailing efficiency. As the trigger, Ca^{2+} is thus thought to release the mechanism. The best evidence for this is the fact that the lipidic steps of membrane merger can be blocked with certain molecules (e.g. lysophosphatidylcholine) despite triggering of the associated upstream machinery by Ca^{2+}; washout of the LPC then results in the rapid completion of fusion despite the absence of the trigger. Currently, the best candidate for a Ca^{2+} "sensor" is the protein synaptotagmin that is associated with the SNARE complex and also with specific membrane lipids. It is thought that Ca^{2+}-triggered interactions of specific domains in the synaptotagmin molecule with lipids may promote some of the membrane rearrangements that then initiate membrane fusion [5]. Certainly this would explain the association of synaptotagmin with the synchronous SV release that occurs with the opening of voltage-gated Ca^{2+} channels. The existence of additional sensors is also postulated based on the estimated numbers of Ca^{2+} ions that are thought to effect the release reaction; these estimates currently remain somewhat model-dependent.

Fusion

The triggered fusion of the SV and the PM is the defining step of regulated exocytosis. Specifically, this requires the triggered focal merger of the SV bilayer membrane with that of the PM, at a highly restricted and specialized domain within the AZ. Without this, there is no release of neurotransmitters, no signaling between neurons, and thus no effective neural circuitry. The actual molecular mechanism mediating bilayer merger has been studied for decades and has relied heavily on biophysical analyses of membrane properties and associated mathematical modeling to reach our current understanding of the process. It is now reasonably clear that the inter-membrane SNARE complex itself does not drive membrane fusion [4,6], nor does it seem do other protein components, despite their contributions to delimiting the site, controlling the timing, and facilitating the outcome. It is currently most widely accepted that the fusion pore itself is likely to be lipidic. The stalk-pore hypothesis describes a series of transient, high curvature membrane intermediates that yield the lowest energy molecular pathway to fusion pore opening and full expansion [7,8]. At this stage of terminal fusion (e.g. full vesicle collapse), the vesicle and plasma membranes are continuous and only an active retrieval mechanism can reform the vesicle and recycle it for another round of exocytosis (see below).

Yet there is accumulating evidence to suggest another form of tightly coupled fusion and recycling that does not utilize full fusion [9]. "Kiss & Run" has been identified as a transient fusion event that results in only a partial release of vesicle content prior to the reversal or resealing of the fusion pore (sometimes referred to as a "flickering" pore). This is perhaps best thought of as a tight, focal interface between fusion and retrieval in which the SV never loses its identity. Variations on this theme suggest the continued docking or the undocking of the SV following the transient fusion event. There is evidence indicating that kiss & run is a specific response to certain modes of synaptic stimulation. If this is the case, a single synapse is even more versatile and complex in its responses than had been previously imagined, and modulation of the fusion pore may be a key step in signal integration.

Endocytosis

The classical pathway of SV recycling involves the formation of clathrin-coated vesicles near previous release sites, with a ▶fission reaction mediated by dynamin and associated proteins actually severing the new vesicle from the PM [10]. These vesicles are processed through endosomal intermediates before being refilled with transmitter (via specific transporters) and re-entering the RP or RRP as new SV. Recycling of the SNARE complex components, in part through the

concerted actions of NSF and α-SNAP, is particularly important in this process. Another, faster, non-clathrin based mechanism of SV retrieval is also recognized that does not require subsequent passage through intermediate compartments; SV are quickly refilled and thus rapidly re-enter the RRP. Kiss & Run may be a highly specialized form of this latter recycling mechanism.

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Synaptic Regeneration

Definition

Generation of new synaptic contacts after loosing synapses by nerve damage such as disease or injury.

►Regeneration
►Synaptic Elimination

Synaptic Release

Definition

Synaptic vesicles release their contents in response to depolarization of the presynaptic membrane.

►Synaptic Transmission: Model Systems

Synaptic Scaling

Definition

The differential modulation of the individual synaptic gains in a population of synapses. This process occurs to stabilize the neuronal network.

►Activity-Dependent Synaptic Plasticity

Synaptic Specificity

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Synonyms

Target specificity

Definition

Specificity of synaptic connections between neurons and their target cells. In a narrower definition, it refers to the formation of synaptic structures between neurons and their specific cellular or subcellular targets.

Characteristics

Description of the Process

The proper functioning of the nervous system depends on precise interconnections between distinct types of neurons. Therefore, understanding the molecular mechanisms of synaptic specificity – the specificity with which connections form between neurons – is a central issue in modern neuroscience. The magnitude of the complexity involved in this process is daunting. In the human brain, each of the roughly 10^{11} neurons establishes connections with, on average, over a thousand target cells in a highly characteristic manner. Remarkably, much

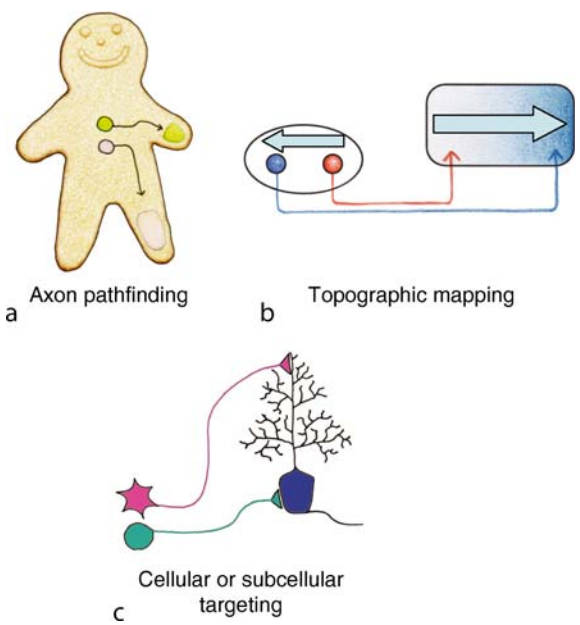
of the intricate patterning of these synaptic connections can be generated in the absence of activity or experience; thus the information necessary for this precise wiring must be largely encoded by the genetic program. It was Roger Sperry who first showed that synaptic specificity could be generated in a predetermined manner, independent of the experience of the animal [1]. After a series of experiments on the retinotectal projection in frogs, he proposed the highly influential "►chemoaffinity hypothesis" [see Glossary]. The theory posits that individual target cells and their innervating nerves must carry matching sets of molecular markers or have "chemoaffinity" to establish specific connections between them. This idea motivated subsequent studies on the molecular mechanisms of synaptic specificity.

Synaptic specificity is generated in a stepwise fashion through three major stages of neuronal recognition (Fig. 1) [2,3].

Neurons first extend axons over long distances along stereotyped pathways toward their target region (axon pathfinding). Some neurons then search for a specific location or position within a field of target cells that represents a map of sensory information (topographic mapping).

Finally, neurons select individual target cells with which to make synaptic connections (cellular targeting). In many cases, presynaptic axons not only distinguish potential target cells but also recognize the appropriate subcellular region of the target cell (for example, the cell body versus dendrites; subcellular targeting).

The focus of this essay is mainly on the third step–cellular and subcellular targeting – addressing the topic of synaptic specificity in its narrower sense. Please refer to other essays for detailed accounts of the first two steps of the generation of synaptic specificity. Also see the essay on "target selection".



Synaptic Specificity. Figure 1 Generation of synaptic specificity. Synaptic specificity is generated in a stepwise fashion through three major stages: axon pathfinding (a), topographic mapping (b) and cellular and subcellular targeting (c).

Regulation of the Process

Axons extend toward their targets by attractive and repulsive guidance cues expressed along the pathway, as well as by cues from the target cells themselves [2]. Axons recognize and respond to these cues with a specialized terminal structure, the growth cone. The growth cone bears receptors that bind to the guidance cues and elicit signal transduction cascades that regulate growth cone steering. The guidance cues expressed by target cells, together with their receptors on the presynaptic cells, determine target specificity and are collectively called target recognition molecules. Compared to the wealth of information on the molecules and signaling that regulate axon pathfinding and topographic mapping, relatively little is known about molecules involved in selection of discrete target cells. However, functional analysis of several candidate molecules begins to illuminate the molecular mechanisms of target recognition (as described below in more detail). As initially postulated by Sperry, target specificity indeed appears to be regulated by the action of the molecular labels on the target (or nearby) cells and their receptors on specific presynaptic cells. Some of such labels are cell adhesion molecules that promote interaction between specific pre- and postsynaptic cells.

How the tremendous diversity of synaptic connections is coded by such cellular labels on neurons and targets is an important but unsolved problem. Is it coded by differential and/or combinatorial use of a relatively small number of molecules? Or are there diverse sets of complementary molecules expressed on individual cells? Several large families of cell surface proteins have been implicated in synaptic specificity, including the cadherin-related neuronal receptors (CNRs), neurexins/neuroligins, odorant receptors and *Drosophila* Dscams. For example, alternative splicing of the *Drosophila* cell adhesion molecule Dscam potentially generates 38,016 isoforms [4]. However, whether these large gene families indeed mediate synaptic specificity remains to be determined. On the other hand, there is evidence that molecules without such immense diversity can function as target recognition molecules (as described below in more detail).

