M2

►Long Loop Reflexes

Machinery of the Neuronal Secretory Pathway

►Synaptic Proteins and Regulated Exocytosis

Mackintosh Model

Definition

Developed to account for attentional phenomena (latent inhibition, perceptual learning), this model of classical conditioning views variations in the effectiveness of CS-US pairings in terms of variations in CS processing. The model asserts that attention to a CS is modifiable and it specifies rules for how CS processing is influenced by experience. Attention to a CS will decrease if it is a poor predictor of the US and increase if it is the best predictor of the US.

►Theory on Classical Conditioning

Macrophages

Definition

Macrophages are derived from circulating monocytes and differentiate into tissue macrophages (including microglia in the central nervous system (CNS) during development). Normally, macrophages are at a resting state. Upon infection, tissue injury or other disturbance in the tissue, macrophages can be activated and become more effective in eliminating damaged tissue, infected cells or tumor cells. Activated macrophages are characterized by increased phagocytosis, increased secretion of inflammatory mediators and cytotoxic substances, and increased ability to activate the adaptive immune response. Macrophage functions can be further enhanced or inhibited by certain cytokines.

Macula Organs

Definition

Epithelia of sensory cells covered by an otolithic structure (utricle, saccule, lagena) arranged in different spatial positions, forming an integral part of the peripheral vestibular sensory apparatus in the inner ear of all vertebrates. The detection of static and dynamic changes of the position of the otolith by the sensory cells makes this organ sensitive to linear head acceleration and constant changes of head position relative to gravity.

►Functional and Neurochemical Organization of Vestibulo Pathways

Maculae

Definition

Specific areas located in two regions (the sacculus and the utriculus) of the membranous labyrinth where labyrinthine (macular) receptors are located.

►Peripheral Vestibular Apparatus
►Vestibulo-Spinal Reflexes

Macular Receptors

Definition

Labyrinthine receptors located within the maculae of the utriculus and sacculus whose cilia are embedded in a gelatinous structure (the otolith membrane). The membrane contains crystals of calcium carbonate whose density is three times higher than that of endolymph. Linear accelerations imposed on the head or changes in head position with respect to the vertical axis displace the membrane and stimulate the receptors.

►Peripheral Vestibular Apparatus

Magnetic and Electric Senses

Wolfgang Wiltschko[1], Bernd Kramer[2]
[1]Universität Frankfurt, Zoologisches Institut Biologie–Campus der Universität, Frankfurt am Main, Germany
[2]Institut für Zoologie, Animal Behaviour and Behavioural Physiology Research Group, Universität Regensburg, Regensburg, Germany

Synonyms

Magnetoreception; Magnetoperception; Magnetosensitivity; Magnetic orientation; Magnetotaxis; Magnetonavigation; Electroreception; Electric sensitivity; Electric orientation; Electrolocation; Electrocommunication

Definition

Many animals use magnetic or ►electric fields to obtain information about their environment. Although the senses for both types of fields are discussed here in one chapter, the role of these physical features in animal behavior is fundamentally different. The magnetic field used is the ►geomagnetic field; it provides a reliable source of information utilized by the animals in numerous ways for orientation in space and possibly time. The electric information used by animals, on the other hand, is normally not provided by the ►physical environment, but comes from other animals or is produced by the user of the information for ►active electrolocation. The ►electroreceptor organs of marine elasmobranch fish, termed ►ampullae of Lorenzini, might additionally act as magnetoreceptors. At the same time, while the ecophysiology of magnetic and electric senses is generally known, at least in the most prominent animal groups studied, our knowledge about the neurobiological base differs greatly. The neurobiology of the electrical sense is comparatively well understood, and a prominent example of neurobiology, whereas our knowledge on the neurobiology of the magnetic senses is still rather limited; here, most of our knowledge comes from behavioral experiments.

Magnetic Senses

For animals that are able to perceive magnetic parameters, the geomagnetic field provides an omnipresent source of navigational information. Its field lines exit the earth at the southern magnetic pole, run around the globe and reenter at the northern magnetic pole. This vector quality provides directional information to be used as a ►magnetic compass, whereas total ►intensity and/or ►inclination, showing a gradient from the poles to the equator, can provide positional information on a large-scale ►magnetic "map" to be used for navigation. The latter two magnetic parameters may also serve as "►sign posts" or triggers, marking specific locations or regions where they elicit specific responses. In a similar sense, even magnetic anomalies could serve to characterize a specific location. Furthermore, the daily variation of the geomagnetic field – in the temperate zones a decrease of magnetic intensity from sunrise to noon, followed by a corresponding increase – have been discussed as potential *Zeitgebers* for the circadian clock. In summary, in order to make optimal use of the wealth of information offered by the geomagnetic field, animals need sensors for magnetic direction as well as sensors for magnetic intensity or intensity changes.

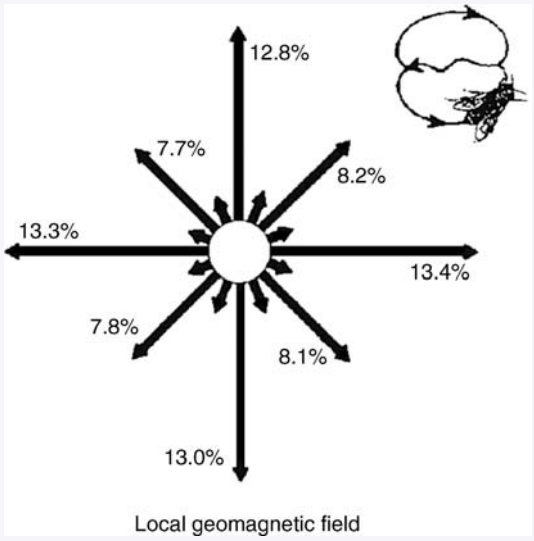
The use of the magnetic field for locating directions is rather widespread among animals. The associated behavior can be classified either as alignment responses or as a magnetic compass orientation. Alignment responses are characterized by an axial preference of the prominent magnetic directions, with the dances of honeybees on a horizontal comb being a classic example: without view of the sky, the largest activity is found along the magnetic N–S and the E–W axes (Fig. 1).

When, however, the magnetic field is used for compass orientation the animals can prefer any arbitrary direction with respect to the direction of the magnetic field. The behavioral context of the animal determines the specific angle relative to magnetic north. The selected course, or "set direction," of the compass can be of different origin: it can be innate, imprinted or learned.

The best studied examples for magnetic compass orientation is that of birds (Fig. 2).

It is a so-called "►inclination compass," as the birds do not use the polarity of the magnetic field, but the inclination of the magnetic field lines in space to derive directions. This type of compass response does not distinguish between magnetic North and South, but between "poleward," where the axis of the field lines forms the acute, and "equatorward," where it forms the

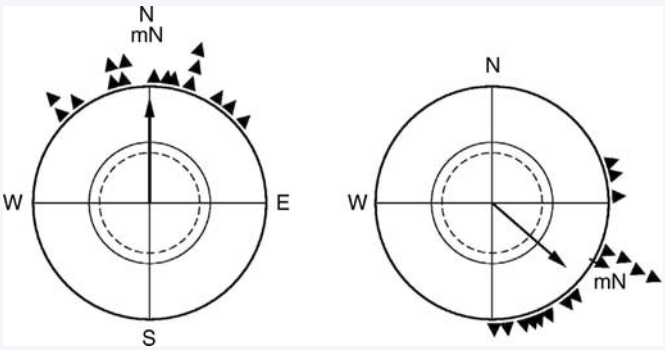
obtuse angle with gravity. At the same time, the avian magnetic compass functions only in a narrow ►intensity window; this functional window is finely tuned to the ambient magnetic intensity where the birds live. These findings from behavioral experiments imply specific characteristics of the receptors mediating magnetic compass orientation in birds. Various other animals are also able to perceive the direction of the magnetic field and use it as a magnetic compass. Two types of compass ►mechanisms have been described: marine turtles and amphibians have an inclination compass like birds, but mole rats, some fish and all invertebrates studied so far use a "►polarity compass" that is based on the polarity of the magnetic field lines, similar to our technical compass. This suggests the existence of at least two different receptor mechanisms among vertebrates [1].



Magnetic and Electric Senses. Figure 1 Dancing directions of bees on a horizontal comb in the absence of directing visual stimuli under diffuse light in the natural geomagnetic field. 24,601 individual dances were recorded; the arrows are proportional to the percentage of dances in the various directions. For the main classes the percentage is given numerically. The results clearly demonstrate a spontaneous preference of the main-direction N, E, S, W and a still remarkable preference of the intermediate direction NE. SE, SW, NW (after [37]).

Birds use their magnetic compass for homing and for migration. Avian navigation is usually described as a two-step process: the direction to the goal is first determined as a compass course (= set direction); then, this course is located with a compass and converted into a heading for flight. Orientation within the home range and homing means that the compass course varies according to the position of the animal relative to home; it is determined by a navigation process or remembered from previous visits. For migration, the migratory direction as fixed set direction is innate; the respective course is genetically encoded and passed on from one generation to the next. Here, the geomagnetic field serves as external reference system and, together with celestial rotation, ensures that this genetic information is converted into the species-specific migratory direction [2]. In birds, the magnetic compass is also involved in establishing the directional relationship between sun azimuth and the circadian clock for the sun compass and in calibrating a stellar compass for nocturnal migrants. The biological significance of the avian magnetic compass lies in its role as a basic component of a complex navigational system (see [1]).

In non-avian species, magnetic compass orientation also provides a directional reference in various



Magnetic and Electric Senses. Figure 2 Orientation behavior of 16 European Robins in spring, tested in the natural geomagnetic field (*left*) and in an experimental magnetic field with the horizontal component shifted to the SE (*right*). mN, magnetic North. The triangles at the periphery of the circle mark the headings of the individual birds. The arrows represent the mean vectors calculated from the 16 headings. The length of the vector is proportional to the radius of the circle. The two inner circles are the 5% (dashed) and the 1% significance levels of the Rayleigh test (after [35]).

behavioral situations. It is used by salmon fry that prefer innate directions to find their way in complex lake-river systems [3] and by hatchlings of sea turtles that use an imprinted magnetic course to head away from the shore to the open sea. Another famous example is the well-studied "y-axis"- orientation that is typical for animals living at the border of land and water, e.g., salamanders, beach hoppers and isopods: here, the animals move along a magnetic axis perpendicular to the shoreline toward water or land, depending on their physiological needs (Fig. 3; [4]).

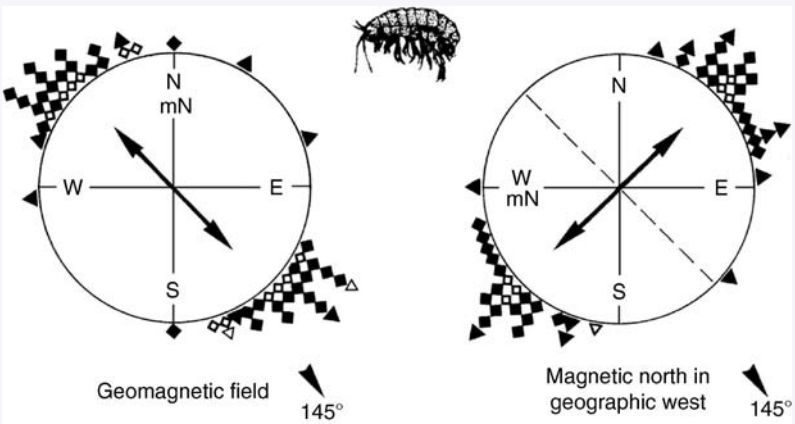
In birds as well as in other vertebrate species, the magnetic compass may be used in a navigational strategy called "path integration," based on directional information obtained during the outward journey. Recording the net direction of the displacement could be based on endogenous (idiothetic) cues alone, or on external (allothetic) factors. In very young pigeons, wood mice, box turtles and young alligators, the geomagnetic field was shown to provide the external reference for path integration (see [1]). Blind mole rats of the genus *Spalax* were shown to use idiothetic factors alone over short distances, but to turn to the magnetic field as external reference on more extended excursions [5].

A special case of directional orientation with the help of the magnetic field is found in ►magnetic bacteria. While all animals detect the direction of the magnetic field with specialized receptors and act according to this information, magnetic bacteria contain chains of tiny crystals of magnetic material. By the force of the geomagnetic field lines, they are passively rotated and aligned along the field lines by magnetic crystals; they then propel themselves along the field lines down into the mud (see [6]). Their orientation is thus fundamentally different from that of animals.

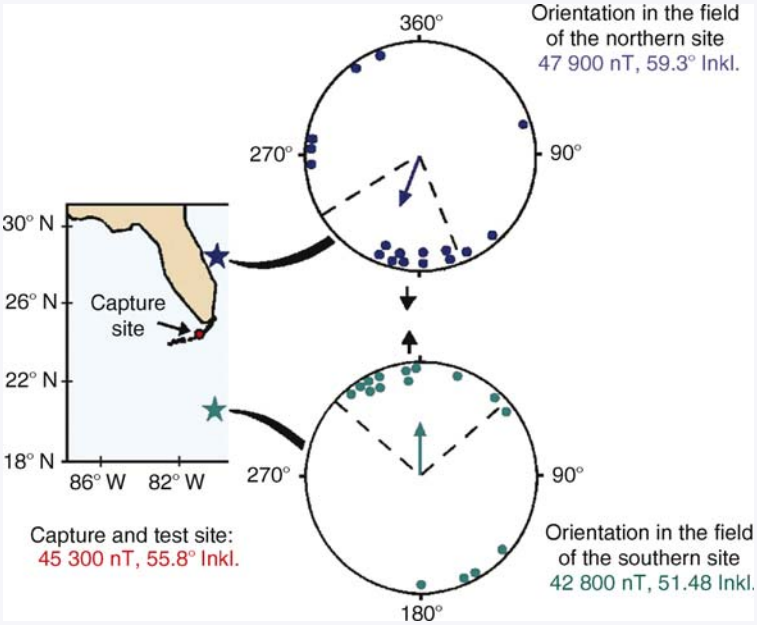
The geomagnetic field is not only used as a source of directional information. An increasing body of evidence suggests that non-directional features of the geomagnetic field are also utilized by animals. Because of the gradients running from the poles to the equator, magnetic intensity and/or inclination can serve as components in a potentially world-wide ►navigational map. The use of magnetic "map"-factors has been discussed for birds since the nineteenth century and is indicated by some findings with homing pigeons, other birds, marine turtles and alligators; Fig. 4 gives a recent example of navigation based on magnetic factors in an invertebrate for the first time.

Navigational "maps" are typical for territorial animals; their biological function is to ensure that the animals find back to their home territory after extended excursions or displacements. Such "maps" are established by experience, involving learning and memory. In these learning processes, the magnetic compass might be involved as reference system, allowing animals to record the regional directions in which navigational factors show a maximum change.

Aside from their role as components of the navigational "map," magnetic intensity and inclination or a combination of both may serve as "sign posts" or triggers to elicit specific preprogrammed responses in certain areas characterized by these magnetic features. A famous example is the responses observed in young sea-turtles from Florida that spend their first year of life



Magnetic and Electric Senses. Figure 3 Orientation of the equatorial sandhopper *Talorchestia martensii* in the laboratory in a centrally lit arena. Test in the local geomagnetic field (*left*); test with magnetic North shifted 90° counterclockwise to geographic west (*right*). The theoretical escape direction to the sea of 145° is marked by the arrowhead outside the circle; the symbols at the periphery indicate the mean headings of individual sandhoppers: triangles unimodal behavior; diamonds axially bimodal behavior, with both ends of the axis indicated; solid symbols samples significant according to Rayleigh test; open symbols non-significant samples. The double-headed arrows represent the mean axes, the dashed diameter in the right diagram marks the axis of the respective controls (after [4]).



Magnetic and Electric Senses. Figure 4 True navigation by magnetic parameters indicated in spiny lobsters. The lobsters were tested near their capture site in magnetic fields replicating the ones of two distant geographic locations (*marked with asterisks*). In the circular diagrams, the small arrows outside of the circle indicate the home directions from the simulated sites. Dots at the periphery of the circle mark the headings of single lobsters; the arrow represents the mean vector proportional to the radius of the circle, with the dashed radii indicating the 95% confidence interval of the mean direction (after [19]).

M

in the Atlantic gyre. When freshly hatched turtles were exposed in the laboratory to magnetic fields simulating those at the edge of the gyre, they altered their headings and chose directions that would have brought them toward the center of the gyre, thus helping them stay within suitable waters (see ►"Entry" Magnetic maps). Similar preprogrammed responses have also been described for migratory birds that change direction or respond physiologically by increasing their fat load when encountering specific magnetic conditions.

A further role of the magnetic field in orienting animal movements has been discussed for the extended migrations of whales between their polar feeding grounds and the temperate regions where they spend the winter; following magnetic contours was suggested as navigational strategy (see [1]).

Organisms like magnetic bacteria need no perception mechanism at all, as they are passively aligned by the force of the geomagnetic field. In contrast, animals that actively respond to magnetic parameters need to obtain information about the direction or the intensity of the geomagnetic field. By what kind of mechanism they detect these features is not yet entirely clear, however. Experiments with birds suggest that magnetic compass orientation requires a stable direction of the magnetic field, but would tolerate changes in intensity and inclination to a certain degree. For the magnetic components of the navigational "map," on the other hand, detecting minute changes in intensity is crucial, whereas the direction of the field appears not to be important. Considering the physical aspects of magnetoreception, three mechanisms have been suggested: induction, ►magnetite-based mechanisms and ►radical-pair processes.

Electric current induction through the Faraday Effect as primary process for magnetoreception is an option only for marine fish. It has been discussed for elasmobranch fish, because the ampullae of Lorenzini, the electroreceptor ►organs of sharks and rays (see below), are highly sensitive to electric fields. With a threshold of as low as 5 nV/cm, these receptor organs are, at least theoretically, sensitive enough to distinguish the voltage induced by the normal swimming speed when moving in different directions and thus provide the information required for magnetic compass orientation (see [1]).

►Magnetite is a specific form of Fe_3O_4, with its magnetic features depending on particle size. Small crystals of less than 40 nm are superparamagnetic (SPM), which means that they do not have a stable magnetic moment; their magnetic moment fluctuates due to thermal instability, but can be stabilized by static ambient magnetic fields like the geomagnetic field. Particles of an intermediate size of 40–120 nm form

so-called single domains (SD) and have a stable magnetic momentum; theoretically, they could align themselves along the magnetic field lines like minute compass needles. Larger particles above 120 nm become multi-domain and have no pronounced net magnetic moment, because the moments of the various domains largely cancel each other.

Considerations on ►magnetite-based magnetoreception usually favored single domains, and several models have been suggested how single domains could mediate magnetic information. E.g., attached to hair cells or specialized membranes, they would be able to transduce the magnetic torque to mechanical torque and thus act as a compass. By magnetic remanence measurements, single domain particles were indicated in the tissues of numerous animals (see [7]). In vertebrates, magnetite was found in the nasal and orbital region, a region which is innervated by the ophthalmic branch of the *nervus trigeminus*, from which electrophysiological responses to magnetic stimulation involving changes in intensity were recorded. Structures that may be candidates for a ►magnetite-based magnetoreceptor based on single domains have been described for fish (e.g. [8]). In the upper beak of homing pigeons a structure has been identified which contains clusters of superparamagnetic magnetite; it may serve as modified pressure receptor measuring magnetic intensity [9].

The radical-pair hypothesis postulates magnetoreception by specialized photopigments. By photon absorption, molecules are raised to the excited singlet state, where some of them undergo a transition into the excited triplet state. The probability to reach the triplet state, and with it, the triplet yield, depends on the alignment of the photopigments with respect to the magnetic field lines. In the spherical or hemispherical structure, the triplet yield would form a specific pattern that was centrally symmetric to the axis of the field lines, thus forming a ►chemical compass. By comparing the triplet yield in the various spatial directions, animals could obtain information on the direction of the magnetic field [10]. Because of their biochemical properties, cryptochromes are discussed as possible candidates for the photopigments underlying these processes. The radical-pair model is indirectly supported by behavioral findings indicating that the magnetic compass of salamanders and birds is ►light-dependent: short-wavelength monochromatic light allows normal orientation, whereas the use of long-wavelength light abolishes orientation behavior [11]. The recent observation that the magnetic compass of birds can be disrupted by high-frequency magnetic fields points directly to a radical-pair process underlying magnetoreception [12].

In salamanders, the receptors mediating compass information appear to be situated in the pineal, the ancestral "third eye" of vertebrates [13]. In birds, too, magnetosensitive cells have been found in the pineal; however, in two species of passerine birds, magnetoreception was shown to occur almost exclusively in the right eye [14]. Since the optic nerves of birds cross over almost completely, this means that magnetic information is processed predominantly in the left hemisphere of the brain. The tectofugal part of the visual system shows a marked anatomical lateralization, with the relevant pathways in the left hemisphere more pronounced than in the right [15] which might also be associated with processing magnetic compass information. Electrophysiological recordings from the *tectum opticum* and the nucleus of the basal optic root (nBor), a nucleus belonging to the tectofugal system, revealed units that were stimulated by changing the direction of the ambient magnetic field [16].

Altogether, the available findings on magnetoreception suggest a variety of mechanisms based on different principles. It seems plausible to assume that the magnetic compass and the magnetic part of the "map" require different types of magnetoreceptors, because they utilize different physical features of the magnetic field. This asks for different primary processes and different ways of neuronal processing. So far, evidence from birds suggests that a ►radical-pair mechanism in the right eye provides compass information, whereas magnetite-based receptors associated with the trigeminal system provides intensity information for the "map." A radical-pair mechanism is also discussed for the compass of salamanders, but what kind of mechanisms other animals might use is not yet known.

Electric Senses

In contrast to the geomagnetic field, the electric field of the earth is highly variable. Its variability is caused by differences in the activity of thunderstorms and related phenomena, and the ►field intensity depends on many factors like air humidity, temperature and conductivity of the surface. The polarity of the electric field is directed vertically downward. In view of this, it is hard to see how the electric field could provide information that is useful to animals. Yet a number of animals were found to be electroreceptive. Only in the past 50 years, peculiar structures (sensory pores) in the skin of some aquatic vertebrates that had been known for a long time were identified as electroreceptor organs (see entry "Electroreceptor organ"). Such electroreceptor organs are found in all groups of lower aquatic vertebrates and in certain amphibians, while they are lacking in most of the modern fish (such as the Teleostei within the Neopterygii). In two, possibly three, not closely related lineages of Teleostei, they obviously reevolved independently, namely in the ►Mormyriformes from the Osteoglossomorph branch and the ►Siluriformes (catfish) and ►Gymnotiformes from the Neognath branch. Because of the insulating properties of air,

electroreceptor organs are generally lacking in terrestrial vertebrates such as reptiles, birds and mammals, the only exceptions being the ►Monotremata, the ►Echidna and the ►Platypus, where electroreceptor organs have been recently described (see entry "►Electroreception and Electrolocation in the platypus and the echidna").

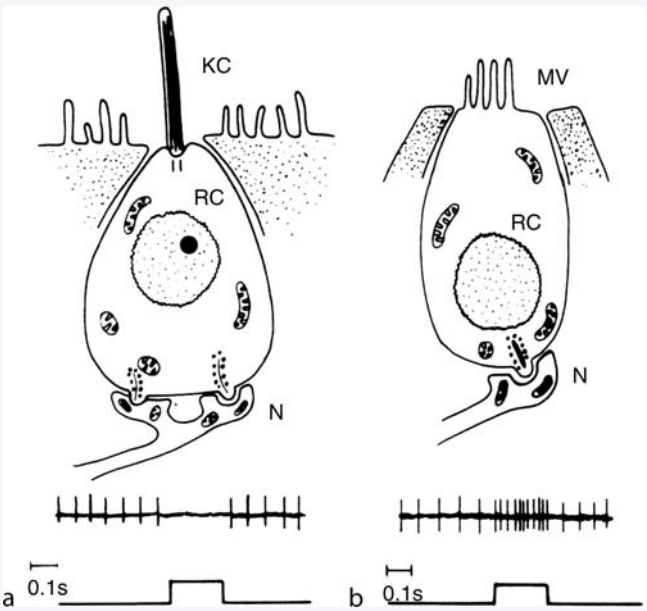
Electroreceptor organs are voltmeters; the receptor cells are modified hair cells and are part of the ►octavolateral sensory system that is responsible for hearing and the sense of equilibrium. Electroreceptor organs are contacted by sensory nerves only.

There are several types of electroreceptive organs. ►Ampullary electroreceptor organs are extremely sensitive to weak gradients of the electric field. The ampullae of Lorenzini of the marine elasmobranch fish have thresholds of about 5 nV/cm, the analogous "►ampullary" receptor organs of freshwater teleosts may reach 1–5 μV/cm maximum sensitivity. Reflecting their different origin, the structure of ampullary electroreceptor cells differs in the various groups: in non-teleosts, they bear a kinocilium, sometimes in addition to microvilli, whereas in electroreceptive teleosts, the secondarily evolved electroreceptor cells have only microvilli, but no kinocilium (Fig. 5).

The ampullary organs as a whole, as well as their teleost analogs, consist of a layer of receptor cells lining an ampulla which is embedded in the skin and connects to the outside by a canal. In marine fish, this canal is long, in fresh-water fish, it is short. The adequate stimulus is the voltage difference between the inside of the skin and the surface of the fish. The lumen of the ampulla and of the canal connecting to the surface is filled with a highly conductive jelly so that the electric potential at the lumenal surface of the receptor cells is almost identical with that on the outside of the skin. Because of the relatively high conductivity of the skin of marine fish, their ampullary canals must be longer than those of freshwater fish to achieve similar sensitivity. Also, whereas the ampullary organs of the ancestral forms of vertebrates are stimulated by negative voltages on the outer skin, those of teleosts are stimulated by positive voltages.

Animals with ampullary organs make use of their high sensitivity to detect minute changes in the ambient electric field, thereby locating prey by detecting the normal electric activity of living organisms, like prey buried in sand or active at night. The detection of electric fields that are produced by other organisms rather than the animal itself is called ►passive electrolocation. Orientation responses along local electric fields, even magnetoreception based on the voltage induced by moving in various directions with respect to the geomagnetic field have been described (see above).

Most ►Electrogenic fishes are not only sensitive to ambient electric fields, but also generate their own



Magnetic and Electric Senses. Figure 5 Ampullary electroreceptor cells (*RC*) of nonteleosts (a) bear an apical kinocilium (*KC*), sometimes in addition to microvilli (*MV*), whereas electroreceptive teleosts (b) have only microvilli and no kinocilium. The spontaneously active, afferent nerve fibers (*N*) increase their firing rate when the electrical stimulus (in this case a square-wave pulse of 200 ms) is positive outside the ampulla in teleosts, while in nonteleosts a negative stimulus is required for a similar response (from [36] modified).

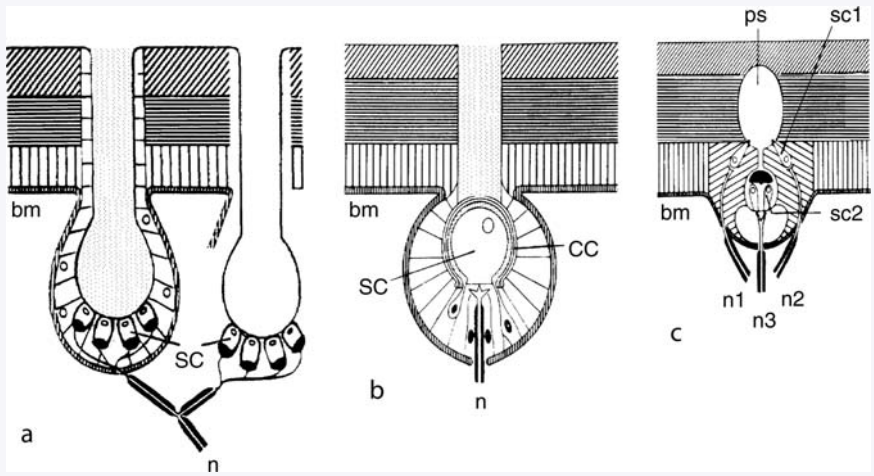
electric fields by specialized ►electric organs (see entry "Electric fish"). Any living tissue generates ►electric fields of low intensity by maintaining the ionic balance of its cells, and by field potentials from nerve and muscle activity; these fields' strength ranges from 0.5 mV to several mV (as measured between the body and a distant electrode). Electrogenic fish, however, possess electric organs consisting of orderly arranged, closely packed groups of modified muscle cells (nerve endings in one taxon). These fishes can discharge their electric organs in a controlled way; thereby producing electric fields ranging from a few mV up to 500 V. Electrogenic fish are found among both cartilaginous and bony fishes; prominent examples for species producing strong electric fields are the electric rays (genus *Torpedo*) and the electric eel (*Electrophorus electricus*).

The rhythmic discharge of electric organs (►EOD) generates species-characteristic electric signals that are highly stereotyped (see entry "►Electric organ discharge"). Among the teleosts, both gymnotiform and mormyriform fish have a second type of electrosensitive receptor organ besides the ampullary organs, namely ►tuberous electroreceptor organs. These receptor organs are specifically tuned to the frequency spectrum (15–20,000 Hz, depending on the species) generated by the discharge of their own electric organ.

The ►tuberous electroreceptor organs occur in two types: one acts as ►time marker unit of high sensitivity and short and constant latency, whereas the other type acts as ►amplitude coder that is relatively insensitive in absolute terms, but encodes minute changes in the intensity of the fishes' own electric organ discharges. Like ampullary receptor organs, ►tuberous receptor organs are located in the skin and form part of the ►lateral line system whose afferences project to the ►electrosensory lobe of the lateral line (ELL). With these tuberous electroreceptor organs, the fish detects impedance inhomogeneities in its environment by recording the associated modulations of their electric organ discharges in amplitude and phase. Thus, these fishes are capable of active electrolocation. Probably the predominant function of producing and perceiving electric fields is ►electrocommunication. With their electric organs, fishes produce signals either of the pulse- or the wave type that can be perceived and decoded by their neighbors (see entry "Electrocommunication and Electrolocation").

The tuberous electroreceptor organs of the African Mormyridae are the ►knollenorgane and the ►mormyromasts (Fig. 6).

Knollenorgane fire one action-potential per EOD pulse. As the mormyrid fish brain blanks the reafferences from self-generated electric organ discharges, only the pulses from other fish gain access to the higher centers of the brain. Knollenorgane thus serve electrocommunication. The second type of tuberous electroreceptor organ, the mormyromasts, has a higher threshold and therefore responds primarily to the fish's own EODs (those of other fish being centrally blanked); they appear to be primarily responsible for active electrolocation. Mormyromasts comprise two kinds of electroreceptor cell that are innervated separately. Mormyromasts are capable of coding for both resistive



Magnetic and Electric Senses. Figure 6 Schematic electroreceptor organs in freshwater teleosts, located in invaginations (or ampullae) of the epidermis. (a) Small pit organ, the teleost equivalent of the ampullary electroreceptor organ of similar structure that is common to all classes of lower aquatic vertebrates (but lacking in neopterygians, including teleosts). (b) Knollenorgan, one kind of tuberous electroreceptor organ present in mormyrid fish. (c) Mormyromast, the other kind of tuberous electroreceptor organ in mormyrid fish [33].

and capacitive loads associated with nearby objects, and fish can discriminate between live and dead material by their difference in capacitive impedance.

The central-nervous processing of information from the various types of electric organ takes place in different structures of the brain; e.g., the input from mormyromasts and knollenorgane, involving active electrolocation and ►communication, are processed separately. In gymnotiform fishes, many of which generate discharges of the wave type, electrosensory reafferences are encoding time (phase) and amplitude (of the wave discharge envelope) by different receptor organs whose afferences are processed separately by different parts of the brain, analogous to the hearing system of other vertebrates. This separate neuronal processing of phase- and amplitude information is thought by one theory (theory I) to be important for the so-called "►jamming avoidance response" (JAR) that was mainly studied in the gymnotiform wave fish *Eigenmannia virescens.* A fish will tend to shift its own discharge frequency away from a stimulus too close in frequency such that the two signals beat against each other faster, in an attempt to restore its active electrolocation performance (according to theory I; see entry ►Temporal coding in electroreception). By contrast, theory II stresses that the jamming avoidance behavior has long been shown to be sexually dimorphic and to differ between juveniles and adults, and envisions its sensory mechanism and functional adaptation to be radically different (for aspects of theory II, see also entry ►Electric communication and electrolocation). For example, incompatible with theory I is the observation that the JAR threshold is identical to stimulus detection threshold, that is, it is defined by the more sensitive ►T receptor organs. Consequently, phase (timing) information (that is coded for by the ►T receptor organs) has been found to be both necessary and sufficient for evoking and guiding the JAR, and information on amplitude modulation of the beat envelope from the rather insensitive P receptor organs is not available in the threshold range and well above (as would be required by theory I, but not theory II; P receptor organs or probability coders report the amplitude modulation of the EOD by a stimulus of similar frequency only at sufficiently strong modulation depth, that is, sufficiently strong stimulus/EOD intensity ratios). Furthermore, the JAR may be evoked by a stimulus of exactly the fish's own frequency (that is, the frequency difference equals 0 Hz), even when maintained dynamically constant by a frequency clamp; an observation theory I cannot explain but which does not present a problem for theory II. According to theory II, by purely temporal analysis of beat features, the zero-crossings times of the individual oscillations within a beat wave that are reported by T receptor organs, the fish extracts (i) the strength of the stimulus signal harmonic closest to its own fundamental discharge frequency (only that stimulus harmonic is driving the JAR), (ii) the frequency difference and its sign, (iii) the waveform of the stimulus signal. The JAR is thought by theory I to support active electrolocation in the presence of "jamming" conspecifics in the near field (the reach of active electrolocation is limited to a few cm). Theory II, however, has demonstrated that the JAR supports electrocommunication and the detection of EOD waveforms generated by neighbors from a much greater distance (far field sensitivity). This discussion exemplifies the dual nature of the electric system that is adapted for both functions.

References

1. Wiltschko R, Wiltschko W (1995) Magnetic orientation in animals. Springer, Berlin Heidelberg New York
2. Weindler P, Wiltschko R, Wiltschko W (1996) Magnetic information affects the stellar orientation of young bird migrants. Nature 383:158–160
3. Quinn TP (1982) Intra-specific difference in Sockeye Salmon fry compass orientation mechanisms. In: Brannon EL, Salo EO (eds) Proceedings of the Salmon and Trout Migratory Behavior Symposium, University of Washington, Seattle, pp 79–85
4. Pardi L, Ugolini A, Faqi AS, Scapini F, Ercolini A (1988) Zonal recovering in equatorial sandhoppers: interaction between magnetic and solar orientation. In: Chelazzi G, Vannini M (eds) Behavioral adaption to intertidal life. Proceedings of the NATO Science, Plenum, New York London, pp 79–92
5. Kimchi T, Etienne AS, Terkel T (2004) A subterranean mammal uses the magnetic compass for path integration. Proc Nat Acad Sci USA 101:1105–1109
6. Mann S, Sparks NHC, Board RG (1990) Magnetotactic bacteria: microbiology, biomineralization, palaeomagnetism and biotechnology. Adv Microb Physiol 31:125–181
7. Kirschvink JL, Jones DS, MacFadden BJ (1985) Magnetite biomineralization and magnetoreception in organisms. Plenum, New York
8. Walker MM, Diebel CE, Haugh CV, Pankhurst PM, Montgomery JC, Green CR (1997) Structure and function of the vertebrate magnetic sense. Nature 390:371–376
9. Fleissner G, Holtkamp-Rötzler E, Hanzlik M, Winklhofer M, Fleissner G, Petersen N, Wiltschko W (2003) Ultrastructural analysis of a putative magnetoreceptor in the beak of homing pigeons. J Comp Neurol 458:350–360
10. Ritz T, Adem S, Schulten K (2000) A model for vision-based magnetoreception in birds. Biophys J 78:707–718
11. Wiltschko W, Wiltschko R (2002) Magnetic compass orientation in birds and its physiological basis. Naturwissenschaften 89:445–452
12. Ritz T, Thalau P, Phillips J, Wiltschko R, Wiltschko W (2004) Avian magnetic compass: resonance effects indicate a radical pair mechanism. Nature 429:177–180
13. Deutschlander, ME, Borland SC, Phillips JB (1999) Extraocular magnetic compass in newts. Nature 400:324–325

14. Wiltschko W, Munro U, Wiltschko R, Kirschvink J (2002) Magnetite-based magnetoreception in birds: the effect of a biasing field and a pulse on migratory behavior. J Exp Biol 205:3031–3037
15. Güntürkin O (1997) Morphological asymmetries of the tectum opticum in the pigeon. Exp Brain Res 116:561–566
16. Semm P, Nohr D, Demaine C, Wiltschko W (1984) Neural basis of the magnetic compass: interaction of visual, magnetic and vestibular inputs in the pigeon's brain. J Comp Physiol 155:283–288
17. Markowski B, Baier B, Kramer B (2007) Differentiation in electrical pulse waveforms in a pair of sibling dwarf stonebashers, *Pollimyrus castelnaui* and *P. marianne*: possible mechanisms and functions (Mormyridae, Teleostei). Behaviour 145:115–135
18. Bennett MVL (1971) Electroreception. In: Hoar WS, Randall DJ (eds) Fish physiology, vol V. Academic, London New York, pp 493–574
19. Boles LC, Lohmann KJ (2003) True navigation and magnetic map in spiny lobsters. Nature 421:60–63
20. Bullock TH, Hopkins CD, Popper AN, Fay RR (eds) (2005) Electroreception. Springer, Berlin Heidelberg New York
21. Heiligenberg W (1991) Neural nets in electric fish. MIT, Cambridge, Mass.
22. Hopkins CD (1999) Signal evolution in electric communication. In: Hauser MD, Konishi M (eds) Design of animal communication. MIT, Cambridge, Mass., pp 461–491
23. Kramer B (1990) Electrocommunication in teleost fishes: behavior and experiments. Springer, Berlin Heidelberg New York
24. Kramer B (1996) Electroreception and communication in fishes. Gustav Fischer Verlag, Stuttgart, Jena, Lübeck, Ulm
25. Kramer B (1999) Waveform discrimination, phase sensitivity and jamming avoidance in a wave-type electric fish. J Exp Biol 202:1387–1398
26. Ladich F, Collin SP, Moller P, Kapoor BG (eds) (2006) Communication in fishes. Science, Enfield, New Hampshire, USA
27. Lissmann HW (1958) On the function and evolution of electric organs in fish. J Exp Biol 35:156–191
28. Meek J, Grant K, Bell C (1999) Structural organization of the mormyrid electrosensory lateral line lobe. J Exp Biol 202:1291–1300
29. Moller P (1995) Electric fishes: History and behavior. Chapman & Hall, London
30. Peters RC (1993) Orientation in catfish and dogfish. Orientation and navigation. The Royal Institute of Navigation, Oxford, pp 33–43
31. Scheich H (1977) Neural basis of communication in the high frequency electric fish, *Eigenmannia virescens* (jamming avoidance response). I. Open loop experiments and the time domain concept of signal analysis. II. Jammed electroreceptor neurons in the lateral line nerve. III. Central integration in the sensory pathway and control of the pacemaker. J Comp Physiol A 113:181–255
32. Stoddard PK, Zakon HH, Markham M, McAnelly L (2006) Regulation and modulation of electric waveforms in gymnotiform electric fish. J Comp Physiol A 192:613–624
33. Szabo T (1974) Anatomy of the specialized lateral line organs of electroreception. In: Fessard A (ed) Handbook of sensory physiology, vol III/3. Springer, Berlin Heidelberg New York, pp 13–58
34. von der Emde G, Schwarz S (2001) How the electric fish brain controls the production and analysis of electric signals during active electrolocation. Zoology 103:112–124
35. Wiltschko W, Wiltschko R (1999) The effect of yellow and blue light on magnetic orientation in European robins, *Erithacus rubecula*. J Comp Physiol A 184:295–299
36. Bullock TH, Heiligenberg W (eds) (1986) Electroreception. John wiley, New york
37. Martin H, Lindauer M (1977) der EinfluB des Erdmagnetfeldes auf die schwereorientierung der Honigbiene (Apis mellifica). J Comp Physiol 122:145–187

Magnetic Bacteria

Michael Winklhofer
Department für Geo- und Umweltwissenschaften – Sektion Geophysik, Ludwig-Maximilians-Universität Munich, Munich, Germany

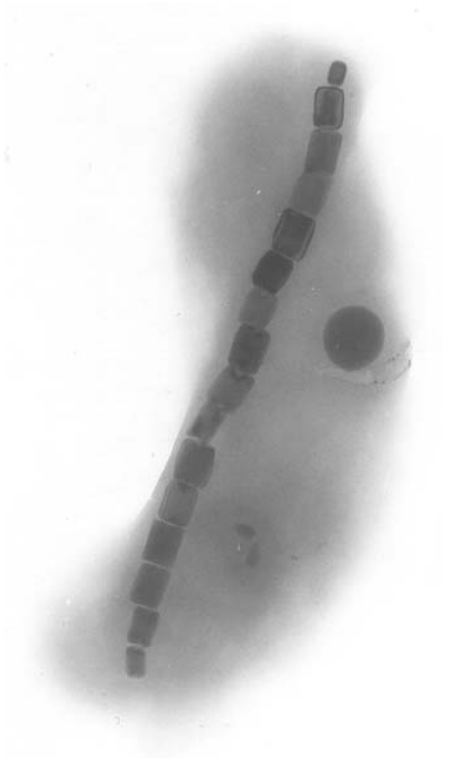
Synonyms

Magnetotactic bacteria

Definition

Magnetic bacteria are a morphologically and phylogenetically diverse group of motile Gram-negative prokaryotes. Their common feature is intra-cellular ►ferrimagnetic crystals, made of ►magnetite (Fe_3O_4) or ►greigite (Fe_3S_4), called magnetosomes. Rather than being ingested from food, magnetosomes are synthesized within the cell and are most often arranged in a single chain or two chains, apparently fixed within the cell (Fig. 1).

A chain of magnetosomes carries a permanent ►magnetic moment and thus acts as an internal compass needle, rotating the cell into alignment with the geomagnetic field axis. Due to this magnetic torque, magnetic bacteria are constrained to move along magnetic field lines when swimming. They are actively motile rather than being pulled or pushed by the magnetic field. Magnetic bacteria can move both parallel and antiparallel to the magnetic field, corresponding to downward (north seeking) and upward (south seeking) motions in the ►geomagnetic field, which has inclined lines of forces except at the magnetic equator, where field lines are horizontal. Their magnetically enforced one-dimensional locomotion, makes magnetic bacteria highly



Magnetic Bacteria. Figure 1 Wildtype magnetic vibroid bacterium. The cell contains a linear chain of magnetite crystals, so-called magnetosomes. The chain length is 2 μm, the average length of the magnetosomes is 120 nm. Note that the magnetite crystals at the ends of the chain are smaller than average and therefore may represent nascent crystals. Courtesy of M. Hanzlik.

efficient at migrating to suitable chemical conditions in a vertically stratified water column or sediment, and so gives magnetic bacteria an advantage over their nonmagnetic counterparts that pursue purely chemotactic strategies such as run-and-tumble. The behaviour of magnetic bacteria is often referred to as ►magnetotaxis, which is misleading by implying motion as a *reflex* action to a magnetic field, and ignoring the fact that magnetic orientation in magnetic bacteria is a passive process. Stimuli to which magnetic bacteria react instead are high or low concentrations of free oxygen. It is therefore more appropriate to speak of magnetically assisted ►aerotaxis.

Characteristics

Magnetic bacteria, discovered by Salvatore Bellini in the late 1950s, are widespread in both marine and freshwater habitats (see [1] for a review), and have even been identified in soils. They usually occur at zones where the gradients of oxygen or sulphide concentration are steepest, be it in the topmost few centimetres of lake sediments or deep-sea sediments, or be it at the oxic-anoxic-transition-zone (OATZ) within a chemically stratified water column as encountered in poorly ventilated marine environments.