Higher-Level Processes

For proper neural wiring to occur, the guidance cues expressed along axon pathways and targets and their

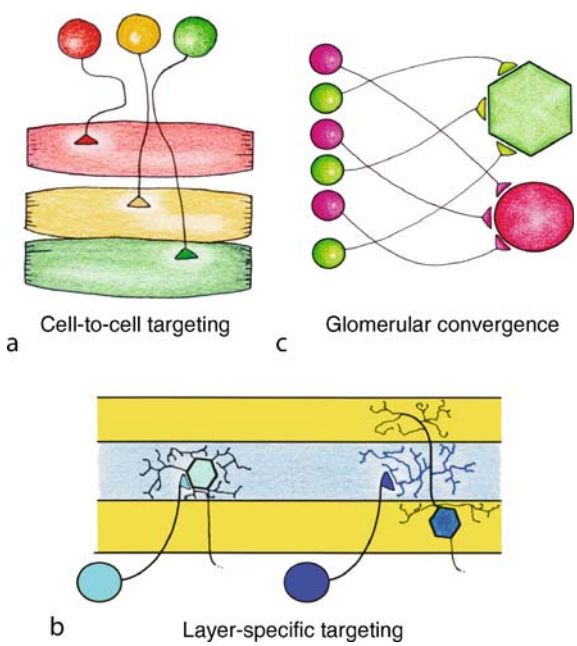
receptors in the presynaptic cells, have to be expressed at the right place at the right time. This process is regulated in part by the action of transcription factors as they specify the fate of individual neurons. For example, combinatorial expression of LIM-homeodomain transcription factors, the LIM code, determines the axon pathways of motor neurons toward their distinct muscle targets in vertebrates as well as in *Drosophila*. However, the specific downstream axon-guidance molecules that are regulated by these transcription factors are not yet defined.

Examples of Synaptic Specificity: Selecting Discrete Targets

Cell-to-Cell Targeting

Upon reaching the target region, neurons must choose specific synaptic partners from among a number of potential targets in the vicinity. In the cerebral cortex, for example, chandelier cell interneurons form synapses only with pyramidal neurons and in the cerebellum, ascending fibers connect only with Purkinje cells. The molecular mechanisms of cell-to-cell targeting are currently best characterized in the *Drosophila* neuromuscular system (Fig. 2a) [5].

In each segment of *Drosophila* larvae, ~40 motor neurons specifically innervate 30 muscle cells. Each motor neuron contacts many different muscles in the target region before forming synapses with only one or a few targets, suggesting the presence of specific cues present on individual target cells. Molecular and genetic studies have indeed identified several cell-surface or secreted proteins that are expressed in different subsets of muscles and can either attract or repel specific motor neurons. These include cell adhesion molecules with leucine-rich repeats (LRR), connectin, toll and capricious, a cell adhesion molecule of the immunoglobulin superfamily fasciclin3 (Fas3) and the attractive and/or repulsive secreted guidance molecules known as netrins and semaphorins. Connectin, Fas3 and capricious are also expressed on the presynaptic axons that innervate the muscles that express the same molecule and appear to mediate homophilic and attractive interaction between the synaptic partners. On the other hand, netrins, semaphorins and toll are expressed only on the target cells; they promote or inhibit synapse formation by binding to heterophilic receptors on the growth cone. These candidate target recognition molecules appear to function in a partially redundant manner to determine synaptic specificity; although gain-of-function mutations or ectopic expression of these molecules dramatically affects target specificity, loss-of-function mutations generally lead to only minor defects. Consistent with this idea, presynaptic motor neurons are able to integrate the information provided by multiple attractive and repulsive muscle cues.



Synaptic Specificity. Figure 2 Examples of discrete targeting. Synaptic specificity can be generated by different forms of neuronal targeting. (a) Cell-to-cell targeting as in the case of a *Drosophila* neuromuscular connection. (b) Layer-specific targeting as found in the tectum and the cerebral cortex. (c) Glomerular convergence in the olfactory system.

Layer-Specific Targeting

Layer-specific (also called lamina-specific) innervation is a common form of neuronal targeting, since many targets in the central nervous system, such as the tectum and the cerebral cortex are divided into multiple layers [6]. Arriving axons thus form specific synaptic connections by selecting the right layer(s). In some cases, the postsynaptic cells and their dendrites are themselves confined to a particular layer (Fig. 2b, left). In other cases, postsynaptic cells have dendritic branches that extend through multiple layers (Fig. 2b, right). In the latter case, presynaptic cells must recognize not only the specific target cell but also its correct dendritic segments for synapse formation (subcellular specificity). Several candidate target recognition molecules that are expressed in a layer-specific manner in vertebrates have been reported, including N-cadherin, sidekicks (Sdks) and ephrins. Of these, the best characterized are Sdk1 and Sdk2, which are homologous immunoglobulin superfamily cell adhesion molecules that are expressed in different subsets of retinal cells [7]. Sidekick proteins are concentrated at synapses that form between Sdk-expressing pre- and post-synaptic cells. Ectopic expression of Sdks in normally Sdk-negative presynaptic cells redirects their terminals to Sdk-positive layers.

A good model system for layer-specific targeting is photoreceptor targeting in the *Drosophila* visual system [4]. Eight photoreceptors (R cells; R1–8) that comprise the simple eye project to distinct layers of the optic lobe; R1–R6 project to the first optic ganglion (the lamina) and R7 and R8 project to distinct layers in the second optic ganglion (the medulla). Large-scale genetic screening has been used to identify several receptors and cell adhesion molecules that are involved in this targeting process, including the cadherins N-cadherin and flamingo and the receptor protein tyrosine phosphatases LAR and PTP69D [4]. Although the expression of these molecules is not restricted to particular R cells or target layers, the mutant phenotypes indicate that they function in specific aspects of R cell targeting. On the other hand, the LRR cell adhesion molecule capricious, which was originally identified for its role in neuromuscular specificity (as described above), is specifically expressed in R8 cells and their target cells in the medulla [8]. Both loss-of-function and gain-of-function analyses suggest that capricious regulates layer-specific targeting by mediating specific axon-target interaction.

Glomerular Convergence: Targeting in the Olfactory System

The odorant receptors constitute a large receptor family (~1,000 in mammals). Olfactory neurons that express a particular receptor are scattered in a large area of the nasal epithelium. Yet, their axons converge onto specific target glomeruli in the olfactory bulb (Fig. 2c). The odorant receptor itself has been implicated in this targeting process [9]. When a single odorant receptor is deleted, the neurons that normally express it fail to converge on their target glomerulus. On the other hand, replacing a normal olfactory receptor with an ectopic one causes olfactory neurons to target neither the normal glomerulus nor the one expected for the new receptor. Instead, they map to an ectopic glomerulus located in between. These results suggest that while odorant receptors are important in glomerulus targeting, they are not the sole determinants.

Targeting Mediated by "Guidepost Cells"

In some cases, synaptic specificity between two neurons is determined by the function of a third cell. The HSNL motor neurons in *C. elegans* form synaptic connections with VC4 and VC5 neurons and the vulval muscle vm2, in the vicinity of the vulval epithelial cells [10]. The vulval epithelial cells, but not the target cells themselves, are important in synaptic positioning. Thus, the epithelial cells serve as guidepost cells that induce the formation of specific synaptic sites. SYG-1 and SYG-2, a pair of transmembrane proteins of the immunoglobulin superfamily that heterophilically bind to each other, have been implicated in this process. SYG-1 is expressed in presynaptic HSNL motor neurons and SYG-2 in the guidepost epithelial cells. Both are necessary for normal synapse formation by the HSNL neurons. Ectopic expression of SYG-2 induces the accumulation of SYG-1 and presynaptic markers in HSNL adjacent to that region.

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Synaptic Transmission: Model Systems

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Synonyms

Model presynaptic release sites

Definition

Model systems are being used to define the structural and functional attributes of synapses, which are specialized points of physical and functional contact between two communicating neuronal elements.

Characteristics

Cell-cell communication is essential to all nervous system functions. Synapses allow signals to be transmitted from neurons to their targets, providing the minimal building blocks necessary for neural integration. ►Chemical synapses, which consist of presynaptic and postsynaptic compartments separated by a synaptic cleft, are highly specialized structures that mediate the transmission of signals from presynaptic termini to postsynaptic targets via chemicals known as ►neurotransmitters. The structural and functional features of synapses are conserved in vertebrates and invertebrates.

At most chemical synapses, an action potential that invades a presynaptic terminal leads to a depolarization that causes voltage-activated calcium channels to open. A calcium influx increases the intracellular calcium concentration, resulting in the generation of calcium microdomains or nanodomains, which facilitate the fusion of transmitter-containing synaptic vesicles to the presynaptic membrane. After fusing to the membrane, the synaptic vesicles release their contents (neurotransmitters) into the synaptic cleft via exocytosis. The transmitters released by exocytosis diffuse to the postsynaptic membrane where they bind to ►postsynaptic receptors; thus, directly or indirectly, alters the excitability of the postsynaptic cells. At ►excitatory synapses, transmitter binding to postsynaptic receptors allows a net inward current, which depolarizes the membrane toward the action potential threshold (►Excitatory postsynaptic potential (EPSP)); whereas at ►inhibitory synapses, transmitter binding to postsynaptic receptors allows a net outward current, which drives the membrane potential away from threshold and maintains a membrane potential that is negative relative to the threshold value (►Inhibitory postsynaptic potential (IPSP)). Thus, the synapse mediates communication between the presynaptic and postsynaptic cells.

A variety of forms of the synapse have been identified. Depending on the nature of the postsynaptic cell, the synapse can be divided into two major categories: the ►neuro-muscular synapse (Neuromuscular junction, NMJ), which refers to a synapse formed between a presynaptic neuron and a postsynaptic muscle cell, and the ►neuronal synapse (►Central synapse), which refers to a synapse formed between two neurons.

Much of our understanding of the basic properties of synaptic transmission is the result of a large body of work done on neuromuscular junctions, largely due to its anatomical simplicity and accessibility. Using these models, the principle structures of presynaptic features, release mechanisms of acytelcholine, and synaptic efficacy of transmission have been determined. For instance, studies on frog neuromuscular junctions demonstrated the quantal release of synaptic vesicles by Del Castillo and Katz in 1954, vesicle fusion to cytoplasma membrane by Heuser and Reese in 1973, acetylcholine-dependent single-channel activity by Neher and Sakmann in 1976, the calcium requirement for release by Katz and Miledi in 1967, and the collocalization between the presynaptic calcium channels and postsynaptic acetylcholine receptors by Robitaile and colleagues in 1990. In addition to principle studies of neurotransmission, NMJs with specific features have also been used to investigate modulatory mechanism of synaptic transmission. For instance, Atwood and colleagues in 1967 showed that crustacean phasic and tonic glutamatergic motor neurons are innervated to a common muscle cell, but evoke different postsynaptic excitatory responses. The phasic EPSPs are large and often exhibit synaptic facilitation, whereas the tonic EPSPs are small and usually exhibit synaptic depression. These distinct properties have made crustacean NMJ models useful to study synaptic specialization. A number of genetic models of invertebrates have been used to identify molecules that are involved in regulating and mediating neurotransmission at neuromuscular junctions. For instance, the role of synaptotagmin in the NMJ transmission were investigated in *Drosophila* by Littleton and Colleagues in 1993, and Schwarz's group in 1994, and in *C. elegans* by Nonet and colleagues in 1993 and Jorgensen and colleagues in 1995.

Many of the principle properties that have been established for synaptic transmission at neuromuscular junctions are shared by central synapses. However, recent studies have shown that certain features of central synapses are distinct from those of neuromuscular junctions. For instance, Ceccarelli and colleagues in 1973 showed that presynaptic vesicles in neuromuscular junctions are locally reused at the synapse at which they are recycled. Work by Krueger and colleagues in 2003 indicated that functional synaptic vesicles in hippocampal neurons exhibit considerable mobility and can transit from the stable ►synaptic release sites along axons to other sites. Presynaptic proteins associated with neurotransmission are also shared amongst the neighboring terminals. Another example is the size of the quantal response, an elementary unit of synaptic transmission. The variability of the quantal size in the NMJs is low (the coefficient of variation is ~0.3), whereas that in the central synapses is ranged widely (the coefficients of variation are from 0.23 to 0.6), dependent on the preparation used. In addition, certain molecules that are critical to synapse formation in neuromuscular junctions play different roles in central synapses. For instance, agrin is essential to neuromuscular junction formation as showed by McMahan in 1990. Serpinskaya and colleagues in 1999 reported that central synapses, however, form in the absence of agrin.

Our limited understanding of the presynaptic mechanisms of neuronal (central) synapses can be

attributed to the complex anatomical structures and small size of most of neuronal synapses, which makes the synapses less accessible to electrophysiological recordings. Unlike the situation in neuromuscular junctions, in neuronal synapses the structures of both the presynaptic and postsynaptic neurons are highly variable. A stereotypical presynaptic element is the nerve terminal of axon, which forms synapse with a postsynaptic dendrite (axonal-dendrite synapse), a postsynaptic soma (►Axonal-soma synapse), or a postsynaptic axon (►Axo-axonal synapse). However, atypical synapses can form between a presynaptic dendrite and a postsynaptic axon (►Dendro-axonal synapse), or between cell somata (►Soma-soma synapse). Although afferent axons are only rarely postsynaptic to dendrites, the ultrastructures of dendro-axonal synapse have been described in dorsal horn of cats and monkeys by Ralton III's group in 1984, and of rats by Cruz and colleagues in early 1990s. *In vivo* axo-axonal synapses have been described in both invertebrates and vertebrates. For instance, ultrastructures of synaptic vesicle clustering in crayfish and in spider crabs have been shown at both axonal sites by Atwood's group in 1970s. Depolarization of an inhibitory efferent axon projection to the excitatory terminals results in modulation of excitatory transmitter release. Ralton III's group detailed the axo-axonal structures in rats, monkeys, and cats. The same group in early 1980s also reported multiple forms of synaptic connections in the macaque spinal cord, including axo-dendritic, axo-axonal, axo-somatic, and dendro-axonal synapses. One of the short-comes of these native synapse preparations in higher animals is to determine the presynaptic release properties due to the small size of the synapses and the complex anatomy, which does not permit direct access to the synaptic sites for functional analysis.

Our understanding of synaptic transmission in neuronal synapses largely relies on the availability of synapse models in which functional properties of synaptic transmission can be detected by direct electrophysiological recordings at the presynaptic release sites. This entry will focus on the major neuronal synapse models used to study the mechanisms and control of transmitter release in the neuronal synapse.

Native Neuronal Synapse Models

Squid Giant Synapse

The squid giant synapse forms between a presynaptic second-order giant fiber and a postsynaptic third-order giant nerve. These synapses are particularly large (100s μm). Synaptic transmission in the squid giant synapse was first recorded by Bullock and Hagiwara in 1957. Later studies using this synapse model demonstrated the correlation between the presynaptic depolarization, presynaptic calcium concentration and postsynaptic potential. For example, Llinas' group in early 1980s showed that calcium entry is directly related to the release of transmitter and confirmed the power relationship between calcium concentration and transmitter release by Katz and Miledi in 1970.

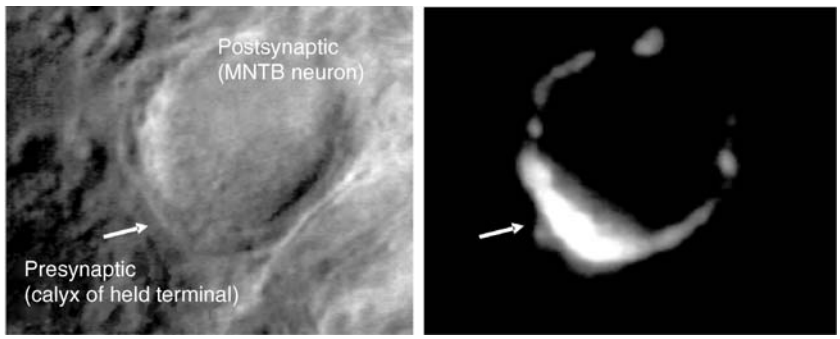
Calyceal Synapses

Giant calyceal synapses were first described in the nucleus magnocellularis of the avian auditory system. A classical example is the chick ciliary synapse as described by Marin and Pilar in 1964 and by Stanley and Goping in 1991. In this giant chick synapse, the presynaptic element envelops the postsynaptic ciliary neuron and contains a typical fast-transmitting cholinergic nerve terminal. Glutamatergic synapses are also observed in neurons of the chick nucleus magnocellularis (nMAG), one of the avian cochlear nuclei that receives somatic, calyceal innervation from the auditory nerve fibers as reported by Zhang and Trussell in 1994.

Hans Held (1894) first described calyceal synapses in the mammalian auditory brainstem, and these giant synapses were further characterized by Lorente de No in 1980, and Spirou and colleagues in 1990. The "endbulb of Held" synapses form between auditory fibers (presynaptic) from the spiral ganglion in the inner ear and the bushy cell soma (postsynaptic) of the ventral cochlear nucleus, and ►calyx of Held synapses form between a projection of globular bushy cells (presynaptic) in the anterior ventral cochlear nucleus and the cell soma of a principal neuron (postsynaptic) in the medial nucleus of the trapezoid body (MNTB) (Fig. 1).

The calyx of Held is a typical example of an axonal-soma synapse, from which Forsythe (1994) pioneered the first patch clamp recordings from nerve terminals. The globular bushy nerve terminals in this synapse release glutamate, resulting in fast AMPA and slow NMDA excitatory postsynaptic currents.

One of the major advantages of the calyx of Held as a model for the study of synaptic transmission is the accessibility of its large presynaptic terminal (10–15 μm), which permits patch-clamp recordings, capacitance measurements of exocytosis in combined with calcium imaging, and uncaging studies. These features have made the calyx of Held a popular synapse model of central synaptic transmission in the last decade. For instance, this model system has been used to study the quantal properties of transmission by Schneggenburger and colleagues in 1999, the calcium sensitivity of transmitter release by Bollmann and colleagues in 2000, the regulation of presynaptic calcium level and vesicle release by Takahashi's group in 1996, and the presynaptic mechanisms of short-term synaptic plasticity by a number of groups including Barnes-Davies and Forsythe in 1995, Turecek and Trussell in 2001, and Xu and Wu in 2005. The calyx of Held has also been used to study the developmental and



Synaptic Transmission: Model Systems. Figure 1 The calyx of Held synapses in the auditory brainstem slice. Left: DIC image; Middle: epifluorescence image of the same synapse with presynaptic terminal loaded with Lucifer Yellow. Arrow: the presynaptic calyx of Held nerve terminal enveloping the postsynaptic MNTB neuron. The cell diameter: ~15 mm (Courtesy of Lu-Yang Wang).

maturational changes that occur in presynaptic function as reported by Taschenberger and von Gersdorff in 2000, and Joshi and Wang in 2002. Manipulation of the presynaptic release mechanism at the molecular level is the major challenge in using this model system.

Retinal Bipolar Cells

The retinal bipolar cells of goldfish have a single, large and bulbous synaptic terminal, 8–12 μm in diameter, allowing patch-clamp recordings to be made on either dissociated bipolar cells or detached terminals as reported by Matthews' group in 1994. The ribbon-type terminals of the retinal bipolar cells, which secrete glutamate via the fusion of small, clear-core vesicles to the presynaptic membrane, have been used to study the mechanisms of calcium-dependent exocytosis and synaptic vesicle recycling.

Neurohypophysial Nerve Terminals

The nerve terminals of neurohypophysis (the posterior pituitary gland) extending from supraoptic and paraventricular nuclei release peptide neurohormones into the capillaries of the hypophyseal circulation. Arginine-vasopressin and oxytocin are the two major peptides found in neurohypophysial secretory granules. Some neurohypophysial nerve terminals have endings as large as 8–10 μm in diameter. Neurohypophysial synapse preparations have been used to study the calcium-dependent release mechanisms of peptide hormones in the work by Lemos and Nordmann in 1986 and Jackson and colleagues in 1991.