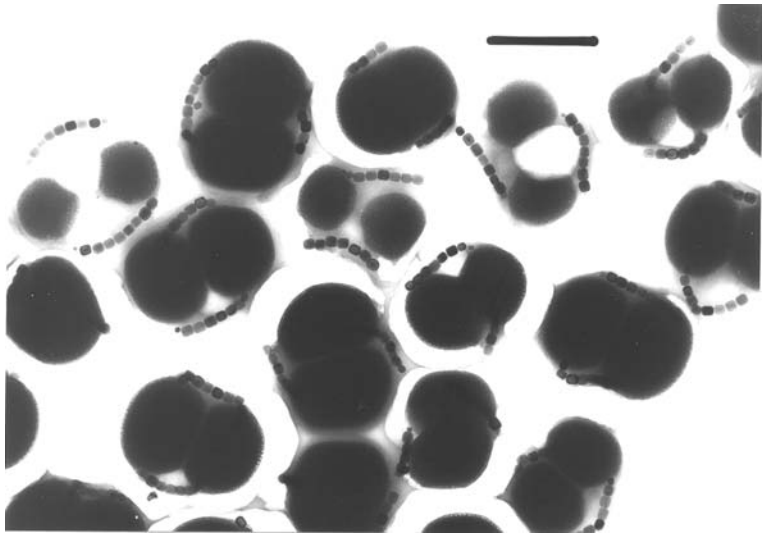
Behaviour

The behaviour of magnetic bacteria from sedimentary habitats has not been accessible to *in situ* observations, and has had to be inferred from *in vitro* experiments under the light microscope. The easiest way to study magnetic bacteria is to place a wet sediment sample on a microscope slide and apply a horizontal magnetic field. Magnetic bacteria then swim out of the sediment and eventually collect at the edge of the sample. The swimming speed varies from one species to another, with magnetic coccoid cells (Fig. 2) being the fastest swimmers (around 100 mm/s). In samples taken from the northern hemisphere, the predominant swimming direction is towards the magnetic North Pole, in samples from the southern hemisphere, movement is towards the magnetic South Pole.

At the geomagnetic equator, where the magnetic field is horizontal, equal numbers of both polarities exist. Despite the hemispherical bias, a small percentage of magnetic bacteria can always be found that swim opposite to the prevailing direction.

The swimming behaviour observed under the light microscope was extrapolated to the natural environment, such that magnetic bacteria tend to swim downward along the downward- and upward-inclined geomagnetic field lines in the northern and southern hemisphere, respectively. This way, displaced magnetic bacteria (by bioturbation, wave action, etc.) are guided back into the sediment by persistently swimming downward until they reach their preferential position in the sediment. Such a unidirectional motility is usually referred to as magnetotaxis.

Other tactic responses may, however, override magnetotaxis. In particular, the notion of magnetotaxis needs to be revised when considering magnetic bacteria from aquatic habitats where the OATZ occurs within the water column. The vertical position of the OATZ in the water column may change seasonally, and magnetic bacteria have to migrate accordingly. To maintain position at the OATZ, magnetic bacteria must be capable of reversing their swimming direction once they have reached the border of their preferred chemical zone. Experimental evidence exists that bi-directional motility is coupled with an oxygen gradient: Spormann and Wolfe [2] observed the formation of a distinct band of actively motile cells (magnetic ►spirillum), with individual cells swimming back and forth within the band, parallel and antiparallel to the magnetic field B. It therefore depends on the oxygen concentration $[O_2]$ if cells swim parallel or antiparallel to B. The observed band was arc-shaped, roughly 60 mm across (cell length ~ 2 mm), and formed at a distance of ~100 mm from an air bubble trapped under the cover slide. The edge of the band nearer to the

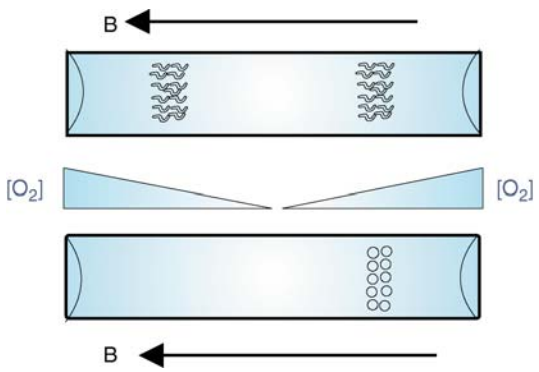


Magnetic Bacteria. Figure 2 Cells of a wildtype magnetic ►coccus, the most abundant type of magnetic bacterium. A cell usually contains two linear chains of magnetosomes, lying at opposite sides within the cell. Cells have typical diameters of 1.5 µm. The average magnetosome dimensions are 100 nm by 80 nm. The dark globules are inclusions rich in phosphorous and sulphur. Courtesy of M. Hanzlik.

air bubble was more sharply demarcated than the far edge, implying that the tolerance of all cells reach an upper limit for tolerance of oxygen but individually varying lower limits. The role of the magnetic field here is to assist active aerotaxis. This behaviour, therefore, was later referred to as magnetically assisted aerotaxis, or briefly, ►magneto-aerotaxis [3].

A similar experiment by Frankel and co-workers [3] resulted in a further distinction between axial and polar aerotaxis and is summarized in Fig. 3.

In their standard essay, a magnetic field B is directed along a capillary tube, into which oxygen diffuses from the open ends, thereby building up an oxygen-concentration [O_2] gradient from the centre of the tube towards each end. While magnetic spirilla form aerotactic bands at both ends (axial magneto-aerotaxis), magnetic cocci from the northern hemisphere form only one band, located at that end of the tube where the [O_2] gradient is opposite to B (polar magneto-aerotaxis). While the band of spirilla remain intact after reversal of B, the band of cocci disperses. The reversed-field condition appears to impair their sensing mechanism for aerotaxis, which under normal field conditions triggers reversal in swimming direction.



Magnetic Bacteria. Figure 3 Axial (*top*) and polar (*bottom*) magneto-aerotaxis. *Top*: Formation of aerotactic bands by spirilla is symmetrical and maps the two microoxic zones in the tube. *Bottom*: Band formation by cocci occurs only in that microoxic zone where the magnetic field direction is opposite to the oxygen-concentration [O_2] gradient (after ref. [3]).

Behaviour and Ecology

The large majority of naturally occurring magnetic bacteria display polar magnetotaxis, with the advantage being that an oxygen gradient is not necessary for efficient orientation in the ►anoxic zone, thereby enabling a rapid return of the cell over large distances to the preferred ►microoxic conditions, without wasting energy by constant movement along gradients [4]. On the other hand, if greater than optimal oxygen concentrations are encountered, the cells - then in an "oxidized state" - will display the typical down-seeking response. Reversing the swimming direction can be accomplished by switching the rotational sense of the flagella. That the sense of flagellar rotation can be

regulated by an oxygen sensory system has been observed in other aerotactic bacteria.

By analogy with sulphide-oxidizing bacteria, it was suggested that magnetic bacteria perform excursions to the anoxic zones of their habitat in order to accumulate reduced sulphur compounds as an electron donor [4]. The bacteria, then in a "reduced state," would again reverse their swimming direction and move up to the microoxic zone where oxygen is available to them as an electron acceptor. In fact, many magnetic bacteria contain inclusions of sulphide (Fig. 2).

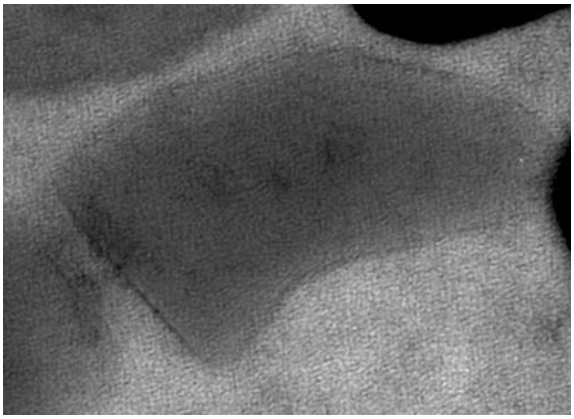
Magnetosomes

The grain-size and crystal habits of magnetosomes as well as their arrangement within the cell may vary remarkably among the different morphological types of bacteria. Cells from a given strain, however, show little variation in crystal size, habit, and arrangement of chains. This implies that biomineralization of magnetosomes is genetically controlled. The biochemical details of magnetosome synthesis, however, remain elusive. It has been suggested that their biomineralization occurs in membrane vesicles [5], because magnetosomes in many species are enveloped by a bilayer membrane consisting of phospholipids and proteins, at least several of which appear to be unique to this membrane [6]. A vesicle would not only provide chemically stable conditions for magnetosome growth, but could also explain why magnetosomes do not grow above a certain maximum size. On the other hand, the hook-shaped magnetosomes of *Magnetobacterium bavaricum* (Inset in Fig. 4) do not appear to be surrounded by a membrane, and it is possible that magnetite crystals start growing from some template. From growth experiments monitored with Moessbauer spectroscopy [5], it was recently concluded that magentite precipitates directly in empty magnetosome vesciles. This is in contrast to greigite-producing magnetic bacteria, in which a series of non-magnetic phases of approximately FeS composition has been identified as crystalline precursors to ferrimagnetic greigite [7].

Evolutionary Aspects

Interestingly, magnetite and greigite are the strongest ferrimagnetics of all the naturally occurring iron oxides and iron sulphides, respectively, and it is only these two phases that have consistently been identified in magnetic bacteria. Magnetotaxis obviously gives magnetic bacteria an edge over their nonmagnetic counterparts. If it were only for iron metabolism, there would be no need for the cells to sequester excess iron in a ferromagnetic form.

Not only are magnetosomes made of strong ferrimagnetics, they also appear to be magnetically optimised for the purpose of magnetotaxis: they are magnetic single domains (SD), that is, the magnetization within each magnetosome is uniform and so the magnetic moment of the particle assumes the maximum value attainable. Thus, the available magnetic material is used in the most efficient way.



Magnetic Bacteria. Figure 4 Magnetobacterium bavaricum. A cell may contain up to a thousand magnetite crystals, which are arranged in several rope-shaped bundles of chains. Inset: The hook-shaped magnetosomes are characteristic of this unusual type of magnetic bacterium. The average magnetosome dimensions are 100 nm by 40 nm. A dark layer at the crystal base may represent a template from which the magnetite crystal may have nucleated. Courtesy of M. Hanzlik.

Magnetic bacteria achieve this magnetic optimisation by limiting the grain size of magnetosomes to values below ~150 nm, while it usually ranges between 40 nm and 120 nm. Above ~ 150 nm, non-uniform magnetization structures develop in magnetite crystals, resulting in lower magnetic moments. This means that magnetic material would be "wasted" by growing magnetosomes much larger than ~ 150 nm. If on the other hand the grain size were below some 30 nm, the particles would be in a ▶superparamagnetic (SP) state and could not carry a stable magnetic moment because of thermal fluctuations constantly buffeting the magnetization, leading to frequent spontaneous magnetization reversals within the particle. A magnetosome chain grows as new magnetosomes are synthesized at either end (see Fig. 1). A newly forming magnetosome has to go through the SP stage (provided that it has already transformed into a ferrimagnetic from the non-magnetic precursory phase), but grows in the magnetic stray field produced by the adjacent, mature magnetosome. As it grows further and eventually crosses the SP-SD threshold size (roughly 30 nm), its magnetization becomes locked in, and so has the same magnetic polarity as the mature magnetosome. By growing

this way, a magnetosome chain will always consist of individual magnetic dipoles pointing in the same direction. That the particles in a chain are all polarized in the same direction has been directly imaged by means of transmission electron holography [8]. In addition to the optimal grain-size range for magnetosomes, there is also a theoretical optimum for the number of magnetosomes per cell: Between 10 and 20 magnetosomes, with a typical grain size of 50 nm, are sufficient to constitute a permanent magnetic dipole strong enough to keep the cells aligned with the comparatively weak geomagnetic field. With the exception of the unusual *M. bavaricum*, which contains up to a thousand magnetosomes per cell (Fig. 4), this optimum is achieved in most types of magnetic bacteria. It is therefore fair to say that magnetic bacteria have evolved their peculiar traits under the influence of the Earth's magnetic field, which prompts the question of how magnetic bacteria adapt to periods of low geomagnetic field strength. In periods of reduced field strength, magnetic bacteria that produce more magnetosomes or grow larger magnetosomes than normal have an advantage. At present, such a scenario is to some extent realized in Rio de Janeiro, Brazil, where the field strength is anomalously low (0.25 G): The magnetosomes in one morphological type of bacterium had average dimensions of 120 nm in length and 110 nm in width, a volume nearly ten times greater than average [9]. Other bacteria from the same region, however, had rather averagely sized magnetosomes in usual numbers per cell. The field strength is obviously not low enough to cause a selection of magnetic bacteria with stronger magnetic moments. If, on the other hand, sediment samples that initially contained magnetic bacteria are kept in a *zero* magnetic field, the population of magnetic bacteria appears to decline rapidly, but it is not known whether magnetic bacteria become extinct or just stop producing magnetosomes, or whether non-magnetic mutants take over. Similar experiments with Northern-hemisphere sediments incubated in *reversed-field* conditions yielded an initial decrease in the population density of magnetic bacteria. With increasing duration of the experiment, South-seeking bacteria emerged in greater numbers and eventually supplanted North-seeking bacteria [10]. Thus, in the case of a geomagnetic field polarity reversal, the few cells in a natural population that have wrong polarity, (such as due to a malfunction in cell division) can take over and guarantee the survival of the species. That applies to polarily magnetoaerotactic bacteria, whereas "two-way swimmers" (axial magnetoaerotaxis) should remain unaffected. However, detailed paleomagnetic records and numerical geodynamo simulations strongly suggest that there is more to a geomagnetic polarity transition than a mere polarity flip. The global change in polarity is often foreshadowed by large directional variations and a period of decreasing field strength down to values of 10% of present-day values or even less, which may last thousands of years. The fossil magnetosome record in sediments analysed thus far is too scarce to clearly monitor adaptation of magnetic bacteria or evolutionary changes. Research is further complicated by the fact that bacterial magnetite, because of the small particle size, is prone to dissolve under increasingly reducing pore-water conditions with increasing burial.

References

1. Bazylinski DA, Frankel RB (2004) Magnetosome formation in prokaryotes. Nat Rev Microbiol 2:217–230
2. Spormann AM (1987) Unusual swimming behaviour of a magnetotactic bacterium. FEMS Microbiol Ecol 45:37–45
3. Frankel RB, Bazylinksi DA, Johnson MS, Taylor BL (1997) Magneto-aerotaxis in marine coccid bacteria. Biophys J 73:994–1000
4. Spring S, Bazylinski DA (2000) Magnetotactic bacteria. In: Dworkin M et al. (eds) *The prokaryotes*: an evolving electronic database for the microbiological community, 3rd edn. (release 3.4). Springer, Berlin Heidelberg New York, [www.prokaryotes.com], (released 10. Sep. 2001)
5. Faivre D, Böttger LH, Matzanke BF, Schüler D (2007) Angew Chem Int Edn 46:8495–8499
6. Jogler C, Schüler D (2007) Genetic Analysis of Magnetosome Biomineralization. In: Schüler D, Magnetoreception and Magnetosomes in Bacteria, 133–161, Springer, Berlin
7. Pósfai M, Buseck PR, Bazylinski DA, Frankel RB (1998) Reaction sequence of iron sulfide minerals in bacteria and their use as biomarkers. Science 280:880–883
8. Dunin-Borkowski RE, McCartney MR, Frankel RB, Bazylinski DA, Pósfai M, Buseck PR (1998) Magnetic microstructure of magnetotactic bacteria by electron holography. Science 282:1868–1870
9. Farina M, Kacharo B, Lins U, Broderick R. de Barros HL (1994) The observation of large magnetite (Fe3O4) crystals from magnetotactic bacteria by electron and atomic force microscopy. J Microsc 173:1–8
10. Blakemore RP (1982) Magnetotactic bacteria. Annu Rev Microbiol 36:217–238

Magnetic Compass

Definition

An animal with a magnetic compass has an ability to maintain a heading relative to the Earth's magnetic field (such as a course toward the north or the south).

►Magnetic Map

Magnetic Displacement Experiments

Definition

Experiments in which animals are subjected to the magnetic fields that exist in distant geographic areas, with a view toward determining if the animals possess a magnetic map.

►Magnetic Map

Magnetic Field Inclination

Definition

The angle formed between the field lines and the surface of the Earth, also known as dip angle.

►Magnetic Map

Magnetic Map

Kenneth J. Lohmann,
Catherine M. F. Lohmann
Department of Biology, University of North Carolina, Chapel Hill, NC, USA

Synonyms

Geomagnetic map; Geomagnetic positioning system; Magnetic positioning system; Magnetic position-finding

Definition

A convenient, shorthand term used to indicate that an animal has the ability to derive positional (as opposed to directional) information from the Earth's magnetic field. The term is now increasingly used in a broad and metaphorical way.

Characteristics

The Earth's magnetic field provides animals with two potential types of information. The simplest of these is directional or compass information, which enables an animal to maintain a consistent heading in a particular direction such as north or south. Magnetic compasses are phylogenetically widespread and exist in several invertebrate groups, as well as in all major groups of vertebrate animals.

Alone, a compass is often insufficient to guide an animal to a specific destination or to steer it reliably along a long and complex migratory route. For example, a sea turtle migrating through the ocean towards a distant target can be swept off course by currents, and a migratory bird's heading can be altered by wind. Navigation can therefore be enhanced by an ability to determine geographic position along a desired pathway of travel or relative to a destination. For today's humans, this need is usually met through a global positioning system (GPS), which provides users with their geographic position and can also continuously compute the direction to a goal. For some migratory animals, positional information inherent in the Earth's magnetic field provides a similar, although considerably less precise, way of assessing geographic location. Animals that can derive positional information from the Earth's field (as opposed to directional information) are often said to have a ►magnetic map.

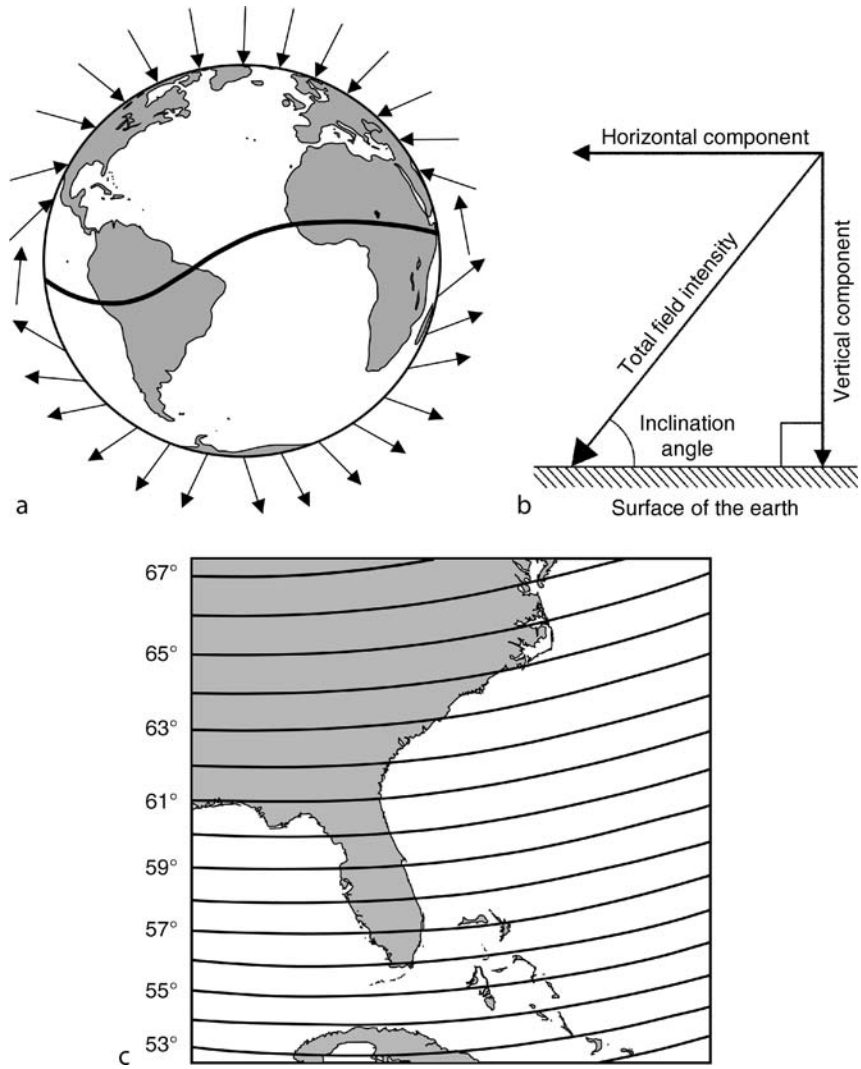
It is important to recognize that the term magnetic map is now increasingly used in a broad and metaphorical way [1,2]. The term does not imply that an animal necessarily has a detailed mental representation in its head equivalent to a human roadmap or high-resolution topographic map. Instead, the information in a magnetic map may be minimal and very general [1]. For example, it might simply tell the animal that it is approximately north or south of the area where it lives (possibly without encoding distance), or that the animal has arrived at a point in a migratory route where it should orient westward. Moreover, information from a magnetic map is often used in combination with other sensory information.

Positional Information in the Earth'S Magnetic Field

Several geomagnetic elements vary in a predictable way across the surface of the globe and might hypothetically be used in position-finding [3]. For example, at each location on the earth, the magnetic field lines intersect the earth's field at a specific angle of inclination (Fig. 1).

At the magnetic equator, the field lines are essentially parallel to the Earth's surface and the inclination angle is said to be 0°. The field lines become progressively steeper, however, as one moves toward the magnetic poles; at the poles themselves, the field lines are perpendicular to the Earth's surface. Thus, inclination angle varies predictably with latitude, and an animal able to detect this field element may be able to determine if it is north or south of a particular area.

In addition to inclination angle, at least three other magnetic field elements might hypothetically be used in assessing position. These include: (i) the intensity (strength) of the total field; (ii) the intensity of the horizontal field; (iii) the intensity of the vertical field.



Magnetic Map. Figure 1 (a) Diagrammatic representation of the Earth's magnetic field illustrating how field lines (represented by *arrows*) intersect the Earth's surface, and how inclination angle (the angle formed between the field lines and the Earth) varies with latitude. At the magnetic equator (the curving line across the Earth), field lines are parallel to the Earth's surface and the inclination angle is 0°. The field lines become progressively steeper as one travels north toward the magnetic pole, where the field lines are directed straight down into the Earth and the inclination angle is 90°. (b) Diagram illustrating four elements of ►geomagnetic field vectors that might, in principle, provide animals with positional information. The field present at each location on Earth can be described in terms of a total field intensity and an inclination angle. The total intensity of the field can be resolved into two vector components: the horizontal field intensity and the vertical field intensity. (Whether animals are able to resolve the total field into vector components, however, is not known.) (c) Map of ►magnetic field inclination along the southeastern coast of the United States. The isolines represent isoclinics (lines of equal magnetic field inclination). In this part of the world the isoclinics trend east-west, while the coastline is aligned approximately north to south. As a result, each area of coastline along the eastern seaboard is marked by a unique inclination angle. A similar pattern exists for the isolines of total intensity. A sea turtle navigating along the east coast to a particular feeding or nesting area might thus hypothetically do so by detecting a single magnetic element such as inclination or intensity [1].

For animals that can perceive the direction of true geographic north (for example, by perceiving the area of the northern hemisphere night sky that does not rotate), additional magnetic parameters such as declination (the difference between true north and magnetic north) might also potentially be used.

The pattern of variation in magnetic field elements differs greatly in different geographic areas and may

thus influence what an animal can do with magnetic positional information in a given situation [1,4]. In some areas, the four magnetic elements listed above vary in similar directions over the surface of the earth. In others, such as the Indian Ocean, the gradients of inclination and intensity are oriented almost perpendicularly, so that each location is marked by a unique magnetic field. Thus, in some areas, an animal might be able to determine its position in only one dimension (for example, whether it is north or south of a goal). In others, bicoordinate magnetic navigation using two elements of the Earth's field might be possible. The matter is further complicated in some areas by the existence of magnetic anomalies arising from geological formations. Whether an animal can use a magnetic map to help solve a given navigational task, and the capabilities and limitations of such a system, may thus be influenced by a complex set of variables that differ among geographic settings.

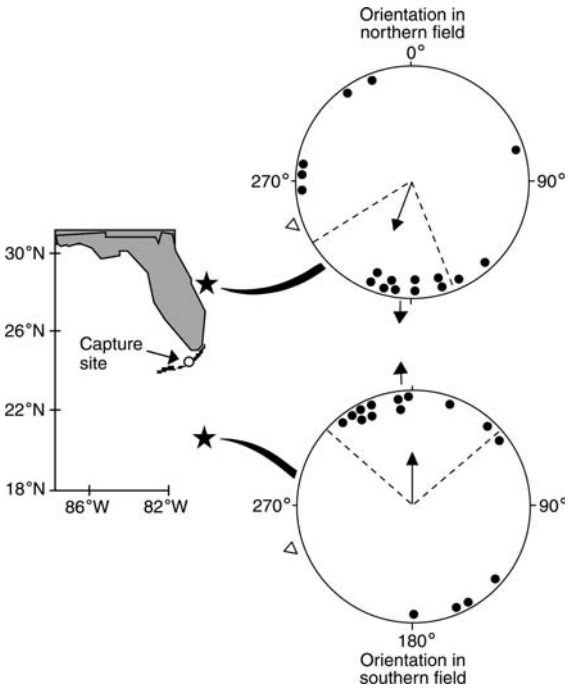
Experimental Evidence for Magnetic Maps

The idea that animals derive positional information from the Earth's magnetic field was first proposed more than a century ago, but until recently, the concept remained controversial. Several early studies provided indirect correlative evidence consistent with the idea of magnetic maps. For instance, homing pigeons released in areas with slight magnetic anomalies appeared to have difficulty establishing a homeward course, and pigeon orientation was more dispersed on days when solar storms disrupted the Earth's field slightly – enough to potentially interfere with a magnetic map but not enough to affect a ►magnetic compass [3]. These findings generated much discussion, but it was not until researchers began exposing navigating animals to the actual magnetic fields found at different geographic locations that more definitive evidence began to emerge. These "►magnetic displacement experiments" provide a powerful tool for investigating magnetic maps because they do not involve physically displacing animals to new areas where numerous cues and factors may vary. Instead, animals can be tested under carefully controlled laboratory conditions in which only the magnetic field is altered.

Among animals that home to specific areas, the most compelling evidence for magnetic maps has come from studies with spiny lobsters [5], juvenile sea turtles [6], and newts [7]. Spiny lobsters inhabit dens in coral reefs and forage out from them at night, often returning to the same den before sunrise. These lobsters are capable of "true navigation," meaning that they can determine the direction to a capture site even if displaced to locations where they have never been. In one experiment [5], lobsters captured in their dens were taken to a nearby arena surrounded by a magnetic coil system that could be used to generate magnetic fields replicating those found in distant geographic locations. Lobsters exposed to a field that exists approximately 400 km north of the testing site oriented southward, whereas those exposed to a field that exists approximately 400 km south of the testing site oriented northward (Fig. 2).

In effect, the lobsters were apparently tricked into thinking that they were at distant locations when they encountered the magnetic fields that exist at those sites. These results provide strong evidence that lobsters have a magnetic positioning system that enables them, at a minimum, to determine if they are north or south of their goal.

Similar results have been obtained with juvenile green sea turtles [6]. After several years in the open ocean, these young turtles return to the southeastern



Magnetic Map. Figure 2 Evidence for a magnetic map in spiny lobsters (*Panulirus argus*). Lobsters from the middle Florida Keys were subjected to magnetic fields that exist in locations north or south of the location where they were captured. Lobsters subjected to the field from the northern site oriented approximately southward, whereas those exposed to the field from the southern site crawled approximately north. The *open triangle* outside each orientation diagram indicates the actual direction to the capture site from the test site. In each case, lobsters responded as if they had been displaced to the locations marked by the stars rather than orienting in the direction that was actually toward the capture site. The *arrow* in the center of each circle represents the mean angle of the group. *Dashed lines* represent the 95% confidence interval for the mean angle. Figure is modified from [5].

M

coast of the United States to take up residence in feeding grounds. Turtles are known to return to these locations after experimental displacements and long seasonal migrations. In a recent experiment, turtles captured in their feeding grounds were tethered in an arena and exposed to magnetic fields that exist at locations north or south of their home areas. As with the lobsters, turtles exposed to a field that exists north of the capture site oriented southward, whereas those exposed to a field south of the capture site oriented northward. Thus, juvenile turtles evidently possess a magnetic map which permits an assessment of position relative to specific geographic destinations.

Sea turtles and spiny lobsters migrate over considerable distances, but a magnetic map may also exist in a kind of salamander that moves only over distances of about 1–3 km. Red-spotted newts exposed to an inclination angle found far north of their home area oriented southward, whereas those exposed to an inclination angle found south of their home area walked northward [7]. Although the fields used in these experiments did not precisely match those that exist in nature, these initial results are consistent with the hypothesis that newts, like lobsters and sea turtles, also have some type of magnetic map.

Magnetic Maps and Migratory Pathways

Positional information in the Earth's magnetic field is also used by some animals during long-distance migrations that do not involve well-defined endpoints such as a particular home site. For example, young loggerhead sea turtles (*Caretta caretta*) from Florida, U.S.A., do not live in coastal feeding areas as older turtles do. Instead, they undertake a circular migration around a large region of the Atlantic Ocean. Newly hatched loggerheads, when exposed to magnetic fields replicating those found in three widely separated oceanic regions, responded by swimming in directions that would, in each case, facilitate movement along the migratory pathway [8]. Thus, young sea turtles appear to inherit responses that enable them, in effect, to exploit regional magnetic fields as navigational markers; such fields elicit changes in swimming direction at crucial geographic boundaries.

A similar use of magnetic positional information occurs in the pied flycatcher *Ficedula hypoleuca*, a migratory bird. Captive flycatchers exposed to a sequence of magnetic fields matching those they normally encounter while migrating shifted orientation in the same direction and at the same time as conspecifics during the natural migration [9]. Such shifts in orientation did not occur in birds maintained in the ambient field at the migration start point, or in birds maintained in a field replicating that at the migratory endpoint. Thus, for the pied flycatcher, the results suggest a complex interaction between an endogenous time program and magnetic parameters, in which the birds must apparently experience sequentially the fields of specific locations at the appropriate times in order to orient appropriately at each point in the migration.

In at least one species of bird, regional magnetic fields appear to act as a behavioral trigger of a different kind. The thrush nightingale *Luscinia luscinia* migrates south across the Saharan desert, a vast region over which food is seldom available. Birds held in Sweden but exposed to a sequence of regional fields along the migratory route, the last from a location just north of the desert, gained significantly more weight than control birds held under identical conditions but in the local Swedish field [10]. Thus, the results imply that a regional field just north of the Sahara, or perhaps a sequence of fields normally encountered during the migration, triggers changes in behavior and physiology that result in the birds accumulating fat needed for their trans-desert flight.

Given the phylogenetic distance between lobsters and the three vertebrate groups known to exploit positional information in the Earth's field, it appears likely that magnetic position-finding has evolved at least twice. Moreover, natural selection has apparently sculpted this ability for multiple uses in different animals, depending upon whether the animal needs to move along a migratory route, navigate to a specific home area, or store fat in preparation for a particularly difficult segment of a migration. The recent nature of these findings suggests that additional investigation will be fruitful, and that researchers have only begun to uncover the ways in which animals exploit magnetic maps.

References

1. Lohmann KJ, Lohmann CMF (2006) Sea turtles, lobsters, and oceanic magnetic maps. Mar Freshw Behav Physiol 39:49–64
2. Mouritsen H (2001) Navigation in birds and other animals. Image Vis Comput 19:713–731
3. Wiltschko R, Wiltschko W (1995) Magnetic orientation in animals. Springer, Berlin
4. Lohmann KJ, Hester JT, Lohmann CMF (1999) Long-distance navigation in sea turtles. Ethol Ecol Evol 11:1–23
5. Boles LC, Lohmann KJ (2003) True navigation and magnetic maps in spiny lobsters. Nature 421:60–63
6. Lohmann KJ, Lohmann CMF, Ehrhart LM, Bagley DA, Swing T (2004) Geomagnetic map used in sea-turtle navigation. Nature 428:909–910
7. Fischer JH, Freake MJ, Borland SC, Phillips JB (2001) Evidence for the use of magnetic map information by an amphibian. Anim Behav 62:1–10
8. Lohmann KJ, Cain SD, Dodge SA, Lohmann CMF (2001) Regional magnetic fields as navigational markers for sea turtles. Science 294:364–366

9. Beck W, Wiltschko W (1988) Magnetic factors control the migratory direction of pied flycatchers (*Ficedula hypoleuca* Pallas). In: Ouellet H (ed) Acta XIX Congressus Internationalis Ornithologica, University of Ottawa Press, Ottowa, Canada, pp 1955–1962
10. Fransson T, Jakobsson S, Johansson P, Kullberg C, Lind J, Vallin A (2001) Magnetic cues trigger extensive refuelling. Nature 414:35–36

Magnetic Moment

Definition

A measure of the torque exerted on a magnet when placed in a magnetic field.

►Magnetic Bacteria

Magnetic Orientation

►Magnetic and Electric Senses

Magnetic Position-finding

►Magnetic Map

Magnetic Positioning System

►Magnetic Map

Magnetic Remanence

Definition

Magnetism in the absence of an external magnetic field.

►Magnetite

Magnetic Resonance Imaging

Peter Fransson
MR Research Center, Cognitive Neurophysiology, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

Definition

Magnetic Resonance Imaging (►MRI) is an imaging method that is based on the principles and properties of water. It uses a combination of magnetic fields and radiofrequency electromagnetic pulses to produce images that show how water, or more precisely hydrogen, is distributed in the human body.

Purpose

The medical usage of MRI is to locate and diagnose pathological changes in the human body. Recent advances in MRI technology have opened up the possibility of investigating physiological processes. Pertinent examples are measurements of macroscopic flow (MR angiography), in-vivo MR spectroscopy (MRS), perfusion, diffusion of water [►Diffusion weighted magnetic resonance imaging (DW-MRI)] and changes in cerebral hemodynamics related to changes in neuronal activity [►Functional magnetic resonance imaging (fMRI)].

Principles

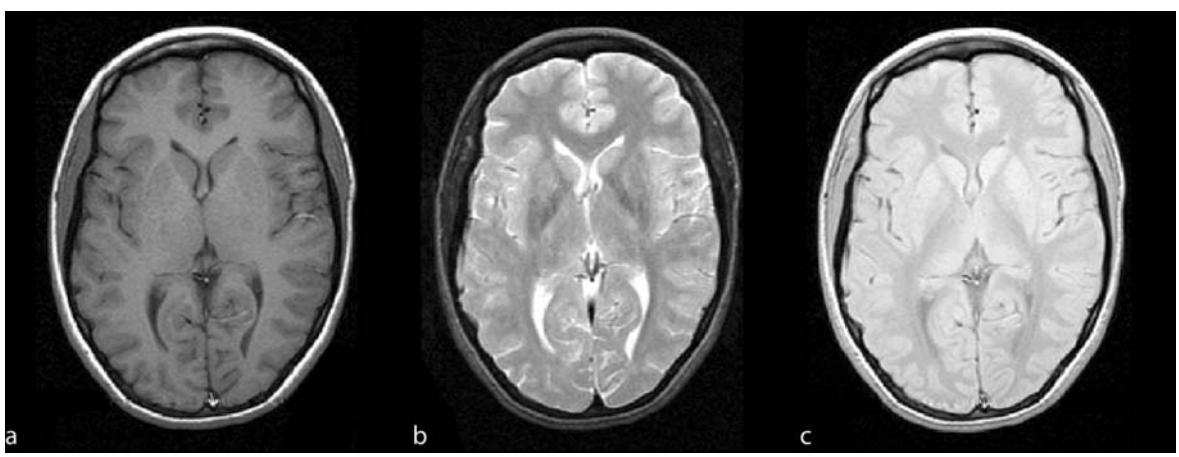
Magnetic Resonance Imaging (MRI) is founded on the same principles as ►Nuclear Magnetic Resonance (NMR), a technique that has been primarily used by chemists to study the three-dimensional structures of chemical compounds since the beginning of the 1950s [1,2]. It should be noted that the NMR phenomena occurs in different atom types, but since virtually all medical imaging is based on the magnetic properties of hydrogen atoms in the human body, this essay will only discuss hydrogen-based MRI.

The hydrogen nucleus consists of a single charged particle. In addition, the proton in the hydrogen nucleus possesses a nuclear magnetic spin, i.e. it spins around its own axis. Together, these properties of the proton entail that each proton behaves like a small magnet, much like a microscopic compass needle with a south and north pole. If protons are positioned in an external magnetic field, the protons will be aligned to the magnetic field, and start to precess around the external field with a precession frequency (►Lamor frequency) that is governed by the strength of the applied magnetic field. A field-strength of 1.5 Tesla, typical for clinical MR scanners, would imply a proton resonance frequency of approximately 63.87 MHz. In the presence of a magnetic field, the ensemble of protons split up into

two different energy levels, where the population of protons in the lower energy level is aligned parallel to the external magnetic field, whereas the population of protons in the high energy level is aligned anti-parallel to the external magnetic field. Subsequently, if a radiofrequency (RF) pulse is applied with a frequency that exactly matches the Lamor frequency of the precessing protons, a subpopulation of protons can be brought to jump from the low to the high energy level. This can be thought of as a process of energy absorption. The uptake of electromagnetic energy from the RF pulse is often called excitation, and it is said that the protons are at "resonance". After RF-excitation, the energy equilibrium between the two energy states is altered and the protons will again strive to reach an equilibrium state. A return to the equilibrium state is accomplished by an emission of energy in the form of a new radiofrequency pulse. This process, in which the protons jump back from the high to the low energy level, is termed relaxation in the MR literature. The emitted energy from the excited protons is subsequently detected as an induced current in a receiver coil, and this current is the basis for the MR signal.

The deciding factor for MR-image contrast between tissue types is the chemical environment for each excited proton. Immediately after RF-excitation, two relaxation processes start simultaneously. First, a net loss of magnetization, i.e. energy dissipation from the protons, is accomplished by a transportation of the extra energy to the surrounding tissue or "lattice" through spin-lattice relaxation (►T1-relaxation). Second, protons will feel the microscopic field from neighboring protons, which in turn causes an exchange of energy between protons. The exchange of energy between neighboring protons is called spin-spin relaxation or ►T2-relaxation. Protons residing in different tissue types have different T1 and T2-relaxation properties. For example, in white brain matter hydrogen is primarily found in the triglyceride chains of fat molecules due to the presence of myelin sheaths. The presence of fat will reduce the T1 and T2-relaxation times in white compared to grey brain matter. The local value of the T1 and T2-relaxation constants are, together with the local concentration of protons (proton density), the major factors that contribute to soft tissue contrast in MR images. The effect of different T1 and T2 relaxation times for the tissue types found in the human brain is shown in Fig. 1.

In order to spatially resolve the MR signal from the object being imaged, magnetic gradients are introduced during the image acquisition process [3]. Applying a magnetic gradient in an arbitrary direction in space implies that the magnetic field strength will vary spatially along the chosen direction. Since the proton precession frequency is proportional to the magnetic field strength, the proton precession (Lamor) frequency will increase or decrease depending on which direction we move along in the magnetic gradient. By applying linear gradients along all three dimensions in space during image acquisition, a spatial encoding is effectively enforced by the fact that the proton precession frequency is now uniquely dependent on its location in space. Hence, the raw data collected during the MRI acquisition takes the form of a sample of its discrete Fourier transform. The final step in the



Magnetic Resonance Imaging. Figure 1 Images demonstrating the basic image contrast mechanisms available in MRI. Fig. 1a shows a T1-weighted, axial section of human brain where the MR signal is primarily governed by the local T1-relaxation times of the hydrogen atoms that reside in each voxel. Similarly, Fig. 1b shows the typical contrast achieved in a T2-weighted MR image, for the same section as in Fig. 1a, where the MR signal is dependent on the local T2-relaxation time of hydrogen. Note that the image contrast between gray and white brain matter is reversed for the T2-weighted image compared to the T1-weighted image. A proton-density-weighed image where the MR image signal intensity is proportional to the absolute concentration of hydrogen atoms in each voxel is shown in Fig. 1c.

MR image acquisition process is to translate the recorded frequencies to spatial information, and this is performed by reconstructing the images by using the two-dimensional Fourier transform. Virtually any image orientation is possible with MRI by employing pertinent linear combinations of magnetic gradients in the x, y and z-direction. The feasibility to set arbitrary slice orientation profiles is shown in Fig. 2, where a T1-weighted image of the human brain is shown in an axial, coronal and sagittal orientation.

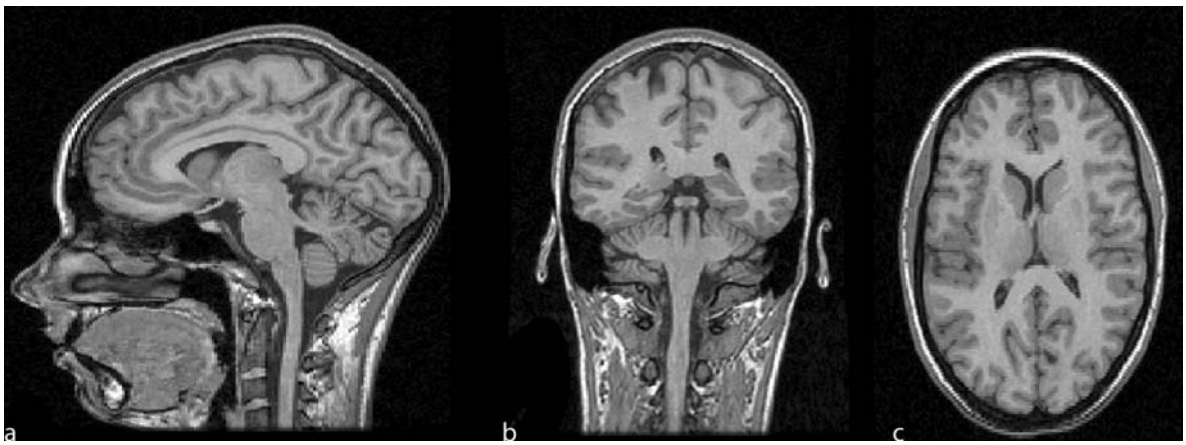
The workhorse in MR imaging is the so called spin-echo sequence [4], which by using two RF-pulses produces superior image contrast and spatial resolution with excellent diagnostic quality. However, conventional spin echo images typically take minutes to acquire. Consequently, throughout the history of Magnetic Resonance Imaging, numerous approaches have been developed to achieve increases in image acquisition speed. The rationale for this work has primarily been to relieve patient discomfort in the MR scanner by reducing scan time. More recently, a second motive for faster image acquisition has been the possibility of monitoring parameters such as perfusion, flow and diffusion. Methodological advances in image acquisition techniques in the mid-eighties such as the FLASH (Fast Low Angle Shot) gradient echo [5] and the RARE (Rapid Acquisition with Relaxation Enhancement) spin echo technique [6] decreased the scan time ten-fold. Ultra-rapid image acquisition schemes such as ►EPI (Echo-Planar Imaging), which allows single image acquisition in a tenth of a second, were conceived in 1977 [7] but it was not possible to make it available on a commercial scale until rather recently due to high demands on magnetic gradient hardware.

Advantages and Disadvantages

During the last decades, MRI has expanded its usability to include the ability to examine and record physiological parameters in the brain. Two examples are given below:

Functional MRI

MRI has recently become an important research tool in the field of cognitive neuroscience. In 1990, Seiji Ogawa and colleagues discovered the MR contrast mechanism that is commonly referred to as BOLD fMRI [8]. ►BOLD (Blood Oxygenation Level Dependent) imaging takes advantage of the fact that hemoglobin, which contains four iron ions, has different magnetic properties depending on whether it has an oxygen molecule attached to it or not. If oxygen is attached to an hemoglobin molecule, it is called oxy-hemoglobin and is slightly diamagnetically similar to the rest of the human body, and thus does not interact with an externally applied magnetic field. However, if the hemoglobin molecule has released its oxygen to the surrounding tissue, it is paramagnetic and called deoxy-hemoglobin. Consequently, a deoxy-hemoglobin molecule in the presence of a magnetic field will cause a local, microscopic inhomogeneity of the magnetic field. This inhomogeneity leads to a change in resonance frequency of the hydrogen atoms in the immediate vicinity of the deoxy-hemoglobin molecule. The deoxy-hemoglobin induced local change in resonance frequency will in turn lead to a reduction in the local MR signal intensity. However, since the increase in cerebral blood flow upon an increase in neuronal activity is much larger than the increase in oxygen consumption, the net result is an MR signal increase due to a wash-out of paramagnetic deoxy-hemoglobin. By employing fast



Magnetic Resonance Imaging. Figure 2 High-resolution, T1-weighted MR images of a human brain in (a) sagittal, (b) coronal, and (c) axial slice orientations. An arbitrary spatial image orientation is possible in MRI through pertinent choices of linear combinations of magnetic gradients applied in the x, y and z-direction during image acquisition.

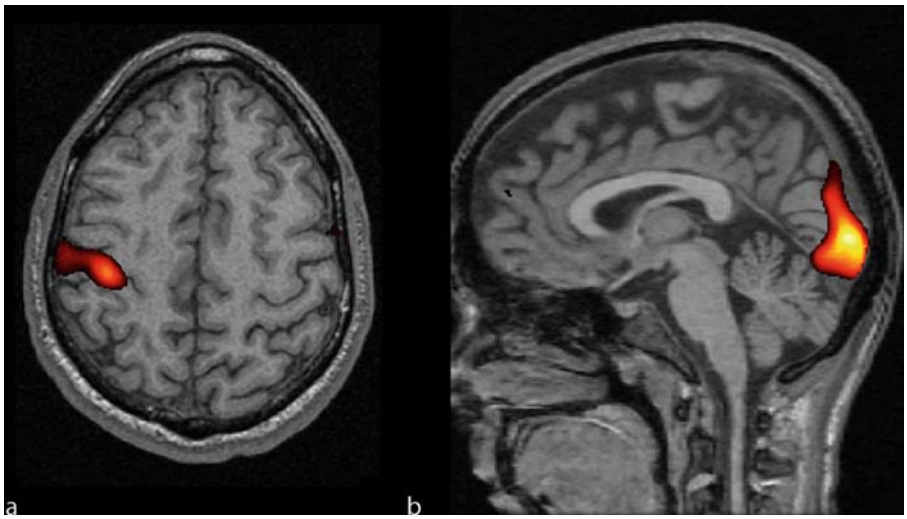
MR acquisition schemes such as echo-planar imaging [7], the whole brain can be scanned in 2–3 s with BOLD sensitivity. Thus, fMRI is usually performed by repeated echo-planar image acquisitions, which provide the possibility of detecting changes in hemodynamic activity that follow changes in external stimuli and/or cognitive processing. Examples of functional Magnetic Resonance Imaging for stimulation of the visual and motor systems in the human brain are given in Fig. 3.

Diffusion Weighted Imaging and Diffusion Tensor Imaging

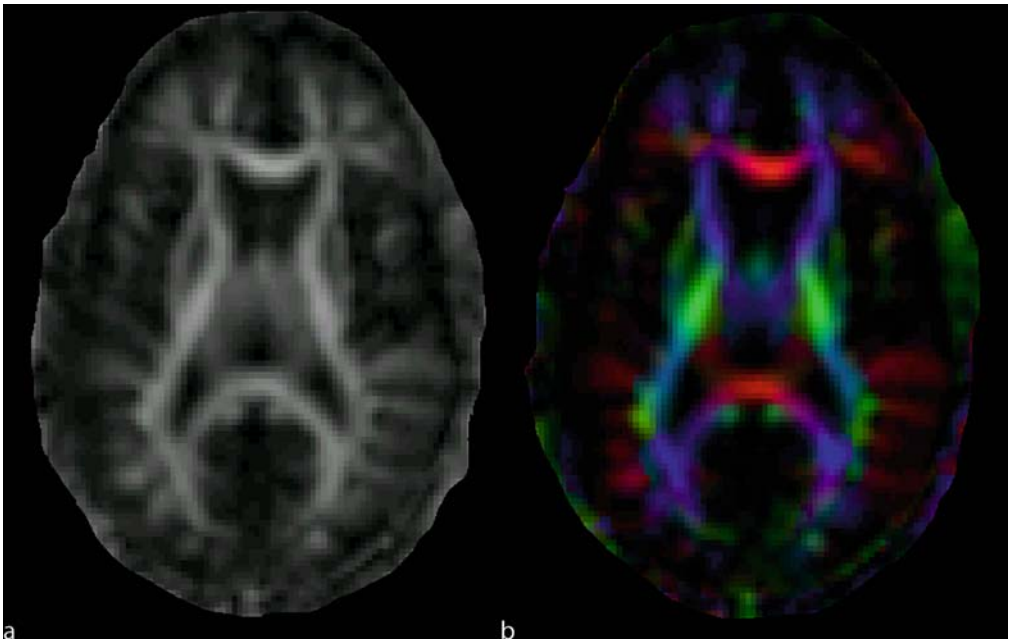
Another rather recent addition to the family of MRI techniques aimed at investigation of human physiology is diffusion-weighted MRI (DW-MRI) [9]. Image contrast in DW-MRI is based on differences in diffusivity of water molecules in the human body (random translational movement of molecules based on Brownian motion). For example, diffusional movement of water is relatively more restricted by cellular membranes in gray and white brain matter compared to cerebrospinal fluid. MR imaging sequences can be made sensitive to differences in diffusional movement by including additional magnetic gradients that encode for movement along an arbitrarily chosen spatial direction. Thus, the mechanism behind DW-MRI is that the MR signal from stationary hydrogen atoms is not affected by the additional gradients, whereas the MR signal from hydrogen atoms moving along the direction of the applied diffusion encoding gradient will be reduced. Moreover, the signal reduction for moving hydrogen is proportional to the speed of movement. If no preferred direction exists for diffusion of water, e.g. in cerebrospinal fluid, diffusion is said to be isotropic. That is, the size of diffusional movement is similar in all directions. However, water diffusion can also be anisotropic. This is the case for water in white matter tracts, where the movement of water is much less restricted along a line parallel to the fiber bundles compared to an orthogonal direction. A complete characterization of the spatial distributions of diffusional movement in each image voxel can be obtained by measuring the so-called ►diffusion tensor (DT-MRI). Diffusion tensor calculations require at least seven (six different directions and one image acquisition measurement without any diffusion gradients) separate MR image acquisitions. An average value of diffusion anisotropy based on diffusion tensor calculations is usually displayed using a scalar value such as the fractional anisotropy (FA) index, which shows the magnitude of the diffusion tensor that can be attributed to anisotropic diffusion (Fig. 4a). The spatial direction of the diffusion tensor can be indicated by using a color-coding scheme as depicted in Fig. 4b, where, for example, the color red indicates fibers running in the left-right direction (genu and splenum part of the corpus callosum).

Limitations

Since the MRI technique is based on the usage of strong magnetic fields, caution must be exercised when bringing



Magnetic Resonance Imaging. Figure 3 Color-coded statistical parametrical maps superimposed on anatomical T1-weighted MR images showing significant functional activation of the motor cortex (a) and the primary visual cortex (b) using the functional Magnetic Resonance Imaging (fMRI) technique. fMRI was used to record changes in neuronal activity as observed by local changes in blood oxygenation (Blood Oxygenation Level Dependent, BOLD) for either right hand finger-thumb opposition versus rest (a) or presentation of a visual, flickering checkerboard versus darkness (b).



Magnetic Resonance Imaging. Figure 4 Water diffusion anisotropy in an axial section of the human brain measured with Diffusion Tensor Magnetic Resonance Imaging (DT-MRI). The mean degree of anisotropy is shown as an FA-map (Fractional Anisotropy) in Fig. 4a, where the white matter fiber tracts show a high degree of diffusional anisotropy due to the parallel arrangement of fiber bundles in white brain matter. The spatial orientation of the diffusion tensor for the same section is shown in Fig. 4b, where color represents the preferred direction of diffusion of water molecules, predominantly in white fiber tracts (red: left-right, blue: anterior-posterior, and green: inferior-superior). Courtesy of Zoltan Nagy.

metal objects into the MR scanner room. All ferromagnetic objects will experience both a translational force and a twisting force (torque) in the presence of the magnetic field created by the MR scanner. Moreover, the magnetic field may compromise the function of cardiac pacemakers. In addition, non-ferromagnetic metal objects will produce inhomogeneities in the vicinity of the magnetic field causing in-plane signal displacement and signal drop-out. These image artefacts are called susceptibility-induced image artifacts, and are also present in air-tissue interfaces, e.g. near the ear canals and the nasal cavities. This is a particular problem for functional MRI that is sensitive to macroscopic (tissue-air interfaces) as well as microscopic (deoxy-hemoglobin) magnetic field inhomogeneities.

References

1. Bloch F, Hanson WW, Packard ME (1946) Nuclear Induction. Phys Rev 69:127
2. Purcell EM, Torrey HC, Pound RV (1946) Resonance absorption by nuclear magnetic moments in solid. Phys Rev 69:37
3. Lauterbur PC (1973) Image formations by induced local interactions: examples employing nuclear magnetic resonance imaging. Nature 243:190–191
4. Hahn EL (1950) Spin Echos. Phys Rev 20(4):580
5. Hennig J, Nauerth A, Friedburg H (1986) RARE imaging: a fast imaging method for clinical MR. Mag Reson Med 3:823–833
6. Haase A, Frahm J, Matthaei D, Hänicke W, Merboldt KD (1986) FLASH imaging. Rapid NMR imaging using low flip-angle pulses. J Magn Reson 67:258–266
7. Mansfield P (1977) Multi-planar image formation using NMR spin echoes. J Phys C 10:L55–L58
8. Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 87:9868–9872
9. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis EA, Laval-Jeantet M (1986) MR imaging of intravoxel incoherent motion: application to diffusion and perfusion in neurological disorders. Radiology 161:401–407

Magnetic Resonance Spectroscopy (MRS)

Definition

It produces spectra that reflect levels of metabolites and thus provides information on tissue properties.

Magnetic Stimulation

►Transcranial Magnetic Stimulation

Magnetite

Michael Winklhofer
Department für Geo- und Umweltwissenschaften – Sektion Geophysik, Ludwig-Maximilians-Universität, Munich, Germany

Synonyms

Iron ferrite, mixed-valence iron oxide; Loadstone, lodestone

Definition

Magnetite is a ferrimagnetic mineral with chemical formula Fe_3O_4.

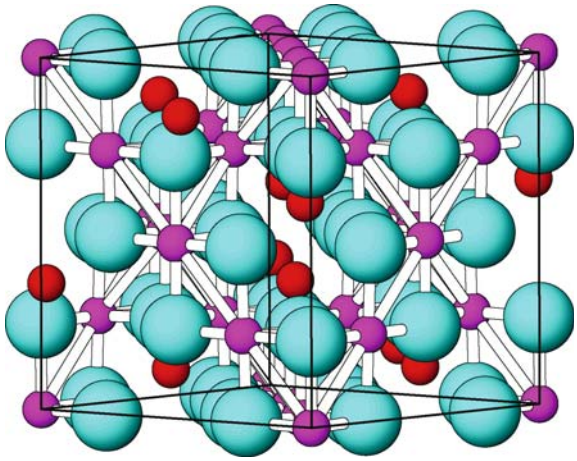
Characteristics

Occurrence

Magnetite (empirical formula Fe_3O_4) is the oldest magnetic mineral known to man. Being the most abundant magnetic mineral in terrestrial rocks of igneous and metamorphic origin, magnetite has helped paleomagnetists to reconstruct the ancient geomagnetic field from rocks, and with it, the past positions of the continents on the globe. As an ore, magnetite is economically valuable, containing 72 wt% of iron. In sediments, magnetite may be of detrital (inorganic) or biogenic origin. Magnetic bacteria, algae, and some higher organisms such as molluscs have been shown to synthesize magnetite of high chemical purity, although the biochemical pathways of biogenic magnetite formation remain to be elucidated. Magnetite may form the basis of a magnetic-field receptor in homing pigeons and migratory animals. Magnetite is also technically important in electrochemical applications (electrodes, catalysts) and magnetic storage media. Owing to its half-metallic character and high ►Curie temperature, magnetite is currently being considered for spintronic applications.

Crystal Structure and Ferrimagnetism

The mixed-valence iron oxide magnetite (structural formula $FeO{\cdot}Fe_2O_3$) crystallizes in the inverse ►spinel structure, i.e., $(8\ Fe^{3+})^{[4]}[8\ Fe^{2+} + 8\ Fe^{3+}]^{[6]}\ 32\ O^{2-}$, with () and [] denoting tetrahedrally and octahedrally coordinated sites (A and B sites), respectively (Fig. 1).



Magnetite. Figure 1 Lattice structure of magnetite. *Green*: Oxygen anions; *red*: tetrahedral sites; *pink*: octahedral sites (courtesy of Dr. R. Pentcheva). The cube defines the system of the crystallographical ⟨100⟩ axes.

The unit cell (edge length 8.396 Å) is a cubic-close packed lattice of 32 oxygen anions (8 formula units), which are slightly distorted toward the octahedral interstices to accommodate a third of the iron cations on tetrahedral interstices. The 16 B sites per unit cell (p.u.c.) are occupied by an equal number of randomly distributed Fe^{2+} and Fe^{3+} cations, and the remaining 8 Fe^{3+} cations p.u.c. are on A sites. The A-site moments are aligned anti-parallel to the B-site moments, neutralizing the magnetic spin moment of the Fe^{3+} cations in the B-sites. The net magnetic spin moment is therefore carried by the Fe^{2+}, resulting in a net magnetic spin moment of exactly 4 μ_B (►Bohr magneton) per formula unit Fe_3O_4. A small contribution from the orbital moments results in a total magnetic moment of 4.07 μ_B per formula unit Fe_3O_4 (value extrapolated to 0 K). This ferrimagnetic structure of magnetite was first suggested by Néel [1] and later confirmed by neutron scattering experiments.

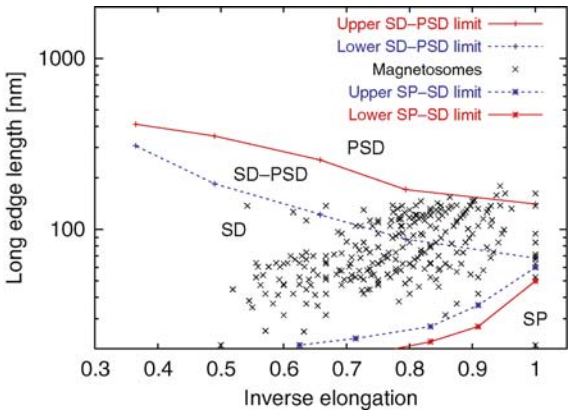
The ►ferrimagnetism of magnetite breaks down at a critical temperature of $T_C = 580°C$ (Curie temperature), above which magnetite is paramagnetic. At $T_V = 125$ K, magnetite undergoes a first-order phase transition, the so-called ►Verwey transition, below which the Fe^{2+} and Fe^{3+} cations on octahedral sites order, and so reduce the symmetry of the lattice from cubic to monoclinic. On warming through T_V, the electrical conductivity of magnetite increases by two orders of magnitude. The black color of magnetite, as well as its moderate electrical conductivity above T_V, is due to electron hopping between the Fe^{2+} and Fe^{3+} cations in the octahedral sites, that is, the cations exchange their valence between the +II (ferrous) and +III (ferric) oxidation states. The temperature of the Verwey

transition decreases with increasing oxidation parameter δ in $Fe_{3(1-\delta)}O_4$. The fully oxidized form of magnetite with δ = 1/9, called maghemite (formula unit Fe_2O_3), does not undergo a Verwey transition, but is an electrical insulator and roughly 10% less magnetic than stoichiometrically pure magnetite. The unit cell of maghemite has a defect spinel structure and can formally be written as $(8\ Fe^{3+})^{[4]}[40/3\ Fe^{3+} + 8/3\ ]^{[6]}\ 32O^{2-}$, where stands for a lattice vacancy. If ordered on a tetragonal superlattice, the vacancies in the maghemite lattice give rise to additional reflexes in X-ray diffraction (XRD), by which maghemite can be distinguished from stoichiometrically pure magnetite. However, not all maghemite crystals show vacancy ordering, and the unit-cell parameter reported in the literature ranges from 8.330 Å to 8.340 Å, reflecting differences in how the samples were synthesized or in the precursory minerals (magnetite or iron-oxyhydroxides, FeOOH) from which maghemite is naturally formed.

From the above, it is clear that discrimination between magnetite and maghemite may not always be straightforward by means of diffraction methods. The situation is even more complicated when it comes to identifying tiny amounts of magnetic material in tissue [2]. The amount of material in tissue is not sufficient for XRD (let alone spectroscopical techniques such as Moessbauer spectroscopy) and electron diffraction, as the only remaining crystallographical identification technique is not accurate enough to resolve the small differences in lattice spacing between magnetite and maghemite. Here, magnetometric measurements can be used to further constrain the nature of the magnetic material (see below).

Domain State

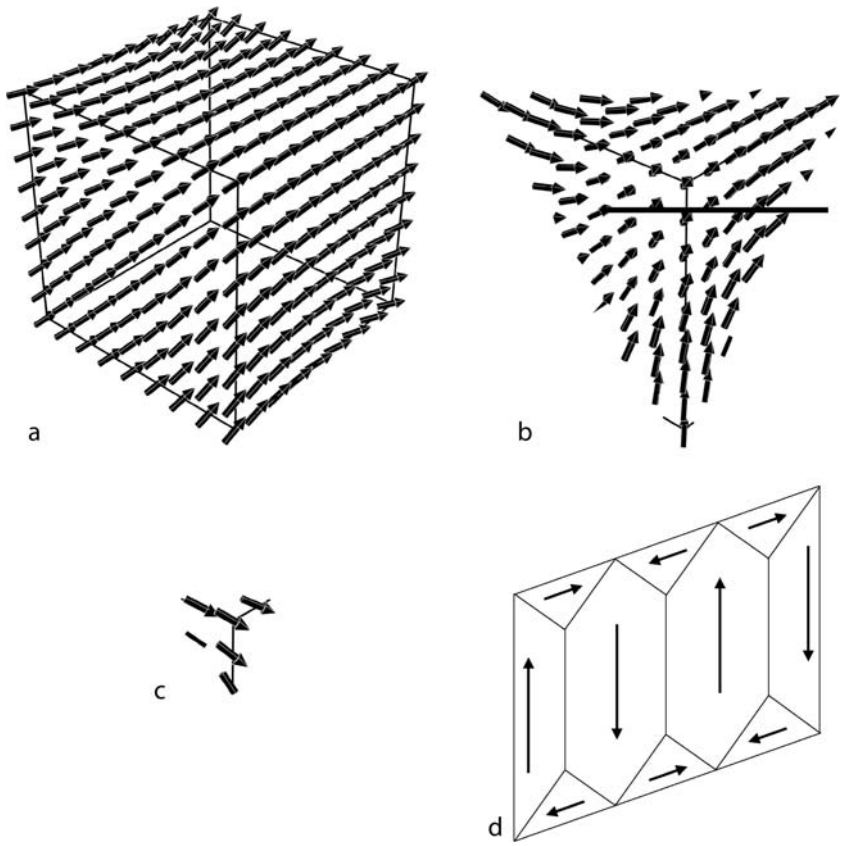
Magnetic properties of magnetite crystals such as ►magnetic remanence and coercive force are largely controlled by domain state, which in turn depends upon grain size and shape. Figure 2 shows a magnetic phase diagram for submicron-sized single crystals of magnetite as a function of grain size and axial ratio, calculated with a micromagnetic model [3,4]. Magnetite cubes with an edge length smaller than 68 nm are magnetic single domains (SD) and so have a nearly uniform magnetization structure (Fig. 3a). Departures from the uniform magnetization structure near the corners and edges of the cubes become larger with increasing grain size (Fig. 3a,b). As the grain size increases above 68 nm, however, SD magnetization states become energetically less favorable, but can still exist up to a threshold edge length of 140 nm (Fig. 2), where they finally give way to non-uniform magnetization structures such as magnetic vortices (Fig. 3c).



Magnetite. Figure 2 Phase diagram for magnetic domain state in submicron-sized rectangular crystals of magnetite as a function of axial ratio (width/length) and long edge length calculated for room temperature (according to [3,4]). The upper two lines demarcate the stability of single domain (SD) magnetization states against pseudo-single-domain (PSD) states [3], the lower two lines against superparamagnetic behavior [4]. The crosses represent data from edge-length measurements on magnetite particles (magnetosomes) in magnetic bacteria [5]. With a few exceptions, magnetosomes fall into the stable SD field or in the field where SD states coexist with vortex states (SD–PSD field).

In a magnetic vortex, the magnetization structure is curling, thereby efficiently reducing the stray field outside the particle, however, at the expense of the magnetic moment. Particles containing such magnetic swirls are also referred to as pseudo-single-domain (PSD) particles. Magnetite crystals with grain sizes larger than 1 μm host several uniformly magnetized, lamellar domains (multi-domain, or "MD" particles) with adjacent domains in the interior having opposite polarity (see Fig. 3d).

While single-domain particles carry the maximum magnetic moment per particle volume (►saturation magnetization), the specific magnetic moment of a vortex decreases rapidly with grain size [3], and is nearly zero in MD particles. For the purpose of magnetotaxis, in magnetic bacteria it is therefore most efficient to have SD particles. This can be achieved by limiting the particle size to 140 nm and by increasing the particle elongation. It therefore comes as no surprise that magnetite crystals in magnetic bacteria, so-called magnetosomes, usually have grain sizes below 140 nm and are elongated [5]. It is true that vortex states are energetically more favorable in magnetite cubes with an edge length greater than 68 nm, but one has to bear in mind that the magnetization in growing magnetosomes already occupies a SD state, as the particle size exceeds the threshold of 68 nm.



Magnetite. Figure 3 Domain state in submicron-sized cubes of magnetite as defined by the magnetization structure: (a) single-domain (SD) state with nearly uniform magnetization; (b) SD "flower" state; (c) pseudo-single-domain (PSD) state containing a spin-curling structure (vortex). For comparison (d) shows a cross section (viewing plane 110) through a multi-domain (MD) magnetite (grain size >1 μm), which contains lamellar magnetic domains and so-called closure domains near the surface to minimize magnetic pole density on the surface.

There are energy barriers preventing the (metastable) SD state from collapsing into a vortex, up to a critical size of 140 nm. That the magnetization in magnetosomes from the SD–PSD field is SD has convincingly been demonstrated by transmission electron holography [6]. Likewise, it is necessary to emphasize that the magnetic phase diagrams were calculated for isolated crystals in zero external field. Magnetosomes are usually arranged in chains, and so strongly magnetically interact. The interactions are such that the SD state will be stabilized.

Superparamagnetism

If, on the other hand, the edge-length becomes less than some 50 nm, magnetite cubes cannot retain a temporally stable SD magnetization at room temperature because the magnetization structure is constantly buffeted by thermal fluctuations, leading to frequent spontaneous magnetization reversals in the particle. Such behavior is called Néel superparamagnetism. In a magnetic field, an assemblage of SP particles carries a magnetization, which will decay logarithmically with time after the magnetic field is switched off. Although ►superparamagnetism does not represent a true domain state but rather describes a thermal relaxation phenomenon, it is sensible to include it into the magnetic phase diagram, defining the lower end of SD stability (Fig. 2).

It is important to note that Néel superparamagnetism refers to the stability of magnetic remanence with respect to the coordinate system of the particle. If the particles are not embedded (as in a solid rock matrix), but dispersed in a fluid, then the magnetic remanence of an assemblage of particles will decay through Brownian motion in the fluid. Magnetically stable SD particles, which are able to rotate freely in a viscous medium, are therefore subject to the Brownian type of superparamagnetism. Using magnetic relaxometry, one can distinguish Néel and Brownian relaxation by their different relaxation time characteristics.

Magnetic Measurements as a Diagnostic Tool

Thermomagnetic curves allowing for Curie-point determination are a widely used tool in rock magnetism for identifying different magnetic crystals with different

Curie temperatures. Due to the high Curie temperature of magnetite, this rock magnetic technique is not suitable in biomagnetism for detecting magnetite in tissue.

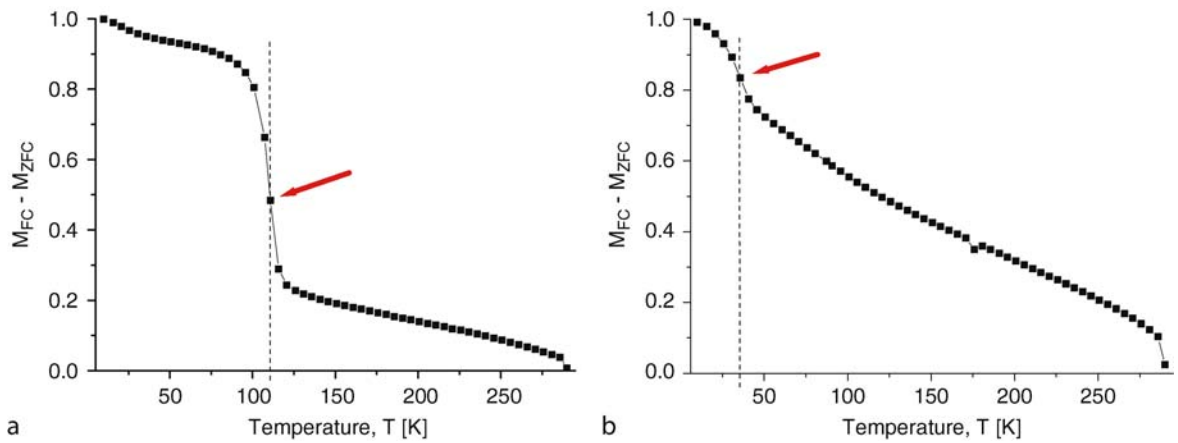
The electronic and structural changes at the Verwey transition are also accompanied by abrupt changes in magnetic properties, which can be used to identify magnetite by measuring magnetic properties at low temperatures (►ZFC–FC measurements). Figure 4a shows a conspicuous discontinuity in magnetic remanence associated with the Verwey transition. This is, however, not the case with magnetite particles smaller than some 30 nm (Fig. 4b).

With decreasing grain size, not only thermal fluctuations, but also surface effects become important and affect the (magnetic) Verwey transition, first by lowering the temperature of the Verwey transition, and eventually by suppressing it altogether. Magnetic relaxation may also obscure the Verwey transition in SP particles. Nevertheless, low-temperature magnetic measurements are an excellent tool to identify and characterize SP particles. With decreasing temperature, thermal fluctuations diminish and SP particles are able to retain a magnetic remanence. The temperature at which SP particles become stable SD particles is called the blocking temperature. On heating above the blocking temperature, the magnetic remanence acquired at temperatures below the blocking temperature becomes unblocked and relaxes (linear-logarithmic decay). The spectrum of blocking temperatures contains useful information on the SP particle-size spectrum (magnetic granulometry). Interpretation of low-temperature measurements may not be straightforward when additional phases are present that become magnetic at low temperatures (such as the iron-storage proteins ferritin or hemosiderin).

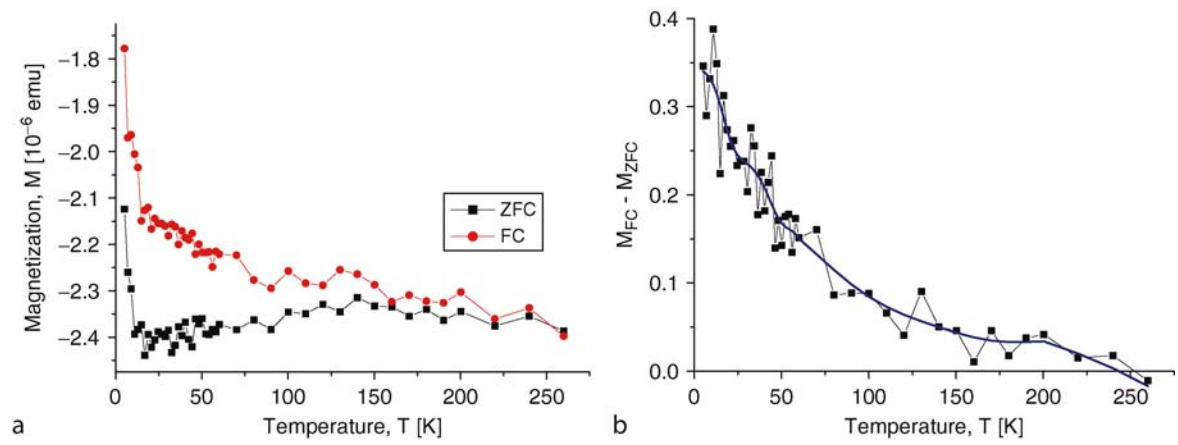
Theory

Magnetoreception Based on SD Magnetite

Following the example of magnetic bacteria, it was postulated that chains of SD magnetite particles might form an efficient basis for magnetoreception in animals [7]. A chain of magnetite particles would produce a torque in the geomagnetic field, which via mechanosensitive structures such as Pacinian corpuscles, hair cells, etc., could be transduced into a nerve signal. Despite the conceptual beauty of the model, a chain of magnetite particles has never been identified directly in animal tissue. It is true that SD crystals of magnetite have been extracted from brain tissue of bone fish, but the crucial questions have remained unanswered thus far, namely: (i) do the magnetite crystals have a physiological function and is it related to the magnetic sense? (ii) how had the magnetite crystals been arranged in situ before the tissue was dissolved and a magnetic extract made? (iii) what is the nature of the connection in the nervous system? In a more timely approach to unearth the elusive magnetic sense, iron-rich magnetic particles, probably SD magnetite, were detected by in-situ measurements on magnetically active nerve cells in the nose of trout [8]. Surprisingly, the particles detected were not arranged in a chain, but appeared to



Magnetite. Figure 4 Low-temperature magnetic measurements on synthetic magnetite samples, (a) median grain-size 60 nm (interacting SD particles), and (b) median grain-size 20 nm (interacting SP particles). A magnetic remanence was acquired during ZFC–FC cycling in a field of 1 mT. The SD sample is characterized by a pronounced discontinuity at 110 K (*arrow*) associated with the Verwey transition. The SP sample on the other hand shows no apparent discontinuity, except for the change in curvature at 35 K (*arrow*). When it comes to identifying magnetic material in tissue, magnetization curves similar to the one on the left will make the case for magnetite, while curves resembling the one on the right can only be taken as evidence of very-fine grained material, however, not necessarily of magnetite (Winklhofer and Maher, unpublished data).



Magnetite. Figure 5 Low-temperature magnetic measurements indicating the presence of SP crystals in the upper beak skin of homing pigeon [2]. (a) ZFC–FC cycling in a field of 5 mT. The mean concentration of magnetic material in the tissue is so little that the signal is dominated by the diamagnetic background and the variations in the signal are just above the noise level. (b) The resulting remanence curve (inset), obtained by subtracting the ZFC curve from the FC curve (raw data: squares; smoothed data: blue line), shows that most of the magnetic remanence is blocked well below 100 K. This is consistent with SP particles smaller than 10 nm grain size.

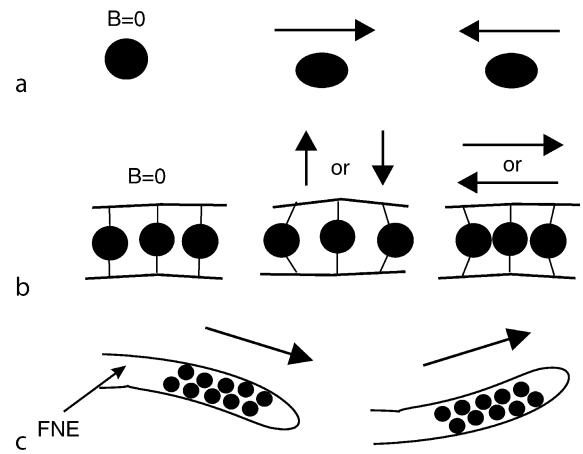
form an irregular cluster in the cell body of the neuron. Yet, the magnetic inclusions are a first structural candidate for the postulated magnetoreceptor in trout.

Magnetoreception Based on SP Magnetite

Using an approach combining bulk magnetic measurements (Fig. 5), histological staining techniques and electron microscopy, it was possible to identify a putative magnetoreceptor in the beak skin of homing pigeons [2,9], namely clusters of SP crystals of magnetite (or maghemite) located in free nerve endings of the ophthalmic branch of the N. trigeminus.

Free nerve endings in the skin are sensitive to mechanical stimulation and so can convert, in principle, magnetic-field induced deformation into a nervous signal. There are several ways of producing mechanical deformation by SP clusters interacting with the magnetic field, as has been demonstrated theoretically and experimentally using droplets of magnetic fluids as a model system [10]. A single cluster of SP particles will assume a shape that depends upon the magnetic field direction and intensity (Fig. 6a).

The micrographs in [9,10] show that the clusters do not occur singly, but form coherent groups of some 20 clusters. The clusters will therefore be magnetically interacting [10], which opens new ways of producing mechanical deformation. If embodied in an elastic matrix (such as the cytoskeleton), adjacent clusters will attract or repel, depending on the relative orientation of the magnetic field axis to the (imaginary) axis connecting the clusters (Fig. 6b). This way, stress is produced on the cytoskeleton and can be measured using cellular mechanotransducers. If contained in a viscous medium, the clusters self-organize into a chain-like arrangement parallel to the magnetic field. Due to the shape anisotropy of the arrangement, a magnetic torque is produced when the relative orientation between the chain and field axis changes. The



Magnetite. Figure 6 Possible ways of transforming a magnetic field into mechanical deformation based on SP clusters. (a) Single cluster in zero field (B = 0) and in an applied magnetic field. (b) Magnetically interacting SP clusters in an elastic matrix coupled to the membrane of the dendrite; the matrix is under dilatation (compression) if B is perpendicular (parallel) to the axis joining the clusters. (c) Magnetically interacting SP clusters in a viscous medium within a free nerve ending (FNE), which behave as a single mechanic unit. The magnetic field exerts a torque on the double chain of clusters, and by aligning the chain into the magnetic field, the FNE will be bent. Note that all the mechanisms are independent of the polarity of the magnetic field.

torque tries to realign the chain into the magnetic field axis and bends the free nerve ending (see Fig. 6c). In conclusion, there are several possibilities for transducing the magnetic field based on SP clusters. The theoretical predictions have been successfully confirmed by experiments on model systems, and it is about time to start in-situ experiments in order to find out which mechanism is realized.

References

1. Néel L (1948) Propriétés magnétiques des ferrites: ferrimagnétisme et antiferromagnétisme. Ann Phys (Paris) 3:137–198
2. Hanzlik M, Heunemann C, Holtkamp-Rötzler E, Winklhofer M, Petersen N, Fleissner G (2000) Superparamagnetic magnetite in the upper beak tissue of homing pigeons. Biometals 13:325–331
3. Fabian K, Kirchner A, William W, Heider F, Leibl T, Hubert A (1996) Three-dimensional micromagnetic calculations for magnetite using FFT. Geophys J Int 124:89–104
4. Winklhofer M, Fabian K, Heider F (1997) Magnetic blocking temperatures of magnetite calculated with a three-dimensional micromagnetic model. J Geophys Res B102:22695–22709
5. Petersen N, Weiss DG, Vali H (1989) Magnetic bacteria in lake sediments. In: Lowes et al. (ed) Geomagnetism and Palaeomagnetism. Kluwer, Dordrecht, pp 231–241
6. McCartney MR, Lins U, Farina M, Buseck PR, Frankel RB (2001) Magnetic microstructure of bacterial magnetite by electron holography. Eur J Mineral 13:685–689
7. Yorke ED (1979) A possible magnetic transducer in birds. J Theor Biol 77:101–105
8. Diebel CE, Proksch R, Green CR, Neilson P, Walker MM (2000) Magnetite defines a vertebrate magnetoreceptor. Nature 406:299–302
9. Fleissner G, Holtkamp-Rötzler E, Hanzlik M, Winklhofer M, Fleissner G, Petersen N, Wiltschko W (2003) Ultrastructural analysis of a putative magnetoreceptor in the beak of homing pigeons. J Comp Neurol 458:350–360
10. Davila AF, Fleissner G, Winklhofer M, Petersen N (2003) A new model for a magnetoreceptor in homing pigeons based on interacting clusters of SP magnetite. Phys Chem Earth 28(16–19):647–652

Magnetization Transfer Imaging (MTI)

Definition

Is an MRI technique based on the selective saturation of protons bound to macromolecules such as myelin. In damaged brain tissue, for example, the increased concentration of protons in free water leads to a quantifiable reduction of MT saturation effects.

Magneto-aerotaxis

Definition

Aerotaxis guided by a magnetic field.

►Magnetic Bacteria

Magnetoencephalography

Andreas A. Ioannides[1,2]
[1]Laboratory for Human Brain Dynamics, Brain Science Institute, RIKEN, Saitama, Japan
[2]Laboratory for Human Brain Dynamics, Aesthetic Analysis of Ideas: Scientific Cultural services Ltd, Nicosia, Cyprus

Synonyms

Magnetoencephalography; MEG

Definition

Magnetoencephalography (MEG) encompasses a family of non-contact, non-invasive techniques for detecting the magnetic field generated by the electrical activity of the brain, for analyzing this MEG signal and for using the results to study brain function.

Purpose

The overall purpose of MEG is to extract estimates of the spatiotemporal patterns of electrical activity in the brain from the measured magnetic field outside the head. The electrical activity in the brain is a manifestation of collective neuronal activity and to a large extent it is the currency of brain function. The estimates of brain activity derived from MEG can therefore be used to study mechanisms and processes that support normal brain function in humans and help us understand why, when and how they fail.

Principles

Basic Physical Principles

Brain function is expressed through electrical activity within and between *neurons*. The same neuronal generators responsible for the generation of the MEG signal are also responsible for changes in the electrical potential on the scalp that can also be measured non-invasively as the ►Electroencephalogram (EEG) by attaching electrodes to the scalp. The well-understood laws of electromagnetism define how electric currents in the brain generate EEG and MEG signals.

The determination of the EEG and MEG signal from the knowledge of the sources, the electrical properties of their biological environment and the configuration of the measuring devices is known as the forward problem. The estimation of generator strength, location and timecourse from the EEG and MEG signal and the knowledge of electrical properties of their biological environment and the configuration of the measuring devices is known as the inverse problem. The laws of electromagnetism define what can be asked of the data and how the forward and inverse problems should be tackled, in particular what *a priori* assumptions can be made about the generators. The basic elements of the hardware used for the detection of the MEG signal will first be described. The forward problem and then the inverse problem will then be considered, describing in each case the theoretical framework established by the laws of electromagnetism and its implications for useful MEG (and sometimes EEG) applications.

Recording and Strength of MEG Signal

As will be described later the MEG signal is generated by the collective activity of a large number of neurons. Nevertheless, the strength of the MEG signal is extremely weak compared to typical terrestrial magnetic fields. The earth's magnetic field is about a billion times as strong, while the usual urban environment at frequency ranges that overlap the ones of interest in MEG is still many orders of magnitude higher than the strongest MEG signal from a normal human brain. A pre-requisite for useful MEG measurements is therefore the availability of sensors that can detect the weak magnetic fields generated by the brain. Also required are methods that can exclude the large ambient fields and tools that can separate out the signal of interest from any remaining interfering signals from the environment and other signals generated by the body of the subject that are often considerably stronger than the signal of interest.

The basic MEG measurement relies on the detection of the electrical current in a small loop of wire, typically about one centimeter across, induced by the change in the magnetic field component perpendicular to the loop surface. Measurement of the induced current determines the value of the change in the magnetic field. Usually a set of coils is used arranged as a ►gradiometer to emphasize nearby signals from the brain at the expense of distant sources. The detection of the minute magnetic field changes outside the head generated by electrical currents in the brain is measured by coupling the coil or gradiometer to an extremely sensitive "superconducting quantum interference devices" (►SQUID). ►SQUIDS as the name implies rely for their exquisite sensitivity on ►superconductivity and together with their sensing coils must be kept at extremely low temperatures, just a few degrees above absolute zero. To achieve this, sensing coils and SQUIDS are kept in a thermos-like container, the ►dewar, which under normal operating conditions is filled with liquid helium. In modern systems the bottom of the dewar is shaped into a helmet with well over one hundred, nowadays a few hundred sensing coils evenly distributed on its inner surface. Just a few millimeters away, on the other side of the insulating layer, at normal room temperature a subject can safely place his/her head inside the helmet. Each sensing coil samples the local magnetic field and the full set of sensing coils can be "scanned" a few thousand times a second. Each scan delivers an independent measurement of the instantaneous magnetic field just outside the head.

The second requirement, separating the signal of interest from the larger ambient background and other interfering signals is achieved by a combination of passive shielding, use of gradiometer design either in hardware for the sensing coils coupled to the SQUIDS or in software using additional reference channels. Other signal processing techniques, e.g. Independent Component Analysis (ICA) coupled to the use of information from auxiliary channels like the ►electro-oculogram (EOG) and electrocardiogram (ECG) can effectively eliminate biological and other artifacts. The combination of the exquisite SQUID sensitivity with these hardware and software methods allows the measurement of the magnetic field generated by the brain with little contamination.

In a modern MEG hardware typically a few hundred sensing coils, each coupled to its own SQUID, are housed at the bottom of the helmet-shaped dewar distributed so that they capture evenly the magnetic field just outside the head. The magnetic field for just one "timeslice" can be mapped by recording the signal from each sensor independently from, and for all practical purposes simultaneously with, the signal of each other sensor. In one second a few thousand such timeslices can be recorded so that successive timeslices provide a movie of the instantaneous change in the magnetic field just outside the head. Since, as we will shortly describe, the speed of propagation from the generators to the sensors is the speed of light, the MEG signal change corresponds to the instantaneous change of the electrical current density in the brain generated by neuronal activity. The peaks of the signal generated by the brain are about two orders of magnitude higher than the device noise level, so the map of the magnetic field not only has exquisite time resolution (a fraction of a millisecond) but is also a very clean map of the topography of the magnetic field just outside the head.

The Forward Problem

It is useful to separate the full current density into two terms. In general we are interested in the first term,

known as impressed currents because they describe the active currents generated by energy-demanding neuronal activity. The remaining currents make up the second term; they describe the passive flow of currents that flows as a result of the impressed currents in the biological medium. Impressed currents of an individual neuron cannot be directly detectable by either MEG or EEG because they are too weak. Even under the most favorable conditions, a detectable signal can only be generated by the collective activity of many tens, possibly many hundreds of neurons spread over at least 1 mm^2 of cortex. At this spatial scale the appropriate terms that best separate the full current density into active and passive elements are referred to as primary current density and volume current or return current respectively. The primary current density depends on both intracellular currents and the local extracellular currents. The intracellular currents are closely related to the local impressed currents. Since these ionic flows are along axons and dendrites the net contribution from a single neuron is a sum of vectors each pointing along the long axis of the corresponding active dendrite or axon. The overall primary current density generated by intracellular currents is the vector sum of contributions from active neurons, which is therefore strongly dependent on the overall arrangement of neurons. The extracellular currents flow along the local conductivity gradients is determined mainly by cell membranes. For each focal neuronal activity, the local arrangement of cells determines the combined effect of both intracellular and extracellular currents and therefore shapes the resulting primary current density. The source space is a convenient label for the region of space where the primary current density can be non-zero, and it includes the entire brain. Primary currents can be thought of as the generators of the volume or return currents, i.e., the large-scale passive electrical current flowing in the "volume conductor," in the brain at large and bounded by the highly resistive skull. These large-scale passive electrical currents do not contribute to the magnetic field, except where they "twist" at boundaries with sharp changes in conductivity, especially the skull. In the special case that only concentric spherical boundaries of changes in conductivity are present, the magnetic field generated outside a conductor is given by an analytical expression [1]. Furthermore, the laws of electromagnetism and spherical symmetry define explicitly which generators can produce an external magnetic field and which are magnetically silent, i.e. they do not produce an external magnetic field no matter how strong they are. Specifically, radial components of the current density are magnetically ►silent sources. The non-zero contribution of tangential components of the current density can be written analytically in a form that depends on the center of the conducting sphere(s) and it does not depend on either the conductivities of the different compartments or the radii of the concentric shell(s), as long as the magnetic field is computed outside the conductor (last spherical shell). Finally the magnetic field in the *radial* direction depends only on the primary currents. The skull is smooth and nearly spherical so the convenient and relatively simple spherical model can provide an excellent estimate for the second term, except around openings like the eye sockets or parts of the skull that deviate substantially from the spherical model.

In contrast to the MEG forward problem the EEG forward problem poses real difficulties in practice. The computation of EEG signal is more complicated because it depends closely on details of the conductivity profile. The differences in the forward problem for MEG and EEG signals have two main consequences. First, the relationship between neuronal activity is easier to model for MEG. On the one hand the skull is transparent to magnetic fields and highly resistive to electrical currents (that must cross it to produce the scalp EEG) and on the other the effect of the conducting medium can be approximated by simple models for accurate computations of the magnetic field but have to be described in detail for the computation of the surface potential. Second, the EEG is influenced strongly by both radial and tangential electric currents while MEG is only sensitive to tangential sources.