Hippocampal Brain Slices

Hippocampal brain slices have been used to study the presynaptic mechanisms involved in synaptic plasticity in the CA1 region since the work by Creager and colleagues in 1980. Direct patch-clamp recordings have been achieved on the mossy fiber terminal in the hippocampal CA3 region by Geiger and Jonas in 2000. This study demonstrated that slow recovery from inactivation of presynaptic K^+ channels regulates presynaptic strength by enhancing presynaptic calcium influx. The major limitation of this model is again the small presynaptic site.

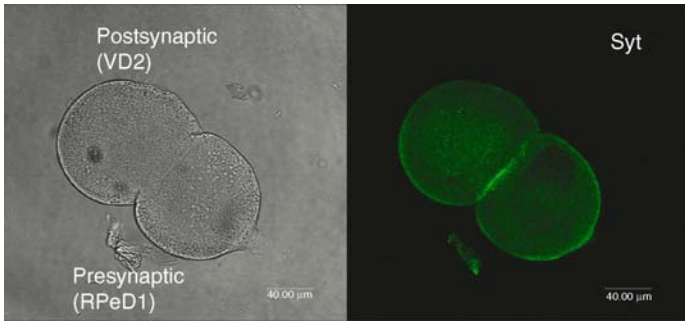
Synapse Models in Primary Cell Culture

Neurite-Neurite Synapses

Synaptic connectivity has been extensively studied in synapses formed in primary dissociated neuronal cell culture. Rotten hippocampal neuronal cultures are commonly used to study synapse function and structure *in vitro*. Unfortunately, the identities of the synapses in these cultures are usually unknown until the recording is completed. In addition, glial cells are required to establish these cell cultures, and functional synapses take up to weeks to form, increasing the variation and complexity found in these preparations. Simpler invertebrate neuronal cell culture models, such as those derived from mollusks, are also used to study synaptic function and synapse formation. Invertebrate *in vitro* systems offer some major advantages, including neurons that are usually individually identifiable, synapses that form in the absence of glial cells, and neurites that proceed with large growth cones. However, even in simple mollusk model systems, the neurite-neurite synapses are small, and electrophysiological recordings are often performed at cell somata that lie some distance from the synapse. The number of synapses in these cultures and the time it takes for the synapses to form between neurites varies between preparations. The formation of synapses depends primarily on neurite outgrowth. The temporal and spatial sequences of synaptic dynamics are difficult to observe directly. Thus, in an ideal model, the synapse would form between the cell bodies of identified neurons in the absence of neurites, namely a soma-soma synapse.

Soma-Soma Synapses

In culture, synapses form between neuronal somata in the absence of neurites. The major advantage of



Synaptic Transmission: Model Systems. Figure 2 A soma-soma synapse between identified *Lymnaea stagnalis* neurons in culture. Left: light image; Right: confocal image showing synaptotagmin clustering at the presynaptic site. Scale bar: 40 mm (Courtesy of Peter Gardzinski and Zhong-Ping Feng).

this model is that the synapses are large and relatively easily accessible for electrophysiological recordings and calcium imaging. The soma-soma synapse model, which most often employs neurons derived from molluscs, was pioneered in leech [1] and subsequently refined in the snails *Helisoma* [2] and *Aplysia* [3]. Feng et al. [4] adapted the soma-soma synapse approach to *Lymnaea stagnalis*. Functionally well-defined presynaptic and postsynaptic neurons can be individually isolated and paired in a soma-soma configuration in cell culture (Fig. 2).

Simultaneous electrophysiological recordings can be directly performed on the pre- and postsynaptic sites. Specific synaptic connections, similar to those observed *in vivo* and *in vitro* between neurites reported by Syed's group in early 1990s, have been detected between the identified neurons. In addition, voltage-induced calcium hotspots [5] and synaptic vesicle aggregation, labeled by FM1-43 signaling [6] or synaptotagmin [7], have been observed at the presynaptic sites. Formation of inhibitory and excitatory synapses has been showed to require distinct trophic factors [4,8]. The synaptic efficacy of *Lymnaea* soma-soma synapses is regulated by the cAMP-PKA signal transduction pathway [9] and glial cells [10]. Our recent study showed that the C2A and C2B calcium binding loops of synaptotagmin play different roles in synapse formation and synaptic transmission between soma-soma synapses [7]. The *Lymnaea* soma-soma synapse provides an unrivaled functional model for investigating the molecular mechanisms underlying synapse function.

Isolated Synapse Preparation

Synaptosome

Synaptosomal preparations are made from isolated nerve terminals and axonal varicosities *in vitro*. The well-sealed synaptosomes contain 70–100% of presynaptic boutons and terminals, and closely resemble the nerve terminal or varicosity from which they were derived. This model system has been used to identify proteins and mechanisms involved in exocytosis since the work of Whittaker's group in 1964. Direct patch clamp recording was first made by Nicholls and Sihra in 1986. Synaptosomes are derived from non-uniform sources of nerve terminals and varicosities and contain a mixture of multiple-types of synapses and transmitters; these features limit its usefulness in studies on the specificity of synaptic release mechanisms.

In summary, every model has its own particular strengths and limitations. The major advantage of the *in vitro* soma-soma synapse model between *Lymnaea* neurons is that the giant synapse forms between individually identifiable cells. In contrast to native giant synapses, the soma-soma synapse model allows direct assessment of the timing of synapse development, thus offering an ideal model not only for studying the cellular and molecular mechanisms of synaptic function, but also allowing investigations of the maturation of synapses formed between adult neurons.

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Synaptic Vesicle

Definition

Synaptic vesicles are membrane-bound organelles found in presynaptic terminals. They accumulate neurotransmitters and neuromodulators, and release these substances into synaptic cleft by a Ca^{2+}-dependent exocytosis.

►Synaptic Vesicle Recycling

Synaptic Vesicle Recycling

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Definition

Proteins of Synaptic Vesicle (SV) component are synthesized in the neuronal cell body and transported to the terminal by axonal transport. In addition, SVs are reformed by recycling of SVs after exocytosis at the nerve terminal. The recycling process includes endocytosis of SVs, refilling with neurotransmitter, translocation to release sites, and reformation of pools of SVs.

Characteristics

Quantitative Description

Time Course of SV Recycling

The time course of SV recycling varies depending on the type of synapses, or on the intensity and duration of the stimulus. In optical measurements by using fluorescence dye, the time required for a SV to be endocytosed, transported, and prepared for a new round of release was estimated to be shorter than 40 s at the frog neuromuscular junction, and in cultured rat hippocampal neurons [1], rapid recycling (few sec) was also detected in cultured hippocampal neurons. The time for recycling becomes much longer at prolonged stimulation. The first step of SV recycling is the endocytosis at the plasma membrane of nerve terminals. The half time of endocytosis after a brief burst of exocytosis is approximately 20 s or a few seconds [2]. With capacitance measurement at the giant terminal of goldfish bipolar neurons and at saccular hair cells, the time constant of the endocytosis following exocytosis was estimated as brief as 2 s. For SV attachment to the plasma membrane and pre-fusion may be required approximately 10–20 ms and for Ca^{2+}-triggered fusion less than 1 ms, most of SV recycling consists of reformation of release-ready SVs and neurotransmitter uptake.

SV Pools

The active zones of nerve terminals are considered as release sites for neurotransmitter. Few SVs (5–10) are attached to the active zone and considered as release-ready SVs. There are clusters of some 200–500 SVs that are situated next to the active zone. The majority of SVs are located in the cytosol of the nerve terminals. From functional determinations, SVs are divided into three groups (pools), the Immediately Releasable (a few percent of the total), the Readily Releasable (10–20%), and the Reserve pools (all the rest) in nerve terminals of fly and frog neuromuscular junctions, goldfish retina, and mammalian hippocampal and calyx of Held synapses [3].

Higher Level Structures

Neurons release neurotransmitters only at nerve endings, which are situated far from the cell body. The supply of SVs by transportation from the cell body to nerve endings is not enough to maintain continuous release of neurotransmitters for a long time. How can nerve endings sustain a high rate of release of transmitters for a prolonged period without exhausting their supply of SVs? Some forms of local recycling of SVs must occur at the nerve ending.