The laws of electromagnetism endow both EEG and MEG signals with a direct relationship with the neuronal sources. Specifically, the electric and magnetic fields propagate from the (neuronal source) generator site with the speed of light. Since the sensors are just some centimeters away, for all practical purposes the effect is immediate: a change in the source electrical activity in the brain produces an immediate change in the MEG and EEG signal. This is in sharp contrast with other neuroimaging methods like ►positron emission tomography (PET) and ►functional magnetic resonance imaging (fMRI) that rely on changes in blood flow or content (*e.g.* radioactive labeling or oxygenation) and therefore produce indirect correlates of neuronal activity with delays that are at best a good fraction of a second in the case of fMRI and minutes in the case of PET.

Finally, the forward problem is linear as a direct consequence of the linearity of the laws of electromagnetism. In other words the electric and magnetic field generated by any combination of instantaneous current elements is simply the sum of individual contributions from each element. In the case of continuous primary current density, the instantaneous electric and magnetic field can be computed by integrating the contributions from each small volume element in the source space. In the case of a spherical model the source space for MEG includes only regions where neurons and possibly white matter exists, any intervening regions and boundaries

are not part of the source space as long as they do not generate primary currents.

Inverse Problem

In contrast to the forward problem, the inverse problem has no unique solution, a mathematical fact that was already demonstrated over 150 years ago [2]. Simply stated, it is impossible to reconstruct uniquely the electrical current density inside the head from MEG and/or EEG measurements. Even if we knew exactly the electrical potential on the surface of the head and the magnetic field everywhere outside the head we would still be unable to determine the currents inside the head. In practice, non-uniqueness is much less of a problem than would appear from the dry mathematical statements. By definition silent sources cannot be recovered and noise and sparse sensor coverage further limit what can be reliably extracted about the non-silent part of the current density vector. Nevertheless what is often required of the data is to provide reliable estimates about which areas of the brain were preferentially activated by some stimuli or tasks and when. This limited objective is often satisfied with estimates of the timecourse of the non-silent part of the source configuration. The key question in practice is how accurately and reliably one can recover the non-silent part of the primary current density.

A unique solution of the biomagnetic inverse problem can be obtained by introducing constraints for the form of the generators. Two types of constraints are particularly popular [3]. The first assumes that the generators are one or more point-like sources, or current dipoles. ►Dipole source localization solutions are often interpreted as representatives for their neighborhood and are referred to as equivalent current dipoles (ECD). The second family of popular source localization methods assumes that the continuous current density can be written as a linear sum of (weighted) functions, each defining the sensitivity profile, or lead fields, of the sensors. These methods, known as ►minimum norm or weighted minimum norm solutions, are popular because they lead to a linear system of equations which allows standard pseudoinverse techniques to define the inverse operator that can then be applied directly to the data. Theoretical scrutiny of the mathematical foundation of the inverse problem shows that neither current dipoles nor linear solutions are adequate. Minimum norm is not appropriate for tomographic localization for a rather subtle reason; although the forward problem is linear the optimal algorithm for tackling the inverse problem cannot be linear [4]. The laws of electromagnetism provide no justification for expressing the full primary current density vector as a weighted sum of lead fields, only the direction of the primary current density can be so represented and this leads inevitably to a non-linear relationship between the measurements and the distribution of generators. This conclusion was reached first on the basis of simulation studies leading to the standard form of ►magnetic field tomography (MFT) [5]. In the last 10 years accurate MFT reconstructions have been demonstrated with many applications and extended to single timeslices of ►single trial data [6,7].

Neural Mechanisms

A detectable MEG signal requires concerted action from many neurons numbering at a minimum many tens probably many hundreds. These neurons must be arranged in a similar way in space and they must be activated in near synchrony. The very presence of a good size MEG and EEG signal is evidence for dual organization of neurons: a spatial organization in the way they are grouped together in space and large scale synchrony in the way their activity is organized in time. It is generally believed that relatively slow changes in electrical activity associated with ►post-synaptic potentials (PSP) at the ►apical dendrites of large ►pyramidal neurons are the main contributors to the MEG signal. Large pyramidal neurons are prime candidate generators of MEG signals because their elongated shape is ideal for producing strong primary currents. Furthermore they are arranged in parallel in the cortex so the net impressed current from nearby large pyramidal neurons will tend to sum up constructively. It is very likely that a large part of the MEG signal is indeed due to slow PSPs in the apical dendrites of pyramidal neurons, especially at frequencies well below 100 Hz. For this standard mechanism, typical estimates require about a million *synapses* to be simultaneously active to produce a measurable MEG signal [3]. MEG activity at frequencies well above 100 Hz is likely to be produced by synchronous ►action potentials [7].

Advantages and Disadvantages

Advantages

MEG is a completely non-invasive method. With appropriate analysis methods it can provide simultaneously accurate localization of different brain regions and exceptional temporal resolution. The MEG signal depends weakly on the conductivity changes in the brain and simple models can provide accurate estimates of the magnetic field generated by a source in the brain. The insensitivity to radial sources adds to the discriminability of MEG, especially for sources in sulci.

Disadvantages

The need for shielding and use of liquid helium makes MEG an expensive technology both in terms of the cost of hardware and the operating costs. Another disadvantage of MEG is the need for the subject to stay

motionless while data are collected. MEG is insensitivity to radial currents so generators close to the center of the head (e.g. ►thalamus) and at the crest of gyri are close to silent sources. The patterns of activity identified with MEG are not very meaningful on their own because they lack anatomical context. The background anatomy must be provided by other methods, usually ►MRI and the process of combining the background anatomy and the functional information requires considerable effort to ensure accurate coregistration between the two modalities for each subject and experiment.

►Magnetoencephalography

References

1. Sarvas J (1987) Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. Phys Med Biol 32:11–22
2. von Helmholtz H (1853) Ueber einige Gesetze der Vertheilung elektrischer Ströme in körperlichen Leitern, mit Anwendung auf die thierisch-elektrischen Versuche. Ann Phys Chem 89:211–233, 353–377
3. Hamalainen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography – theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys 65:413–497
4. Taylor JG, Ioannides AA, Muller-Gartner HW (1999) Mathematical analysis of lead field expansions. IEEE Trans Med Imaging 18:151–163
5. Ioannides AA, Bolton JPR, Clarke CJS (1990) Continuous probabilistic solutions to the biomagnetic inverse problem. Inverse Probl 6:523–542
6. Ioannides AA (2001) Real time human brain function: observations and inferences from single trial analysis of magnetoencephalographic signals. Clin EEG 32:98–111
7. Ioannides AA, Fenwick PBC, Liu LC (2005) Widely distributed magnetoencephalography spikes related to the planning and execution of human saccades. J Neurosc 25(35):7950–7967

Magnetonavigation

►Magnetic and Electric Senses

Magnetopause

Definition

The outer boundary of the magnetosphere, which is teardrop shaped and highly variable in altitude, because of variations in solar wind speed. Roughly 10 R_E (Earth radii) on the dayside, ~1000 R_E on the night side.

►Geomagnetic Field

Magnetoperception

►Magnetic and Electric Senses

Magnetoreception

Definition

The ability to detect magnetic fields.

►Magnetic Map
►Magnetic and Electric Senses

Magnetosensitivity

►Magnetic and Electric Senses

Magnetosphere

Definition

The uppermost part of the atmosphere, which is fully ionized and where all charges are controlled by the geomagnetic field.

►Geomagnetic Field

Magnetotactic Bacteria

►Magnetic Bacteria

M

Magnetotaxis

Definition
Unidirectional motility along magnetic lines of force.

►Magnetic Bacteria
►Magnetic and Electric Senses

Magnification Factor

Definition
The cortical magnification factor describes how much cortical area is related to a certain area on the receptor sheet. The magnification factor depends on the receptor density of the corresponding body surface, which is also related to the behavioural relevance of the respective sensory inputs and on the divergence of the afferent projections arising from the subcortical relay structures (spinal cord, brain stem, thalamus).

►Somatosensory Reorganization

Magnitude (Amplitude) Spectrum in Acoustics

Definition
A description of the relationship between magnitude (pressure or sound intensity) and frequency of the sinusoidal components of a complex sound wave.

►Acoustics

Magnocellular Cells

Definition
Large cells located in two layers of the lateral geniculate nucleus (LGN) of primates that have been proposed to be part of a pathway (the M pathway) from the retina to visual cortex concerned with visual motion.

►Geniculo-striate Pathway
►Lateral Geniculate Nucleus (LGN) – Magnocellular Neuron
►Retinal Ganglion Cells
►Visual Motion Processing
►Evolution of the Visual System: Mammals – Color Vision and the Function of Parallel Visual Pathways in Primates

Magnocellular Division of the Ventral Lateral Geniculate Nucleus (Cat)

►Intergeniculate Leaflet

Magnocellular Pathway

Definition
The magnocellular visual pathway takes its input from retinal ganglion cells with large cell bodies. The pathway proceeds through layers 1 and 2 of the lateral geniculate nucleus (LGN) to layer 4cα of primary visual cortex.

►Geniculo-striate Pathway
►Lateral Geniculate Nucleus (LGN) – Magnocellular Neuron
►Retinal Ganglion Cells
►Striate Cortex Functions
►Visual Motion Processing

Main Olfactory Bulb

Definition
►Olfactory Bulb

Main Olfactory System

Definition
Specialized in the detection of odorants. Signals generated by olfactory sensory neurons in the olfactory

epithelium are transmitted to the main olfactory bulb, and then relayed through the primary olfactory cortex to higher cortical areas involved in conscious perception as well as limbic areas that control basic drives and emotions.

►Odor

Maintenance of Wakefulness Test

Definition

Standardized test of the ability of subjects to stay awake while in a sleep-conducive environment, e.g. a darkened room.

►Sleep-Wake Cycle

Major Depression

Definition

A psychiatric diagnosis indicating a state of depressed mood diagnosed according to DSM IV criteria.

►Major Depressive Disorder

Major Depressive Disorder

Heinz Boeke
University Hospital of Psychiatry Zurich, Hospital for Affective Disorders and General Psychiatry Zurich East, Zurich, Switzerland

Synonyms

Major depression; Endogenous depression; Unipolar depression; Melancholia

Definition

Major depression is the most severe category of depression and is marked by a combination of symptoms that occur together and last for at least two weeks without significant improvement.

Symptoms from at least five of the following categories must be present for a major depression, although even a few of the symptom clusters are indicators of a depression, but perhaps not a major depression:

- Persistent depressed, sad, anxious, or empty mood
- Feeling worthless, helpless, or experiencing excessive or inappropriate guilt
- Hopeless about the future, excessive pessimistic feelings
- Loss of interest and pleasure in usual activities
- Decreased energy and chronic fatigue
- Loss of memory, difficulty making decisions or concentrating
- Irritability or restlessness or agitation
- Sleep disturbances, either difficulty sleeping, or sleeping too much
- Loss of appetite and interest in food, or overeating, with weight gain
- Recurring thoughts of death, or suicidal thoughts or actions

Characteristics

History/Background

Descriptions of what is today known as depression or mood disorders appear in many ancient documents. About 400 BC Hippocrates used the terms mania and melancholia to describe mental disturbances. Around 30 AD, in his work "De re medicina" the Roman physician Celsus described melancholia (from the Greek "melan" meaning "black" and "chole" meaning "bile") as a depression caused by black bile.

In 1899, the German psychiatrist Emil Kraepelin, building on the ideas and theories of earlier French and German psychiatrists, described manic-depressive psychosis; according to Kraepelin, a dementing or deteriorating course in manic-depressive psychosis differentiated it from dementia praecox (as schizophrenia was then called). Kraepelin also described a depression that later came to be known as involutional melancholia as a form of depression beginning in late adulthood.

Epidemiological studies have shown that depressive disorders are more common and have a less favorable course than previously assumed. Concepts of diagnosis have also changed over time. The entity of endogenous depression, part of Kraepelin's systematic, triadic nosology (1913), was abandoned in favor of depressive episodes, as defined in ICD-10 (WHO 1992), and major depression as defined in DSM-IV (APA 1994). These became the new major diagnostic categories for depressive disorders. The heterogeneity of the depressive syndrome has resulted in a continuous demand for new attempts at classification. When the current DSM-IV and ICD-10 systems for the classification of depressive disorders are considered from the

controversial historical perspective, it becomes clear that the distinction between unipolar and bipolar disorders has prevailed and that classification on the sub-syndrome level has been taken up again, albeit in a somewhat modified form. The main change occurring in the transition from ICD-9 to ICD-10 was the abandonment of the distinction between endogenous and neurotic forms of depression: this distinction was considered to be too etiologically oriented, and could not be adequately validated on an empirical basis.

Diagnostic Considerations

There is no general agreement about the best method of classifying depressive disorders. Three broad approaches have been made: first to base classification on etiology, second on symptoms and third on the course of the disorder.

Both ICD-10 and DSM-IV classify depressive episodes on the basis of severity and whether or not ►psychotic features are present. It is also possible to specify whether a depressive episode has ►melancholic (DSM-IV) or ►somatic (ICD-10) ►features. In DSM-IV, an episode of major depression with the appropriate clinical symptomatology can be specified as ►atypical depression. In ICD-10 atypical depression is classified separately under "other depressive episodes." Both ICD-10 and DSM-IV allow the diagnosis of ►recurrent brief depression. Nowadays it is argued that the phenomenologically-based concept of "major depression" has led to sterility in depression research and clinical practice, and that there is a need for a paradigm shift in modeling and classifying the depressive disorders [1].

Epidemiology

Major depressive disorder is a common disorder, with a lifetime prevalence of about 15% and perhaps as high as 25% for women. The incidence of major depressive disorder is 10% in primary care patients and 15% in medical inpatients.

An almost universal observation, independent of country or culture, is that major depressive disorder is twice as prevalent in women than in men. Possible reasons for this are hormonal differences, the effects of childbirth, different psychosocial stressors for women than for men and behavioral models of learned helplessness.

The gender differences have been found in community samples and can thus not be accounted for by the fact that women are more likely to seek help than men. Race, education, income and marital status do not influence prevalence rates for major depressive disorder. Recent epidemiological data clearly indicate that the age of onset of major depressive disorder has decreased in recent years (the "birth cohort" effect) in many Western cultures [2].

The lifetime psychiatric co-morbidity rate for major depressive disorder can be as high as 43% [3], i.e., up to 43% of patients with major depressive disorder have a history of one or more non-mood psychiatric disorders. The one-month point prevalence for concurrent in contrast to lifetime psychiatric co-morbidity is 8%.

There is strong empirical evidence suggesting that psychosocial events or stressors may play a significant role in precipitating the first or second episode of major depressive disorder, but this becomes less important for the onset of subsequent episodes [4]. This means that for the recurrent forms of major depressive disorder, new episodes are less likely to involve a specific precipitant as the disorder becomes more firmly established.

Course and Outcome

Periods of significantly increased risk for the onset of the illness include late adolescence and early adulthood, with a progressively increasing incidence up to the age of 45. The age of 30 is usually considered the typical age of onset, although more recent investigations have implied that the average age of onset is considerably earlier [5]. Contrary to the traditional clinical conception that the highest rates for depression are found in older persons, more recent studies have found the highest rates in younger age-groups [6]. More and more young patients are developing depression at an increasingly earlier age. It seems likely that the increased risk of depression in younger people is environmentally mediated, but the factors involved are unknown [7].

Major depression is 2.5 times more common in separated people living alone [5].

People who have been unemployed for at least 6 months of the 5 years preceding diagnosis are three times more likely to develop an episode of major depression.

Critical life events with respect to inter-personal relationships, particularly the death of a close friend of relative, and physical illness combined with poor social resources (e.g., inadequate social support) and personal resources (e.g., dysfunctional coping behavior) are found primarily in depressive cases [8]. An earlier onset of illness, a slower rather than an acute onset, the presence of dysthymia, the presence of chronic physical illness and above all the presence of a chronic anxiety disorder all significantly increase the risk of chronic depression.

The duration of the episodes varies, but several prospective studies have shown that affective disorders remit completely much more often than anxiety disorders (ratio: 32–46%).

The remission rate (defined as five years without relapse) is 42% for unipolar depressive illnesses.

For those who experience a first depressive episode, the risk of recurrence is 80–90%. About 50% of patients with major depressive disorder become chronic cases:

more than 20–30% do not respond to antidepressant medication, with up to 60% of primary care patients remaining depressed after 12 months and 20% of clinic patients remaining depressed for over two years despite pharmacological treatment. Further, one third of those initially responding to medication relapse within one year, with up to 75% relapsing within five years. Chronic depression leads to psychosocial deficits, which place a tremendous burden on both patients and society. It is not only associated with various somatic illnesses, but also entails massive economic costs. According to the WHO, it is predicted that depression will become the major burden on mental health services by the year 2020.

The risk of suicide has been estimated at 15% and is thus considerably higher than in the normal population. Co-morbid depressive episodes last significantly longer than non-co-morbid depression and have a considerably higher rate of relapse.

Etiology

Genetic Causes

Most family studies have shown that parents, siblings and children of severely depressed patients have a morbid risk of about 20% for mood disorders, as compared with about 7% for the relatives of controls. The concordance rates for manic depressive disorder were 69% for monozygotic twins reared together, 67% for monozygotic twins reared apart, and 13% for dizygotic twins.

Neurodevelopment Factors

It has been proposed that stress-induced changes in the hippocampus may be central to the development of depression in genetically vulnerable individuals. New evidence implicates the pre-frontal cortex (PFC) in addition to the hippocampus as a site of neuropathology in depression. The PFC may be involved in stress-mediated neurotoxicity as stress alters PFC functions and glucocorticoid receptors, the PFC is directly interconnected with the hippocampus, and metabolic alterations can be seen in the PFC in depressed patients. Post-mortem studies in major depression provide preliminary evidence for specific neuronal and gliohistopathology in mood disorders. Three patterns of morphometric cellular changes are noted: cell loss (subgenual PFC), cell atrophy (dorsolateral PFC and orbitofrontal cortex) and increased numbers of cells (hypothalamus, dorsal raphe nucleus, cf. [9]).

Neurotrophic Factors

Several neurotrophic factors (such as nerve growth factor, NGF, brain-derived neurotrophic factor, BDNF, and glio-derived neurotrophic factor, GDNP), as well as cytokines and insulin-like growth factor-1 (IGF-1) increase cell survival. The cAMP response element-binding protein (CREB) is a critical integrator of neuroplasticity that is responsive in a brain region-specific manner to a variety of environmental and pharmacological stimuli, including widely prescribed antidepressant medications. CREB is an ubiquitous key-element of intracellular signal transduction cascades that may contribute to symptoms of depression. The increase in CREB-phosphorylation might be a molecular state marker for the response to antidepressant treatment.

There is emerging evidence – primarily from post-mortem studies – supporting the role of abnormalities in neurotrophic signaling pathways in depression. Recent studies suggest that stress-induced atrophy and loss of hippocampal neurons may contribute to the pathophysiology of depression. At the cellular level, evidence has emerged indicating neuronal atrophy and cell loss in response to stress and in depression. At the molecular level, it has been suggested that these cellular deficiencies, mostly detected in the hippocampus, result from decreased expression of BDNF associated with elevation of glucocorticoids.

Serotonergic Markers

Imipramine binding to blood platelets is generally decreased in depression, as indicated by decreased maximal binding capacity. Similarly, 5-HT-uptake in blood platelets is decreased. These findings correspond to a decreased maximal binding capacity of imipramine to brain tissue. Imipramine binding to platelets is a robust biological marker for depression.

5-HT-Receptors

Due to the efficacy of serotonergically acting drugs in major depression, some 5-HT-receptors have been extensively studied in major depression. Almost all the studies point to a decreased or unchanged expression of the 5-HT-1A-receptor. A trend towards decreased 5-HT-1A-receptor expression appears to be a robust finding in major depression.

Biochemical Markers

Several studies have investigated lipids as biological markers for depression. Hypocholesterolemia has been associated with depression, suicide and affective disorders. Low or lowered cholesterol may be associated with increases of suicides and accidents. Cholesterol levels have been identified as a blood marker for depression and anxiety in a normal population in a primary care setting. A hypertriglyceridemia-driven metabolite cause of depression has also been demonstrated in controlled clinical trials, showing that trigylceride lowering alleviates the symptoms of depression. Recent evidence has suggested an important role for lipids in the etiology and treatment of depression. There is empirical evidence for the hypothesis that unipolar

depression may be associated with abnormalities in lipid-associated signaling systems.

Vitamins: Folic Acid

Several cross-sectional studies have focused on the low blood folate levels in depression patients. In a large Finnish study, depressed patients in the general population with energy-adjusted folate intake below the median had a higher risk of being given the discharge diagnosis of depression during the follow-up period than those with a folate intake above the median. A low dietary intake of folate may be a risk factor for severe depression.

Vitamins B_6 and B_{12}

A group of Danish investigators have suggested that a low level of vitamin B_6 is associated with symptoms of depression. A low plasma level of the vitamin B_6 derivate, puridoxal phosphate (POP), was significantly associated with the depression score. Higher vitamin B_{12} levels were significantly associated with better outcome. Vitamin B_{12} level may thus be positively associated with the probability of recovery from major depression.

G-proteins

Abnormal signal transduction pathways have been implicated in the pathogenesis of major depression. G-proteins are key elements of these pathways in the regulation of cellular responses by transmission of signals from receptors to effector proteins. Several studies have reported altered levels and activities of G-protein subunits in depressive patients.

Although it is well established that depression is a major risk factor for the development of coronary artery disease and that cerebro-vascular disease can be a major contributing factor for the development of depression, the information interplay between the central nervous system and cardio-vascular disease is still limited. In an investigation of the G-protein beta-3-subunit C825T polymorphism and the angiotensine-1 converting enzyme (ACE) ID polymorphism, analysis of both genes showed that the combined actions of ACE and C825T genotypes accumulate in carriers of the ACE-D allele and C825T-TT nomozygates with IC/DD-TT carriers showing a more than fivefold increase in risk for major depression. Thus, the study reports that the same allelic combination of two genes that have been shown to increase the risk for myocardial infarction increase the vulnerability for depressive disorder. This finding strengthens the evidence for the involvement of G-protein-couple signal transduction in the pathogenesis of affective disorders.

Hypothalamic Pituitary–Adrenal Axis

The HPA axis stimulating properties of higher ACE and consecutively higher angiotensine and lower substance peak concentrations may be crucial factors for the HPA system hyperactivity during major depressive episodes.

The corticotropin-releasing hormone binding protein gene is likely to be involved in the genetic vulnerability for major depression.

Neural Imaging Markers

Positron emission tomography (PET) imaging studies have revealed multiple abnormalities in regional cerebral blood flow (CBF) and glucose metabolism in limbic structures and the prefrontal cortex (PFC) in mood disorders. In unmedicated subjects with major depression, regional CBF and metabolism are consistently increased in the amygdala, orbital cortex and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual PFC), compared with healthy controls [10]. These abnormalities implicate limbic-thalamic-cortical and limbic-cortico-striato-pallidal-thalamic circuits involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of major depression. These circuits have also been implicated more generally in emotional behavior by the results of electrophysiological, lesion analysis and brain-mapping studies in humans and experimental animals. Structural imaging studies have demonstrated reduced greymatter volumes in areas of the orbital and medial PFC, ventral striatum and hippocampus, and enlargement of the third ventricle. It is not known whether these deficits constitute developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes per se [9]. Taken together with other pre-clinical data regarding these structures' specific roles in emotional processing, the neuro-imaging and neuropathological abnormalities in major depression suggest that the illness is associated with the activation of regions that putatively mediate emotional and stress responses, whereas areas that appear to inhibit emotional expression (such as posterior orbital cortex) contain histological abnormalities that may interfere with the modulation of emotional or stress responses.

Cognitive Deficits in Major Depression

There is growing evidence that several cognitive domains are significantly impaired in patients with major depression, including attention, memory and executive functioning. Patients with major depression manifest significant impairment in their ability to maintain attention in tasks requiring strenuous mental operations, i.e., tasks requiring selective and sustained attention or implying a large resource-allocation capacity.

Patients with major depression also have widespread executive dysfunction, including working memory, set-shifting and inhibition processes, even during the euthymic state.

It has been suggested that cognitive deficits in major depression may depend on age, severity of illness and psychotic or melancholic features. Cognitive deficits in depression may be associated with both trait and state factors and raise questions regarding the long-term cognitive functioning in patients with major depression. These deficits may be explained by structural or functional changes associated with the severity of illness, ageing effects or a possible cumulative pathologic effect of depression on brain structure and function across recurrent episodes of illness [9].

In summary, none of the biological and neuropsychological markers (see Fig. 1) have been shown to be sufficiently specific to allow inclusion in diagnostic manuals of major depression.

Sleep Abnormalities

Problems sleeping – initial and terminal insomnia, multiple awakenings, hypersomnia – are common and classic symptoms of depression. The sleep electroencephalograms (EEGs) of many depressed persons show abnormalities. Common abnormalities are delayed sleep onset, shortened rapid eye movement (REM) latency (the time between falling asleep and the first REM period), a longer first REM period and abnormal delta sleep.

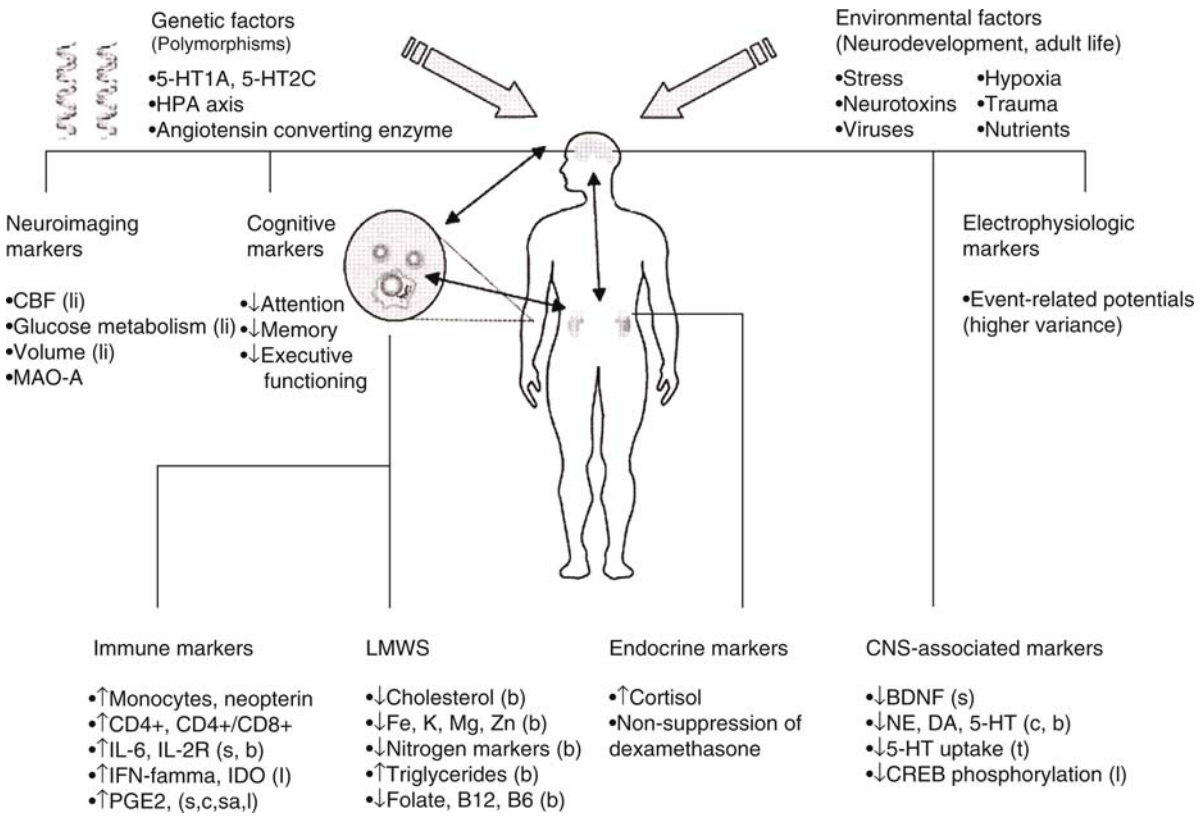
Circadian Rhythms

The abnormalities in sleep architecture in depression and the transient clinical improvement associated with sleep deprivation have led to theories that depression reflects the abnormal regulation of circadian rhythms. Experimental studies with animals indicate that many of the standard antidepressant treatments are effective in changing the setting of internal biological clocks (endogenous zeitgebers).

Psychosocial Factors

Life Events and Environmental Stress

Stressful life events precede more often first rather than subsequent episodes of major depression. According to Post [4], the stress accompanying the first episode results in long-lasting changes in the brain's biology. These long-lasting changes may alter the functional states of various neurotransmitter and intra-neuronal signaling systems, and may even include the loss of neurons and an excessive reduction in synaptic



Major Depressive Disorder. Figure 1 Biological markers of depression.

contacts. This greatly increases the risk of subsequent episodes of a mood disorder, even without an external stressor.

The most compelling data indicate that the life event most often associated with the development of depression is losing a parent before the age of 11. The environmental stressor most often associated with the onset of an episode of depression is the loss of a spouse. Another risk factor is unemployment: persons out of work are three times more likely to report symptoms of an episode of major depression than those working.

Personality Factors

All humans, regardless of their personality pattern, can and do become depressed under appropriate circumstances. Persons with certain personality disorders – obsessive-compulsive, histrionic and borderline – may be at greater risk for depression than persons with antisocial or paranoid personality disorder. The latter can use projection and other externalizing defense mechanisms to protect themselves from their inner rage. Patients with dysthymic and cyclothymic disorder are at risk of developing major depression or bipolar I disorder later.

Stressors experienced by the patient as reflecting more negatively on his/her self-esteem are more likely to result in depression. What may seem to be a relatively mild stressor to outsiders may be devastating for the patient because of particular idiosyncratic meanings attached to the event.

Pharmacotherapy

Since the introduction of the first tricyclic antidepressant, imipramine, in 1957, many new types of antidepressants have been developed. The classes of substances currently available differ little in their antidepressant effect; there is no convincing evidence that one particular class of antidepressant is more effective or has a more rapid onset of effect than the others. The newer antidepressants of the 1980s and 1990s generally have less serious side effects than the "classic" substance groups of the tricyclic agents and the irreversible monoamine oxydase (MAO) inhibitors. Approximately 30–40% of both in- and outpatients fail to respond adequately to an initial 4–6 week treatment with an antidepressant. As many as 10–15% of patients fail to improve sufficiently, even after several different treatment attempts. 12–15% of depressive patients are not yet asymptomatic two years after onset of the illness. The lack of success of antidepressant therapy is often due not to the illness itself, but to suboptimal treatment. If resistance to therapy remains intractable despite attempts at treatment optimization, the use of augmentative or combination therapy should be considered. Among augmentative therapies, the addition of lithium to traditional antidepressants, has been found useful. Combination therapy with various antidepressants has been tried with varying success, as has so-called pindolol augmentation, a combination of the beta-blocker pindolol with a serotonin-reuptake inhibitor (SSRI). The combination of a neuroleptic with an antidepressant has proven useful in the treatment of depression with psychotic features.

Psychotherapy

The majority of patients with an episode of major depressive disorder respond to the first or second attempted treatment. In patients with mild or moderately severe episodes, treatment with antidepressant drugs and brief psychotherapies are adequate and equally effective. In those with severe episodes, antidepressant medication alone or a combination of medication and psychotherapy is recommended. The treatment of chronic depression and in particular of patients failing to respond to adequate drug treatment (approximately 20%) is more problematic. In addition, these patients have marked impairment in psychosocial functioning, incomplete remission even after two years and very high rates of use of healthcare resources. Furthermore, even if there is a partial remission, there remains a high risk of relapse (up to 80%).

Many studies indicate that a combination of psychotherapy (cognitive behavioral psychotherapy, psychodynamic psychotherapy, interpersonal psychotherapy) and pharmacotherapy is the most effective treatment for major depressive disorder. Some data suggest another view: either pharmacotherapy or psychotherapy alone is effective, at least in patients with mild major depressive episodes.

Three types of short-term psychotherapy (cognitive therapy, interpersonal therapy and psychodynamic psychotherapy) have been studied to determine their efficacy in the treatment of major depressive disorder.

References

1. Parker G (2005) Beyond major depression. Psychol Med 35(4):467–474
2. Rush AJ, Golden WE, Walton Hall G et al. (1993) Detection and diagnosis. Depression in primary care, vol 1. US Department of Health and Human Services, Rockville, MD
3. Sargeant JK, Bruce ML, Florio LP, Weissman MM (1990) Factors associated with 1-year outcome of major depression in the community. Arch Gen Psychiatry 47:519–526
4. Post RM (1992) Transduction of psychosocial stress into neurobiology of recurrent affective disorder. Am J Psychiatry 149:999–1010
5. Kessler RC, McGonagle KA, Zhao S et al. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 51:8–19

6. Wittchen H-U (2001) Epidemiology of affective disorders. In: Henn F, Sartorius N, Helmchen H, Lauter H (eds) Specific psychiatric disorders. Contemporary psychiatry, vol 3. Springer, Berlin Heidelberg New York, pp 231–241
7. Klerman GL, Weissman MM (1989) Increasing rates of depression. JAMA 261:2229–2235
8. Angst J, Dobler-Mikola A (1985) The Zurich study. VI A continuum from depression to anxiety disorders? Eur Arch Psychiatry Neurol Sci 235:179–186
9. Mössner R, Mikova O, Koutsilieri E, Saoud M, Ehlis A-C, Müller N, Fallgatter J, Riderer P (2007) Consensus paper of the WFSBP Task Force on biological markers: biological markers in depression. World J Biol Psychiatry 8(3):141–174
10. Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11:240–249

Major Histocompatibility Complex

Ernesto Salcedo, Diego Restrepo
University of Colorado at Denver and Health Sciences Center, Aurora, CO, USA

Synonyms

Human leukocyte antigens (HLA – human); H-2 (mouse)

Definition

A locus of highly polymorphic genes found on the short arm of human chromosome 6 and mouse chromosome 17 that encode proteins involved in the adaptive immune response (see Fig. 1), and certain aspects of brain function.

Characteristics

MHC Proteins

Genes in the MHC encode for proteins involved in the adaptive immune response. MHC proteins fall into two classes: I or II. Class I molecules (MHCI) consist of an MHC-encoded α heavy chain, and a smaller, non-MHC-encoded β chain (β2 microglobulin). Class II molecules (MHCII) are comprised of two MHC-encoded, non-covalently associated polypeptide chains, α and β (Fig. 1b). Both classes of MHC bind proteosomally degraded peptides (MHC peptides) in a binding cleft that is presented on the surface of the presenting cell. The entire MHC-peptide complex is then recognized by T cells as "self" or "non-self." The complex is considered "self" if the bound MHC peptide is a degraded product of an endogenous protein. If, however, the bound MHC peptide originated from an exogenous source, such as protein from bacteria, viruses, or from cells in a tissue graft, then the complex is recognized as "non-self" and the cell presenting the MHC complex is marked for destruction. MHCI molecules have been shown to be present on virtually all nucleated cells, whereas MHCII molecules expression is typically limited to a small subset of immune response cells such as B lymphocytes and macrophages [1].

MHC Polymorphism

The unique collection of MHC alleles possessed by a given individual is known as the MHC haplotype (Fig. 1a). The MHC displays a high degree of polymorphism; alleles differ greatly from individual to individual within a species. The high degree of allelic variation in MHC is thought to be crucial to defeat attempts by foreign organisms to avoid detection by the immune system. In fact, all of the polymorphic residues found in encoded MHC proteins line the interior of the peptide binding cleft and directly interact with the anchor amino acid residues in the bound peptide (Fig. 1c) [1].

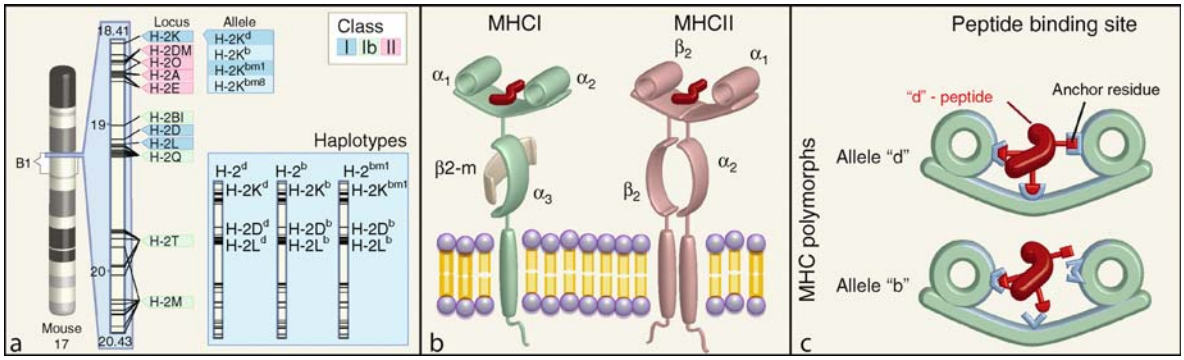
Detection of MHC Haplotype by Smell

Mice and – to some extent – humans are able to detect differences in MHC haplotype between individuals [2]. In mice the detection of MHC identity by smell has been postulated to play a key role in social interactions involving individual recognition, such as mate selection and offspring recognition [3–5]. Indeed, mating preferences dependent on MHC type differences in seminatural populations of mice have been shown to be sufficient to account for much of the MHC genetic diversity [4].

Mice are able to discriminate among individuals with different MHC haplotypes through detection of differences in urine volatiles (these urine volatiles are often termed "odortypes"). The different odortypes elicit distinct maps of activity in the glomerular layer of the olfactory bulb that allow the mice to discriminate between MHC haplotypes [2–3]. In addition to volatiles, released MHC peptides can themselves also be detected by the main and accessory olfactory systems and appear to be involved in detection of MHC haplotype [2]. Intriguingly, MHCI molecules are expressed in the vomeronasal organ of mice and appear to directly interact with chemical receptors classically associated with the detection of pheromones [6].

MHCI and Neuronal Plasticity

The unexpected discovery of activity-dependent MHCI expression in the developing visual system disproved the long held tenet that neurons in an uninjured brain were immune-privileged [7]. Subsequently, other well characterized members of the adaptive immune response have been shown to be expressed throughout



Major Histocompatibility Complex. Figure 1 *The major histocompatibility complex (MHC) is a multigene cluster found on chromosome 17 in mice*. (a) Schematic representation of mouse chromosome 17 including the location and composition of the MHC gene cluster (also named the H-2 region in mice). The banding pattern of the chromosome is shown on the far left. To the right of the chromosomal representation is a partial list of MHC genes. Loci for Class I (*blue and green*) and Class II genes (*pink*) are clustered in the MHC located in the 17 B1 band between 18.41 and 20.43 cm. Each gene (locus) is identified by the prefix "H-2" followed by a capital letter (e.g. H-2K). Different alleles for each of these loci are denoted by a lower case superscript (e.g. H-2K^b). Listed in the two *dark blue panels* to the right of the H-2K locus are a selection of H-2K alleles. Haplotypes inset. Examples of three MHCI allele sets for three different mouse haplotypes: H-2^d, H-2^b, and H-2^{bm1}. (b) Renditions of an MHC class I (MHCI) and a class II (MHCII) transmembrane molecule. In MHCI, two homologous segments (α_1 and α_2) form the peptide-binding region, which consists of two parallel strands of α-helix supported by an eight-stranded β-pleated sheet. The non-MHC encoded β2-microglobulin (β2-m) chain is required for proper presentation of the molecule on the cell surface. In MHCII, the peptide binding region is formed by the interaction between the $\alpha_1$and β_1 subdomains of the two non-covalently associated MHC-encoded polypeptide chains. Polymorphic variation for a particular MHC locus is restricted almost entirely to amino-terminal domains that line the base of the binding cleft or are directed inward from the walls of the α-helices (indicated by blue shading) [1]. Contained within the binding site is an MHC peptide (*red*). (c) Example of the specificity of an MHC peptide to a particular MHC polymorph. "d"-peptide: a hypothetical MHC peptide that, due to its anchor amino acid residues, can only bind a hypothetical MHCI molecule encoded by a "d," but not a "b" allele. This specificity illustrates how MHC peptides, based solely on the configuration of their anchor residues and regardless of their primary amino acid sequence, can provide information on MHC haplotype.

the central nervous system during development and into adulthood. These molecules include the MHCI subunit, β2-microglobulin; the peptide loading enzyme transporter associated with antigen presentation (TAP); critical subunits of the T cell receptor, such as TCRβ or CD3ζ; and the Paired-immunoglobulin–like receptor, another MHCI receptor [7–8].

While the components of adaptive immunity are expressed in neuronal cells, the collective function of these molecules appears to have changed. Loss of MHCI or CD3ζ disrupts the activity-dependent structural reorganization of axons in the lateral geniculate nucleus and the hippocampus [7]. After lesion of the sciatic nerve, fewer neurons are able to regenerate axons in a deficient MHC background [9]. An in vitro examination of cultured hippocampal neurons revealed that MHCI sublocalizes to the soma and dendrites. Moreover, cultured neurons deficient in MHCI had changes indicative of a defect in homeostatic synaptic plasticity. Thus, MHCI molecules appear to function as components of a mechanism that regulates synaptic morphology and physiological function [10].

References

1. Janeway CA, Travers P, Walport M, Schlomchik M (2001) Immunobiology. Garland, New York
2. Restrepo D, Lin W, Salcedo E, Yamazaki K, Beauchamp G (2006) Odortypes and MHC peptides: complementary chemosignals of MHC haplotype? Trends Neurosci 29:604–609
3. Boehm T, Zufall F (2006) MHC peptides and the sensory evaluation of genotype. Trends Neurosci 29:100–107
4. Penn D, Potts W (1998) How do major histocompatibility complex genes influence odor and mating preferences? Adv Immunol 69:411–436
5. Jacob S, McClintock MK, Zelano B, Ober C (2002) Paternally inherited HLA alleles are associated with women's choice of male odor. Nat Gene 30:175–179
6. Olson R, Dulac C, Bjorkman PJ (2006) MHC homologs in the nervous system – they haven't lost their groove. Curr Opin Neurobiol 16:351–357
7. Boulanger LM, Shatz CJ (2006) Immune signalling in neural development, synaptic plasticity and disease Nat Rev Neurosci. 5:521–531
8. Syken J, Grandpre T, Kanold PO, Shatz CJ (2006) PirB restricts ocular-dominance plasticity in visual cortex. Science 313:1795–1800

9. Oliveira AL et al. (2004) A role for MHC class I molecules in synaptic plasticity and regeneration of neurons after axotomy. Proc Natl Acad Sci USA 101:17843–17848
10. Goddard CA, Butts DA, Shatz CJ (2007) Regulation of CNS synapses by neuronal MHC class I. Proc Natl Acad Sci USA 104:6828–6833

Major Tranquilizer

►Antipsychotic Durgs

Male Hypogonadism

Definition

A clinical syndrome due to reduced levels of testosterone. Clinical hallmarks include absence or regression of secondary sex characteristics, reduced fertility (oligospermia, azoospermia), anemia, muscle wasting, reduced bone mass (and bone mineral density), and/or abdominal adiposity. This syndrome has a multifactorial etiology that includes genetic conditions, anatomic abnormalities, infection, tumor, and injury.

Malignant Hyperthermia (MH)

Definition

A pharmacogenetic disease of skeletal muscle with autosomal dominant inheritance that is manifested in humans as an acute hyperthermic reaction, arising from uncontrolled skeletal muscle Ca^{2+} release and contraction, and usually triggered by potent inhalational anesthetics.

►Excitation-Contraction Coupling

Mammalian Respiratory Rhythm Generators

►Respiratory Network Analysis, Isolated Respiratory Center Functions

Mammillary Body

Synonyms

Corpus mamillare

Definition

The mammillary nuclei are located in the medial zone of the hypothalamus. Major afferents arrive via the fornix of hippocampus, while efferents pass largely via the mammillothalamic fasciculus, Vicq d'Azyr bundle to the anterior thalamic nucleus or via the dorsal longitudinal fasciculus (Schütz) to the visceral centers in the brainstem and spinal cord. Component of the Papez neuronal circuit. Involved in affective actions and learned processes.

Damage to the mammillary body, e.g. in the case of alcoholic encephalopathy, results in affective impairments and marked loss of perceptivity.

►Diencephalon

Mammillary Nuclei

Synonyms

►Nuclei mamillares; ►Nuclei of mammillary body

Definition

A distinction is made between the following nuclei of the mammillary body:

- Mammillary body, medial nucleus
- Intermediate mammillary nucleus
- Mammillary body, lateral nucleus
- Posterior nucleus

The medial nuclear region is especially pronounced in humans and connected via the thalamus with the prefrontal cortex. Selective dysfunction of the mammillary body, medial nucleus results in Korsakoff syndrome (amnetic syndrome with anterograde and retrograde impaired memory, and diminished drive).

►Diencephalon

Mania

►Bipolar Affective Disorder

Manic-depressive Illness (MDI)

►Bipolar Affective Disorder

MAP

Definition
Microtubule-associated Protein.

►Microtubule

Map Refinement

Definition
The process by which the initial crude topographic map of a sensory surface to structures in the central nervous system, is refined later in development.

MAPK

Definition
►Mitogen Activated Protein Kinase

Mapping Study

Definition
An experimental procedure in which electrodes are placed into the cortex of a living brain to record the electrical activity of neurons in response to various stimuli.

►Evolution of Association Pallial Areas: Parietal Association Areas in Mammals

Maps

Definition
Neurons may be arranged so that they represent the outside world in a systematic, topographic manner. Those arrangements are called neural maps. The most famous maps may be the representation of the body surface in the somatosensory cortex.

Marburg's Variant

Definition
This is a fulminant, widespread demyelinating disease without remissions which is fatal within 1–2 years. Lesions in Marburg's multiple sclerosis (MS) are more destructive than those usually seen in MS with widespread myelin destruction, severe axonal loss, edema, massive macrophage infiltration and extensive necrosis. Lesions on magnetic resonance images (MRI) increase in size and become confluent reflecting large areas of demyelination.

►Multiple Sclerosis

MARCM

►Mosaic Analysis with a Repressible Cell Marker

Masking of Sounds

Definition
This refers to the increase in the level of a "target" sound (measured in dB) that is required to overcome effects produced by a second sound.

►Psychoacoustics

Masking (Positive/Negative)

Elaine Waddington Lamont[1], Shimon Amir[2]
[1]Institute of Neuroscience, Carleton University, Life Sciences Building, Ottawa, ON, Canada; Department of Psychiatry, McGill University, Montréal, QC, Canada
[2]Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, Montreal, QC, Canada

Synonyms

Disguising

Definition

The attenuation (negative) or enhancement (positive) of a measure of the circadian master clock by an exogenous stimulus or factor.

Characteristics

Masking is a term applied to a number of phenomena in circadian research, whereby some clock-controlled variable of interest is obscured, but not necessarily altered, by an exogenous factor. Masking can be superimposed on ►entrained or ►free-running rhythms, and can be identified by the sudden change in behavioral state that occurs with its onset or offset. Often the effectiveness of the masking stimulus is dependent on the circadian phase of the variable of interest. Masking can limit the interpretation of experimental results, which has necessitated the adoption of particular experimental protocols in order to reveal the endogenous circadian rhythm of the variable of interest. Two areas where masking has had a significant impact on experimental methodology are masking of locomotor activity by light in rodents and the masking of the core body temperature (CBT) rhythm by posture and sleep in humans.

Photic Masking of Locomotor Activity

Photic masking is caused by the direct enhancement or inhibition of locomotor activity by light, and is mediated by the visual system, as it is abolished by orbital enucleation [1], but not by lesions of the master circadian clock, the ►suprachiasmatic nucleus (►SCN) [2]. Devising means of reducing masking effects has led to the development of special methodologies including the use of constant darkness, constant light, and skeleton photoperiods. In ►diurnal species like canaries, light produces positive masking, inducing or increasing locomotor activity, while darkness inhibits activity [3]. In ►nocturnal species, the effect of light is inhibitory, particularly when exposure occurs during the active phase, while darkness results in a release from inhibition or "unmasking" [4]. Positive masking by light has been observed in nocturnal rodents at very low light levels, inviting speculation that the utility of low light levels for successful foraging, compared to total darkness, can result in increased locomotion [1].

Interestingly, in rodents, positive and negative masking appear to be mediated by different aspects of the visual system. Negative masking is independent of the image-forming visual pathway, as suppression of locomotor activity was observed in mutant mice that have nearly total degeneration of both rods and cones [1]. In fact, negative masking appears to be mediated by melanopsin-expressing ►retinal ganglion cells, as melanopsin knock-out mice show an impaired masking response to light, compared to wild-type mice. Negative masking of activity occurs in melanopsin knock-outs during the first part of a 3 h light pulse, but activity gradually increases to darkness levels, despite the continued presence of light. In contrast, wild-type animals show negative masking throughout the three hour light pulse [5]. This suggests that melanopsin-expressing retinal ganglion cells are necessary for the maintenance of photic inhibition of locomotor behavior, but not for the initiation of masking. Interestingly, positive masking requires the classical ►photoreceptors. Positive masking is intact in wild-type mice and in melanopsin knock-out mice [5], but is absent in rodless mice [1].

Masking of Circadian Core Body Temperature

Masking is a confounding variable in human circadian rhythms research because of the enormous difficulty of eliminating or even effectively modeling the effects of exogenous variables on the circadian core body temperature (CBT) rhythm. CBT is frequently used as a marker of the phase and amplitude of the circadian clock in humans because it is more readily measured in a continuous manner than circadian rhythms of ►melatonin or cortisol secretion, which must be sampled frequently via plasma, saliva, or urine. CBT is directly controlled by the SCN master clock, and easily measured with a rectal probe, but is influenced by a large number of exogenous variables including the ►light/dark cycle, sleep, activity, social interaction, posture, ambient temperature, and humidity [6]. Three methods have been used to control masking effects in humans: the ►constant routine (CR) procedure, the ►forced desynchrony procedure, and ►mathematical purification. The "gold standard" of these is the CR, which holds masking effects constant in order to reveal the CBT rhythm. After maintaining a regular sleep-wake schedule for several days to weeks, subjects enter a temperature, light, and humidity controlled laboratory where they remain awake in a semirecumbent posture throughout the 30–72 h assessment. Movements are kept to a minimum and meals are replaced by isocaloric

snacks at regular intervals. Using this technique, Czeisler and colleagues have been able to accurately determine the human phase response curve to light [7]. A major limitation of the CR is that effects of fatigue and sleep deprivation are not controlled. In contrast, a forced desynchrony protocol allows for the measurement of masking effects of sleep by placing subjects on a sleep-wake schedule either much longer, or much shorter than 24 h, to which the master ►circadian pacemaker is unable to entrain. In this way, the intrinsic circadian period of CBT is revealed and the effect of sleep can be observed at all circadian phases [8,9]. While both of these techniques are very powerful, they are limited by the necessity of being carried out in a laboratory over extended periods of days to weeks. In contrast, mathematical purification, which removes masking effects mathematically, can be performed on any data set, whether obtained in the laboratory under rigorous conditions, or in the field. Unfortunately, although purification is very powerful, it is limited by the availability of the data used to describe masking effects. For example, physical activity raises core body temperature. Therefore, to subtract the effect of activity from the endogenous CBT rhythm, the effect of that activity on temperature must be known. While some work has been done to measure the effects of posture and activity on temperature, normative values for a particular population of interest may not be available [6]. Also problematic is that many purification methods assume that exogenous factors affecting CBT are independent of each other and of the phase of CBT. If this assumption is violated, a purification model that was simply additive could potentially obscure changes in phase. Using a 90 min day protocol, Moul and colleagues [10] demonstrated that the masking effects of sleep and posture on CBT are not consistent across the day, but in fact also show circadian rhythms. The greatest rate of temperature decrease occurred several hours before the CBT minimum, while the subject was lying in bed awake, and gradually decreased after sleep onset. While a model for purification of CBT could certainly incorporate this type of data, rigorous testing and comparison with accepted laboratory based protocols like the CR will be necessary to determine the reliability and validity of any purification method, particularly when used with clinical populations, where observations about the phase relationships between CBT and masking variables may differ from that observed in normal subjects.

References

1. Mrosovsky N, Foster RG, Salmon PA (1999) Thresholds for masking responses to light in three strains of retinally degenerate mice. J Comp Physiol A 184:423–428
2. Redlin U, Mrosovsky N (1999) Masking by light in hamsters with SCN lesions. J Comp Physiol A 184:439–448
3. Aschoff J, von Goetz C (1989) Masking of circadian activity rhythms in canaries by light and dark. J Biol Rhythms 4:29–38
4. Aschoff J, von Goetz C (1988) Masking of circadian activity rhythms in hamsters by darkness. J Comp Physiol A 162:559–562
5. Mrosovsky N, Hattar S (2003) Impaired masking responses to light in melanopsin-knockout mice. Chronobiol Int 20:989–999
6. Hanneman SK (2001) Measuring circadian temperature rhythm. Biol Res Nurs 2:236–248
7. Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sanchez R, Rios CD, Freitag WO, Richardson GS, Kronauer RE (1986) Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 233:667–671
8. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE (1999) Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 284:2177–2181
9. Dijk DJ, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526–3538
10. Moul DE, Ombao H, Monk TH, Chen Q, Buysse DJ (2002) Masking effects of posture and sleep onset on core body temperature have distinct circadian rhythms: results from a 90-min/day protocol. J Biol Rhythms 17:447–462

Mast Cell

Definition

Mast cells are a type of resident tissue leukocyte, widely distributed in a variety of tissues/organs. Mast cells have large numbers of cytoplasmic granules containing histamine, bradykinin, prostaglandins, and etc., which can be released upon mast cell activation (a process called degranulation). Many of these substances released have effects such as vasodilation and smooth muscle contraction. In an activated state, mast cells can also secret certain types of cytokines that shape further adaptive immune responses.

Master-Slave Oscillators

Definition

Master oscillators are those that set the phase and period of circadian rhythms by driving effectors for multiple

rhythmic processes, or by coordinating slave (secondary) oscillators that drive effectors. Slave oscillators drive local rhythms, and do not coordinate the phase of oscillators elsewhere.

►Internal Desynchrony

Mastication

James P. Lund[1], Arlette Kolta[2]
[1]Faculty of Dentistry, McGill University, Montréal, QC, Canada
[2]Faculté de Médecine Dentaire, Université de Montréal, Succursale Centre-ville, Montréal, QC, Canada

Synonyms

Chewing; rhythmic jaw movements

Definitions

The initial stage of digestion in which pieces of food are mechanically broken down and mixed with saliva by the rhythmical action of the teeth.

Characteristics

Quantitative Description

Humans and most other mammals except carnivores grind or chop food between their upper and lower teeth prior to swallowing. The incisor teeth are used to bite off pieces of food that are then transported back in a series of simple movements (Fig. 1a) by the tongue and facial muscles to the premolar and molar teeth, where reduction of the food takes place (Fig. 1b) during a series of repetitive movements of the mandible, at about 1.5 Hz in adult humans. The general form of each movement cycle depends on the type of food being eaten: brittle foods tend to be chopped, while tough foods are chewed with wider lateral strokes. As the size of the particles declines with successive cycles, the amplitude and velocity of the opening and closing movements of the jaw fall, and forces applied between the teeth drop. The tongue forms the food and intermixed saliva into a bolus during a pause in the opening phase of the cycles preceding swallowing (Fig. 1c).

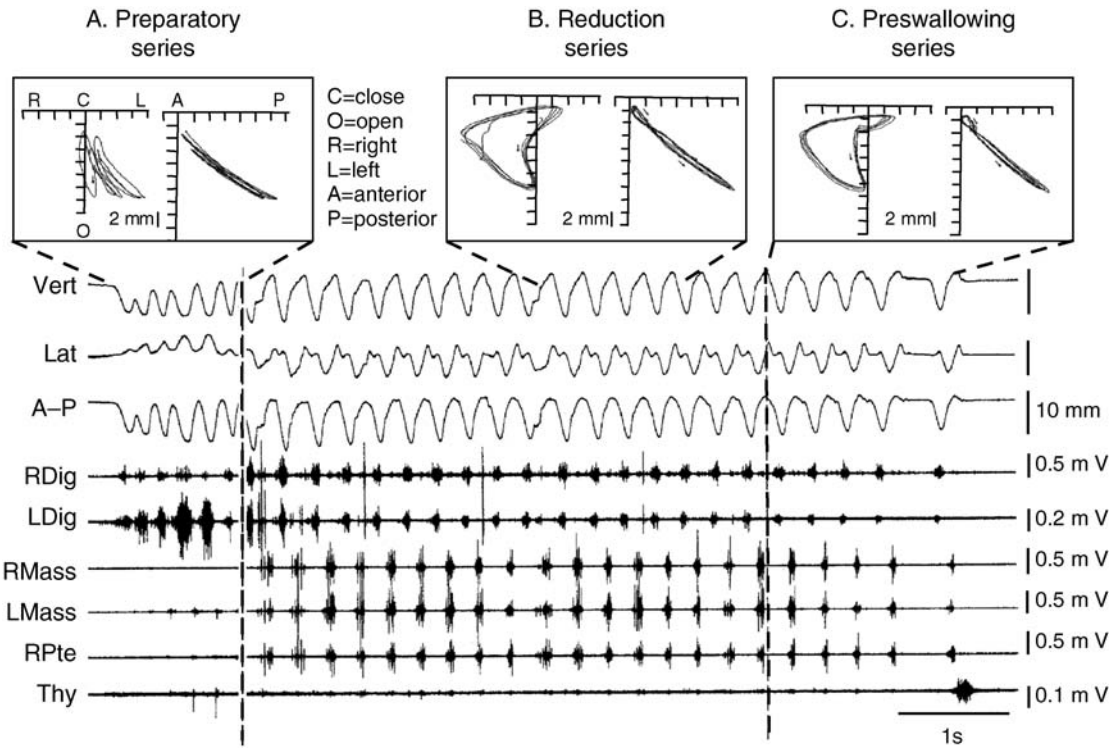
Higher Level Structures

The essential circuits controlling mastication are located in the ►hindbrain, and the basic rhythmical alternation of jaw opening and closing movements can be produced by a hindbrain Central Pattern Generator (CPG) in the absence of sensory feedback [1–3]. However, when scientists began to use repetitive electrical pulses to stimulate the brain in the nineteenth century, they found that mastication was represented in the cerebral cortex of primitive mammals and in more evolved species, including humans [3,4]. In lower species, the various patterns of natural mastication are represented at distinct sites in an orderly fashion. In primates, the cortical masticatory area is found at the lateral end of the ►precentral gyrus, but it does overlap with the more medial representation of individual jaw, tongue and facial muscles in the primary motor cortex, and also extends into the adjacent sensory cortex in the ►postcentral gyrus [5]. Neurons in both the cortical masticatory and adjacent motor cortex receive inputs from orofacial sensory receptors, and lesions or cold block of both regions disrupt ingestion, mastication and swallowing.

Lower Level Structures

The essential parts of the masticatory CPG lie between the rostral poles of the Vth (trigeminal) and VIIth (facial) cranial motor nuclei. There are two CPGs, one for each side, that are connected by axons that cross the midline. Each CPG is made up of many neurons. There are a large number in the lateral ►reticular formation (RF) that surrounds the Vth motor nucleus (Motor V), in the adjacent spinal trigeminal nucleus (Spinal V) and in the dorsal cap of the Vth main sensory nucleus (Main V), which change their pattern of firing during ►fictive mastication (Fig. 2).

Many of these neurons control V motoneurons directly [2]. Some fire tonically, but most of them fire rhythmical bursts of action potentials that coincide with either the jaw closing or jaw opening phases of the "fictive" masticatory cycle [6,7]. Most of the neurons receive inputs from oral mechanoreceptors or ►muscle spindles, and from the motor cortex [7]. The CPG also includes the central axons of muscles spindle afferents, which appear to transmit messages from their terminals in Spinal V and lateral RF backwards to their other terminals in Motor V [2]. The motor neurons in turn control the activity of four groups of muscles: one to open the jaws- the digastric, and three closers-the temporalis, masseter and pterygoid groups, and four groups of teeth (Incisors, Canines, Premolars, and Molars). The jaw closing groups are complex, multi-component muscle systems that are capable of moving the mandible in all three planes. All are innervated by the trigeminal nerve, except for a portion of the digastric muscle that is innervated by the facial nerve. The jaw closing groups are very powerful and also fatigue resistant. Mastication requires coordinated actions of the tongue and facial muscles. Saliva is mixed with the food during mastication, and salivary enzymes begin the first stage of chemical digestion. However, the main function of saliva is to provide lubrication during mastication and swallowing. Activation of ►periodontal pressoreceptors causes reflex salivation.



Mastication. Figure 1 Records of movements of the lower incisor teeth of an awake rabbit and of jaw muscle electromyographic (EMG) activity during the mastication of a pellet of rabbit chow. The sequence of movements is divided into Preparatory, Reduction and Preswallowing series of cycles. The Preparatory cycles have only two phases, Opening and Closing; the Reduction series has a Slow Closing phase in which the food is ground up, and during the Preswallowing phase, the jaw pauses during opening to allow the bolus to be formed. Vert, Lat and A-P- movement of the teeth in the vertical, lateral and anterior-posterior directions. RDig, LDig- right and left digastric EMGs. RMass, LMass- right and left masseter EMGs. RPte- right medial pterygoid EMG. Thy- thyrohyoid muscle EMG (swallowing marker). In A, B and C, the output of two pairs of axes is combined to show movement of the teeth viewed from the front (left) and from the left side (right). Data from Schwartz G et al. (1989) Journal of Neurophysiology 62:273–287.

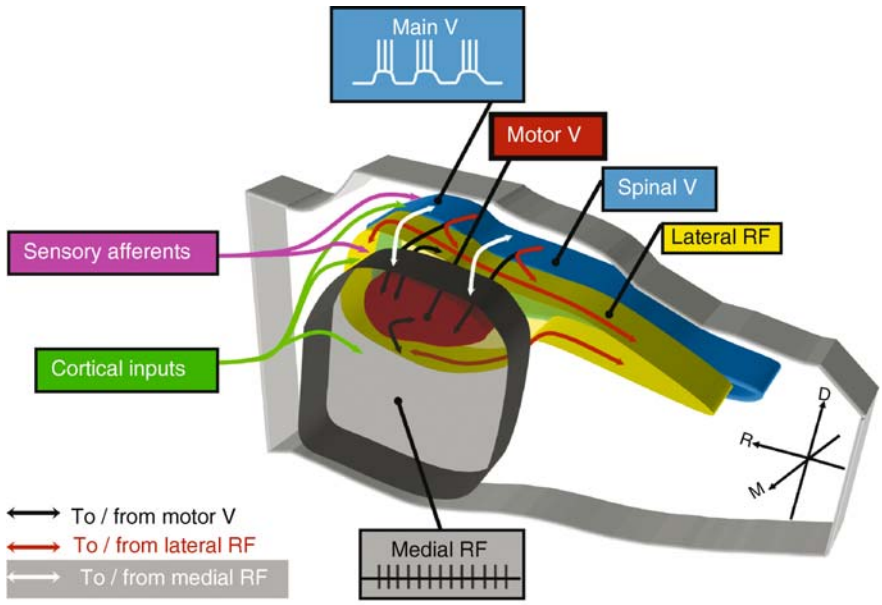
The medial RF at the level of Motor V also seems to be implicated in the control of mastication [3,8], but we do not know yet if it is an essential part of the CPG. This region does not project directly to V motoneurons, but it is reciprocally connected with the lateral subgroups [9]. It gets direct inputs from the motor cortex, but not from sensory afferents [8]. Many neurons in the dorsal half of the medial RF fire in either the jaw opening or the jaw closing phases, while most ventral neurons fire tonically. These tonic neurons appear to inhibit the lateral subgroups during mastication, while the phasic dorsal neurons have mixed effects [8].

Higher Level Processing

The primary motor cortex has a primary role in coordinating the ingestion and the transport phase of mastication, while the masticatory cortex is more important in food reduction, preswallowing and swallowing [4, 5]. The corticobulbar pathways from these regions of the cortex innervate all of the brainstem masticatory cell groups bilaterally (Fig. 2), and the firing pattern of many brainstem neurons is modified by the short-latency inputs from the cortex during fictive mastication [4,5,7,8].

Lower Level Processing

The motoneurons of the jaw closing muscles occupy the anterior and dorsal portions of Motor V, while the jaw opening motoneurons are confined to the ventral and caudal parts. During fictive mastication, the CPG causes jaw opening motoneurons to fire in very high frequency (up to 250 Hz) bursts, which are superimposed on slow rhythmical depolarizing potentials that return to resting levels during the jaw closing phase [3]. The slow rhythmical oscillations are mediated by excitatory amino acids. The jaw closing motoneurons are only weakly depolarized by similar slow potentials during the closing phase of fictive



Mastication. Figure 2 A model of the hindbrain CPG for mastication and associated structures. The figure shows the right side of the brain viewed from the midline and slightly from behind. The Main sensory (blue-Main V) and Spinal trigeminal nuclei (blue- Spinal V)) and adjacent lateral reticular formation (yellow-lateral RF) receive direct inputs from sensory afferents and from the sensori-motor cortex that are capable of activating the CPG. The three regions are reciprocally connected, and all project directly to Motor V. Some neurons in Main V have the intrinsic ability to generate slow depolarizing potentials and bursts of spikes (Inset). The medial RF has direct inputs from the cortex, but not from sensory receptors. It is reciprocally connected with the lateral nuclei, but not with Motor V. Neurons in the middle of the nucleus can fire tonically even when isolated from other neurons. R-rostral, M-medial, D-dorsal.

mastication: however, they are much more active during jaw closing in real mastication, because of excitatory feedback from sensory receptors (see below). This feedback is cut off by strong glycinergic inhibition of the motoneurons during jaw opening [3]. Trigeminal motoneurons receive a dense serotoninergic innervation, and express several receptor subtypes. Serotonin has little effect on the activity of quiescent neurons, but it plays an important role by modulating firing generated by other transmitters. It also modifies the masticatory rhythm [2,3].

The CPG can be turned on by tonic stimulation of sensory receptors in the mouth and muscles [1], and during mastication, several groups of afferents provide feedback to motoneurons, the CPG and to higher centers (Fig. 2). The pattern of firing that emerges from the motoneurons is the result of these interactions. The effects of three groups of afferents (muscle spindles, periodontal pressoreceptors and nociceptors) have been well described.

There are no, or very few, muscle spindles in jaw opening muscles, but jaw closing muscles contain many. These provide monosynaptic excitatory glutamatergic feedback to jaw closing motoneurons, and to many interneurons in the trigeminal sensory nuclei and lateral RF [2,6,7]. During the jaw opening phase of mastication, these receptors are stretched, and they fire at high frequency [10]. This activity facilitates the CPG, but the monosynaptic excitation of the jaw closing motoneurons is prevented by hyperpolarization (see above). Many spindle afferents continue to fire as the jaw closing muscles shorten because the ►fusimotor neurons are driven strongly by the CPG. This muscle spindle input lengthens the jaw closing motoneuron bursts and greatly increases firing frequency [1,10].

Periodontal pressoreceptors are located in the ligament surrounding the roots of the teeth. They signal the direction and intensity of loads generated during mastication. Tapping on the teeth causes a bi-synaptic inhibition of the jaw closing muscles that is abolished by the glycine antagonist, strychnine, but heavy pressure on the teeth does not cause inhibition during mastication. Instead, these receptors cause the jaw closing phase to lengthen, and jaw closing motoneurons to fire at higher frequency. It appears that the CPG shuts the inhibitory pathway, and opens an excitatory one during mastication [1,10].

The CPG also modulates inputs from other oral mechanoreceptors and particularly from nociceptors (pain afferents). When nociceptors are stimulated during chewing (e.g., by biting the tongue), they strongly inhibit the jaw closing muscles [1].

Process Regulation

Tonic stimulation of inputs to the CPG coming from sensory receptors, from the cortex and other forebrain and midbrain structures is converted into rhythmical mastication by the CPG [1–3]. It is not known how this happens, but there is evidence that special properties of the network and of individual neurons may be involved. For example, when the pattern of mastication changes, say from grinding on the left teeth to grinding on the right, about half of the active lateral RF and Spinal V neurons change their rhythmical firing pattern, while the others stop participating in the CPG [7]. This suggests that the CPG uses at least two methods to generate different patterns of mastication: addition and subtraction of its constituent neurons, and changes in firing frequency of active elements. There are extensive interconnections, both excitatory and inhibitory, between all of the lateral subgroups of the CPG [9] that must be important in this reorganization, and perhaps also in generating the rhythm. However, some CPG neurons seem capable of generating self-sustained membrane oscillations either spontaneously, or in response to tonic inputs, and this can lead to regular bursts of firing at about the masticatory frequency [6,9]. Most of these are in the dorsal cap of Main sensory V, which is the only region of the nucleus that seems to be part of the CPG [6]. Most of the interactions within these circuits involve amino-acid neurotransmitters. Excitatory synapses seem to release glutamate, while inhibitory inputs are either glycinergic or ►GABAergic [2,9].

Function

The function of mastication is the mechanical breakdown of food to prepare it for digestion.

Pathology

Disorders of mastication are not a frequent symptom of neurological disease, although strokes that cause lesions of the cortical masticatory area are associated with difficulty in initiating mastication and swallowing [5]. Abnormal orofacial movements, which sometimes resemble purposeless mastication, are a symptom of tardive ►dyskinesia, which is associated with damage to the striatum caused by long-term treatment with neuroleptic drugs.

Chronic pain of the jaw muscles and joints slows mastication and reduces chewing forces, and loss of salivary tissue (autoimmune disease, radiation) makes it hard to chew and swallow. Many millions of people throughout the world are handicapped because the ability to masticate falls as teeth are lost.

Therapy

There is no effective treatment for tardive dyskinesia. Lost teeth can be replaced by prostheses.

References

1. Lund J (1991) Mastication and its control by the brainstem. Crit Rev Oral Biol Med 8:718–724
2. Lund JP, Kolta A, Westberg KG, Scott G (1998) Brainstem mechanisms underlying feeding behaviours. Curr Opin Neurobiol 8:718–714
3. Nakamura Y, Katakura N (1995) Generation of masticatory rhythm in the brainstem. Neurosci Res 23:1–19
4. Lund J, Enomoto S (1988) The generation of mastication by the central nervous system. In: Cohen AH, Rossignol S, Grillner S (eds) Neural control of rhythmic movements in vertebrates. Wiley, New York, pp 41–71
5. Narita N, Yamamura K, Yao D, Martin RE, Masuda Y, Sessle BJ (2002) Effects on mastication of reversible bilateral inactivation of the lateral precentral gyrus in the monkey (*Macaca fascicularis*). Arch Oral Biol 47:673–688
6. Tsuboi A, Kolta A, Chen CC, Lund JP (2003) Neurons of the trigeminal Main sensory nucleus participate in the generation of rhythmic motor patterns. Eur J Neurosci 17:229–238
7. Westberg KG, Clavelou P, Sandstrom G, Lund JP (1998) Evidence that trigeminal interneurons form subpopulations to produce different forms of mastication. J Neurosci 18:6466–6479
8. Scott G, Westberg KG, Vrentos N, Kolta A, Lund JP (2003) Effect of lidocaine and NMDA injections into the medial pontobulbar reticular formation on mastication evoked by cortical stimulation in anaesthetized rabbits. Eur J Neurosci 17:2156–2162
9. Bourque MJ, Kolta A (2001) Properties and interconnections of trigeminal interneurons of the lateral pontine reticular formation in the rat. J Neurophysiol 86:2583–2596
10. Hikeda O, Morimoto T, Kato T, Masuda Y, Inoue T, Takada K (1999) Behavior of jaw muscle spindle afferents during cortically induced rhythmic jaw movements in the anesthetized rabbit. J Neurophysiol 82:2633–2640

Matching to Sample

Definition

Matching to sample discrimination (MTS) is a kind of conditional discrimination. In MTS training, a sample stimulus is given first, then two or more different choice stimuli are given to animal. One of the choice stimuli is the same as the sample stimulus and the animal has to choose that stimulus to get reward.

►Discrimination

Material Body

Definition
A continuous collection of material particles. Technically, such a collection is known as a material "continuum" or, more precisely, a differentiable manifold.

►Mechanics

Material Evolution

Definition
A concept used in theories of growth and remodeling, whereby certain phenomena (such as motion of dislocations, addition of matter or rearrangement thereof) take place in the material body, in addition to its deformation in space. An evolution law prescribes the time-evolution of the material isomorphisms of a body.

►Mechanics

Material Frame Indifference

Definition
A constitutive principle according to which the constitutive functionals are independent of the observer, whether it be inertial or not.

►Mechanics

Material Isomorphism

Definition
A map between the neighborhoods of two points bringing the material responses into exact coincidence. Also called a material transplant.

►Mechanics

Material Symmetry

Definition
A material isomorphism of a point with itself.

►Mechanics

Material Time-Derivative

Definition
The derivative of a field with respect to time while following a specific particle. In the Lagrangian description, the material time-derivative coincides with the partial derivative of the field with respect to time. In the Eulerian description an additional term needs to be added to take into consideration the fact that the particle is moving in space.

►Mechanics

Materialism (Dialectical, Eliminative, Emergentist)

Jürgen Schröder
University of Karlsruhe, Heidelberg, Germany

Synonyms
Materialist monism

Definition
Materialism is a metaphysical doctrine opposed to idealism according to which everything that exists is material, i.e. there are only material but no spiritual substances. Angels, gods, incorporeal souls and spirits are denied. Secondly, materialism is a methodological attitude that is critical of tradition and authority. According to this attitude, explanations of mental phenomena should be given without reference to occult powers whose existence cannot be independently (from the facts to be explained) ascertained.

Description of the Theory
Dialectical Materialism
Dialectical materialism is a doctrine that originated in the nineteenth century in the works of Marx and especially

Engels [1,2,3]. Both authors approved of Hegel's dialectical method but rejected his idealism. They held that matter is primary and that mind and consciousness are dependent on matter. Marx's materialism was empiricist in the sense that all real knowledge is based on sense experience, it was realist in that he believed in a mind-independent material world. Furthermore he rejected supernaturalism (the doctrine that some events like, for example, the plague are to be explained by the intervention of God or the Devil) and mind-body dualism.

The dialectical aspect of dialectical materialism was especially emphasized by Engels who understood dialectical materialism as superseding mechanical materialism as it was defended e.g. by Vogt, Büchner, or Moleschott. At the core of mechanical materialism is the idea that every phenomenon of nature, including life and mind, can be reduced to arrangements of the simple constituents of matter and explained by the laws of mechanics. As opposed to this sort of reductive materialism, dialectical materialism holds that there is real novelty in the development of the world and human history, e.g. new substances result from chemical combinations, life as a novel phenomenon results from the combination of a complex of chemical processes and minds result from the complex functioning of brains. Mechanical materialism turned out to be false because electromagnetic phenomena cannot be explained by the laws of mechanics. The underlying idea, however, that every phenomenon can be ultimately reduced to physical arrangements and physical laws has survived until today in the doctrine of physicalism.

Engels claimed that there were three fundamental dialectical laws of nature [3]: (i) The sudden change of qualities of phenomena when certain quantities in them reach a certain threshold, (ii) the law of the interpenetration of opposites, (iii) The law of the negation of the negation. Examples of the first law are the change from liquid to solid state when water is cooled down, the transformation of mechanical motion into heat, and the occurrence of a social revolution after the oppression of the people reaches a certain threshold. The interpenetration of opposites is an idea that Hegel used in order to explain how change and development are possible. For example, the movement of a body in space, Hegel thought, is only possible if the body is at one and the same instant at a certain place and at another place. For if it were at each instant at only one place then there would be only a series of stationary states but no movement. According to Engels (and Hegel) the opposites (the different places) have to interpenetrate one another if movement is to be possible.

The law of the negation of the negation is a law that applies especially to those changes in nature that give rise to novel phenomena and to progress in some sense. Examples of this law are the process in which a plant produces seeds giving rise to further plants, the process in which the early materialism of the Greeks was superseded by idealism which was superseded in turn by dialectical materialism, and the development of geological formations.

Of these three laws the second and the third seem to be unacceptable for different reasons. The second law amounts to the idea that there are contradictions in nature and to the idea that two sentences that contradict each other can both be true. From a contradiction, however, any sentence whatsoever can be logically derived and that means that the idea of truth, the idea that truth is a property only of *some* descriptive sentences and not of all, is abandoned. The third law suffers from a different defect. A law that is applicable to virtually everything and that accordingly cannot be refuted by any possible observation is cognitively useless. It is uninformative and its explanatory power is zero.

Eliminative Materialism

Eliminative materialism shares the rejection of supernatural entities like gods and angels with dialectical materialism. It also rejects the existence of soul substances in addition to physical substances. Whereas dialectical materialism with its three laws and its emphasis on novelty and progress is a positive doctrine (although a poor one), eliminative materialism is a negative doctrine. It says that certain things are not what we take them to be. Furthermore, the scope of eliminative materialism is much narrower than the scope of dialectical materialism. Eliminative materialism is a thesis about a certain part of the mental, viz. the propositional attitudes and qualia. The thesis about propositional attitudes says that since they are posits of a folk theory, viz. folk psychology, and since every folk theory in the past was wrong, folk psychology will also be wrong. Besides, Churchland argues that folk psychology does not explain certain things (e.g. why we need sleep), that it has been in a state of stagnation for more than 2,000 years and that it is not reducible to the neurosciences (which is bad for folk psychology because the ontology of the latter is beyond any doubt) [4]. But – and this is the decisive move – if the theory (folk psychology) gets the properties of its posits quite wrong then the terms that are used in folk psychology like "belief," "fear," "hope," "desire" etc. do not refer. They do not designate any part of reality. They are empty. And their being empty means that propositional attitudes don't exist.

The corresponding thesis about qualia, viz. that they don't exist, is similarly argued for. Qualia, i.e. sensory qualities like tickles or color qualities, are supposed to have certain properties as e.g. that one cannot be wrong about one's own sensations. But there is nothing that has this property. So qualia *in the traditional sense* don't exist [5]. This line of attack on qualia is, however, easily rebutted by admitting that qualia *in this sense*

don't exist and by insisting that states with a characteristic feel and a subjective character do exist.

The basic strategy of eliminativists is, first, to say that propositional attitudes are posits of a theory with which we explain behavior and then to argue that this theory is quite probably false. The final step concludes from the alleged falsity of the theory to the emptiness of the terms of the theory and thereby to the non-existence of the entities those terms were supposed to refer to. This strategy can be criticized at every step.

First, as an alternative to the idea that we predict and explain the behavior of others by applying a theory (folk psychology) some theorists have urged that we run a simulation of the other's mental processes within ourselves, i.e. we take the information about the other person's situation in terms of her goals and beliefs and then ask ourselves what *we* would do in a similar situation [6]. In order to exclude the possibility that this simulation is done with an underlying theory of behavior, the proponents of the simulation approach point out that human behavior is very sensitive to slight changes in situations and that an incorporation of all the possible details of a situation into either the theory or the computational process of deriving conclusions would be just too complex a task.

Second, contrary to Paul Churchland's claim that our folk psychology (if we accept that we use a theory in the prediction of everyday behavior) is probably false, other theorists have insisted that it is a highly successful and deep theory without parallel in its domain (i.e. everyday behavior) [7].

Third, even if one takes folk psychology to be a false theory, it is far from clear what consequences its falsity has. A theory can be false in many ways. It may be that one peripheral claim of the theory is false or that many are. Or it may be that a central postulate has to be given up. The theory of electrons from 1900 ascribed trajectories to electrons, but the theory from 1934 rejected trajectories. Both theories, however, were about the same entities, viz. electrons. The term "electron" did not lose its reference by the fact that the theory from 1900 was found to be false. On the other hand, the theory of combustion before Lavoisier postulated a substance called "phlogiston" that was thought to be released in a combustion process. Oxygen, however, was thought to be absorbed by the burning material. In this case, the phlogiston theory of combustion was not only false, but the term "phlogiston" was said to refer to nothing. In order to adjudicate the plausibility of eliminative materialism it would be necessary to argue that folk psychology gets things so fundamentally wrong that the propositional attitudes will share the fate of phlogiston.

One way to argue for this conclusion takes its cue from cognitive science. There are certain models of cognitive processes like memory and inference according to which the information that is needed for various tasks is distributed over a network of nodes (connectionist models). In these networks there are just no entities to which the two characteristic properties of propositional attitudes, viz. a certain content and a certain causal role, can be ascribed. If connectionism with distributed representations turns out to be the best paradigm in cognitive science then this may be a decisive reason against the existence of propositional attitudes *thus* conceived (as distinct entities with a particular content and a particular causal role) [8].

On the other hand, propositional attitudes needn't be conceived in this way. They needn't be states with distinct causal roles, but may be rather like parallelograms of forces, i.e. devices that we use in order to make predictions but that do not themselves belong to the furniture of the world [9]. However, this move, viz. an instrumentalist conception of propositional attitudes, amounts to abandoning the reality of the attitudes altogether if one adopts a causal criterion of reality, i.e. that being real requires being causally efficacious.

A common objection to eliminative materialism urges that the eliminative materialist makes an assertion when expressing the thesis that there are no propositional attitudes. According to common sense assertions express beliefs. The eliminativist thus falls victim of the contradiction that he or she believes that there are no beliefs. Against this Patricia Churchland pointed out that we need a successor concept for the concept of belief [10]. Once we dispose of such a concept we can say that an assertion expresses a type of cognitive state T which is not a belief. Thus the contradiction would disappear. However, the problem with this answer is that nobody has any idea what such a successor concept would be like. So this answer does not seem to amount to much more than handwaiving.

Emergentist Materialism

Emergentist materialism in the broad sense is the doctrine that although there are only material substances there are various types of such substances with properties that cannot be reduced to properties of their parts together with composition laws describing the interaction of the parts [11]. According to a weaker sense of "emergentist materialism" any materialism that acknowledges properties of wholes which are not properties of their parts is emergentist [12]. In the early 1920s, before the advent of quantum mechanics and quantum chemistry, C.D. Broad believed that certain properties of chemical compounds, in particular their chemical behavior, could not be predicted in principle from knowledge about the properties of the atoms and knowledge about how the atoms interact in a molecule. "In principle" meant that empirical regularities like "whenever atoms of type x, y, z etc. combine in proportion P, then the resulting compound will show behavior B in circumstances C" were disallowed for the

prediction. These regularities were also called "ultimate laws" because they were not reducible to or explainable by other facts. The British emergentists like Samuel Alexander and Convy Lloyd Morgan thought that predictions of chemical, biological, psychological or sociological properties could be made on the basis of such empirical laws but they also thought that these laws were brute facts that cannot be further explained. According to the British emergentists a property of a whole was emergent if and only if (i) it was not also a property of its parts and (ii) it was not deducible from the properties of the parts and general composition laws. If a property of a whole was only deducible from the properties of the parts and an ultimate law connecting these properties with the property of the whole then it was said to be emergent. The important point about composition laws was that they be general. In the case of chemistry this meant that they should be valid for all chemical compounds and not only for a certain kind of compound.

A prima facie strength of emergentist materialism was that it allowed to account for the major distinctions in our common sense picture of the world: the distinction between the living and non-living, and the distinction between organisms with a mind and organisms without a mind. Life and mind were considered to be major emergent properties.

A problem with emergentism thus construed is whether emergence is a property of reality itself or whether it is rather a property of our knowledge of reality. Certain properties that were considered to be emergent in the past such as the chemical properties of chemical compounds or the property of life with its more specific properties of growth, reproduction, metabolism etc. have turned out to be non-emergent according to Broad's criterion of non-deducibility. This fact supports the hypothesis that emergence has to do with our knowledge rather than with reality itself [13].

As far as the mind and the brain are concerned, emergentist materialism claims that among all properties of all things there is a certain class, viz. the qualities of sensations, which is not deducible from physical properties and furthermore that these qualities will remain undeducible and therefore emergent forever [14,15]. The more specific idea is that it will appear forever contingent that the special character of, for example, a visual sensation is connected with a particular brain process. It is claimed that we cannot give any reason why a visual sensation should be correlated with brain process A and another visual sensation with a brain process B instead of the reverse.

There is, however, an ambiguity as to the concept of qualia involved in this claim. The quality of an sensation can be described relationally by comparing it to other qualities of the same domain. Colors, for example, can be arranged in a circle such that any color that is on the opposite side of the circle is maximally dissimilar to a given color with respect to the other colors. All the relational properties of a sensory quality constitute its relational profile. It seems plausible that a state with a certain relational profile cannot be realized just by any brain state but only by such brain states that have enough structure in order to guarantee the relational profile of the respective sensory quality. Qualitative states with different relational profiles should accordingly be correlated with brain states that have different structures. If we identify a sensory quality with a certain relational profile there probably are explanations of sensory qualities that remove the impression of contingency that constitutes the so-called explanatory gap [16].

On the other hand, qualia may be taken non-relationally. One may conceive of a quale as a structureless property that has a certain intrinsic character. Even then qualia would not be completely without relations. But the only relations would be relations of difference without any specifications of greater or smaller difference. The emergentist claim would then be that with respect to these intrinsic, non-relational qualities any correlation with some brain process or other would be arbitrary, i.e. there would be no reason why the intrinsic quality of red should be correlated with brain process A instead of B.

According to this line of reasoning the only really emergent properties would be the intrinsic qualities of experience. But the underlying idea may also be used to show that any real property whatsoever is emergent relative to more fundamental properties. For, imagine any property, e.g. the property of being magnetic or the property of having some mass m. In order to characterize this property, you may specify a certain relational profile. You may say what the causal role of this property is and you may say how it differs from other properties in its domain. But you may also assume that this property has a certain intrinsic character over and above its relational profile. You may even assume that this intrinsic character is the bearer of the relational profile. In contrast with the case of qualia you don't know what this intrinsic character is like, you only think of it indirectly via its role of being the bearer of the relational profile. All the same, if you take any set of supposedly more fundamental properties and any composition rules there will be no reason why it is correlated with intrinsic character A instead of intrinsic character B. So the reason for the appearance of contingency of qualia relative to the brain states they are correlated with is their intrinsic character and not their being mental. Accordingly, every real property, i.e. every property with a distinct causal role is emergent relative to some set of more fundamental properties as it appears equally contingent that its intrinsic character is correlated with that set of more fundamental properties.

But if every real property is emergent then the concept of emergence does no useful work anymore, e.g. to demarcate the major layers of reality.

References

1. Marx K (1845) Die heilige familie. Frankfurt
2. Engels F (1878) Herrn eugen dührings umwälzung der wissenschaft. Leipzig
3. Engels F (1985) Dialektik der nature. Berlin
4. Churchland PM (1981) Eliminative materialism and the propositional attitudes. J Phil 78:67–90
5. Dennett D (1988) Quining qualia. In: Marcel A, Bisiach E (eds) Consciousness in comtemporary science. New York, pp 42–77
6. Gordon RM (1986) Folk psychology as simulation. Mind Lang 1:158–171
7. Fodor J (1987) Psychosemantics. Cambridge, Mass
8. Ramsey W, Stich S, Garon J (1990) Connectionism, eliminativism and the future of folk psychology. Philos Perspect 4:499–533
9. Dennett D (1981) Three kinds of intentional psychology. In: Healy R (ed) Reduction, time, and reality. Cambridge, pp 37–61
10. Churchland PS (1986) Neurophilosophy. Cambridge, Mass
11. Broad CD (1925) The mind and its place in nature. London
12. Bunge M (1980) The mind–body problem. Oxford
13. Schröder J (1998) Emergence: non-deducibility or downwards causation? Philos Q 48:433–452
14. DuBois-Reymond E (1872) Über die grenzen des naturerkennens. In: Strich F (ed) Deutsche akademier-eden, München, 1924
15. Levine J (1983) Materialism and qualia: the explanatory gap. Pacific Philos Q 64:354–361
16. Hardin CL (1988) Colour for philosophers. Indianapolis

Materialist Monism

►Materialism (Dialectical, Eliminative, Emergentist)

Maternal Transcript

Definition

Transcribed mRNA that is provided to the embryo directly by the mother.

►Alternative Splicing and Glial Maturation

Mathematical Model

Definition

A mathematical model is a mathematical tool (expression) representing the behavior of a physical system. Differential or difference equations are commonly used as models. Some mathematical models result from laws of physics. Others are obtained by experimenting on the system.

►Adaptive Control

Mathematical Purification in Circadian Rhythm

Definition

A procedure for mathematically removing the influence of exogenous factors on rhythmic circadian variables of interest. The correction is generally based on normative data measuring the size of the effect of the exogenous factor on the variable of interest, and applied according to currently theory on the timing of that influence. For this reason, the accuracy of mathematical purification is limited by the quality of the experimentally derived data used to develop the purification formula.

►Masking (Positive/Negative)

Mathematical System in Biomechanics

Definition

A defined set of mathematical equations.