Lower Level Components

According to the vesicle hypothesis, neurotransmitter is contained in SVs and transmitter release occurs by exocytosis of SVs. After exocytosis, SVs are slowly retrieved from the plasma membrane, mainly by formation of clathrin-coated pits. The retrieved SVs are processed in the terminal to generate new SVs, either by direct uncoating of clathrin-coated SVs or via intermediate ►endosomes (cistemae) that later give rise

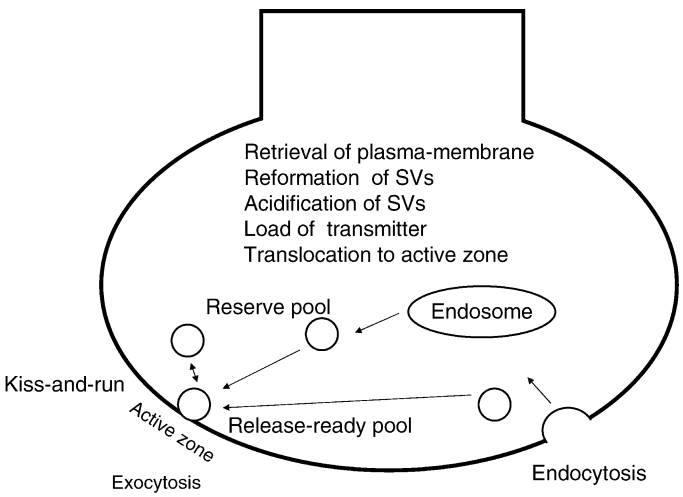
to new SVs [4]. In addition, a faster clathrin-independent retrieval mechanism, including "►kiss-and-run," where SVs fuse only temporarily with the presynaptic membrane before retrieval has also been suggested [5] (Fig. 1). The frequency of stimulation may determine vesicle endocytosis through two different recycling routes. Ceccarelli et al. [5] used low frequency stimulation, and found no requirement for endocytic intermediates. Heuser and Reese [4] used high frequency stimulation, and found that vesicle reformation was required for endocytic intermediates. Electron microscopic observations revealed that two endocytic pathways exist in single presynaptic boutons of *Drosophila*. During recovery, after blockade of endocytosis in a temperature-sensitive dynamin mutant, *shibire*, one pathway of endocytosis was found to be fast, did not rely on endosomal intermediates, and refilled a pool of vesicles near the active zone. A slower pathway refilled a vesicle pool distal to the active zones, through cisterna-like intermediates [6]. The pool recovered via the fast pathway supplied SVs for evoked release (at low frequency, and may constitute a ►readily releasable pool). The second pool may constitute the ►reserve pool of SVs for transmitter release at a high frequency.

Higher Level Processes

The recycling of SVs in presynaptic terminals is regulated by retrograde signals from postsynaptic cells. Fluorescence imaging and pharmacological analysis showed that a nitric oxide (NO) signal generated postsynaptically regulates endocytosis, and at least one later step in SV recycling in rat hippocampal neurons in culture. In goldfish retinal slices, fast endocytosis of SVs in presynaptic terminals is inhibited by postsynaptically released GABA-mediated chloride influx.

Lower Level Processes

In the kiss-and-run cycling of SVs [5], no endocytic process is necessary. During kiss-and-run cycling, SVs transiently release transmitter through a narrow pore, and the empty vesicle either detaches from the active zone or remains in place and is refilled with transmitter. Recently recycled SVs occupy a privileged location near the active zone, which would neatly explain their preferential reuse. The importance of clathrin-mediated endocytosis in recycling of SVs is well established. Assembly of endocytotic machinery proteins including clathrin, adaptor proteins (AP-2), endophilins and formation of clathrin-coated pits are necessary for retrieval of SVs from the plasma membrane by dynamin. For further steps of recycling of SVs after retrieval of clathrin-coated SVs, the clathrin-coated SVs are processed for uncoating. An interaction between Hsc70 and auxilin are suggested to be required for uncoating. Genetically induced disruption of genes encoding these proteins in *Drosophila* resulted in severe impairment of SV recycling. In either case of clathrin-mediated or kiss-and-run cycled retrieval of SVs, after fission of SVs by dynamin, empty SVs acidify via proton pump activity (vacuolar ATPase) to generate an electrochemical gradient across the SV membrane. SVs are then filled



Synaptic Vesicle Recycling. Figure 1 Synaptic Vesicle Recycling. There are alternative pathways for SV recycling; kiss-and-run cycling and full fusion followed by endocytosis. During kiss-and-run cycling, SVs transiently release transmitter through a narrow pore, and the empty vesicle either detaches from the active zone or it remains in place and refills with transmitter. Kiss-and-run cycling occurs at the active zone, is dependent on dynamin, but does not require clathrin assembly. After exocytosis, SVs are slowly retrieved from plasma membrane, mainly by formation of clathrin-coated pits. The retrieved SVs are processed in the terminals to generate new SVs, either by direct uncoating of clathrin-coated SVs or via intermediate endosomes (cistemae) that later give rise to new SVs.

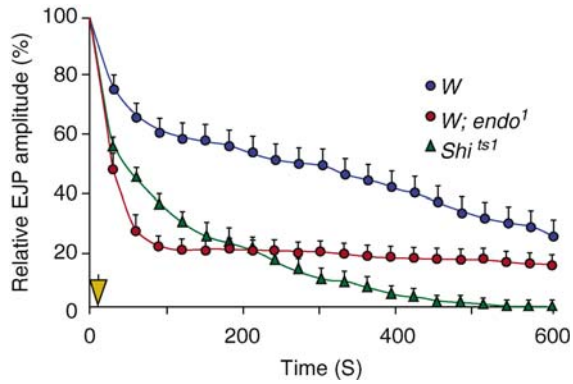
with neurotransmitters by active transport, which is mediated by transporters specialized for individual transmitter, utilizing energy of H^+ gradient. There are specific transporters for glutamate (GLUT 1, 2 and 3), ATP, and acetylcholine, a common transporter for glycine and GABA, and one for all catecholamines. SVs filled with neurotransmitters are translocated to the area near to active zones. Although participation of cytoskeleton and motor proteins in this active transport process has been suggested, direct evidence has not yet been obtained.

Process Regulation

Following incorporation of the SV membrane into the plasma membrane by exocytosis, the endocytic process could be blocked by removing extracellular Ca^{2+}. The block could then be released by re-adding low concentrations of extracellular Ca^{2+} [7]. One of the roles of Ca^{2+} influx in endocytosis of SVs is in assembly of endocytotic machinery proteins at the plasma membrane. When Ca^{2+} influx linked to endocytosis was selectively blocked at the *Drosophila* neuromuscular junction, components of SV were incorporated into the plasma membrane but no clathrin clusters were formed [8]. Ca^{2+} influx accelerates endocytosis at rat cultured hippocampal neurons. However, elevation of the intracellular Ca^{2+} level to a few hundred nM inhibits endocytosis in goldfish bipolar terminals.

Function

The most striking demonstration of the importance of recycling of SVs in animal behaviors came from the phenotypic characterization of temperature-sensitive *Drosophila shibire* mutants (shi^{ts}) [9]. Shi^{ts} flies are normal at a permissive temperature of 19°C, but become rapidly paralyzed at the non-permissive temperature of 29°C. Exocytosis occurs normally at 29°C, but endocytosis is impaired, leading to a rapid depletion of SVs. The roles of clathrin-mediated endocytosis of SVs and kiss-and-run cycling of SVs in synaptic transmission are clearly demonstrated in *endophilin* mutants. Endophilin is a key molecule for clathrin-mediated-endocytosis. Electrophysiological recordings at the neuromuscular junction in *endophilin* mutants demonstrated that a lack of clathrin-mediated endocytosis does not affect neurotransmitter release at low levels of synaptic activity. However, when stimulated at a high frequency, *endophilin*-null neuromuscular junctions undergo a strong synaptic depression, highlighting the importance of clathrin-mediated recycling. However, neurotransmitter-release is not completely abolished (►neurotransmitter release, elementary step). Neurotransmission remained at the 15–20% level throughout the stimulus. In contrast, at restricted temperatures in *shibire*, neurotransmission is completely abolished after intense-stimulation [10] (Fig. 2).



Synaptic Vesicle Recycling. Figure 2 Roles of Endocytosis of SVs, Kiss-and-Run Cycling and Clathrin-Mediated Endocytosis, in Synaptic Transmission. Amplitude of the excitatory junctional potential (EJP) evoked by nerve stimulation at 10 Hz. Values are relative to the EJP amplitude measured at 1 Hz before applying the tetanus. Blue circles, w; red circles, $endo^1$; green triangles, $shit^{s1}$, recorded at the non-permissive temperature. The yellow arrow indicates the approximate time at which full depletion of the total vesicle pool in $endo^1$ mutant terminals would occur at 10 Hz stimulation in the absence of vesicle retrieval by using $shit^{s1}$; endo1 animals [10].

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Synaptodendrosome

►Synaptosome

Synaptogenesis

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Synonyms

Synapse formation

Definition

Formation and maturation of synaptic contacts during development in the central and peripheral nervous system.

Synapse is the specialized contact between neurons through which they communicate. Synaptogenesis is a process in which synaptic contacts form and mature. The formation of synaptic contact is a complex process requiring the coordinated assembly of components on either side of the ►synaptic cleft. Synapse assembly begins when the immature presynaptic process contacts the postsynaptic neurons, leading to formation of an active zone where ►neurotransmitters are released into the synaptic cleft. During the postsynaptic process, receptors and signaling molecules are induced and localized, conferring the capacity to transduce the given signal into a postsynaptic response. The morphological rearrangements take place once synaptic targets establish their initial contact. During these maturational changes, functional molecules are also rearranged in synapses.

Characteristics

Following proliferation, migration and differentiation, a developing neuron reaches its final destination in the nervous system. To establish contact with its synaptic partners, a neuron must extend axonal (presynaptic) and dendritic (postsynaptic) processes towards targets located significant distances away. Extending axons and ►dendrites are guided towards their targets. The journey of both ►axons and dendrites towards its synaptic partner is regulated by a series of intermediate targets by cell–cell interaction and gradients of diffusible chemotrophic factors, which can be attractive or repulsive in nature [1–3]. Synaptogenesis involves a series of vary gradual structural, functional, and molecular changes in differentiation and maturational processes.

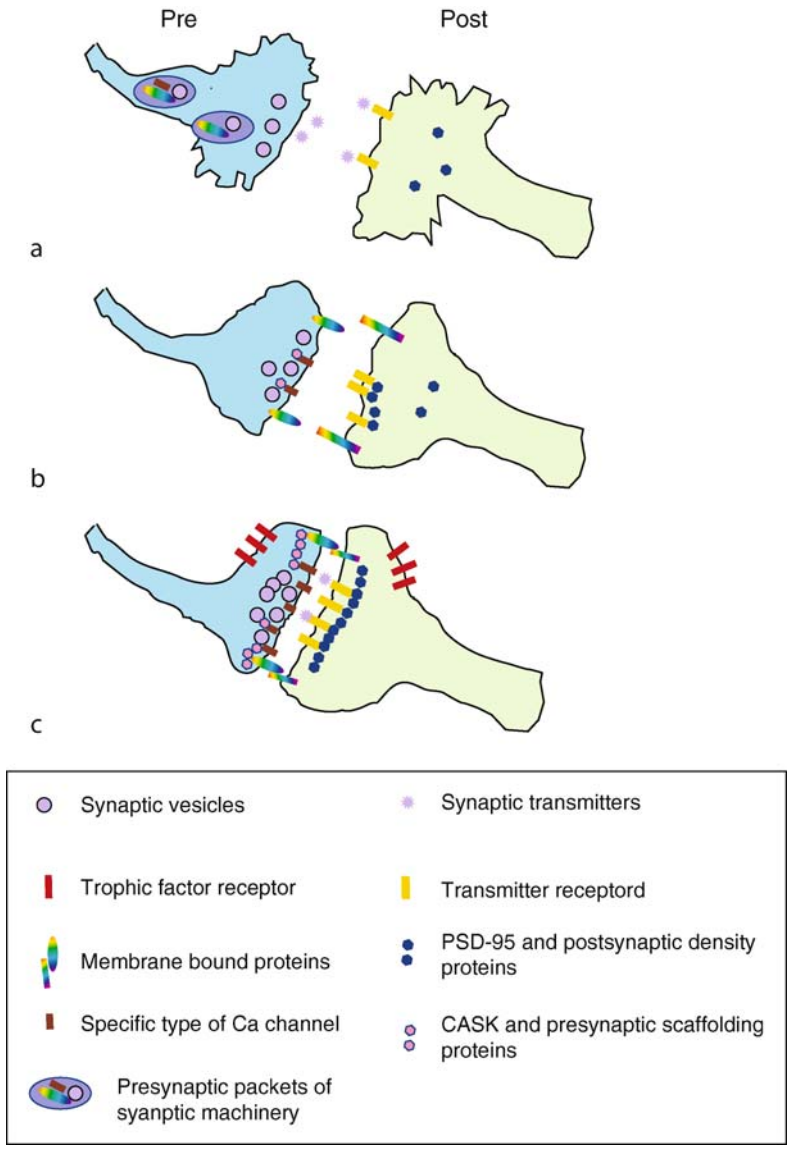
Cell-Cell Interaction during Synapse Formation

The formation of synapses involves an interaction between the presynaptic and the postsynaptic elements. Postsynaptic densities without presynaptic processes, and free presynaptic processes with associated ►synaptic vesicles, have been observed ultrastructurally in the developing brain. Prior to synaptic contact, receptor molecules of neurotransmitter are present on the surface of postsynaptic processes, and synaptic vesicles in the isolated presynaptic processes release synaptic transmitters before synapse formation. Transmitter-receptor interaction attracts appropriate target processes by binding to and stimulating postsynaptic processes. These two pre- and postsynaptic elements must first come into close proximity. Both pre- and postsynaptic processes play active roles in identifying and attracting their potential synaptic partners through a series of cell-cell interactions, either diffusible (neurotransmitter, ►neurotrophic factor) or ►cell adhesion molecules (N-CAM, cadherin, SyCAM, neurexin, neuroligin) [1] (Fig. 1). Whilst making contact, these molecules stabilize pre- and postsynaptic scaffolding proteins such as CASK and PSD-95M. Subsequent formations of synaptic contacts and interactions between neurotrophic factors and receptors leads to clustering of specific (non-L type) ►Ca channels and synaptic vesicles in presynaptic processes and transmitter receptors in postsynaptic processes [4]. Other molecules localize in pre and postsynaptic elements during cell–cell interactions (Fig. 1).

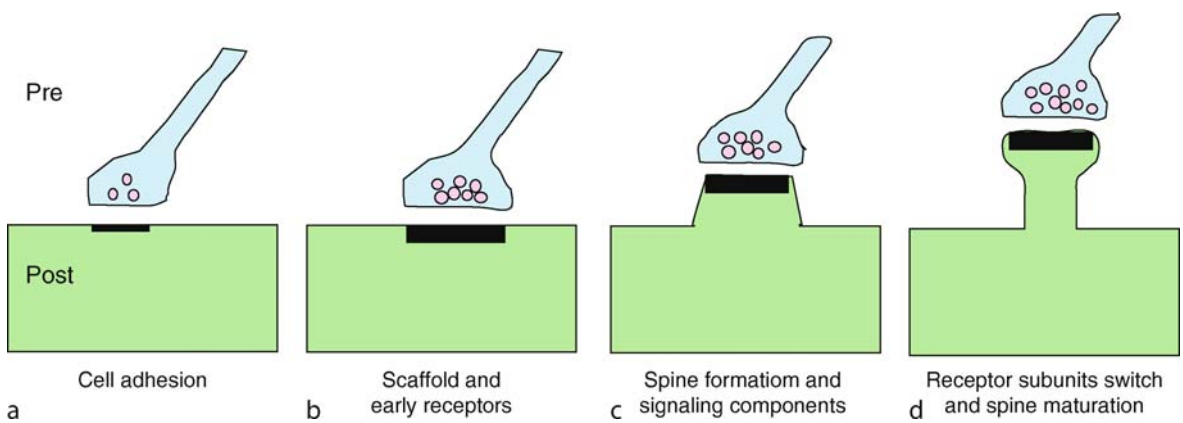
1. Pre- and postsynaptic growth processes approach each other. Transmitter-receptor interaction attracts appropriate target processes by binding and stimulating postsynaptic processes. Various components of pre- and postsynaptic specialization, including presynaptic packets containing synaptic machinery and channels, and postsynaptic proteins are mobile prior to contact.
2. As extending growth processes contact, the processes smooth, and asymmetric interactions between cell adhesion molecules mark the synaptic sites and stabilize pre- and postsynaptic scaffolding proteins.
3. Subsequent formation of synaptic contacts and interactions between neurotrophic factors and receptors lead to clustering of specific (non L type) Ca channels and synaptic vesicles in presynaptic processes and transmitter receptors at the postsynaptic processes.

Differentiation and Maturation of Synapse

There is no general rule about the order of maturation of the pre- and postsynaptic structures, but in each case, the order is apparently invariant. A number of factors may have to act in combination to result in the functional maturation of the synapses (Fig. 2).



Synaptogenesis. Figure 1 Steps of synaptic contact formation.



Synaptogenesis. Figure 2 Maturation of spine synapses.

An approximate sequence of assembly of postsynaptic components is related to maturational changes in synaptic structure. (i) Pre- and postsynaptic processes form morphologically unspecialized but functioned contact. The earliest synapses recognized ultrastructurally contain only few synaptic vesicles. (ii) Putative scaffolding proteins such as PSD-95, GKAP/SAPAP, and Shank families localize to synapse early with an increase of size of PSD. Synaptic vesicles begin to accumulate at presynaptic processes. (iii) Many spine associated components such as actinin, drebrin, and CaMKII cluster at synapses late in development, concurrent with the outgrowth of spines. (iv) Rapid neurotransmitter receptor accumulation occurs in the spines. NMDA type glutamate receptors undergo a subunit switch from NR2B to NR2A associated with maturation of spines.

Functional activity may be necessary to ensure full maturation and permanent stability of the synapses.

Morphological Maturation

1. The number of synaptic vesicles increases in development and differentiation.

   The earliest synapses recognized ultrastructurally contain only a few synaptic vesicles. The number of synaptic vesicles increases with development. In the rat cerebral cortex, a fourfold increase in the number of vesicles per terminal has been observed [5,6].
2. The size of pre- and ►postsynaptic density increases in maturation [6].
3. The outgrowth of ►dendritic spines occurs in the late stage of development.

   Dendritic spines develop gradually following initial synapse formation. Quantitative electron microscopic studies show that spine synapses develop from shaft synapses by outgrowth through a stage of stubby spine [7].
4. The shape of spine changes dependent on the activity of stimulation.

   Activity can regulate the pre- and postsynaptic structure and synapse formation. However, there is not yet a consensus on how activity influences synaptic constituents. The variation may reflect differences in cell type, developmental state, experimental preparation, time course, and mode of activity manipulation [8,9].

Molecular Differentiation

1. Changes in cell adhesion molecules occur. The actions of cell adhesion molecules is not limited to initial contact formation, but is also involved in specific target recognition and regulation of synaptic size and strength [5].
2. Maturational changes in structural proteins occur. Scaffolding protein (PSD-95, GKAP/SAPAP, Shank families) localize to synapses early, functional protein (CaMKIIa and syndecan-2) cluster at synapses late in development, concurrent with maturation of dendritic spines [1].
3. Receptor subunits switch in association with the changes of the presynaptic terminal. Many spine associated components such as actinin, drebrin, and CaMKII cluster at synapses late in development, concurrent with the outgrowth or maturation of dendritic spines. NMDA type glutamate receptors also undergo a subunit switch from NR2B to NR2A [2].
4. Neurotrophins (NGF, BDNF, NT3, 4/5) have been implicated in multiple aspects of synaptic development. BDNF induces axonal and dendritic branching and remodeling, increases the efficacy of synaptic transmission, and modulates the functional maturation of synapses [10].

Critical Period of Synaptogenesis in Developing Brain

The onset of synaptogenesis occurs according to a remarkably invariant timetable. In each region of the mammalian brain, there is usually a difference of less than a few days between individuals of the same species in the appearance of the first synapses on any particular type of neurons. Synapses appear suddenly and increase rapidly in numbers. Excessive production of synapses, followed by elimination of redundant synapses, occurs in many regions.