►Distribution Problem in Biomechanics

Mathematical Theory of Communication

►Information Theory

Matrix

Definition

Body of the ligament that consists of water, collagen, proteoglycans, fibronectin, elastin, actin and other glycoproteins. In a ligament, the majority of the matrix is composed of collagen.

►Articular Cartilage
►Ligaments

Matrix Metalloproteinases

Definition

The family of enzymes contributing to both normal and pathological remodeling of the extracellular matrix and playing a key role in the migration of normal and malignant cells through the body. Matrix metalloproteinases are the members of a family of at least 15 Zndependent endopeptidases that function extracellulary. Their catalytic domains have a similar structure but the topology of the active site clefts differs, accounting for some of the differences in substrate specificities.

Maturation of Cells – Differentiation of Cells

►Nervous, Immune and Hemopoietic Systems: Functional Asymmetry

Mauthner Cell

Definition

Giant interneurons, arranged in a pair on either side of the brainstem, that mediate directed escape turns (Cstart escape) in fish and larval amphibians. Mauthner cells respond to acoustic, vibrational and various other sensory signals and initiate muscle contractions along the flank of the animal, resulting in a C-shaped bend of the body (see C-start escape).

►Auditory-Motor Interactions
►Startle Response

Mayer Waves

Definition

Blood pressure oscillations of low frequency (0.1 Hz in humans and cats, 0.4 Hz in rats). These waves are slower than the respiratory rate and are not synchronous with each breath but affect the ventilatory pattern.

►Pontine Control of Respiration

Maze Learning

Definition

A maze is a spatial puzzle. Mazes are typically two-dimensional and involve a player, termed a “traveler”, who attempts to move from a start location to a goal. A labyrinth is a particular type of maze with tortuous, walled alleyways and a single route from start to goal. Mazes have long been used as tests of learning, memory and intelligence. Common animal mazes include the T maze, the plus maze, Hebb-Williams mazes, the sunburst maze, the radial-arm maze, the water maze and the Barnes maze. Three important chapters in animal psychology involve mazes. Beginning in the 1920s Karl Lashley trained rats in labyrinths to explore their general learning capabilities. He found that no particular part of rat neocortex was necessary or sufficient to support maze learning and memory, and, from this observation, derived the principal of equipotentiality (also known as mass action). In the 1940s and 1950s two contentious groups (the behaviorists and the cognitivists) used a broad array of mazes to test whether rats learn about space by means of response learning or map learning. Finally, in recent years the radial-arm maze, the Barnes maze and the water maze have been used extensively to asses the role of the hippocampus in spatial learning and memory.

►Spatial Learning/Memory

M-channels

Definition

M-channels (M for muscarine) are non-inactivating, voltage-sensitive K^+ channels that exist in many types of neuron in the central nervous system and in peripheral sympathetic neurons, and generate the only sustained current in the range of action potential initiation. In the absence of acetylcholine, M-channels open at resting membrane potential and dampen neuronal excitability. Acetylcholine inhibits M-channel activity by activation of the muscarinic M_1 receptors. The M-current can be modulated by various receptor types, either by suppression or enhancement. There are two main ways of modulation: receptor-mediated modulation and the control of current amplitude by intracellular Ca^{2+}.

►Acetylcholine
►Action Potential
►Muscarinic Receptors
►Neuronal Potassium Channels

Meaning (Verification Theory)

Markus Schrenk Dphil
Research Fellow, Department Philosophy, University of Nottingham, University Park, Nottingham, UK

Synonyms

Verificationist theory of meaning; Verification principle; Verification criterion; Verificationism

Definition

The verification theory of meaning aims to characterize what it is for a sentence to be meaningful and also what kind of abstract object the ►meaning of a sentence is. A brief outline is given by Rudolf Carnap, one of the theory's most prominent defenders:

> If we knew what it would be for a given sentence to be found true then we would know what its meaning is. […] thus the meaning of a sentence is in a certain sense identical with the way we determine its truth or falsehood; and a sentence has meaning only if such a determination is possible. [1: 420]

In short, the verification theory of meaning claims that the meaning of a sentence is the method of its verification.

Description of the Theory

Verificationism can only be fully appreciated in the larger context of the philosophical credo it emerged from, namely twentieth Century ►logical empiricism (also known as ►logical positivism) [2].

An empiricist subscribes at least to the following doctrine: intuition or pure reasoning, can reveal what the world is like. All *factual* ►knowledge has its sole source in sense experience. For example, if you want to understand how the human brain works, there is no other way to knowledge than via observation, especially via empirical experiments.

This *epistemic* doctrine (see ►epistemology) about the nature and source of factual knowledge had already been put forward by the ►classical empiricists in the seventeenth and eighteenth Centuries. The novelty of twentieth Century logical empiricism is a shift in focus from this doctrine about knowledge to a doctrine about (scientific) language. More exactly, the logical empiricists tried to underpin the validity of the doctrine about factual knowledge with a doctrine about sentence ►meaning. This is where the verification theory of meaning has its place.

Suppose we stipulate that the meaning of a ►statement (a sentence, a ►proposition) is given by the observations we have to make to find out if it is true. Or stronger, that a sentence has to be discarded as meaningless unless one can offer a description of what fact or state of affairs has to be observable so that this sentence can be said to be true or false. That is precisely what the verification theory of meaning demands: "The meaning of a proposition is the method of its verification." [3: 148]

Suppose furthermore, that all factual knowledge is expressed in meaningful sentences. Then, together with the verification theory of meaning, we arrive back at the epistemic doctrine from above: factual knowledge has its justification in observation. Thus, verificationism is the linguistic counterpart of the empiricists' doctrine about knowledge.

Both logical empiricism and the verification theory of meaning are, however, outdated theories. This is not because the general idea behind them – that empirical knowledge depends on sense experience – has been given up by philosophers. Rather, verificationism in its strongest form faced a few unsolvable technical difficulties. A closer look at the verification theory of meaning, as well as exemplary applications of the theory will unveil some of these problems.

Verificationism and the Hierarchy of Language

Historical Background. The verificationist theory of meaning has a by-product: logical empiricists perceive language to be hierarchically structured. Observational terms are at the basis of that structure, and all other terms further down the hierarchy are translatable into

M

terms of this basis. ►Logic and ►conceptual analysis is the central tool to arrive at such translations of non-observational terms to observational terms. What does this mean?

Take a sentence like "This apple is red." The verification theory of meaning claims that it is meaningful if and only if we can describe which state of affairs has to be observable so that the sentence can be said to be true. In this case, the task seems to be rather easy: "This apple is red" is, indeed, a meaningful sentence – it is true just if the apple in front of us is really red, i.e. precisely if, under normal light conditions, it appears red to us, and false if not.

However, not every sentence contains terms that refer to directly observable features of easily observable objects. For those sentences it is difficult to see how the verificationist criterion can be met. For example, what kind of observation verifies sentences like "This fluid has a temperature of 100°C" or, worse, "The electron's mass is $m_e = 9.11 \times 10^{-31}$kg"?

For these sentences to meet the verificationist criterion of meaning, an intermediate step seems unavoidable: scientific terms which do not refer themselves to directly observable features of the world have to be analyzed or reduced to descriptive terms that do so (See ►operationalism). Those sentences that contain non-observational terms can, with the help of these analyses, be translated into sentences that are observational. Only then can the verification criterion of meaning be applied.

The following example illustrates what we mean: "object O has temperature T" can be analyzed into the phrase "if a mercury thermometer is placed into or nearby object O the mercury will rise (or fall) to mark T." With the help of this analysis we can translate "This fluid has a temperature of 100°C" into "if a mercury thermometer is placed into this fluid the mercury will rise (or fall) to mark 100." The latter sentence clearly indicates which possible observation would verify it. Hence, according to verificationism, the sentence has meaning.

The actual translation of all terms (or sentences) to observational terms (or sentences) is, of course, a utopian dream. In any case, the general possibility of such a reduction would suffice to support the empiricists' credo. Attempts to prove the general possibility have indeed been given [4].

Verificationism and Metaphysics. It is easy to see how both the conceptual analysis of terms and the verificationist doctrine about sentence meaning could be used as a tool to criticize or even ridicule metaphysical philosophy. Indeed, to try to show that metaphysics does not make any sense at all was part of the empiricists' programme. Terms like *god*, *nothingness*, or *meaning of life* are so the empiricists not suitable for analysis into observational terms and are, hence, not apt to figure in meaningful, verifiable sentences and philosophical research in general. They can, at best, be used to express a general attitude towards life, a *Lebensgefühl*, but they have no factual content [5].

Verificationism and Behaviorism. There is a close relation between verificationism and behaviorism (see ►behaviorism, ►logical). The aforementioned idea of a reduction of all scientific terms and sentences to observable terms and sentences means, too, that psychological terms, i.e., terms concerning the human ►mind, have to be translatable into observational language. This is precisely what behaviorism asks for: attributions of mental states to people (like "Agnes is happy") must be translated into statements about people's observable behavior or, at least, their dispositions to behave.

Take the sentence "Alfons desires a good bottle of wine." Such an ascription of a mental state to a person can only be admitted into scientific language if we can, according to the verificationist theory of meaning, describe the way we determine its truth or falsehood in observable terms. Hence, in order to give the meaning of that sentence we would have to say something along the following lines: "Alfons desires a good bootle of wine" is true if and only if (i) Alfons reaches for a bottle of wine when he sees one standing on the table, (ii) Alfons utters the words "Yes, please!" when someone offers him a glass of Riesling, (iii) Alfons seeks a wine shop when he has got the money and time, etc. This list amounts to a catalogue of observable stimulus and response connections (see ►testability). It thereby offers testing conditions and so gives the meaning of the initial sentence. In this way, statements about mental states are generally thought to be reduced to sentences about behavior (or dispositions to behave).

Problems with Behaviorism and Verificationism

There are, however, severe problems for behaviorism and consequently for verificationism. For a start, note that the list given above seems to be endless. Wine lovers do various other things additional to those listed above. Yet, when can we stop and be sure to have reached the full meaning of the sentence which is to be analyzed? Is it not rather doubtful that there is a comprehensive catalogue of stimulus-response entries?

Furthermore, some wine lovers might not always be disposed to do the things listed: they might have interfering wishes, other preferences or they might obey certain prohibitions. Alfons could be a wine lover but he might not touch any alcohol for religious reasons. Hence, some sort of proviso will have to be added to the stimulus conditions: if Alfons sees a bottle of wine *and* no other wish or desire or prohibition or promise etc. prevents him from pouring himself a glass then he will do so. However, the verificationist is still not off

the hook, since the word *preventing*, which occurs in the proviso clause, is again an unobservable mental ►predicate (we were not talking about Alfons being observably chained to the chair but about other desires preventing him). In trying to reduce a statement about one mental state to observational language we had to use the non-observational mental terms, and it is questionable whether we can ever escape. (Kind of this vicious regress is already a danger for the analysis of non-mental non-observational terms).

Verificationism and Physics: Further Problems

Aside from the realm of the mental, verificationism has difficulties with statements from the very ►science which should cause the least problems, namely physics. Consider a law hypothesis like "All masses attract each other." Which kind of observation would conclusively establish this sentence's truth and hence it's meaning? No doubt, this difficulty relates back to the traditional problems of ►induction of how to conclude from some observed events to all of them (including unobserved ones). In the guise of a puzzle about meaning, the problem of induction is, however, aggravated: not only is it difficult to define what would provide conclusive evidence for "All masses attract each other", for verificationism, the lack of such a characterization would mean that law hypotheses do not form meaningful sentences. Hence, they should be dropped from scientific language. And yet, this is unacceptable for general and universal hypotheses are, arguably, central to any scientific enterprise. Note that similar problems arise from sentences about past events for which observations are also in principle impossible.

There have been attempts to reformulate verificationism in weaker forms to avoid these consequences: observations should only be *somehow relevant* to the determination of the truth or falsehood of sentences [6,7: 18–19]. However, instead of going further into detail of those reformulations (which have anyway been unsuccessful in the end) it is worth turning to problems on a more abstract level. The first concerns the status of the verificationist doctrine itself. The second challenges tacit presuppositions of verificationism which turned out to be untenable.

Verificationism Applied to Itself

Ironically, the verificationist doctrine itself falls short of its own high demands. Take the statement: "Sentences have meaning only in so far as they are empirically verifiable." Are there possible observations which could prove the truth of this very sentence? It seems not. But then the doctrine itself lacks meaning, i.e. it is a statement like metaphysical claims without any sensible content. The logical empiricists' response to this charge was to claim that the verification criterion is prescriptive rather than descriptive in character. It is meant to be a recommendation to scientists of what is best to be counted as proper scientific language; it is not meant to be a factual statement. Note inside that vertification is a similar answer have offered for other indispensable non-factual claims, like mathematical or logical statements, or sentences which state conceptual truths. (See ►necessity; ►necessity, conceptual).

Verificationism and Meaning Holism

Still more problematic for verificationism is a thesis called *meaning* ►*holism*. Take again the sentence "if a mercury thermometer is placed into this fluid the mercury will rise (or fall) to mark 100." which is supposed to give the meaning of "The fluid is 100° C". Suppose your observation speaks against its truth. You place a thermometer into the fluid, Yet, the mercury does move only a little but not to 100. Unsurprisingly, it is possible to make, adjustments at various other points in our belief-system such that we could, in principle, nonetheless affirm to the sentence that the fluid is 100: we could, for example, doubt that the pressure is appropriate for the measurement and the pressure remains constant; we could suppose that the thermometer is broken; we could claim that thermometer's scale has been wrongly calibrated, etc.

The upshot of this ►thought experiment is that the verificationists' assumption that isolated sentences alone face the tribunal of observational evidence is not justified. It is always a whole bunch of interrelated sentences – a whole belief system – which is tested by observation. This is a thesis which came to be known as meaning ►holism and was argued for by W. V. O. Quine [8]. Single sentences are too small a unit to be verifiable by experience. Instead "the unit of empirical significance is the whole of science." [8: 42]. But if this is so, the verification theory of meaning which is defined for single sentences is false from the outset.

Verificationism Rejected

The *prima facie* attractive verificationist doctrine proves to be untenable for various reasons: (i) It turned out to be difficult if not impossible to apply the verificationist theory of meaning in a concrete case: this has been shown in the example from behaviorism. Endless lists and regresses threaten the success of an analysis. (ii) It was necessary to rewrite the verificationist doctrine several times, as underlined by the example of law statements which would otherwise have to be discarded as being nonsense. (iii) The self-application of the doctrine reveals its own non-empirical status; and finally, (iv), the hidden presupposition that sentences are the units of observational verification had to be dropped, and so verificationism as a whole.

The Remnants of Verificationism

It should be mentioned that some verificationist ideas still live on and are indeed worth pursuing. For philosophical theories of sentence meaning it is essential to hold on to the strong link between truth and meaning: some philosophers claim that giving the truth conditions of a sentence (not the *verification conditions* for its truth, though) is giving the meaning of that sentence [9]. The philosopher Michael Dummett even revived a verificationism which is, in some respects, akin to the logical empiricist's doctrine. As a result, Dummett had to adopt anti-realist positions (compare ►realism) when it comes, for example, to statements about laws of nature (►Law, Natural; ►Law, Lawfulness) or the past: he claims that statements whose truth cannot decisively be verified are neither true nor false [10].

References

1. Carnap R (1936) Testability and meaning I. Philos Sci 3:419–471
2. Ayer AJ (ed) (1959) Logical positivism. Free Press, New York
3. Schlick M (1936) Meaning and verification. Philos Rev 45:339–369
4. Carnap R (1928) Der logische Aufbau der Welt. Weltkreis, Berlin (repr. Meiner, Hamburg 1998)
5. Carnap R (1932b) Überwindung der Metaphysik durch logische Analyse der Sprache, Erkenntnis 2:219–41 (English translation in [2])
6. Hempel CG (1950) Problems and changes in the empiricist criterion of meaning. Revue internationale de philosophie 4:41–63 (appears slightly modified as Empiricist criteria of cognitive significance: problems and changes. In: Hempel CG (ed) (1965) Aspects of scientific explanation. Collier-Macmillan, London; Free Press, New York)
7. Ayer AJ (1936) Language, truth and logic. Victor Gollancz, London (repr. Penguin, London 2001)
8. Quine WVO (1951) Two dogmas of empiricism. Philos Rev 60. (repr. in Quine, WVO (1953) From a logical point of view: nine logico-philosophical essays. Harvard University Press, Cambridge, MA
9. Davidson D (1984) Truth and meaning. In: Davidson D (ed) Inquiries into truth and interpretation. Clarendon Press, Oxford, pp 17–36
10. Dummett MAE (1993) The seas of language. Clarendon Press, Oxford

Measure of Equilibrium

►Vestibular Tests Static and Dynamic Posturography

Measurement Techniques (Biomechanics)

Walter Herzog
Professor, Faculty of Kinesiology, University of Calgary, Canada

Synonyms

Optical techniques; Force; Acceleration; Sonomicrometry; Strain

Definition

►Optical methods in biomechanical analyses include high-speed film and video. In the past decade, various motion analysis systems that track passive or active markers have become the preferred mode to capture human and animal movements.

"►Force" cannot be defined by itself. However, the effects of forces can be described. Most importantly, force is described by Newton's second law, which states that, for a particle system, the resultant force acting on a system is proportional to the acceleration of that system. Therefore, forces manifest themselves by accelerating but also by deforming systems.

►Acceleration is the second time derivative of displacement, or the first time derivative of velocity. Acceleration is an instantaneous vector quantity.

►Sonomicrometry is a technique that uses ultrasound transmission from one piezoelectric crystal to another to measure distances and strains. The principle of sonomicrometry rests on the idea that ultrasound pulses travel in a straight line and constant speed through a medium. Therefore, by measuring the time it takes the ultrasound signal to go from one crystal (transmitter) to another (receiver), the distance between the crystals can be calculated.

►Engineering strain is defined as the change in length of a material from its original reference length divided by the original reference length; that is:

$$(L - L_0/L_0)$$

Where: L_0 is the original reference length, and L is the current length of the material.

Purpose

Optical methods in biomechanics are used to quantify the movements of the system of interest. These movements may be on the whole system level, for example human walking, or may be on the microscopic level and include cell motility and division, or the movements of a ►molecular motor protein (e.g. kinesin) on its motor track (microtubule). From movements, forces can often be calculated through the

so-called ►inverse dynamics approach [1], when direct ►force measurements are difficult or impossible.

Force measurements in biomechanics represent a basic tool to quantify the mechanics of a biological system. Forces in human locomotion provide insight into the loading of the musculoskeletal system and the workings and control of muscles. Forces obtained in micro scale systems may provide an understanding of basic life functions, such as cell division, muscle contraction, and ►ATP synthesis.

Acceleration measurements are often performed in situations where force measurements cannot be made. Accelerations of a system are proportional to the ►resultant external forces acting on the system, and therefore represent a valuable piece of information of the ►kinematics and ►kinetics of the target system.

Sonomicrometry has become an accepted tool for measuring deformations of soft tissues in vivo. For example, sonomicrometry is frequently used to measure deformations of the heart on a beat-by-beat basis, or to measure the strains in muscle fibers in freely moving animals.

►Strain measurements in biomechanics are fundamental to define the constitutive properties of hard and soft tissues. The ultimate strain defines the strain at which a material fails, while stress-strain measurements provide ►Young's modulus, a basic material property.

Principles

Early optical methods for movement analysis in biomechanics include single shot photography, chronophotography, and stroboscopy. Photography has the distinct disadvantage that only a single picture of a movement is available, or in the case of multiple exposures, several photographs may be available, but typically with a poor time resolution.

Chronophotography uses a conventional photographic camera with a rotating disc shutter placed in front of the film. The shutter can be rotated typically at very high frequencies and the film is exposed every time the opening of the shutter is in front of the film. Thus, a movement is captured on a still photograph. The limitations of chronophotography include that the movement of interest must be in a given direction, so that exposures do not start to overlap in time, that the movement is relatively fast compared to the shutter speed, and that movements are best captured in an artificial environment where the background makes a very good contrast with the system of interest.

Stroboscopy is also based on multiple exposures of a still film. However, the exposures are obtained through pulsed flashes in an otherwise dark room, thus the system of interest is exposed each time the flash comes on, and is invisible when the flash is off. Stroboscopy, in principle, allows for very high frequencies of data collection. However, in practice, the same limitations as for the chronophotography apply. In addition, stroboscopy can only be performed in a laboratory setting and for movements that can be performed easily in partial darkness.

In the 1970s and 1980s, most biomechanical analyses of movements were performed with high-speed cameras. These cameras typically used 16mm film and were intermittent pin registered or rotating prism cameras. The intermittent pin registered cameras use a mechanical device to advance and then hold the film with pins that grab the holes on the side of the perforated film. When the film is held still, one frame is behind the lens and shutter and will be exposed during that time. This process is repeated frame by frame for a maximal time resolution of about 2 ms (i.e. 500 exposures per second).

In the rotating prism camera, light is focused through the lens onto a rotating prism that directs the light onto the continuously moving film. These cameras can reach time resolutions of about 0.1 ms (i.e. 10,000 frames/s).

Today, most movement analyses with optical methods are based on automated video systems that capture passive or active markers, and track them in three-dimensional space through multiple camera systems, and through software that is based on direct linear transformation [2]. These systems are commercially available (hardware and software), and typically operate at set frequencies, with a maximal time resolution of about 200 frames per second. Tracking of the markers is performed automatically, and the tester merely needs to interfere with manual corrections of the marker tracking system when markers start to overlap and cannot be identified uniquely by the tracking software, or when markers are not simultaneously observed by at least two cameras (for three-dimensional analyses).

In the past few years, high-speed digital cameras have also become available. These cameras allow data collection at rates of several kHz (i.e. several thousand frames per second), but because of memory limitations, can typically only operate for a few seconds at the highest sampling frequencies. The advantages of digital video cameras include that the movements can be directly viewed and displayed on a computer, and that the system can be configured such that very fast events may be captured after they have occurred. For example, a digital camera may be set to collect data continuously, but not store the data. Once the event of interest has occurred, data storage may be triggered to include events that occurred several seconds prior to the triggering of data storage, so that the event of interest is included.

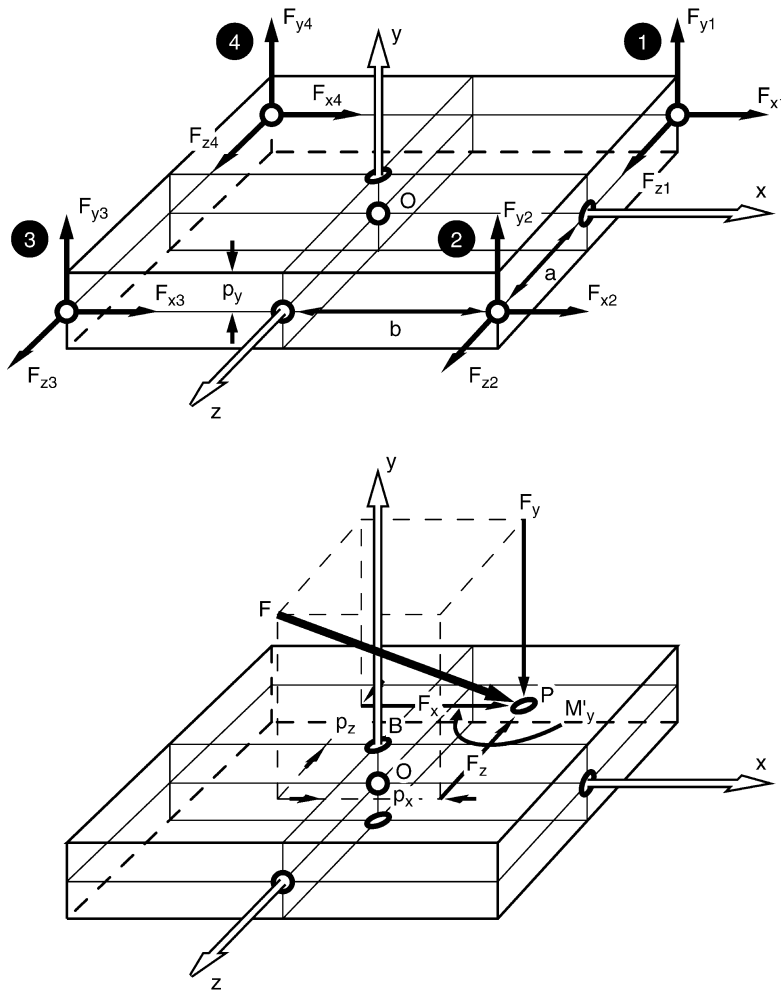
The principles of force measurements are virtually unlimited. They range from mechanical springs, to piezoelectric sensors, to ►optical trapping and atomic

force microscopy. Here, three examples of force measurement principles are given. The first is the ►force platform that is based on piezoelectric force sensors; the second is a strain gauge based ►tendon force transducer for muscle force measurements in freely moving animals and humans; and the third is an optical trapping method using lasers to measure the pico Newton forces in ►molecular motors and springs.

Force platforms have been used in biomechanical research for over a century and have been continuously refined for force and time resolution. Commercial platforms come in a variety of sizes and shapes, and they typically contain force sensors in four corners of a rectangular plate (Fig. 1, *top panel, labels 1–4*).

With this setup of sensors, it is possible to measure the three-dimensional forces and moments in an orthogonal reference system (x, y, z; Fig. 1), as well as the point of application of the force (P, Fig. 1, *lower panel*). Force platforms are typically based on piezoelectric or strain gauge sensors. The piezoelectric effect was discovered in the 1880s by the Curie brothers. Piezoelectric materials are based on non-conducting crystals that generate an electrical charge when strained. Quartz and ceramic materials have piezoelectric properties. For biomechanical applications, quartz crystals are typically cut into discs, and when subjected to forces they produce an electric charge that is proportional to the applied load. Piezoelectric sensors have the advantage that they can be used over a large range of forces. However, they have the disadvantage that the charge "leaks," and thus they are not well suited for long-term static force measurements.

Strain gauge based tendon force transducers have been used for many years to measure the muscle forces

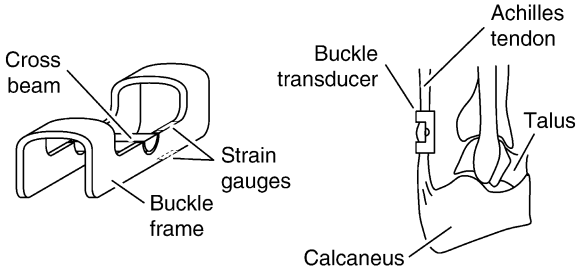


Measurement Techniques (Biomechanics). Figure 1 Force platform with reference frame (x, y, z) and force sensors at each of the four corners (*top drawing*). Resultant force (F) applied to the force platform with the corresponding point of application (P), and force components (F_x, F_y, F_z) (*bottom drawing*).

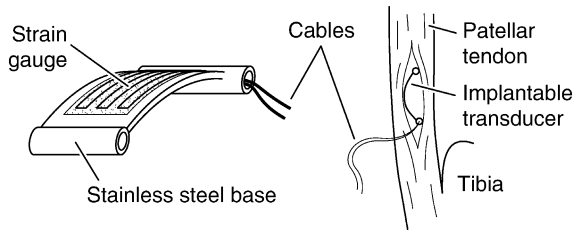
in freely moving animals. Walmsley et al. [3] measured the forces in the cat medial gastrocnemius and soleus, and Herzog and Leonard [4] measured these same forces, plus the plantaris and tibialis anterior forces, for a variety of locomotor conditions. The tendon force transducers used in these experiments are of different shape and size depending on the tendon geometry. However, the principle of these tendon force measurements remains the same. A transducer element is either fixed externally (Fig. 2) or internally (Fig. 3) to the tendon.

Upon force production by the muscle, the transducer element is deformed, this deformation is measured with appropriately placed strain gauges, and the strain gauge output is then calibrated against known forces that are applied to the tendon in a terminal experiment. Measurements of this kind have been instrumental in identifying the forces acting on musculoskeletal structures, such as joints, (e.g. [5]) and in determining strategies of movement control (e.g. [3]).

Optical trapping was developed in the early 1970s by Arthur Ashkin. Optical trapping and the manipulation of small neutral particles is based on the forces of radiation pressure. These forces allow for trapping of a particle of the size of several nm to several μm in diameter at the centre of focus of a laser beam.



Measurement Techniques (Biomechanics).
Figure 2 Schematic illustration of a buckle transducer (*left*) and a possible arrangement on an Achilles tendon (*right*). (From [6], with permission.)



Measurement Techniques (Biomechanics).
Figure 3 Schematic illustration of an implantable force transducer (*left*) and a possible arrangement in a patellar tendon (*right*). (From [7], with permission.)

Optical trapping has been used in atomic physics, but its use in biological applications is of primary interest here. Due to the virtually perfect control that can be exerted with optical traps, they have been used for a variety of biological applications: the unfolding and refolding of proteins and nucleic acids, testing of the strength of ligand to receptor bonding, and the study of a variety of molecular motor functions, and the corresponding forces and basic displacement steps.

Optical traps are perfectly suited to measure forces up to about 200 pN with sub-pico Newton resolution. When combined with adequate displacement sensors, nano metre steps of molecular motors can be detected (e.g. [8]). These techniques have resulted in great advances in our understanding of the basic forces and displacements produced by elementary cycles of a variety of molecular motors. For example, for the myosin II-actin motor associated with muscle contraction, single motor protein interactions are thought to produce forces in the 2–10 pN range, with single step sizes of 3–12 nm and the unbinding force of myosin II from actin in the absence of ATP has been measured as 9.2 ± 4.4 pN.

Accelerations in biomechanics are often determined using high-speed film or video for measuring displacements as a function of time, and then calculating acceleration through the second time derivative of the displacement data. However, this approach is not very accurate for situations where displacements are small and accelerations are high, and taking time derivatives of "noisy" displacement-time data using numerical approaches always introduces errors that are hard to quantify. Therefore, a number of sensors have been used for specific applications in biomechanics to measure accelerations directly rather than determining them numerically through displacement data.

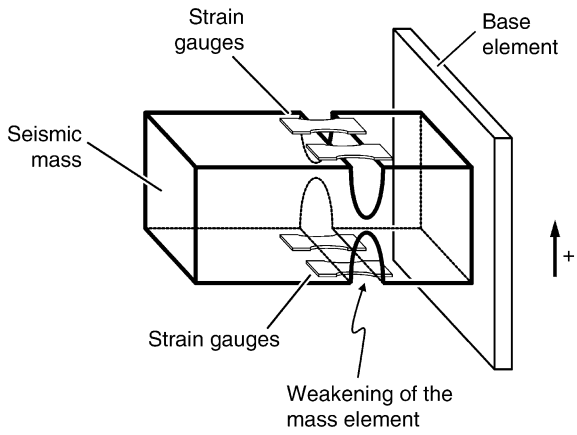
Accelerometers work on the principle that a small inertial mass segment is moved within a sensor, that this movement is captured electronically and is converted, through appropriate calibration, into the corresponding acceleration. Often, accelerometers are built around a seismic mass element as shown in Fig. 4.

The cantilever is fixed to the base element, and the seismic mass is attached to the base through a weakened part in the beam design to allow for deformation of the element as the sensor is accelerated. The deformation is measured through strain gauge elements, as shown in Fig. 4 or piezoresistive elements.

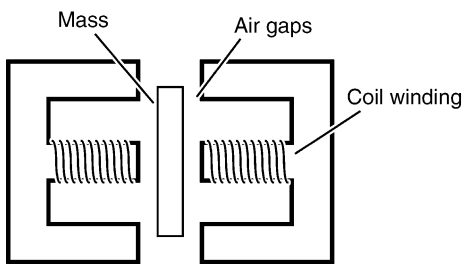
Another principle underlying acceleration measurements is based on a mass element that is positioned between two coils that are attached to the accelerometer base (Fig. 5).

The mass is magnetically coupled between the coils, and when the mass is displaced by acceleration, the magnetic coupling is changed and the corresponding change in the inductive current is measured as a change

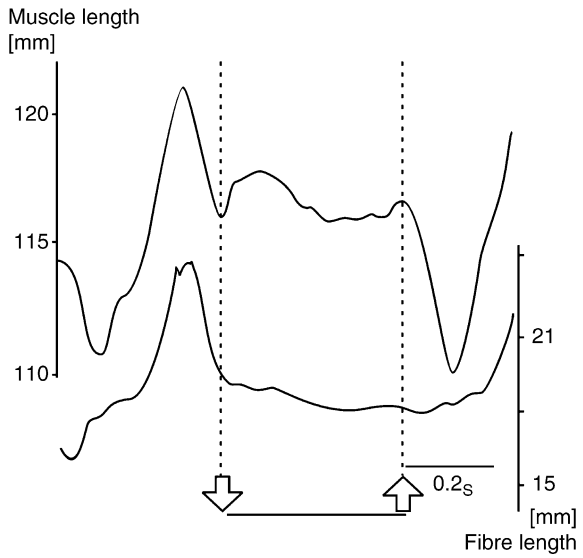
M



Measurement Techniques (Biomechanics).
Figure 4 Illustration of a piezoresistive accelerometer. (From Instruction Manual for Endevco Piezoresistive Accelerometers, 1978, with permission.)



Measurement Techniques (Biomechanics).
Figure 5 Schematic illustration of the construction of an inductive accelerometer.



Measurement Techniques (Biomechanics).
Figure 6 Muscle length (*top trace*) and fiber length trace (*bottom trace*) from the medial gastrocnemius during one-step cycle. The "down" arrow indicates first paw contact, the "up" arrow indicates paw aft at the end of the stance phase. Note how immediately after first paw contact, muscle length increases while fiber length decreases, thereby illustrating the dissociation of muscle and fiber length for specific contractile conditions. (Adapted from [9], with permission.)

in electrical output that can be related to the acceleration of the transducer. Accelerometers can be custom built for applications that require specific frequency and amplitude responses. Proper acceleration measurements are extremely difficult to perform and interpret because it is typically not trivial to attach the sensors rigidly to the target segment and to place them at the point of interest.

Sonomicrometry is a method based on ultrasound transmission between piezoelectric (ceramic) crystals for measurement of length and strain in tissues. For recording, a minimum of two crystal markers are attached to the target sites (for example, on arteries [10] or muscle fibers [11]). One of the crystals emits a short ultrasound pulse while the second crystal receives the pulse. From the known time between transmission and reception of the pulse, and the known speed of ultrasound transmission, the distance between the two markers can be measured continuously. Sonomicrometry can be used with at least 32 crystals, each acting simultaneously as a transmitter and a receiver for all the other crystal markers. Depending on the number of recording crystals, sonomicrometry signals can be measured with a time resolution of better than 1 ms (>1 kHz) and a spatial resolution of 12 μm.

Sonomicrometry has been used extensively to measure the behavior of single muscle fibers (cells) in cardiac and skeletal muscles. With this technique, it was first demonstrated that fiber length changes were not necessarily in concert with the corresponding length changes of the entire muscle (Fig. 6), a result that had great implications for the mechanics of whole muscle contraction, as well as the control of muscles through the ►muscle spindles [9]. Recently, measurements of the strains in vertebral arteries during high speed, low amplitude spinal manipulation of the neck have been instrumental in providing practice guidelines for these types of medical treatments [10].

Strain measurements are fundamental in biomechanics research. They are used to derive constitutive laws for biological tissues, to determine failure properties of materials, to determine stress distributions indirectly, to analyze interface compatibility between artificial and biological materials, and many other applications. Strain on hard tissues, where deformations are less than about 1% of specimen length, can be measured

readily and cheaply with today's technology. However, strain measurements on soft (hyperelastic) materials are much more difficult to measure, as strain transducers are typically hard to fix "rigidly" on soft specimens and might add to the force required to stretch the test specimen.

Strain gauges measure engineering strain (ε), which is defined as the change in length divided by the original length. There are a variety of possibilities of strain measurement and many of these have been used in biomechanical applications. These include electrical resistance strain gauges, extensometers, optical methods, Hall effect transducers, and many more. Strain gauges are used more often in biomechanics than any other strain-measuring device and they will be discussed briefly below.

Electrical resistance strain gauges rely on the general principle that the resistance of an electric conductor is a function of its dimensions and resistivity, or:

$$R = sL/A$$

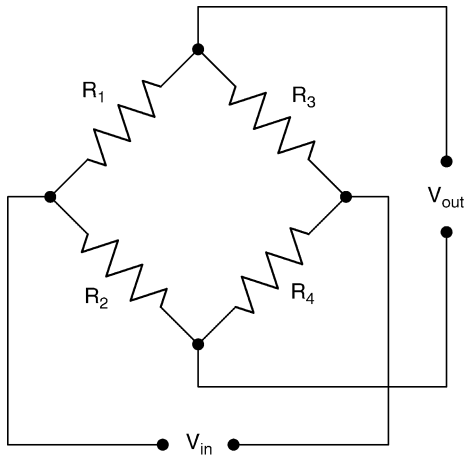
Where R is the electrical resistance, s is the resistivity, L is the length and A the cross-sectional area of the conductor. When a conductor is stretched, L increases and A decreases, and the change in resistance (ΔR) can be captured with the appropriate circuitry and related to the corresponding change in length of the conductor (ΔL):

$$R/R_0 = G_f(L/L_0)$$

Where R_0 is the electrical resistance of the unstrained material, G_f is the gauge factor, and L_0 is the length of the unstrained material. Strain gauge signals are captured with a conditioning amplifier in a ¼, ½, or a full bridge configuration. In the ¼-bridge configuration, only one gauge will be active during testing (e.g. R_1 in Fig. 7). Two of the remaining gauges (R_3 and R_4) would be precision resistors of equal value inside the amplifier, while R_2 would be a dummy gauge.

In the unstrained condition, R_2 is adjusted to have the same resistance as the active gauge, R_1, and the circuit is balanced with a zero output. If R_1 experiences strain, R_1 changes by ΔR and the output, V_{out} is non-zero and depends directly on ΔR. If R_1 and R_2 are active, we have a half-bridge configuration, which is particularly useful when one of the gauges is compressed while the other is stretched, as for example when they are attached to opposite sides of a deflecting beam. When all four gauges are active (Fig. 7), we have a full bridge configuration that maximizes the voltage output of the sensor.

There are two basic types of strain gauges: foil gauges and semiconductor gauges. Foil gauges consist of a thin layer of a metal conductor arranged in an array of connected parallel lines. These gauges are the most commonly used sensors in biomechanical applications. Semiconductor strain gauges are wafers of semiconductor doped to the form of a strain gauge. They have a higher gauge factor than the foil gauges, and thus, have a higher voltage output for a given strain and excitation voltage than the foil gauges. Semiconductor strain gauges can measure strains with a resolution of ~1 microstrain.



Measurement Techniques (Biomechanics). Figure 7 Typical arrangement of four strain gauges with resistances R_1, R_2, R_3, and R_4, respectively, for strain measurements in biomechanics. Depending on the number of active cross-bridges, signals are captured with a conditioning amplifier in a ¼, ½ or a full bridge configuration (see text for details).

References

1. Andrews JG (1974) Biomechanical analysis of human motion. Kinesiol 4:32–42
2. Abdel-Aziz YI, Karara HM (1971) Direct linear transformation from comparator coordinates into object space coordinates. Proceedings of ASP/UI Symposium on close-range photogrammetry. Am Soc Photogrammetry, Falls Church, VA, 1–18
3. Walmsley B, Hodgson JA, Burke RE (1978) Forces produced by medial gastrocnemius and soleus muscles during locomotion in freely moving cats. J Neurophysiol 41:1203–1215
4. Herzog W, Leonard TR (1991) Validation of optimization models that estimate the forces exerted by synergistic muscles. J Biomech 24S:31–39
5. Hasler EM, Herzog W, Leonard TR et al. (1998) In-vivo knee joint loading and kinematics before and after ACL transection in an animal model. J Biomech 31:253–262
6. Salmons S (1969) The 8th annual international conference on medical and biological engineering: meeting report. Biomed Engn 4:467–474
7. Xu WS, Butler DL, Stouffer DC, Grood ES, Glos DL (1992) Theoretical analysis of an implantable force transducer for tendon and ligament structures. J Biomech Eng 114:170–177

8. Finer JT, Simmons RM, Spudich JA (1994) Single myosin molecule mechanics: piconewton forces and nanometre steps. Nature 368:113–119
9. Hoffer JA, Caputi AA, Pose IE, Griffiths RI (1989) Roles of muscle activity and load on the relationship between muscle spindle length and whole muscle length in the freely walking cat. In: Allum JHH, Hulliger M (eds) Progress in brain research. Elsevier Science, B.V. Amsterdam, pp 75–85
10. Symons B, Leonard TR, Herzog W (2002) Internal forces sustained by the vertebral artery during spinal manipulative therapy. J Manipulative Physiol Ther 25:504–510
11. Griffiths RI (1987) Ultrasound transit times gives direct measurement of muscle fiber length in vivo. J Neurosci Methods 21:159–165

Measurement Techniques (Electromyography)

Vinzenz von Tscharner
Human Performance Laboratory, University of Calgary, AB, Canada

Synonyms

Wavelet analysis; Time/frequency analysis; Windowed Fourier analysis

Definitions

Electromyogram (EMG): EMG is the electrical signal in volts recorded by electrodes from a contracting muscle.
Wavelets: Wavelets are short oscillations that have a zero (0) integral, are defined in a limited time window and have a band limited power spectrum. Usually one has a "mother" wavelet and scales and shifts (translates) this wavelet appropriately to obtain a set of wavelets that cover the frequency and time range of the signal of interest.
Tiling: Subdivision of the time-frequency plane into time-frequency boxes covered by the scaled and shifted wavelets.
Wavelet transform: The mathematical method for obtaining the wavelet transformed EMG is a convolution of the EMG with different wavelets.
Scalograms: The intensity that is extracted from the signal by the wavelet transform is displayed in a scalogram as a function of time (abscissa) and scale (ordinate). Scalograms do not show the phase aspects of the wavelet transform (Fig. 1).

The intensity may be displayed in different ways, for example, as a gray scale, where intensity is represented in different shades of gray, black representing the highest intensity and white the lowest one. If colors are available, it is preferable to use color-coding to represent the intensities (e.g. rainbow colors). It has also become common practice to display constant intensities as contour lines similar to contour lines on geographical maps.

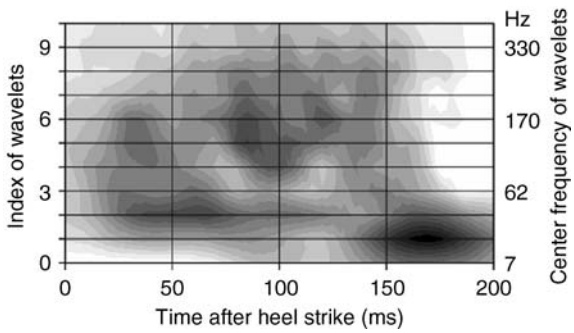
The time intervals on the abscissa are given by the tiling or by constant time increments in a time continuous wavelet transform.

The scale (ordinate) is used to represent the differently scaled wavelets. Frequently, the scale is represented by the actual scaling factor, but an index representing the different wavelets can also be used. If wavelets can be characterized by a center frequency, then the center frequencies can be displayed on the ordinate and thus the ordinate represents a measure of frequency in Hz. These scalograms are also called intensity patterns [1].

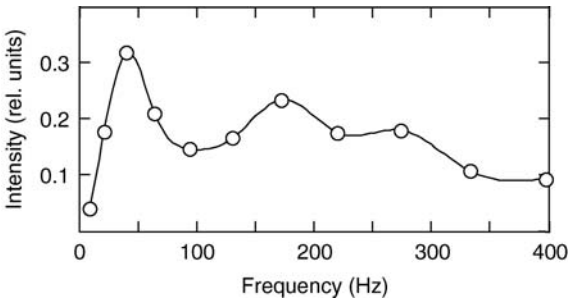
Wavelet domain: The wavelet domain contains the intensity of the EMG that is extracted by one wavelet and displayed over time (wavelet domains are represented as horizontal lines in an intensity pattern).

Intensity spectrum: The Wavelet transform decomposes the power of the EMG signal for each time point (small time window) into a limited set of frequency bands (Fig. 2). The intensity spectrum (wavelet spectrum) is the equivalent of a power spectrum for the Fourier transform. The intensities along a vertical line in an intensity pattern represent the wavelet spectra.

Total intensity: The sum of the intensities of the intensity spectrum is called the total intensity, and is assigned to the specific time point at which the intensity spectrum was measured. The total intensities represent a summation of the intensities across all



Measurement Techniques (Electromyography). Figure 1 Scalogram (average over five trials) of EMGs of the gastrocnemius medialis for a person running at 4 m/s. The signal rises from lower frequencies at 50 ms to higher frequencies at 125 ms, and the high frequency components end at 150 ms. The drop in frequency seen after 150 ms leads to a muscular event that lasts about 50 ms and is typically seen when wearing shoes.