Dramatic increases in synaptogenesis of mammalian cerebral cortex occur during the early postnatal period of development. The critical period of synaptogenesis is postnatal 2 weeks in rodent cerebral cortex and the first year after birth in human visual cortex [11,12].

Activity-Dependent Synaptogenesis in Adult Brain

Recent developments in real time imaging techniques have revealed not only that synaptic structures are motile, but also that a fraction of synapses undergo a continuous elimination and formation process in adult CNS. Activation of neuronal networks enhances dynamic mechanisms at both the presynaptic (remodeling of axonal branching) and postsynaptic (turnover of dendritic spines) level. Structural changes of synapses can occur rapidly within 24 h of sensory stimulation [8,12]. Activity dependent synaptogenesis takes place in adult CNS.

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Synaptoneurosome

►Synaptosome

Synaptosome

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Synonyms

Synaptoneurosome; Synaptodendrosome; Neurosecretosome

Definition

The ►synaptosome is a subcellular particle deriving from the interruption of the axonal termini (see ►Axon) after the brain tissue has been homogenized in a buffer isoosmotic with the plasma. It represents mainly the presynaptic compartment or presynaptic spine but often retains part of the postsynaptic components according to the experimental condition used.

The ►synaptoneurosome is a composite particle containing one or more presynaptic compartments (synaptosome) attached to a postsynaptic element (neurosome) [1]. In the ►synaptodendrosome, the axon terminal adheres to a larger portion of the postsynaptic compartment (dendrite) (see ►Dendrite) [2]. Finally, the ►neurosecretosomes are a subtype of synaptosomes isolated from neurosecretory neurons such as neurons from the neurohypophysis [3].

Characteristics

Quantitative Description

The synaptosomal particles have a variable size according to their composition. The simplest synaptosomes are small bodies with a mean diameter of 0.6 μm or up to 1 μm for the neurosecretosomes [1,3]. As the neurosome vesicle measures around 1 μm, the complete synaptoneurosome has a mean diameter of 1.6 μm [1].

Pre and Postsynaptic Compartment Purification

The quality and composition of the synaptosomal fraction depends on the purification method used. The use of one or multiple step gradients as well as the homogenization of the brain, performed manually or mechanically, leads to a different population of synaptosomes with variable intact postsynaptic compartments.

The traditional procedure utilizes the separation of particles deriving from brain tissue homogenate, through an isoosmotic density gradient [4]. The homogenate is loaded on a sucrose gradient that is then centrifuged at high speed. During the centrifugation, each particle sediments at a specific location along the gradient according to the size and weight leading to the separation of four major subcellular fractions. The bottom fraction (P1) contains mainly nuclei and cell debris, whereas the middle fraction (P2) is a heterogeneous population including myelin fragments, synaptosomes and free mitochondria. At the top, the microsomes, ribosomes and smaller entities form two distinct fractions (P3 and P4). The further separation of the middle fraction (P2) leads to the isolation of synaptosomes.

To improve the quality of synaptoneurosomes fractions, recently, a second density gradient has been employed that makes use of chemicals based on the iodixanol [5]. While the purity of the preparation is very high, the synaptoneurosome recovery is quite low. An alternative method, frequently used for the isolation of synaptoneurosomes, makes use of subsequent filtration steps in isoosmotic buffer. The brain homogenate is passed first through a 100 μm nylon mesh filter and then through a 5 μm filter [1].

Higher Level Structures

The synaptosomes appear as spherical or elongated particles containing the nerve terminal often joined to a partial or complete postsynaptic compartment [4,5]. The particle is coated by a membrane, which seals off at the point where the axon is fractured. This continuous envelope preserves the integrity of synaptoneurosome and thus both the presynaptic and postsynaptic compartments retain their main structural features [4].

The presynaptic element (see ►Chemical synapse, ►presynaptic structure) contains a pool of synaptic vesicles (see ►Synaptic vesicle) that are organized in the active zone (see ►Active zone) close to the presynaptic membrane [1,4].

As mentioned, although in the synaptosome preparation the postsynapse is often not well preserved, the sealed presynaptic compartment is frequently attached to a residual of postsynaptic membrane. In the intact synaptoneurosomes the postsynaptic element is well conserved as shown by a sealed membrane containing a dense structure beneath the membrane, known as postsynaptic density (PSD) (see ►Postsynaptic density) [1]. Figure 1 shows: (i) a drawing of a synaptic contact (pre and postsynaptic compartments) that is piched off during the isolation of synaptoneurosomes, (ii) an image, acquired at the electron microscope, of a synaptoneurosome obtained with a protocol previously described [5] and (iii) a colored drawing of the same electron microscopy image.

Lower Level Components

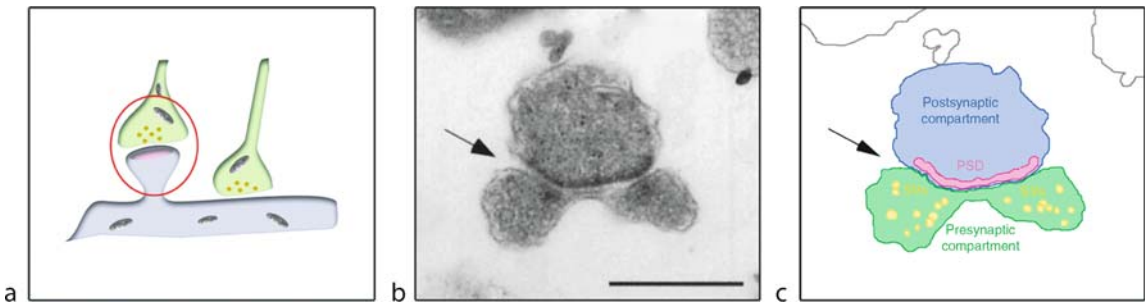
At the ultrastructural level, the synaptosomal particles retain the cytoplasm components and organelles.

In vivo, the presynaptic element presents an active zone (see ►Active zone) containing numerous synaptic vesicles 40–250 nm in diameter: a storage of releasable neurotransmitters (see ►Neurotransmitter). Generally, the synaptosomes contain small vesicles (40–60 nm in diameter), both clear-core vesicles with acetylcholine or amino acid transmitters, and dense-core vesicles (see ►Dense core vesicles) with catecholamines [6,7]. Sometimes larger dense-core vesicles (see ►Large dense core vesicles) have been observed containing neuropeptides (up to 250 nm in diameter) or biogenic amines [6,7]. In the neurosecretosomes the hormones are packaged in large neurosecretory granules (around 150 nm in diameter), with a dense core surrounded by a clear zone [3].

The presynaptic element preserves also the molecular machinery for exocytosis of synaptic vesicles (see ►Presynaptic exocytosis) [7] and the synaptophysin fractions are highly enriched in proteins, involved in neurotransmitter release, such as synaptophysin (see ►Synaptophysin) [5]. In intact synaptophysin, the exocytosis apparatus can maintain its functionality (see below). Within the presynaptic compartment one or more mitochondria are found and supply the energy for the local metabolism [4,7].

The pre and postsynaptic elements in the synaptoneurosome are joined together, as expected in a chemical synapse (see ►Chemical synapse). As mentioned, the Postsynaptic membrane shows a local thickening, the postsynaptic density (PSD), which links the neurotransmitters receptors to signaling protein and cytoskeleton. In fact, the key component of this machinery, known as postsynaptic density protein 95 (PSD-95), (see ►PSD-95) is highly enriched in synaptosomal fractions [5].

In polarized cells, the mRNAs are delivered to specific subcellular compartments to be locally translated. In neurons, mRNAs as well as the translational machinery have been found in dendrites and in axons, especially in growth cone (see ►Dendritic protein synthesis) [8 and references therein]. In synaptoneurosomes, ►dendritic mRNAs, polyribosomes [8 and references therein] and translational factors [9] have been detected and messenger RNAs can be locally



Synaptosome. Figure 1 (a) Drawing of a synaptic contact. The *red circle* indicates the point of rupture of the axon-dendrite contact. The postsynaptic compartment is shown in *light blue* with a visible postsynaptic density (PSD) in *pink*; the presynapse is shown in *green* and contains synaptic vesicles in *yellow*. (b) Electron micrograph of a synaptoneurosome from Bagni et al. (2000) J Neurosci. Copyright 2000 Society for Neuroscience (c) Colored drawing of the previous micrograph. Postsynapse (*light blue*), PSD (*pink*), presynaptic terminal (*green*), synaptic vesicles (SVs) (*yellow*). Scale bar is 0.5 μm.

translated upon synaptic stimulation (see below) [5,8 and references therein]. Lately, small non-coding RNAs such as microRNAs and the Brain Cytoplasmic RNA 1, *BC1*, have also been detected at synapses [2,10].

Higher Level Processes

The synaptosomes maintain their viability and metabolic activity, in media isotonic to plasma, for some hours after isolation [6]. The high membrane potential and the low intracellular calcium concentration indicate the integrity of synaptosomal particles [7].

Importantly, the synaptosomes include mitochondria that supply the energy needed for the metabolic activities of presynaptic terminals. In fact the synaptosomal mitochondria possess a stable membrane potential which sustains the ATP production for the bioenergetic metabolism [7]. As the synaptosomal particles are vulnerable to osmotic shock, the suspension in hypo-osmotic media leads to bursting of synaptosomes and release of intact synaptic vesicles and mitochondria [6].

In conclusion, the viable synaptosome behaves similarly to the synaptic compartment *in vivo* and can react to physiological and not physiological stimulations modulating its own functions (see below).

Lower Level Processes

The synaptosomes retain the ability to release the neurotransmitters by calcium-dependent exocytosis (see ►Exocytosis) as it occurs at synapses [7]. After stimulation, the synaptic vesicles move toward the active zone and, occasionally, the fusion of the vesicles with the membrane can also be observed. The endocytotic recycling of membranes provides the replenishment of vesicles pool (see ►Synaptic vesicle recycling). The synaptosomes release different class of neurotransmitters – cathecolamines, neuropeptides and amino acid transmitters, mainly glutamate [7 and references therein].

As previously mentioned, the synaptoneurosomes retain the majority of cytoplasmic components, including the synaptic mRNAs and the protein synthesis apparatus. Active translation in these particles has been shown by the incorporation of radiolabeled amido acids into proteins [5,8 and references therein]. Interestingly, protein synthesis within synaptoneurosomes is activity-regulated. After stimulation, the translation of subset of synaptic mRNAs encoding for key synaptic proteins increases. Last, but not least, the intact synaptoneurosomes possess functional neurotransmitter receptors and relative signalling complex. As a consequence, they retain the ability to trigger events and processes occurring in the intact neuronal cell (see below).

Process Regulation

Although the synaptosome maintains the metabolic machinery of synaptic terminals, it has lost the axonal input and thus it cannot receive physiological stimuli. Nevertheless, the intact synaptosome possesses functional neurotransmitters receptors that are up to respond to pharmacological drugs. In fact, the synaptosomal membrane has a negative membrane potential whose polarity changes after receptors activation as it happens in the whole neuron [7].

The stimulation can be obtained by alteration of ionic environment increasing potassium ion, by pharmacological inhibition of ion channels such as potassium channel [7] or by administration of physiological or pharmacological receptors agonists. In particular, treatment of synaptoneurosomes with metabotropic glutamate receptor (mGluR) agonists increases the amount of ribosomes associated with mRNAs, i.e. increases general local protein synthesis [8 and references therein]. Moreover, the administration of glutamate activates the translation of specific synaptic mRNAs [5]. At last, synaptoneurosomes maintain also the ability to respond to neurotrophic factors such as brain-derived neurotrophic factor (BDNF) which activates the protein synthesis machinery [9] enhancing the translation of specific mRNAs [10].

Function (Purpose)

The synaptosomes provide a versatile model to study the ultrastructure and the physiological features of the synapses.

The synaptosomal preparations can be used as starting material to isolate synaptic elements such as synaptic vesicles, synaptic mitochondria, purified postsynaptic density and synaptic mRNAs.

The synaptosomes have been used as a model to study synaptic processes. First, the synaptosomes have been extensively exploited to investigate neurotransmitter release, especially the glutamate release, and the regulation of this process [7]. In this context, the synaptosomes also enabled the study of the molecular basis of both endocytosis and exocytosis as the synaptosome is the simplest compartment containing the endocytotic and exocytotic apparatus [7]. Second, the synaptoneurosomes and the synaptodendrosomes have been exploited to identify the synaptically localized mRNAs and to study the regulated local protein synthesis [2,5,8 and references therein]. As the neurotransmitters receptors and the membrane maintain their functionality, the synaptosomal preparations have also been used to investigate the physiological regulation of above-mentioned processes after receptors stimulation or ion channel blockade.

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Synaptosome-associated Protein of 25 kDa (SNAP-25)

Definition

A protein in the SNARE complex. Isoforms of this protein are identified by a number (e.g. 25 or 23) after the term which refers to the molecular weight of the protein in units of kDa.

►Non-synaptic Release
►SNARE Proteins
►Soluble NSF Attachment Protein Receptor (SNARE)
►Synaptosome

Synchronization

►Temporal Coding

Synchronized, Desynchronized Brain Activity

►Brain Rhythms

Syncope

Definition

Acute, brief and transient loss of consciousness and postural tone (general muscle weakness and inability to stand upright) with spontaneous and complete recovery. A syncope is often preceded by faintness which denotes a lack of strength with a feeling of giddiness, swaying ground or surrounding objects, and impending loss of consciousness (presyncope). There are many possible causes of syncope, in particular cardiovascular changes and changes in blood state (e.g., hypoxia, anemia etc.) with a reduced supply of oxygen to the brain. Syncopes may thus be classified as vasodepressor (vasovagal) or neurocardiogenic syncope, postural hypotension with a defect in vasomotor reflexes, cardiac syncope, carotid sinus syncope, and others.

Syndactyly

Definition

Syndactyly describes the congenital or artificial webbing of adjacent fingers. As a consequence, webbed fingers cannot be used independently resulting in temporal coincidence of tactile inputs to these fingers.

►Somatosensory Reorganization

Syndrome of Inappropriate ADH Secretion (SIADH)

Definition

SIADH is characterized by plasma antidiuretic hormone (ADH) levels that are elevated above those

expected on the basis of body fluid osmolality and blood volume or arterial pressure.

►Blood Volume Regulation
►Vasopressin (VP) or Antidiuretic Hormone (ADH)

Synergist Muscles

Definition

Muscles acting to produce the same motion or torque at a joint.

►Impedance Control

Synergy

►Coordination

Synesthesia

Definition

Synesthesia is a condition, in which otherwise normal persons experience sensations in a non-stimulated sensory modality when stimulated by stimuli in another sensory modality or sub-modality. It runs in families, prevails among women and non-right-handers. These synesthetes may see letters or numbers colored (e.g. 5 as green and 6 as red: grapheme-color synesthesia or lexical synesthesia; blind people may have colored impressions of Braille signs), "see" tones as colors (e.g. C-sharp as blue: color-hearing), "hear" colors, "taste" shapes, "smell" the color red, describe music as movements of colored forms in visual space. The most common synesthetic experiences are color-hearing (with clear associations of particular colors with particular sounds) and grapheme-color synesthesia. In synesthetes who clearly associate specific graphemes with specific colors (e.g. "R" is blue), display of the grapheme in another color (e.g. red) may evoke affective reactions (e.g. uneasiness). Evidence is accumulating to indicate that these synesthetic sensations are real perceptions and may be due to hyperactivity of color-sensitive cortical areas or "cross-activation" of brain areas concerned with the associated percepts, thus extending normal processes in multisensory integration by hyperconnectivity between different cerebro-cortical areas. Many well-known artists are known to have been synesthetes, e.g. Alexander Scriabin, Olivier Messiaen, Arthur Rimbaud, Charles Baudelaire, Vladimir Nabokov, Vasily Kandinsky, David Hockney.

►Sensory Systems

Synesthete

Definition

A person with developmental or inherited synesthesia.

►Lexical-Gustatory Synesthesia
►Synesthesia

Synkinesias

Definition

Co-contractions of normally independently controlled muscles. For example, in *jaw winking*, voluntary movements of the lower face coincide with, e.g., eye closure.

Synovial Fluid

Definition

Synovial fluid is the fluid found on the articulating surface of joints. It is closely associated with the

cartilage fluid and is essential for the virtually frictionless movement of joints.

►Articular Cartilage

Synovium

Definition

Thin membranous layer lining synovial joints that secretes synovial fluid and contains nerves and vessels (both blood and lymphatics).

►Joints

Synprint

Definition

A synaptic protein interaction site localized to the large intracellular loop between domains II and III of the α1 subunits of N- and P/Q-type Ca^{2+} channels. Enables binding of syntaxin, SNAP-25 and synaptotagmin to the Ca^{2+} channels, affecting the efficiency of Ca^{2+} entry vesicle release coupling.

►Calcium Channels – an Overview
►Synaptic Proteins and Regulated Exocytosis

Synprint Motif

Definition

Acronym of synaptic protein interaction region: an approximately 225 amino acid stretch in the intracellular domain II-III linker region of the α1-subunit of mammalian Cav2.1 and Cav2.2 channels which binds SNARE proteins. The site is considered unique to vertebrate N-type Ca^{2+} channels and P/Q-type Ca^{2+} channels and seems to be at the origin or the tight coupling between these channels and presynaptic vesicles.

►Calcium Channels – an Overview

Synthetic Quality in Olfaction

Definition

In odor-mixture psychophysics, a synthetic quality occurs when a mixture of odorants smells like something different than the component odorants.

►Olfactory Information

Syphilitic Meningitis

Definition

Syphilitic meningitis mostly occurs within two years of the primary infection and is characterized by nocturnal headache, malaise, fever, stiff neck, and cranial nerve palsies.

Syringomyelia

Definition

An abnormal cystic structure within the center of the spinal cord resulting from the cerebro-spinal fluid (CSF) build-up. It most commonly occurs in the cervical spine. It can be primary or secondary (develops as a result of blockage of the CSF flow). The most common causes include birth defects, tumors and trauma. This condition is associated with Chiari I and II malformations. Typical symptoms include segmental muscular weakness and atrophy with associated specific sensory loss (loss of pain and temperature sensation with preservation of the sense of touch).

Surgical intervention may be needed to alleviate the symptoms and the indications usually depend on the primary cause.

►Gliomas

Syrinx

Definition

A special secondary vocal organ of birds, a modification of the lower part of the trachea, a “lower larynx.”

►Evolution of the Brain: At the Reptile-Bird Transition

System – Nonlinear

Definition

The general class of systems for which the relation between the input variables (initial conditions or external inputs) and output or state variables in not linear.

Common descriptions are by (nonlinear) state equations, differential equations, or difference equations.

►Nonlinear Control Systems

Systemic Lupus Erythematosus (SLE)

Definition

A disease of immune dysregulation characterized by inflammation in several organs and associated with the production of autoantibodies, especially anti-nuclear antibodies.

►Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens

Systems Biology

Definition

Systems biology describes attempts to collate the individual insights obtained from disparate experimental systems with the high throughput datasets obtained from genomics, proteomics, imaging and studies of mutation, and to develop ways of mathematically modeling these data in order to make predictions about the behavior of cells and organs.

►Bioinformatics

Syt

►Calcium Binding Proteins