Measurement Techniques (Electromyography).
Figure 2 Wavelet spectrum extracted from Fig. 1. The *dots* represent the intensities extracted by the wavelets 70 ms after heel strike. The dots are located at their respective center frequencies. The *solid line* represents an interpolation between the dots.

wavelet domains and form a one-dimensional time series. The square root of total intensities of this time series contains the same information as the root mean squared EMG signal [1].

Heisenberg's uncertainty principle: This principle states that the time resolution Δt and the frequency resolution Δf cannot simultaneously be infinitesimally small. The product $\Delta t \cdot \Delta f$ is constant and equals about 1. To exemplify this principle one can think of a sinusoidal signal of finite duration. If the duration is much shorter than the period of the sinusoidal wave one cannot accurately determine its frequency. On the other hand, if the signal duration is very long, and thus the time when the signal occurs is not known, then one can accurately measure its frequency.

Frequency resolution: Frequency is a property of a signal. If signals with distinctly different frequencies are superimposed, the difference can only be resolved if it is larger than the frequency resolution. The frequency resolution is a property of the wavelet and relates to the bandwidth of the wavelet. Scaling wavelets to make them shorter increases their frequency resolution.

Time resolution: Each wavelet has a frequency resolution, Δf, and, according to Heisenberg's uncertainty relationship, a corresponding time resolution, Δt. The time resolution is different for each wavelet domain and represents the shortest time separating two events that are located in the same wavelet domain. Time resolution relates to the finite width in time of the wavelet.

Discrete versus continuous wavelet transforms: Wavelet transforms require a discrete base set of wavelets to fully represent the information contained in an EMG signal. A discrete wavelet transform uses the smallest number of discretely scaled and discretely translated wavelets to transform the signal without loosing information about the original signal. Thus, discrete wavelet transforms require the smallest computational effort retaining the information for reconstructing the original signal. If we focus on the scaling and thus on the spectral aspect first we find that the spacing between the differently scaled wavelets can be so large that the resolution is too broad for projects that aim at a very fine frequency resolution. This handicap can be overcome by using a continuous wavelet transform in which the wavelets are scaled using very small, almost continuous changes of the scaling factors. The continuous wavelet transform is best used for getting a smooth wavelet spectrum, which allows for finding the maximum of the spectrum very accurately.

If two independent EMG signals are recorded, Heisenberg's uncertainty principle does not apply and one can resolve very small spectral differences; for example, differences in the position of the mean of the spectrum that are smaller than the frequency resolution. However, if one analyzes spectra that were recorded within a time interval in the order of the time resolution, then Heisenberg's uncertainty relationship becomes the limiting factor and one cannot have infinitely fine spectral resolution. In this case it does not make sense to use the continuous wavelet transform. Thus, when recording and analyzing movement related patterns of EMG intensities, the continuous wavelet transform is not appropriate.

The discrete wavelet transform is also discrete in time. The time intervals are given by the appropriate tiling. Thus, if one desires to see a smooth continuous development of the wavelet transformed signal in time, one will use almost continuously shifted (translated) wavelets to obtain a time continuous wavelet transform. A time continuous wavelet transform should be used if one is interested in observing the exact timing of muscular activities during a movement. If two EMG signals were separately recorded, for example, for two different external conditions, then the timing difference of muscular events can be measured with an accuracy that exceeds the time resolution imposed by Heisenberg's uncertainty relationship. However, if two muscular events occur in the same EMG recording then Heisenberg's uncertainty applies.

The decision of how "continuous" the wavelet transform should be depends on the desired frequency or time resolution. Unfortunately, one cannot have both simultaneously with great accuracy.

Characteristics

Purpose

The purpose of wavelet analysis of EMG signals is to decompose EMG signals into their frequency components in such a way that temporal aspects of the signal are conserved and resolved [1–3]. For practical cases of analyzing EMG signals, the purpose translates into decomposing the signal in such a way that conclusions about muscle physiological aspects can be drawn. Four

specific purposes relating to physiological aspects are mentioned below.

1. Muscles contain different fiber types that have type specific motor unit action potentials and conduction velocities. Short motor unit action potentials and fast conduction velocities generate high frequency contributions, and broad action potentials and slow conduction velocities generate low frequency contributions to an EMG. Decomposition of an EMG signal into the frequency bands covered by the wavelets provides information about the interplay of muscle fibers generating high or low frequency components in the EMG [4].
2. Muscles are typically only activated during parts of cyclic movements. Decomposition using wavelet analysis can resolve time-dependent muscle activities. Therefore, the time resolution can be selected such that it corresponds to physiological response times for activation and relaxation.
3. Assessment and evaluation of fatigue is a major field of muscle research. Evaluations are typically limited to steady-state recordings of EMG lasting at least 250 ms. Decomposition using wavelet analysis allows detection of the continuous decrease in frequency content that occurs with fatigue. Wavelet analysis is particularly useful when analyzing muscle fatigue for dynamic conditions such as isokinetic contractions [5].
4. Decomposition of EMG through wavelet analysis yields EMG intensity patterns representing the activity of one or multiple muscles at the same time. These patterns can be used as input to pattern recognition methods, which can reveal small differences in muscle activities governing a given movement. For example, male and female runners generate different EMG intensity patterns [6].

Principles

An EMG signal is a recording of the potential generated by ionic fluxes in muscle fibers at the position of the electrode with reference to some other potential (reference potential). These potentials depend on tissue properties between the electrodes and the muscle fibers, and the recorded voltages depend on electrode configuration. The frequency of the EMG depends on the inter electrode distance and on the shape of the electrodes. Proper electrode placement is the key to obtaining high quality signals. The recorded EMG is a signal of the fiber action potentials as measured by "remote" electrodes. However, independent of the distortion of EMG signals as a result of electrode placement, any EMG contains information about the underlying physiological processes and structures.

The theory of wavelet analysis has greatly evolved in the last decade and has been well described by Mallat [7]. Various biomedical applications have emerged using this technology [8]. For time/frequency analyses of EMG signals, an appropriate set of base functions, or wavelets are required. Commercial software packages (MathCad™ or MatLab™) provide wavelets algorithms. There are commercial software packages that use a specific set of wavelets (Biomechanigg Research Inc.) designed for the analysis of EMGs. There are many different types of wavelets, and the selection of the wavelets depends on the purpose of the analysis. If one is mainly interested in frequency aspects, it is an advantage to select wavelets of a damped sinusoidal shape (Morley or Cauchy wavelets). For data compression, one might prefer Daubechies wavelets. The result of the transform depends on the wavelet selection, and there is no consensus as to which wavelets would be the most appropriate for a given situation. Selection is often guided by what is available in software packages, rather than by functionality. Once the wavelets have been selected, the wavelet transform is a straightforward mathematical operation of convolving the measured signal with the wavelets (Convolution, see Karniel in this Encyclopedic Reference). The magnitude of the wavelet-transformed signal (square root of the sum of the squared real and imaginary part) is called the intensity. Phase aspects are not used for the analysis of EMG signals.

Advantages and Disadvantages

The main advantage of the wavelet transformed EMG signal is that physiological processes that change the frequency content of the EMG signal become visible simultaneously in the time and frequency domain. Thus, the classical separation of time- and frequency-domain can be overcome. Wavelet analysis is also an improvement over windowed Fourier transform because the time/frequency compromise is optimized.

Since researchers have used many different types of wavelets, it is difficult to compare results across studies. Nevertheless, wavelet analysis combined with pattern recognition algorithms will probably become the method of choice of EMG signals.

References

1. von Tscharner V (2000) Intensity analysis in time-frequency space of surface myoelectric signals by wavelets of specified resolution. J Electromyogr Kinesiol 10:433–445
2. Constable R, Thornhill RJ (1993) Using the discrete wavelet transform for time-frequency analysis of the surface EMG signal. Biomed Sci Instrum 29:121–127
3. Karlsson S (1999) Enhancement of spectral analysis of myoelectric signals during static contractions using wavelet methods. IEEE Trans Biomed Eng 46(6):670–684

4. Wakeling JM, Kaya M, Temple GK, Johnston IA, Herzog W (2002) Determining patterns of motor recruitment during locomotion. J Exp Biol 205(3):359–369
5. Karlsson JS, Oestlund N, Larsson B, Gredle B (2003) An estimation of the influence of force decrease on the mean power spectral frequency shift of the EMG during repetitive maximum dynamic knee extensions. J Electromyogr Kinesiol 13:461–468
6. von Tscharner V, Goepfert B (2003) Gender dependent EMGs of runners resolved by time/frequency and principal pattern analysis. J Electromyogr Kinesiol 13:253–272
7. Mallat SA (1999) Wavelet tour of signal processing, 2nd edn. Academic Press, San Diego
8. Aldroubi A, Unser M (1996) Wavelets in medicine and biology. CRC Press, Boca Raton, New York, London, Tokyo

Measurement Techniques (Pressure)

Andrea L. Clark
Faculty of Kinesiology and Medicine, KNB 304, University of Calgary, Calgary, AB, Canada

Synonyms

Stress

Definitions

►*Stress/Pressure*: The force per unit area exerted on a material.

►*Diarthrodial Joint*: A joint encased in a ligamentous capsule including an articular cavity.

►*Spatial/Temporal Resolution*: A property of a measurement system that defines its ability to resolve measurements taken at two adjacent points in space or time. The closer the adjacent space or time points, the better the resolution is said to be.

Characteristics

Introduction

Pressure measurement techniques are currently utilized in several major biomechanical fields. For example, pressure sensitive mats and plates are used to measure the pressure distribution between different parts of the body (e.g. the foot or finger) and external surfaces (e.g. the floor, a shoe or a keyboard) [1]. Direct measurement of the contact pressure at articular interfaces within diarthrodial joints of the body (such as the femoral head and acetabulum in the hip joint) continues to remain a challenge in orthopedic biomechanics. Research in this particular field has enabled us to better understand the structure-function relationships of ►articular cartilage and other joint tissues in providing joint motion and the pathomechanical processes involved in joint diseases such as ►osteoarthritis. The main focus of this essay will be to give an overview of this latter area of application.

Measurement Methods

Pressure Sensitive Films

Fuji prescale pressure-sensitive film (Fuji Photo Film Co. Ltd, Tokyo, Japan) is the most extensively used technique to measure contact pressures in diarthrodial joints. The film comes in grades, with each grade covering a different pressure range between 0.2 and 130 MPa (Table 1).

Except for the high-grade film, Fuji film consists of an A- and C-sheet [2]. The A-sheet contains randomly arranged fluid filled bubbles 2–25 μm in diameter. When pressure is applied, the bubbles burst, releasing their fluid content. The second C-sheet contains an active layer that reacts to the fluid to produce a red stain (Fig. 1) [2].

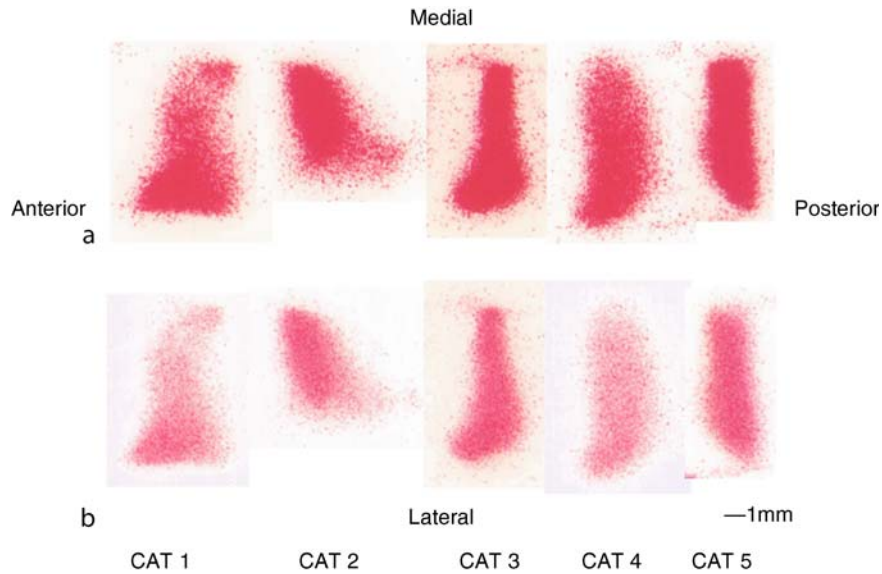
Since different sized bubbles break at different pressures, the amount of fluid released and thus the color density of the stain is dependent upon the pressure acting across that area (Fig. 1). The A- and C-sheets of the film are generally sandwiched between polyethylene layers to protect them from humidity. The film including the sealing materials is ~250 μm thick [2]. Thicker packets of film have been made by stacking films of different grades on top of one another [3]. This technique increases the sensitive range of the Fuji film packet. A much thinner Fuji film, 25–50 μm thick, has recently been introduced, though it has not yet been thoroughly assessed for biomechanical applications [4].

A second pressure sensitive film was developed and applied in the biomechanics field around the same time as Fuji film was first introduced. This sensor consisted of four layers with a total thickness of 285 μm [5]. A layer of fast-drying enamel paint sprayed onto an acetate film acted as a plastic material in this sensor. A nylon screen woven out of monofilament threads with 12 threads per millimetre lay on top of the paint layer with a mylar film on top of that to protect the

Measurement Techniques (Pressure). Table 1 Grades of Fuji film and their pressure ranges [2]

Film grade	Pressure range (MPa)
Ultra-super-low	0.2–0.5
Super-low	0.5–2.5
Low	2.5–10
Medium	10–50
High	50–130

M



Measurement Techniques (Pressure). Figure 1 Typical Fuji film stains from the patellofemoral joints of five cats under 300N of applied force on: (a) low- and (b) medium-grade film. Increasing pressures are associated with increasing stain darkness. Reprinted from the Journal of Biomechanics, 35:1, clark AL, Herzog W and Leonard TR, contact area and pressure distribution in the feline petallofemoral joint under physiologically meaningful loading conditions, Pages 53–60, Copyright (2002), with permission from Elsevier.

sensor from moisture [5]. Pressure applied to the film pressed the threads of the nylon screen into the plastic paint material leaving a series of permanent micro-indentations. The depth of these micro-indentations were then evaluated and related to the magnitude of the applied pressure with ►calibration [5].

Most recently Iscan, an electric film for measuring pressure in joints, has been developed. The Iscan sensor (Tekscan Inc, South Boston, MA, USA) is 200 μm thick, has a sensing area of 56 mm^2, and can take measurements at up to 125 Hz [4]. Each sensor consists of two polyester sheets bonded together with a layer of semi-conductive ink between them. The polyester sheets have electrical conductors evenly distributed across them producing a sensing element at each point where the conductors on both sheets cross each other. As pressure is applied to the sensor, the semi-conductive ink is compressed, altering the resistance between the two polyester sheets [4]. This change in resistance is then related to the applied pressure by a calibration routine.

Discrete Pressure Transducers

In addition to pressure sensitive films, a second major approach to measuring contact pressure in diarthrodial joints has been to place a number of small discrete ►transducers over the articulating surfaces. In the majority of cases, piezoelectric materials have been used to make transducers that are recessed into the superficial layer of the articular cartilage. In one series of studies, 24-flat-bottomed cylindrical wells, ~3.5 mm in diameter, were drilled into the articular surfaces of cadaver femoral condyles and femoral heads [6]. Miniature piezoresistive transducers 400 μm thick were then secured into the wells using cyanoacrylate adhesive. The depth of each well was adjusted so that the face of the transducer was palpably flush with the articulating surface. Two lead wires from each transducer passed across the cartilage surface to a signal-processing unit [6]. The transducers were made of a tightly packed granular piezoresistive material, contained and loaded in parallel through a silastic annular spacer. Transducer resistance changes due to the applied surface pressure were detected by output changes to a simple electronic circuit [6].

In a more recent study, a piezoelectric film replaced the piezoresistive material as the sensing element of these transducers [7]. Piezo film develops an electrical charge proportional to the mechanical stress or strain applied to it. The piezo film was sandwiched between two stainless steel electrodes and sealed in a water resistant capsule. Six of these transducers, 3 mm in diameter and ~300 μm thick, were embedded into the articular surface of cadaver patellae [7]. Wells were drilled into the cartilage as described above; however, an extra 1mm diameter hole was drilled in each well through the subchondral bone to allow the wires to pass through to the other side of the patella [7].

In contrast to these piezoelectric transducers, pressure pipes (1.5 mm in diameter) inserted into holes drilled through the articular cartilage and subchondral bone have also been used as discrete pressure transducers [8]. Physiological saline was utilized as a pressure medium within the pipes and the pipe pressure was measured using a transistor pressure transducer and pressure gauges. This set up was used to measure instantaneous contact pressures between cadaver femoral condyle and tibial articular surfaces [8].

Instrumented Prosthesis

Among the earliest attempts to measure contact pressures in diarthrodial joints was an instrumented femoral hip ►prosthesis [9]. A number of small pressure transducers were introduced in the hollow sphere at the end of the prosthesis to be positioned in the hip joint in contact with the cartilage in the socket. A hole (4 mm diameter) was machined into the inside of the hollow hemisphere leaving a thin diaphragm 445 μm thick. This diaphragm was deflected slightly (0.28 μm/MPa) by the contact pressure with the acetabular cartilage [9]. The displacement of the centre of the diaphragm was detected and measured by a strain-gauged, silicon crystal cantilever beam transducer. Fourteen pressure transducers were evenly distributed across the sphere of the prosthesis. Each transducer was switched on serially and the output sent to a remote data collection station using a radio transmitter and receiver [9]. The transducers were sampled at 253 Hz and the electronics were powered using an induction arrangement involving a pair of magnetically coupled concentric coils. The primary coil circled the upper thigh and was coupled with a smaller secondary coil located on the tip of the stem of the prosthesis inside the femur. The prosthesis was therefore completely self-contained and used no batteries [9].

Advantages and Disadvantages

Disruption of Joint Contact Mechanics

Introducing a pressure sensitive film between two contacting surfaces alters the very pressure distribution that is being measured. This error is primarily caused by the stiffness and thickness of the film. The softer and thinner the film is, the smaller the errors will be. The magnitude of this problem has been evaluated for Fuji film using a theoretical approach [10]. The pressure distribution in the feline patellofemoral joint was calculated for given loading conditions with and without the pressure sensitive film. The film, including sealing materials, was defined as 250 μm thick with a stiffness of about 200 times the stiffness of the articular cartilage. The results of this case indicated that introducing the Fuji film into the joint caused an underestimation of the true pressure distribution by about 10% [10]. Along similar lines, pressures recorded by an instrumented prosthesis are likely to be quite different from those in a natural joint due to the metal on cartilage as opposed to the cartilage on cartilage interface [9].

With discrete pressure transducers, the cylindrical defects made in the articular cartilage and the different elastic moduli of the transducer relative to the surrounding cartilage may alter the local load transmission processes and therefore the pressures being measured [7]. Slight differences in the amount of cement used at the base of each transducer and differences in the congruity match at the cartilage surface may also influence local pressures [7]. While drilling holes through the bone to allow leads to pass out of the joint will keep the leads from disrupting joint contact, it may also cause greater disruption to the fluid flow within the cartilage and between the cartilage and bone in the vicinity of the defect.

When an instrumented prosthesis is implanted, roughly half of the cartilage in the joint is lost [9]. This will almost certainly affect the distribution and quantity of ►synovial fluid between the joint surfaces [9]. The significance of any variation in pressure distribution caused by this redistribution of synovial fluid is currently unknown.

Spatial Resolution of Pressure Measurements

One of the major advantages of pressure sensitive films is that they can record the pressure distribution over the entire contact area within a given joint. In contrast, discrete transducers only record local pressure values from certain points in the joint from which the corresponding whole contact stress patterns must then be reconstructed [6]. In particular, the reported peak local stress values reflect the highest single transducer reading, which may not coincide with the most highly stressed point on the contact surface. Increasing the number of transducers in a joint would improve the spatial resolution of this method, although would also lead to more severe disruption of joint mechanics as discussed above.

Temporal Resolution of Pressure Measurements

The viscoelastic deformational characteristics of articular cartilage suggest that static measurements may not be ideal for estimating the transient pressure distribution that occurs in diarthrodial joints in vivo. One of the major advantages of the pressure measurement techniques that utilize electronics, the pressure pipes or the instrumented prosthesis is that they have the potential to record virtually continuous pressures during joint loading. For example, an Iscan sensor can record measurements at 125 Hz [4] and an instrumented prosthesis at 253 Hz [9]. Pressure films similar to the Iscan, however, have demonstrated drift; a significant time-dependent response to load which may lead to large errors during measurements of dynamic activities

[4]. Fuji film and the film introduced by Ahmed do not allow such time resolution of pressure measurements [5,10,2]. Both of these films record maximal pressures. Therefore, either of these films inside a joint will record the local peak pressures occurring during a loading period rather than any actual pressure distribution or the time history of the pressure distribution.

Other Potential Sources of Artifact

The complex and often multidimensional curvature in many diarthrodial joints is a potential cause of artifacts in pressure measurements. Studies using Fuji film have described artifacts as the film has crinkled while negotiating the curvatures in a joint [10,2]. While not wrinkling, the accuracy of the Iscan sensor may be affected by joint curvature, though it is not clear by how much [4]. Clearly, discrete pressure transducers are not affected as significantly by the curvature of a joint.

The majority of the pressure transducers outlined above are sensitive to things other than pressure. These include temperature, humidity, electromagnetic interference and crosstalk. It is important, therefore, that these variables are either eliminated (e.g. by sealing transducers in water resistant coating), minimized (e.g. by limiting the number of connecting wires routed through a joint) and/or held constant throughout loading and calibration routines.

Adaptability of Technique for In-Vivo Measurements

Ultimately, in trying to understand the in vivo structure-function relationships of joints it is most desirable to conduct experiments that resemble the in vivo situation as closely as possible. Use of the instrumented prosthesis, for example, has enabled pressure measurements to be made in humans during a wide range of daily activities such as riding a bike and using a bedpan. The Iscan sensor has also been inserted into the medial compartment of knees during routine arthroscopic examination. It was used to measure the effects of braces on patient knee loading during normal stance.

References

1. Nigg BM (1999) Pressure distribution. In: Nigg BM, Herzog W (eds) Biomechanics of the musculo-skeletal system, John Wiley & Sons Ltd., Chichester, UK, pp 281–287
2. Liggins AB (1997) The practical application of Fuji prescale pressure-sensitive film. In: Orr JF and Shelton JC (eds) Optical measurement methods in biomechanics. Chapman & Hall, London, pp 173–189
3. Atkinson PJ, Newberry WN, Atkinson TS, Haut RC (1998) A method to increase the sensitive range of pressure sensitive film. J Biomech 31:855–859
4. Wilson DR, Apreleva MV, Eichler MJ, Harrold FR (2003) Accuracy and repeatability of a pressure measurement system in the patellofemoral joint. J Biomech 36:1909–1915
5. Ahmed AM (1983) A pressure distribution transducer for in-vitro static measurements in synovial joints. J Biomech Eng 105:309–314
6. Brown TD, Shaw DT (1984) In vitro contact stress distribution on the femoral condyles. J Orthop Res 2:190–199
7. Manouel M, Pearlman HS, Belakhlef A, Brown TD (1992) A miniature piezoelectric polymer transducer for in vitro measurement of the dynamic contact stress distribution. J Biomech 25(6):627–635
8. Inaba H, Arai M (1989) A method for measuring contact pressures instantaneously in articular joints. J Biomech 22(11):1293–1296
9. Carlson CE (1971) A proposed method for measuring pressures in the human hip joint. Exp Mech 11:499–506
10. Wu JZ, Herzog W, Epstein M (1998) Effects of inserting a pressensor film into articular joints on the actual contact mechanics. J Biomech Eng 120:655–659

Mechanical Impedance

Definition

A dynamic operator that specifies the forces that a mechanical system generates in response to imposed motions. It is normally represented as the transfer function relating the velocity of the system (input) to the force (output). Inertia, damping and stiffness can be identified from the phase relation between output force and imposed velocity. Admittance is the inverse of impedance: an operator specifying a motion in response to imposed forces. Muscle-environment interaction is fundamentally two-way; since the muscle is coupled to the skeleton, which tends to impose motions, muscle is usually best regarded as providing impedance. In the context of vertebrate motion, mechanical impedance determines how the forces applied to a body segment will be transformed into motion.

►Impedance Control

Mechanical Obstruction (or Ileus)

►Bowel Disorders

Mechanically Skinned Fiber

Definition

An isolated single muscle fiber preparation that involves physically peeling or rolling back the sarcolemma (plasma membrane) leaving the other structures relatively unaltered. Upon skinning, the transverse-tubular system seals off which makes it possible to study the normal excitation-contraction coupling process in these fibers (i.e. depolarization-induced Ca^{2+} release).

►Excitation-Contraction Coupling

Mechanics

Marcelo Epstein
Schulich School of Engineering, University of Calgary, Calgary, AB, Canada

Definition

The science that studies the motion of material bodies and its relation with the forces acting on them.

Description of the Theory

As the science of motion and ►deformation of ►material bodies, ►mechanics plays an essential part in the study of those aspects of biological systems that underlie the functioning of living tissues and organs regardless of the fact that they are alive. In biomechanics therefore, mechanics and physiology are complementary disciplines. The barriers between these two main components of biomechanics are not however sharply defined. A chemical reaction involving long, geometrically complex molecules may require a mechanical description of the relative motion of the molecules, while a proper understanding of the macroscopic deformation of an organ may need the incorporation of chemical reactions in the continuum model. In broad terms, mechanics can be divided into two main branches, classical mechanics of particles and rigid bodies and continuum mechanics of deformable media. Both are of relevance to biomechanics. For instance, the description of many physical activities and sports, such as diving or running, can be undertaken fairly faithfully by ignoring the deformability of the tissues involved and considering the human or animal body as an assembly of rigid members joined together by means of ideal hinges and articulations. Models developed under such assumptions fall within the realm of classical rigid body mechanics. The description of the functioning of the heart, on the other hand, is a typical example in which the methods of continuum mechanics are called for. Intermediate between these two realms lies the domain of the so-called rheological models, which represent an attempt at describing deformable systems as if they were made of a discrete array of a small number of idealized deformable elements (such as ►springs and ►dampers).

References

1. Goldstein H (1950) Classical mechanics. Addison-Wesley, Cambridge
2. Truesdell C, Toupin R (1960) The classical field theories. In: Flügge S (ed) Handbuch der Physik, vol III/1. Springer, Berlin
3. Fung YC (1981) Biomechanics. Springer, New York
4. Nigg B, Herzog W (eds) (1994) Biomechanics of the musculo-skeletal system. Wiley, New York
5. Epstein M, Herzog W (1998) Theoretical models of skeletal muscle. Wiley, Chichester

Mechanoelectric Transduction

►Mechanosensory Transduction

Mechanoreceptor Mechanism

►Mechanosensory Transduction

Mechanoreceptors

Definition

A class of sensory receptors whose adequate stimulus is a physical change in the position of a body part or surface, including the various mechanoreceptors in the skin, the auditory and vestibular hair cells of the inner ear, and the stretch receptors in skeletal muscle. The mechanical deformation causes an electrical change within the receptor cell (i.e., the generator or receptor potential), and eventually an action potential in the nerve fiber(s) connected to the receptor organ.

►Sensory Systems

Mechanosensation

Definition

The sensation of a mechanical event (e.g., contact, deformation, stretch or displacement) involving a somatic tissue, such as the skin, oral mucosa, muscle or joint.

Mechanosense

►Evolution of the Mechanosensory and Electrosensory Lateral Line Systems

Mechanosensory Transduction

Hisashi Ogawa
Department of Neurology, Kumamoto Kinoh Hospital, Kumamoto, Japan
Department of Sensory and Cognitive Physiology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Honjo, Kumamoto, Japan

Synonyms

Mechanoelectric transduction; Mechanoreceptor mechanism; Mechanosensitive ion channels; Mechanically-gated ion channels

Definition

Low mechanical energy is received at cutaneous mechanoreceptors and converted into electrical energy in the form of receptor potential. Mechanoreceptors work as sensory transducers to transform mechanical energy to electrical energy. Receptor potential is then converted into a series of impulses at a spike generating site, the first Ranvier node of sensory nerve fibers innervating. Different structures of mechanoreceptors may be suitable to receive different forms of mechanical energy. Comments are also made on the mechanical filter of lamella of corpuscles, the possible functional role of Merkel cells in the Merkel cell-►neurite complex, which yield receptor potentials in response to mechanical stimulator mechanosensitive ion channels.

Characteristics

Quantitative Description

Receptor potentials in response to mechanical stimulation were first discovered at Pacinian corpuscles isolated from the mesentery in cats [1]. Receptor potentials to mechanical stimulation were also recorded from the muscle spindle of frog [2] and from stretch receptors of muscles in crayfish. Receptor potentials are generated locally at the non-myelinated nerve terminals (or at the dendrites of muscle stretch receptor cells), and ►graded depending on the strength of mechanical stimulus. Receptor potentials from the Pacinian corpuscle are rapidly adapting or ►phasic in time course, generated at the onset and offset of mechanical pulses applied (Fig. 1c), whereas those from muscle spindles and stretch receptors are tonic, lasting during the application of muscle stretch.

Thus, it is believed that receptor potentials are phasic in rapidly adapting mechanoreceptors, such as lamellated corpuscles or Meissner corpuscles, but they are tonic in slowly adapting mechanoreceptors, such as Merkel cell-neurite complexes or Ruffini endings, although receptor potentials have not been recorded from most of the cutaneous mechanoreceptors. The size of receptor potentials are dependent on the sodium concentration in the solution bathing the isolated Pacinian corpuscles. Therefore, mechanical forces increase ►membrane conductance, probably by gating the ionic channels permeable sodium ions [3] which have not yet been identified. ►Tetrodotoxin and local anesthetics affect receptor potentials, however, the effects of amiloride which affect Deg/ENaC, mechanosensitive ion channels in *C. elegans* (see below), have not been investigated.

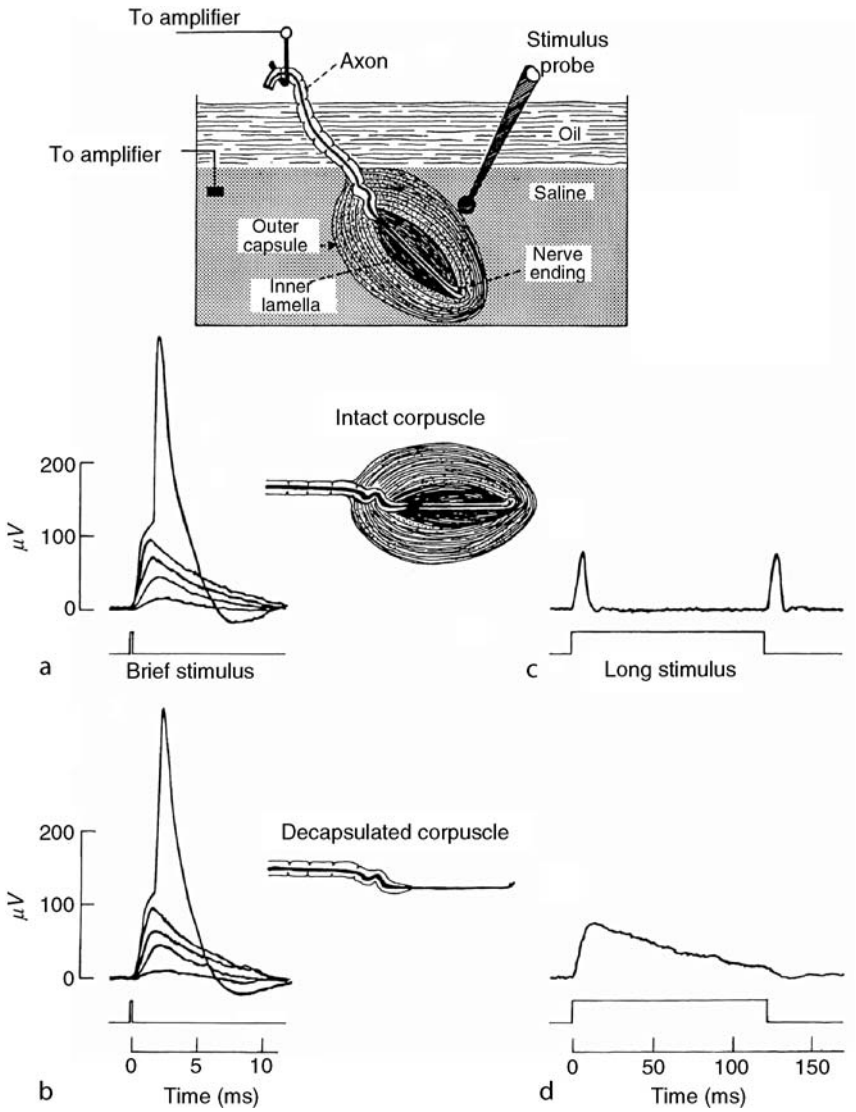
Receptor potentials increase in a graded manner in response to the increased strength of mechanical pulses. The magnitude of the receptor potential is proportional to the strength of mechanical stimulation [1] (Fig. 2).

Receptor potentials spread electrotonically [►Electrotonus, electrotonic (ally)] to the spike generation site, the first Ranvier node, and are recorded as generator potentials. Generator potentials are now converted into spikes when they exceed the threshold for the firing spike. As far as generator potentials exceed the firing threshold, spikes are generated successively, although adaptation at the spike generation sites is different with different mechanoreceptors. The number of spikes generated in a unit time is proportional to the receptor potential height as well as to the mechanical stimulus applied.

Further study of the mechanosensory transduction mechanism may exceed the limit of electrophysiological technique, and may proceed with collaboration of both electrophysiology and molecular biology (see mechanosensitive ion channel).

Lamellate Structure Works as a Mechanical Filter

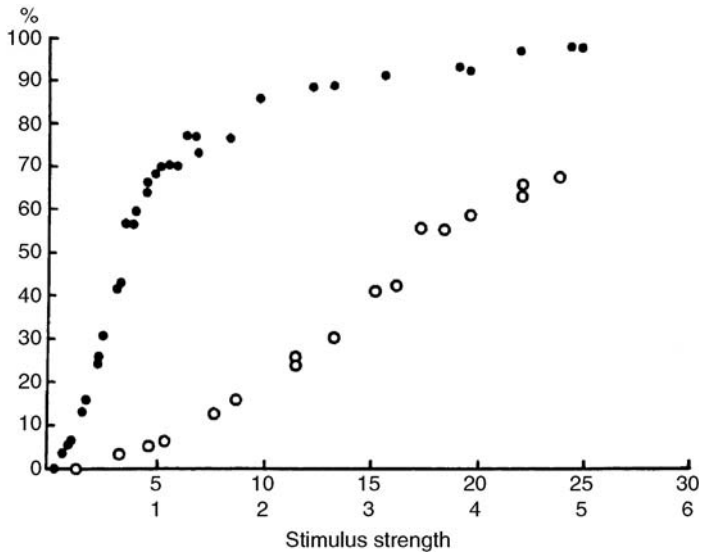
Lamellated corpuscles work as a mechanical filter and transmit a transient change of mechanical forces applied to the unmyelinated nerve terminal in the central core [3]. Application of short mechanical pulses to the



Mechanosensory Transduction. Figure 1 Responses of intact and decapsulated Pacinian corpuscles (PC) to brief and prolonged mechanical stimulation. The upper part of the figure illustrates the gross morphology of an intact PC and the method to stimulate and record from it. A, B; Responses to evoked by graded brief mechanical stimuli at both intact and decapsulated Pacinian corpuscles (A, B). The strongest stimulus evoked a response that exceeded threshold for generation an action potential. C. An intact PC produced a phasic receptor potential at the onset and offset of a prolonged stimulus. D. A decapsulated PC produced a sustained receptor potential. (Reproduced and modified from PB Detwiler 'Sensory transduction', In: HD Patton et al. (eds) Textbook of Physiology, 21st Edition, vol. 1, Excitable Cells and Neurophysiology, WB Saunders Company, Philadelphia 1986, pp 98–129, Fig. 5–9).

outer lamella in the Pacinian corpuscle generates both transient and static phases of mechanical displacement at the outer part of the lamella. But the static phase of the displacement is rapidly decreased as the displacement is transmitted further down to the inner core, and finally only the transient phase of displacement is transmitted to the non-myelinated nerve terminal. Such a mechanical filter action has theoretically also been analyzed. Resection of the outer lamella from the Pacinian corpuscle changes the adaptation of receptor potentials from phasic to tonic form; now, receptor potentials last during the period of mechanical stimulation (Fig. 1b). Thus, the lamella works as a mechanical filter to pass only the high frequency component of mechanical forces to the nerve terminals.

Generation of the RP at offset as well as at onset of mechanical compression is explained by the oval form of nerve terminals [3]. The unmyelinated nerve terminal



Mechanosensory Transduction. Figure 2 Relationship between the stimulus strength applied to crystal or an electromechanical transducer (in voltage) and receptor potential relative to the maximum amplitude (%) in a PaC. Filled circles, relationship in the range of 0~30 volts; open circles, in the range of 0~6 volts. (Reproduced and modified from JAB Gray and M Sato (1952) 'Properties of the Receptor Potential in Pacinian Corpuscles', J. Physiol. 122:610–636, Fig. 8).

is oval in shape, and the longer transverse axis is aligned with the cleft of the inner lamella. The application of mechanical displacement to the shorter axis depolarizes the nerve terminal but the stimulation of the longer axis hyperpolarizes it. Application of mechanical forces displaces the lamella at the onset to increase the pressure inside the lamella, depolarizing the nerve terminal at the shorter axis. When mechanical distortion is over, the lamella return to the original sphere and the pressure inside the lamella is decreased as a whole, which depolarizes the nerve terminal at the longer axis.

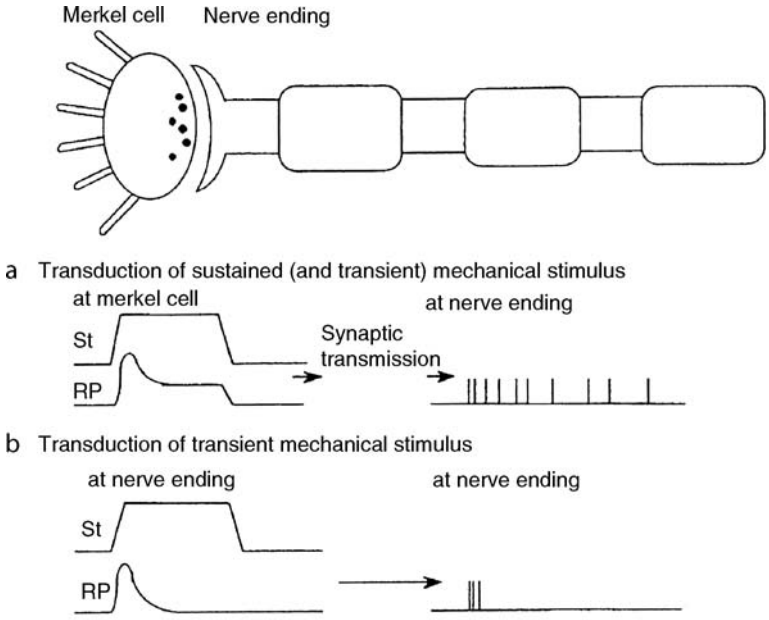
This mechanical filter hypothesis is applicable to all lamellated corpuscles, since all sensory units innervating lamellated corpuscles are rapidly adapting to generate both on and off discharges in response to mechanical pulses.

Functional Role of Merkel Cells at Merkel Cell-Neurite Complexes

Since F Merkel (1875) discovered Tastzellen (Merkel cells) in various vertebrates, it has been known that they are located at the position of the skin to readily receive mechanical deformation or force to the skin from the outside; under the touch dome in hairy skin or under the papillary ridges in glabrous skin. However, there is long-lasting controversy over the issue of whether Merkel cells are receptor cells, merely accessory cells to transmit mechanical forces to the associated nerve terminals or to induce their innervation of the skin during development [4]. Among affirmative evidence for the mechanotransduction hypothesis, included are phototoxic or chemical destruction of Merkel cells to abolish the tonic phase of discharges, chemical or gaseous manipulation of the circulating blood supply or bathing solutions for Merkel cells in situ or in vitro to modify the discharge patterns, and tonic discharges to anodal DC stimulation [4–6]. Among the negative evidence against the hypothesis, however, the failure by phototoxic destruction of Merkel cells to abolish discharges in response to short mechanical stimulations, the capability of Merkel cell-►neurite complex afferents to follow high frequent sinusoidal stimulation, possibly denying the function of synapse between Merkel cells and nerve terminals, and the survival of slowly adapting afferent discharges of irregular form (a specific feature of mechanoreceptor afferents innervating Merkel cell-neurite complexes) in spite of almost all loss of Merkel cells in mice lacking some neurotrophin [4,7]. To compromise the two parties, two-mechanotransduction site hypotheses have been submitted [4] (Fig. 3); Merkel cells are receptor sites for both phasic and tonic transduction and nerve terminals those for phasic transduction.

Mechanosensitive Ion Channels

Application of mechanical forces to mechanoreceptors open mechanosensitive ion channels which is reflected as an increase in membrane conductance, to generate receptor potentials. By using techniques



Mechanosensory Transduction. Figure 3 Schematic illustration of two site-hypothesis in mechanosensory transduction in Merkel cell-neurite complex. Each of the two receptor sites, Merkel cells and nerve ending, transforms different forms of mechanical forces (static + phasic and phasic only). *GP*, generator potential at the spike generation site; *MC*, Merkel cell; *NE*, nerve ending; *RP*, receptor potential; *ST*, stimulation). (Reproduced from H Ogawa (1996) "The Merkel Cell as a Possible Mechanoreceptor Cell", Progress in Neurobiology, 49:317–334. Elsevier Science Ltd, Fig. 15).

M

of both electrophysiology and molecular biology, mechanosensitive ion channels have been extensively studied in nematode (*Caenorhabditis elegans*) and arthropod (*Drosophila*), and some correspondence in mammals has also been studied. However, ion channels gated by low mechanical stimulation have not yet been identified in mammals.

In both *C. elegans* and *Drosophila*, ion channels of two gene families, degenerin/epithelial Na channel (Deg/ENaC) and transient receptor potential (TRP) superfamily, are proposed as the candidates for mechanosensitive ion channels to mechanically gate in a short latency. Corresponding genes in are also found.

Deg/ENaC superfamily [8] have two transmembrane domains with a large extracellular loop for receiving physical stimuli from outside and the N and C terminals facing intracellular space. Among the superfamily, MEC-4 complexes have been identified as a mechanotransduction in *C. elegans*; the assembly is composed of Deg/ENaC subunits MEC-4 and MEC-10 and the accessory subunits MEC-2 and MEC-6. The MEC-4 complex is thought to associate with the extracellular matrix. ►Null mutation in MEC-4, MEC-2 and MEC-6 abolish mechanotransduction in body touch neurons. Since mammalian correspondence, β-ENaC and γ-ENaC, localize at lanceolate nerve endings in the vibrissae, Merkel cells and lamellated corpuscles in the food pad of the rat, they are assumed to act as a mechanotransduction channel. However, the function remains to be studied because of failure in their mutation study.

Three members of the acid-sensing ion channels (ASICs), a related subfamily of Deg/ENaC, are tested for a possible mechanotransduction channel. Na current through the channel is blocked by amiloride and facilitated by an acid lower than pH 5 and Zn. Knockout of respective genes in mice has been carried out to elucidate their involvement. Knockout of ASIC1 did not affect cutaneous touch, but did affect visceral mechanical afferents. Since both ASIC 2 and ASIC 3 are expressed at various mechanoreceptor afferent terminals, such as Meissner's corpuscles, Merkel cell-neurite complex, and hair follicles, several research groups knocked out ASIC 2 and 3 to see the influence on cutaneous mechanoreception. One group found that knockout of either ACIC 2 or ASIC 3 reduced in ►firing rates of rapidly adapting afferents in hairy skin but not in other types of mechanoreceptor afferents. Other groups, however, did not find any disruption of mechanoreceptor afferent activities by knockout of ASIC2 and/or ASIC3.

TRP family [8,9] is comprised of seven families. They are generally nonselective cation channels, having a molecular architecture similar to that of voltage-gated ion channels: subunits have six transmembrane domains with

a putative pore region, and are arranged to form a tetrameric channel. Almost all TRP families are expressed at ciliated structures, such as hair cells in the inner ear, and the vaniloid receptor TRP subfamily (TRPVs) is probably involved in mechanotransduction in vertebrates. TRPV4 are expressed at cutaneous nerve terminals, including Meissner corpuscle, Merkel-cell neurite complex, and Ruffini endings, but not in hair follicle palisade, however, its knockout did not impair mechanotransduction in low threshold mechanoreceptors but did in high threshold pressure receptors or mechanical nociceptors. TRPV4 is also activated by osmotic stimuli which cause cell to swell to regulate osmotic pressure in the brain. Since TRPV4 are usually activated by a second messenger in response to chemicals or temperature, a real mechanosensor is suggested in an upstream element even if it is involved in mechanosensory transduction. Isolated Merkel cells increased intracellular Ca in response to hyposmotic stimuli [10] and Merkel cells have lots of cytoplasmic processes probably corresponding to cilia of hair cells (see Mechanoreceptor, Anatomy in this Encyclopedia). However, it is not known whether TRP is involved in mechanotransduction of Merkel cells.

In spite of efforts, no mechanosensitive ion channels have so far been identified for low threshold cutaneous mechanoreceptors. Attempts to record mechanically-gated ionic currents from dorsal root ganglion (DRG) cells with genes of possible candidates for mechanosensitive ion channels have resulted in vain, probably because mechanosensors are not expressed at the membrane of DRG cells but at the nerve terminals.

References

1. Gray JAB, Sato M (1953) Properties of the receptor potential in pacinian corpuscles. J Physiol 122:610
2. Katz B (1950) Depolarization of sensory terminals and the initiation of impulses in the muscle spindle. J Physiol 111:261–282
3. Hunt CC (1974) The Pacinian corpuscle. In: Hubbard JI (ed) The peripheral nervous system. Plenum Press, New York, pp 405–420
4. Ogawa H (1994) The Merkel cell as a possible mechanoreceptor cell. Prog Neurobiol 49:317–334
5. Senok SS, Halata Z, Baumann KI (1996) Chlorquine specifically impairs Merkel cell mechanoreceptor function in isolated rat sinus hairs. Neurosci Lett 24:167–170
6. Fagan M, Cehusac PMB (2001) Evidence for glutamate receptor mediated transmission at mechanoreceptors in the skin. NeuroReport 12:341–347
7. Kinkelin I, Stucky CL, Koltzenburg M (1999) Postnatal loss of Merkel cells, but not of slowly adapting mechanoreceptors in mice lacking the neurotrophin receptor p75. Eur J Neurosci 11:3963–3969
8. Lumpkin EA, Bautista DM (2005) Feeling the pressure in mammalian somatosensation. Curr Opin Neurobiol 15:382–388
9. Lin S-Y, Corey DP (2005) TRP channels in mechanosensation. Curr Opin Neurobiol 15:350–357
10. Tazaki M, Suzuki T (1998) Calcium inflow of hamster Merkel cells in response to hyposmotic stimulation indicates a stretch-activated ion channel. Neurosci Lett 243:69–72

Mechanotransduction

Definition

The sensing of mechanical stimuli by specialized mechanoreceptor cells, which transduce the stimuli into membrane potential changes (receptor potentials).

►Sensory Systems

Medial Diencephalic Disorder

Definition

Frequently referred to as ‘diencephalic amnesia’, medial diencephalic disorder is a type of amnestic disorder linked to lesions in the medial diencephalic region of the brain. The specific structures and connections in this region that must be damaged to cause memory impairment continue to be investigated. Two structures most frequently implicated include the medio-dorsal thalamic nucleus and mammillary nuclei. The presentation of diencephalic amnesia is similar to medial temporal lobe amnesia, with the usual occurrence of both anterograde and temporally graded retrograde amnesia.

►Amnesia

Medial Eminence

Synonyms

►Eminentia medialis; ►Medial eminence

Definition

Protrusion created by underlying cranial nerve nuclei and pathways.

►Pons

Medial Geniculate Body

Adrian Rees
Auditory Group, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

Synonyms

Auditory thalamus; Medial Geniculate Nuclei

Definition

The medial geniculate body is the thalamic processing centre of the auditory pathway. It receives projections from several nuclei in the auditory brainstem and midbrain (predominantly the inferior colliculus), the auditory cortex, and the thalamic reticular nucleus (TRN). The projections of the MGB include regions of the auditory cortex, the TRN, and the lateral nucleus of the amygdala. The MGB comprises several subnuclei, each of which has distinct structural and functional properties. As well as being important for sound recognition and localization, it also plays a role in the emotional responses to sounds and auditory attention.

Characteristics

Introduction

The innervation of the MGB provides compelling evidence that sound perception depends on more than the upward sweep of sensory information from cochlea to cortex. Although the MGB receives ascending inputs chiefly, but not exclusively, from auditory centers in the brainstem, these are greatly outweighed by the descending inputs it receives from cortical sources. Indeed, the thalamic and cortical centers are so closely interconnected they are often referred to conjointly as the thalamo-cortical loop. Although we know little about the function of these connections, it seems likely they enable prior experience and stimulus history to influence sensory inflow to the cortex. But as well as projecting to the cortex, the MGB also targets the limbic system, a region of the brain involved in controlling emotions, and other subcortical targets such as the auditory sector of the thalamic reticular nucleus (TRN). Thus, the MGB not only has an essential role in auditory perception, but also contributes to learning, memory and attention in the auditory domain.

Our knowledge of the MGB is based on anatomical studies in a variety of mammals from rodents to humans, and physiological studies principally in cat, rat, guinea pig and primate. Species differences exist, but for the sake of clarity the emphasis here will be on the common features.

Location and Subdivisions

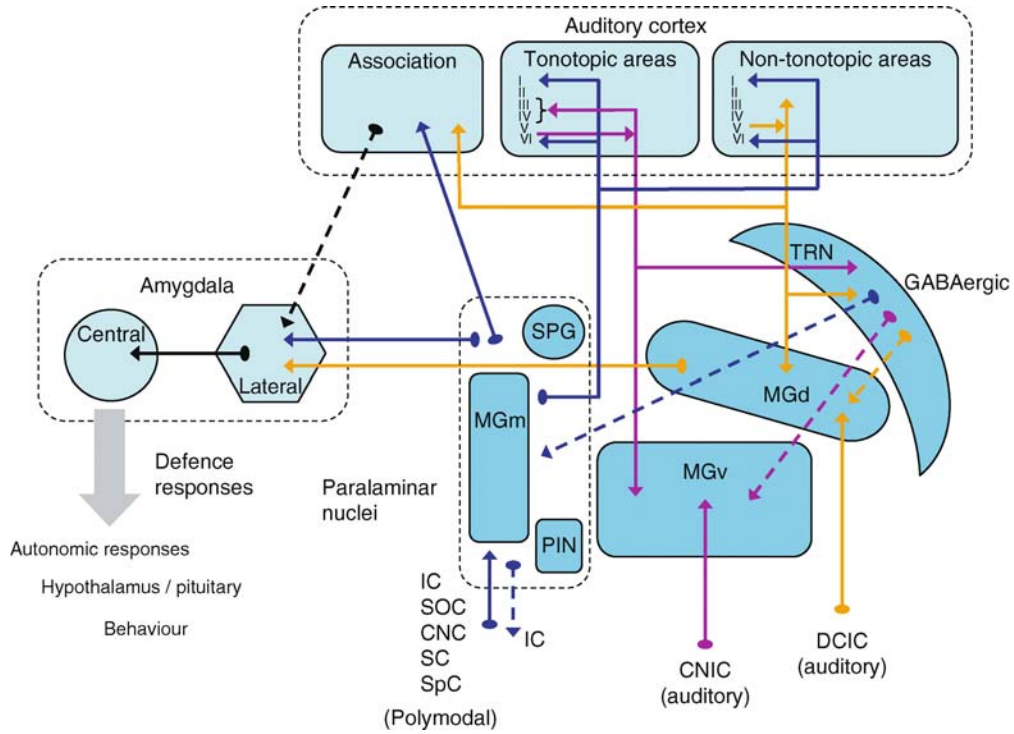
The paired MGBs are the most caudal thalamic nuclei, and are visible as rounded eminences on the lateral edges of the diencephalon at its junction with the mesencephalon. Caudal to each MGB is the superior colliculus, while dorsally and laterally is the lateral geniculate body: the principal visual nucleus of the thalamus.

The MGB is not a single uniform structure, but consists of three divisions, or nuclei: ventral (MGv), dorsal (MGd) and medial (MGm). Within these divisions further subdivisions have been recognized by their distinct cytoarchitecture, connections, and functional properties [1]. In contrast to some structures in the auditory brainstem, the two MGBs are not directly interconnected.

MGv, the largest of the three divisions, is overlain by the flatter dorsal division (MGd), while the narrow MGm lies medial to them. Of the three divisions MGv appears to be primarily sensory. It receives the major ascending (lemniscal) input from the ►inferior colliculus in the auditory midbrain, and sends outputs to the frequency mapped (tonotopic) subdivisions of the auditory cortex on the ipsilateral side, which in turn project back to MGv. MGd receives its inputs primarily from the dorsal cortex of the inferior colliculus and projects predominantly to nontonotopic, or extra-lemniscal, auditory fields and to the limbic system. MGm is characterized by polymodal inputs, and outputs that project to both tonotopic and non-tonotopic regions of auditory cortex. It also targets non-cortical structures including the lateral ►amygdala in the limbic system, and is involved in emotional responses to sound and auditory learning. The TRN comprises a shell of GABAergic neurons enveloping the thalamus laterally and rostrally; the auditory sector being most caudal part of the nucleus. It receives collateral inputs from excitatory thalamo-cortical and cortico-thalamic synapses, while delivering inhibitory feedback to the MGB via $GABA_A$ and $GABA_B$ fibers. Thus, under the influence of these feed forward and feedback connections, TRN modulates information flow from thalamus to cortex. The connections of the MGB are summarized in Fig. 1.

Ventral Nucleus (MGv)

The major ascending input to MGv is from the midbrain, chiefly the central nucleus of the inferior colliculus on the ipsilateral side. Although this projection is predominantly excitatory, there is also a significant GABAergic, inhibitory projection, at least in rat and cat. As with other nuclei in the lemniscal division of the auditory pathway, the incoming fibers are arranged systematically within MGv according to their ►best frequency (BF), so giving rise to a topographic representation of sound frequency (a ►tonotopic map) that reflects the spatial analysis of frequency on the basilar membrane in the cochlea.



Medial Geniculate Body. Figure 1 Connections to and from the medial geniculate body. *Double-headed arrows* indicate bi-directional connections. *Arrows* in the area enclosed by the *dashed line* labeled "paralaminar nuclei" represent connections of all nuclei in this group. Key: CNC, cochlear nucleus complex; CNIC, central nucleus of the inferior colliculus; DCIC, dorsal cortex of the inferior colliculus; IC, inferior colliculus; MGv, MGd, MGm, ventral, dorsal and medial nuclei of MGB, respectively; PIN, Posterior intralaminar nucleus; TRN, thalamic reticular nucleus; SC, superior colliculus; SOC, superior olivary complex; SpC, spinal cord; SPG, suprageniculate nucleus.

The neural substrate underlying this organization is an arrangement of large principal neurons whose flattened, tufted dendrites align with the incoming fibers. In the lateral part of MGv in cat, the species investigated most intensively, the cells and fibers are arranged in curved sheets or laminae orientated approximately dorsal to ventral and rostral to caudal. Neurons responding best to low-frequency sounds are encountered in the most lateral laminae and those with high frequency BFs occur medially. The sequence changes in the neighboring pars ovoidea; a region named for the laminae's distinctive concentric arrangement. The tonotopic mapping reflects this structure with neurons tuned to low frequency in the centre [2]. The tonotopy continues into the lateral part of the Posterior Group of the thalamus, a nucleus that abuts the MGv on its lateral, rostral and medial borders. The similarity of the auditory representation in the posterior group to that in MGv has led to its inclusion as a lemniscal component of the auditory pathway [2]. The tonotopic organization of MGv is reportedly less precise in lightly, or unanesthetized animals.

Other parameters of sounds are distributed across the two dimensional surface of each frequency lamina in MGv. Specific regions of the laminae represent different binaural interactions, e.g., bands of neurons that are excited by sound at either ear are separated by neurons that are excited by sound presented to the contralateral ear and inhibited by sound in the ipsilateral ear.

In cat and primate, MGv has an abundance of small inhibitory (GABAergic) interneurons distributed amongst the lamina-forming principal cells. These neurons form complex nests of connections with the principal cells called glomeruli. In marked contrast, GABAergic neurons are virtually absent in the rat, indicating differences of function across species [1].

In general, neurons in MGv are selective, or tuned, for sound frequency, with the majority showing the same or sharper tuning compared to that of auditory nerve fibers. A variety of different firing patterns to tonal stimuli have also been described including onset (the majority), tonic and off responses [3]. These patterns may reflect the distinct response properties of different units, but they may also be influenced by different functional states of the thalamus. Cells in the MGB, like many in the other thalamic nuclei, are capable of switching between two different modes of firing, "tonic" and "burst," depending on the state of a voltage-sensitive calcium conductance.

Bursts occur when this ion channel is activated by hyperpolarization of the neuron's membrane potential, presumably as consequence of the abundant inhibition derived from intrinsic and extrinsic sources in the MGB. Suggestions for the possible functional relevance of bursting include enhancing sensitivity to weak stimuli, and more effective driving of cortical target neurons. In MGv there is a greater tendency for bursts to fire when the stimulus is near the neuron's best frequency, thus perhaps generating a more robust representation of such sounds.

A caveat to any discussion about the functional role of these different modes of firing is the influence of the animal's conscious state. Membrane potential hyperpolarization appears to be prominent under anesthesia and slow-wave sleep, whereas MGB neurons are more depolarized in awake animals. Recordings in unanesthetized preparations are thus essential to reveal the true physiological response patterns of MGB neurons.

Outputs of MGv project to the tonotopic areas of the auditory cortex; these include A1 and AAF in cat, and the equivalent areas in primates identified as the "core" areas (AI and R, the area rostral to AI). These projections terminate predominantly in layers III–IV; the main input layers of the cortex. The ventral nucleus receives a heavy projection from the same areas of cortex particularly from cells in layer VI, but these patterns of connections are complex, and not simply reciprocal to the sources of input [4]. Collaterals of thalamo-cortical fibers from the MGv terminate in TRN which sends projections back to MGv and the other subdivisions.

We still know little about the functional role of the cortico-thalamic projection, although several studies have demonstrated changes in the tuning and firing rates of thalamic neurons following manipulation of the cortical activity [5]. It seems likely that cortico-thalamic projections mediate the feed-forward as well as feedback of cortical information to the MGB.

Dorsal Nucleus (MGd)

The dorsal nucleus of the MGB has been subdivided into as many as five heterogeneous subdivisions. Like the ventral nucleus, the inputs to MGd originate from excitatory and inhibitory (GABAergic) neurons in the inferior colliculus, but in this case mainly from the dorsal cortex and the nearby lateral tegmental area rather than the central nucleus.

Generally, MGd neurons are not particularly selective for sound frequency and have broad or complex tuning curves; consequently there is little evidence of tonotopic organization in this nucleus, except in the deep dorsal division where neurons with more sharply tuned frequency responses have been recorded [3].

A particular property of MGd neurons is that many fail to respond to simple acoustic stimuli, and their responses habituate to repeated presentation of the same stimulus. Some authors have also reported the preference of MGd neurons for sounds that are spectrally and temporally complex, particularly animal calls and vocalizations [3].

The outputs of MGd are predominantly to the auditory cortex, but they are distributed more diffusely than those of MGv and directed mainly to the non-tonotopic, non-primary areas. For example, in cat there is a particularly strong input to the second auditory area AII, and in primates the strongest projections are to the belt regions surrounding the primary core areas of auditory cortex. The fibers' terminals are more widely distributed within the cortical layers with endings in all six layers [4]. Projections from MGd also go to the insular cortex and to the lateral nucleus of the amygdala indicating that it contributes to emotional responses to sound. MGd receives reciprocal projections from the auditory cortex, particularly from layer V cells, from the perirhinal cortex, the caudate and the putamen. As is the case with MGv, collaterals of MGd output fibers project to the TRN which, in turn, sends projections back to MGd.

Medial Nucleus (MGm)

The medial nucleus of the MGB lies within the paralaminar group of nuclei found medial to the rest of the MGB. The group includes MGm, the suprageniculate nucleus (SPG; included in MGd in some classifications) and the posterior intralaminar nucleus (PIN). Functionally, these nuclei have many features in common and may be parts of the same entity [6].

MGm is a multimodal nucleus; in addition to its auditory input it also receives connections from other sensory pathways including the visual (superior colliculus), vestibular (vestibular nuclei) and ▶somatosensory (spinal cord) systems. Its auditory afferents originate chiefly from the extra-lemniscal external cortex of the inferior colliculus, but it also receives axons from the central nucleus of the inferior colliculus, and auditory centers peripheral to the midbrain including the superior olivary complex and the cochlear nucleus.

Consistent with the input it receives from lemniscal as well as extra-lemniscal divisions of the IC, some neurons in MGm have properties rather like those in MGv, namely relatively sharp tuning and short response latencies. But in general the frequency tuning of MGm neurons is broad, and some have distinctive multi-peaked tuning curves. Tonotopic organization is similarly relatively weak in MGm, although more apparent in the rostral part of the nucleus [3]. Responses are often more labile than those in the MGv, and, like neurons in MGd, often show habituation to repeated stimulus presentation. An important functional difference between neurons in MGm and those in other subdivisions of MGB is the reduced or absent expression of the calcium conductance responsible for the burst mode of firing [6].

A subset of MGm neurons are amongst the largest found in the MGB. An asymmetry in the size and number of these magnocellular neurons has been reported in the brains of dyslexic subjects at post mortem [7]. Compared with controls there was a deficit in the number and size of the neurons in the left MGm. Some assert this finding supports a general magnocellular theory of ►dyslexia. This posits that dyslexia results from a general deficit in magnocellular neurons leading to impaired processing of rapidly changing visual and auditory signals in the thalamus. However, while auditory deficits in processing dynamic stimuli have been reported in dyslexics, they are not always most pronounced for sounds with the most rapid fluctuations of frequency or amplitude. Furthermore, MGm does not appear to be homologous in input or function to the magnocellular layers in the visual thalamus.

The outputs of MGm project widely in the auditory cortex and target both primary, (tonotopic) and secondary (nontonotopic) areas. In contrast to the cortical projections of the other subdivisions, axons from MGm terminate primarily in the most superficial and deepest cortical layers (I and VI). Such a distribution is consistent with evidence that inputs to the cortex from MGm and other paralaminar nuclei contribute to cortical mechanisms mediating the formation of auditory memories, perceptual binding and aspects of attention. Electrical stimulation of the PIN enhances 40 Hz ►gamma oscillations in the cortex in rat, whereas they are attenuated by stimulation of MGv and MGd. These oscillations are hypothesized to reflect the binding of the different sensory representations of an object into a single percept [8]. Similarly, stimulation of TRN also increases cortical gamma oscillations suggesting that the paralaminar group and TRN are part of the same circuit.

Another important role of MGm is its contribution to the circuit mediating ►fear conditioning to acoustic stimuli. In this behavioral paradigm studied in rat, a neutral conditioned stimulus, e.g., a tone, is paired with a fear inducing unconditioned stimulus (mild footshock). After several such pairings, and consequent to the neural plasticity they induce, presentation of the conditioned stimulus alone is sufficient to elicit the fear response. The MGm and other paralaminar nuclei send direct projections to the lateral nucleus of the amygdala in the limbic system, the centre responsible for activating the behavioral and autonomic changes associated with fear responses [9]. The importance of such mechanisms for survival may explain the existence of a direct, and therefore fast, connection between the cochlear nucleus, (the first nucleus of the auditory pathway) and the MGm. An fMRI study in human has reported a correlation between activity in the amygdala and thalamus during conditioning.

There is no dispute that MGm is a source of auditory input to the fear conditioning circuit, but there is disagreement about where the conditioned and unconditioned stimuli become associated. The combined auditory and somatosensory input to MGm could provide a necessary substrate for such an interaction. Receptive field plasticity has been reported for MGm neurons in the form of an enhanced response and selectivity for the frequency of the conditioned stimulus [10]. These changes are persistent and occur with appetitive as well as fear conditioning. Others argue that the association between the conditioned and unconditioned stimulus first occurs in the lateral amygdala, and changes in MGm reflect feedback from the amygdala – although the necessary feedback connection has not been described. Alternatively, plasticity could of course occur at both sites, and differences in the properties of the plasticity observed in the two nuclei are consistent with this possibility.

Information from the MGB also reaches the amygdala via a second (albeit slower) indirect projection from both the dorsal and medial nuclei via the cortex. Other projections of MGm include the basal ganglia and feedback connections to the inferior colliculus.

References

1. Winer JA (1992) The functional architecture of the medial geniculate body and primary auditory cortex. In: Webster DB, Popper AN, Fay RR (eds) The mammalian auditory pathway: neuroanatomy. Springer, New York, pp 222–409
2. Imig TJ, Morel A (1988) Organization of the cat's auditory thalamus. In: Edelman GM, Gall WE, Cowan WM (eds) Auditory function: neurobiological bases of hearing. Wiley, New York, pp 457–485
3. de Ribaupierre F (1997) Acoustical information processing in the auditory thalamus and cerebral cortex. In: Ehret G, Romand R (eds) The central auditory system. Oxford University Press, New York, pp 317–397
4. Winer JA, Miller LM, Lee CC, Schreiner CE (2005) Auditory thalamocortical transformation: structure and function. Trends Neurosci 28:255–263
5. Yu Y-Q, Xiong Y, Chan Y-S, He J (2004) In vivo intracellular responses of the medial geniculate neurones to acoustic stimuli in anaesthetized guinea pigs. J Physiol 560:191–205
6. Smith PH, Bartlett EL, Kowalkowski A (2006) Unique combination of anatomy and physiology in cells of the rat paralaminar thalamic nuclei adjacent to the medial geniculate body. J Comp Neurol 496:314–334
7. Galaburda A, Menard M, Rosen G (1994) Evidence for aberrant auditory anatomy in developmental dyslexia. Proc Natl Acad Sci USA 91:8010–8013
8. Barth DS, MacDonald KD (1996) Thalamic modulation of high-frequency oscillating potentials in auditory cortex. Nature 383:78–81
9. Doron NN, LeDoux JE (2000) Cells in the posterior thalamus project to both amygdala and temporal cortex: A quantitative retrograde double-labeling study in the rat. J Comp Neurol 425:257–274

10. Edeline JM, Weinberger NM (1992) Associative retuning in the thalamic source of input to the amygdala and auditory-cortex – receptive-field plasticity in the medial division of the medial geniculate-body. Behav Neurosci 106:81–105

Medial Lemniscus

Synonyms
Lemniscus med.

Definition
The medial lemniscus arises from the union of the spinothalamic tract (anterior column of the spinal cord, protopathic sensibility), the bulbothalamic tract (gracile nucleus and cuneate nucleus, epicritic sensibility), the trigeminal lemniscus (face) and afferents of the solitary nucleus (gustatory sensibility). Hence it is also called the somatosensory tract. The fibers terminate in the corresponding thalamic nuclei,

which in turn project to the somatosensory cortex.

►Pathways
►Somatosensory Projections to the Central Nervous System

Medial Longitudinal Fasciculus

Synonyms
Fasciculus longitudinalis med.

Definition
A nerve fiber bundle running rostrally to caudally in the brainstem, a little laterally to the midline and below the oculomotor complex (rostrally) and the surface of the fourth ventricle caudally. The riMLF (rostral interstitial nucleus of the MLF) is the rostralmost of the nuclei and is reticulated by the interspersed fibers of the MLF. It borders caudally with a second interstitial nucleus of the MLF, the interstitial nucleus of Cajal from which it is separated by the dorsal to ventral running fibers of the tractus retroflexus. Also, dorsally and medially it is demarcated by the thalamo-subthalamic paramedian artery. The medial longitudinal fasciculus is composed of two fiber components:

- Vestibular component: conducts efferents of the vestibular nuclei to the nuclei for controlling eye and cervical muscles, thus coordinating organ of equilibrium with eye and head movements
- Internuclear component: it coordinates motor cranial nerve nuclei and provides for synchronous eye movement and coordination of pharyngeal muscles while speaking and swallowing

The following tracts course here:

- Interstitiospinal tract
- Reticulospinal tract
- Tectospinal tract
- Lateral vestibulospinal tract
- Medial vestibulospinal tract

►Interstitial Nucleus of Cajal
►Pathways

Medial Nucleus of the Trapezoid Body

Definition
One of the primary nuclei in the superior olivary nuclei located within the fibers of the trapezoid body.

►Superior Olivary Nuclei
►Trapezoid Body

Medial Octavolateralis Nucleus (MON)

Definition
Primary hindbrain recipient zone for mechanosensory neuromast afferents.

►Evolution of Mechanosensory and Electrosensory Lateral Line Systems

Medial Pallium

►Evolution of the Hippocampus

Medial Preoptic Nucleus

Synonyms
POML; Nucl. preopticus med.

Definition
Lies in the preoptic area, involved in thermoregulation, hypovolemic thirst, male sexual behavior, brood care, modulation of go nadotropin secretion. Larger afferents from the amygdala, subiculum, interstitial nucleus of the stria terminalis, lateral septal nucleus, insula. Efferents to the diagonal band, septum, substan-tia innominata, interstitial nucleus, amygdaloid body, brainstem. Has numerous cells with receptors for gonadal steroids. Disruption of this nucleus induces ongoing hypothermia, while stimulation results in hyperthermia.

The menstruation cycle is also interrupted in the event of dysfunctioning of this area.

►Diencephalon

Medial Rectus Muscle

Definition
Medial rectus is one of the six eye muscles.

►Eye Orbital Mechanics

Medial Reticular Formation

Definition
The magnocellular, medial region of the RF stretches across the entire brainstem and enables the following sections to be distinguished:

- Gigantocellular reticular nucleus
- Caudal pontine reticular nucleus
- Oral pontine reticular nucleus

Belonging here are also the mesencephalic nuclei: cuneiform nucleus, subcuneiform nucleus and central medulla oblongata nucleus. This region of the RF is involved in motor and sensory tasks.

►Pons

Medial Septum

Definition
Medial part of the septum, an area in the medial wall of the cerebral hemispheres, contains cholinergic cells in many species.

►Evolution of Subpallial Cholinergic Cell Groups

Medial Superior Olive

Definition
One of the primary nuclei in the superior olivary nuclei located most medially and important for encoding interaural time disparities.

►Interaural Time Difference (ITD)
►Superior Olivary Nuclei

Medial Superior Temporal Area (Area MST)

Definition
An area in the superior temporal sulcus of the rhesus monkey that contains neurons with selectivity for large-field optic flow. Area MST receives its main input from the middle temporal area.

►Optic Flow

Medial Temporal Lobe Amnesia

Definition
Amnesia that results from damage to one or several medial temporal lobe structures crucial for memory; such as, the hippoocampal region and the adjacent perirhinal, entorhinal, and parahippocampal cortices.

The severity of amnesia observed depends on the locus and extent of medial temporal lobe damage. A typical presentation might include anterograde amnesia with temporally graded retrograde amnesia. Generally,

memories for remote events are spared in medial temporal lobe amnesia.

►Amnesia
►Anterograde Amnesia

Medial Vestibular Nucleus

Definition

Cluster of cells located within the medial region of the complex of the vestibular nuclei. It projects to the spinal cord, the cerebellum and the motor nuclei of the extraocular muscles.

►Vestibular Nuclei
►Vestibulo-ocular Reflexes
►Vestibulo-Spinal Reflexes

Medial Vestibulospinal Tract

Synonyms

Tractus vestibulospinalis med

Definition

The efferents going from the medial vestibular nucleus and inferior vestibular nucleus in the direction of the spinal cord form the medial vestibulospinal tract which passes in the medial longitudinal fasciculus of the spinal cord into the cervical and upper thoracic cord, ending here on the motoneurons, innervating the cervical musculature and the upper extremities. The motor fibers of the lateral vestibular nucleus runs in the lateral vestibulospinal tract.

►Medulla spinalis

Mediterranean Diet

Definition

Traditional diet of the inhabitants of the countries around the Mediterranean Sea comprises of fresh fruits and vegetables. Their diet is popular all over the world, after the research linked their better health with their traditional and cultural diet.

►Central Nervous System Disease – Natural Neuroprotective Agents as Therapeutics

Medium Spiny Neuron

Definition

A type of central nervous neuron comprising more than 95% of the neurons in basal ganglia input structures, such as the caudate nucleus, putamen, nucleus accumbens and striatal districts in the olfactory tubercle. The cell body has a diameter in a range between 15 and 18 μm and gives rise to three to five primary dendrites that are aspiny proximally, but densely spiny beginning at about the first branch point.

The dendrites are extensively branched, producing approximately spherical dendritic fields with diameters of 200–300 μm. Medium spiny neurons utilize γ-amino butyric acid (GABA) as an inhibitory neurotransmitter and may co-express a number of peptide neuromodulators, such as enkephalin, substance P, dynorphin and neurotensin. They express dopamine and glutamate receptors and their activities are robustly modulated by dopaminergic projections arising in the midbrain and glutamatergic projections from a variety of sources, including the cortex and intralaminar thalamic nuclei.

The axons of medium spiny neurons give rise to dense terminations characteristic of the striatopallidal and striatonigral projections. Medium spiny neurons are also found in certain other of the deep telencephalic nuclei, such as the central and medial nuclei of the amygdala, bed nucleus of stria terminalis and lateral septum.

►Basal Ganglia
►Ventral Striatopallidum

Medium-Lead Burst Neurons in Eye Movement (MLBNs)

Definition

Neurons that exhibit a burst of spikes beginning no more than 15 ms before the onset of saccades in a preferred direction, but are silent or nearly silent during

fixation or slow eye movements. These include excitatory and inhibitory burst neurons.

►Brainstem Burst Generator
►Saccade, Saccadic Eye Movement

Medulla Oblongata

Definition

The medulla (Latin for marrow) is the caudal most part of the brainstem. Its rostral border is immediately caudal to the caudal edge of the pontine nuclei and its caudal border is marked by the top of the spinal cord just caudal to the pyramidal decussation and the cuneate and gracile nuclei.

►Evolution of the Hindbrain
►Myelencephalon

Medulla Spinalis

►Spinal Cord

Medullary Raphe Nuclei and Respiratory Control

George Richerson
Department of Neurology, School of Medicine, Yale University, New Haven, CT, USA

Definition

Effect of medullary serotonin (5-HT) neurons on motor output from the brainstem respiratory network.

In the accompanying essay of this Encyclopedia, we discuss the effects of medullary 5-HT neurons on the control of breathing. By releasing 5-HT, substance P (SP) and thyrotropin releasing hormone (TRH), they are thought to modulate respiratory output in a sleep state dependent manner, are required for ►hypoxia induced plasticity, and contribute to the stimulation of respiratory output by high CO_2 and/or low pH.

Characteristics

Anatomy

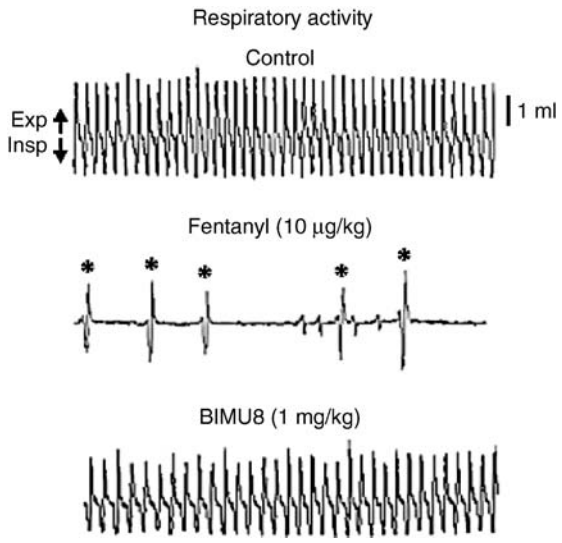
There is a caudal group of 5-HT neurons found in four locations in the caudal pons and medulla: the raphé pallidus, raphé obscurus, raphé magnus and parapyramidal region (►caudal raphé). Using tract tracing methods combined with immunohistochemistry for 5-HT or tryptophan hydroxylase (TPH), caudal 5-HT neurons have been found to project widely to nuclei containing respiratory neurons, including the nucleus ambiguus, nucleus tractus solitarius (NTS), hypoglossal motor nucleus and phrenic motor nucleus [1]. A variety of 5-HT receptor subtypes have been identified within these respiratory nuclei, including 5-HT_{1a}, 5-HT_{1b}, and 5-HT_{4a} [1].

Effect of 5-HT on Breathing in vivo

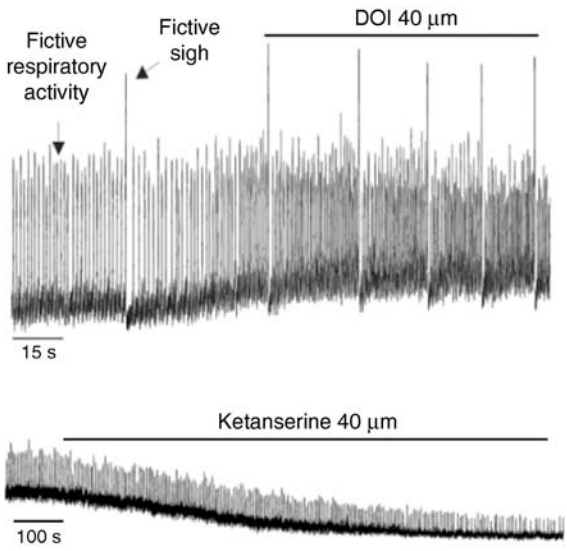
5-HT has a variety of modulatory effects on respiratory output and respiratory neurons *in vivo* [1]. Early experiments showed that blockade of 5-HT synthesis induced an increase in ventilation, suggesting that 5-HT inhibits breathing. Later it was found that stimulation of neurons within the medullary raphé nuclei causes release of 5-HT into the NTS and phrenic motor nucleus, and this could either stimulate or inhibit breathing depending upon where the electrode is placed. In contrast, selective agonists for 5-HT_{1a}, 5-$HT_{2a/1c}$ and 5-HT_{4a} receptors stimulate ventilation (Fig. 1) [1,2]. The precise role of 5-HT and serotonergic neurons remains unclear, because it has been difficult to determine how endogenous release of 5-HT influences breathing *in vivo* under physiological conditions. This has been particularly problematic due to confounding effects of arousal state, separation of the effects of different receptor subtypes, and the interaction with other neuromodulatory inputs (e.g., norepinephrine, acetylcholine, histamine, SP and TRH). However, the consensus is that 5-HT has a primarily excitatory effect on respiratory motor output under most conditions.

Co-localized Neuropeptides

Many 5-HT neurons in the medulla are also immunoreactive for neuropeptides, including SP and TRH. These neuropeptides are co-released by 5-HT neurons, and there are receptors for them on respiratory neurons. For example, neurokinin 1 (NK1) receptors for SP are localized in high concentration within the pre-Bötzinger Complex (pre-BötC) [3]. When administered *in vivo*, SP and TRH both have effects on breathing that are often stronger than 5-HT itself, and are uniformly stimulatory [1]. For example, studies in a variety of species have shown that TRH reverses respiratory depression induced by anesthetics. The relative importance of TRH in mediating the respiratory effects of 5-HT neurons has been difficult to determine, because there are not good antagonists of TRH receptors, but



Medullary Raphe Nuclei and Respiratory Control. Figure 1 5-HT_{4a} receptor activation stimulates breathing *in vivo*. Data is from a rat *in vivo*. Each trace is a recording of lung ventilation. Under control conditions there is regular breathing. Fentanyl leads to severe apnea that required ventilatory support to prevent the animal from dying. Breathing was restored with the 5-HT_{4a} receptor agonist BIMU8. (From Manzke et al, Science, 301:226, 2003).



Medullary Raphe Nuclei and Respiratory Control. Figure 2 5-HT_{2a} receptor activation stimulates respiratory activity *in vitro*. Shown is activity recorded from the pre-Bötzinger Complex in a brain slice from the rostral rat medulla. Fictive respiratory activity is recorded as regular bursts of action potentials (shown here as an "integrated" recording). Application of the 5-HT_{2a} agonist DOI increases the frequency of respiratory output (top trace). Application of the 5-HT_{2a} antagonist ketanserine abolishes respiratory output (bottom trace), due to blockade of the effect of endogenously released 5-HT. (From Pena & Ramirez, J Neurosci, 22:11055, 2002.)

there is some evidence that TRH and SP are released primarily as the firing rate of 5-HT neurons increases to higher levels.

Effects of 5-HT, SP and TRH on Respiratory Neurons in vitro

Compared with *in vivo* experiments, *in vitro* work has more consistently shown that 5-HT, and 5-HT neurons, stimulate the respiratory network. For example, spontaneous respiratory output generated by the pre-BötC in brain slices is stimulated via 5-HT_{2a} (Fig. 2) and NK1 receptors [4,5]. In slices, 5-HT induces ectopic bursting activity in non-pacemaker neurons of the pre-BötC, and TRH induces bursting pacemaker activity in neurons within the respiratory portion of the NTS [1]. 5-HT, SP and TRH also have excitatory effects in the *in vitro* brainstem spinal cord preparation and perfused brain preparations. It is not clear why there are different results from *in vitro* preparations compared to *in vivo*, but it may be related to the more reduced nature of these preparations in which there is less influence of inputs from the periphery and other brain regions.

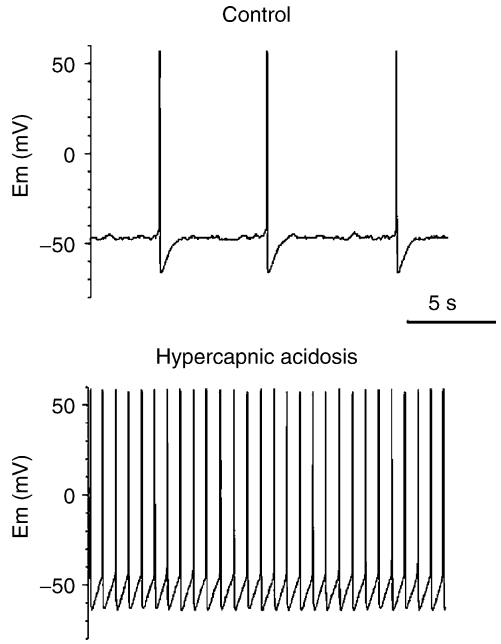
CO_2/pH Chemoreception by 5-HT Neurons

5-HT neurons are normally tonically active *in vivo*, with greater activity during wakefulness and less during sleep, but are relatively unresponsive to most other perturbations and afferent inputs *in vivo*. Two exceptions are that they increase their firing rate *in vivo* in response to inhalation of CO_2 and during repetitive motor activities. This has been shown using extracellular recordings from medullary raphé neurons in behaving cats [6], as well as c-*fos* staining in rats. Interestingly, the response of these neurons to CO_2 is depressed during sleep, in tandem with a decrease in the ►hypercapnic ventilatory response.

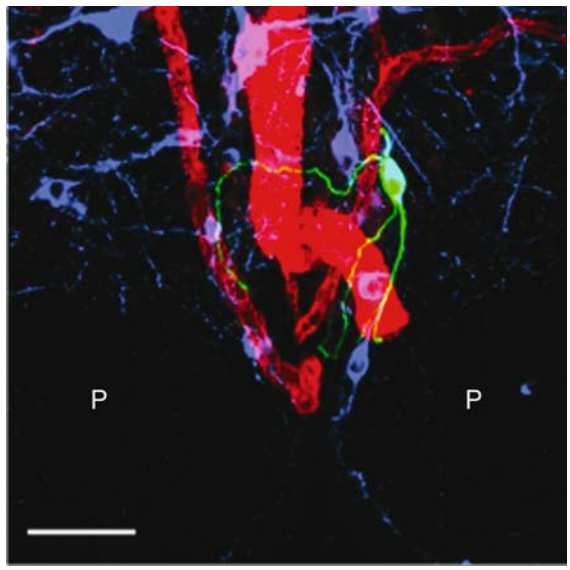
5-HT neurons are intrinsically chemosensitive to CO_2. After chemical or physical isolation from other neurons in brain slices and in cell culture, they respond to ►hypercapnia with an increase in firing rate (Fig. 3) [1]. This response is indirectly due to the decrease in pH induced by increased PCO_2. Based on these and other data, serotonin neurons are thought to be ►central respiratory chemoreceptors (CCRs), i.e., sensors of blood CO_2 that stimulate respiratory output in response to hypercapnic acidosis. This response lowers PCO_2, thus maintaining pH homeostasis.

5-HT neurons in rats have anatomy that suggests they are specialized to detect changes in blood PCO_2. Many 5-HT neurons are located in the midline medulla, which is highly perfused by large arteries, and they have

M



Medullary Raphe Nuclei and Respiratory Control.
Figure 3 5-HT neurons are intrinsically sensitive to acidosis. Shown is the membrane potential of a 5-HT neuron from the medullary raphé grown in cell culture. A decrease in pH from 7.4 to 7.2 induces an increase in firing rate. (From Wang et al, J Physiol, 540:951, 2002.)



Medullary Raphe Nuclei and Respiratory Control.
Figure 4 Serotonin neurons are closely associated with large midline arteries in the medullary raphé and ventrolateral medulla. Shown is a brain slice after recording from a neuron that was stimulated by acidosis. The neuron was identified by filling with biocytin (green). Immunohistochemistry for tryptophan hydroxylase (blue) revealed that it was serotonergic. This neuron had dendrites that were closely associated with large penetrating arteries stained with an antibody for α-smooth muscle actin (red). P – pyramidal tract. Bar – 50 μm. (From Bradley et al, Nature Neurosci, 5: 401, 2002.)

dendrites and cell bodies that are closely apposed to these arteries (Fig. 4). The PCO_2 of arterial blood is inversely proportional to gas exchange in the lungs. This location would avoid confounding effects of changes in local brain metabolism or cerebral blood flow that would influence the PCO_2 near venous blood or brain capillaries, and would thus allow a relatively greater selectivity for monitoring lung ventilation.

5-HT neurons play a role in the increased ventilation induced by hypercapnic acidosis. In slices of the medulla, focal application of acidic solution into the raphé nuclei leads to an increase in frequency of respiratory rhythm generated by the pre-BötC. In rats and goats *in vivo*, focal acidosis in the medullary raphé leads to an increase in ventilation [3]. Specific lesions of 5-HT neurons with the neurotoxin 5,7-dihydroxytryptamine, or genetic deletion of 5-HT neurons, leads to blunting of the hypercapnic ventilatory response *in vivo*. The relative importance of 5-HT neurons in central respiratory chemoreception *in vivo*, compared to other putative chemoreceptors in the brain, has not been determined. However, some data suggest that as much as 50% of the central chemoreceptor response is dependent upon 5-HT in mice. Current work is aimed at defining the relative importance of each of the candidates for central chemoreceptors, and whether this varies under different conditions, such as sleep or disease states.

5-HT and Plasticity of Respiratory Output

Respiratory output is generally considered to be hard-wired, but it has recently been shown to undergo considerable plasticity [3]. For example, after three episodes of mild hypoxia of 5 minutes each, ventilation slowly increases over the next hour despite withdrawal of the hypoxic stimulus. This "long term facilitation" of respiratory motor output is due to strengthening of the synaptic drive to respiratory motor neurons from the medullary respiratory centers, and requires protein synthesis. It has recently been found that this LTF is blocked by 5-HT antagonists [3]. Elucidation of the serotonergic mechanisms involved in LTF may provide new avenues for treatments to strengthen respiratory drive in patients with respiratory weakness, such as that due to incomplete spinal cord injury.

5-HT Neurons and Breathing in Disease

5-HT neurons of the midbrain (dorsal and median raphé) are central to many psychiatric diseases. Those

within the medulla are now known to be involved in the pathophysiology of diseases in which there are breathing abnormalities.

►Sudden infant death syndrome (SIDS) is defined as the "sudden death of an infant under one year of age, that remains unexplained after a complete clinical review, autopsy, and death scene investigation." SIDS is a heterogeneous disorder, including a small subset due to genetic cardiac defects. However, a large percentage of SIDS cases are believed to occur when a developmental defect in the brainstem of otherwise normal infants makes them vulnerable to an exogenous stressor such as obstruction of the airway, a mild infection, or variations in ambient temperature. The stressor can then lead to a decrease in ventilation, hypoxia and hypercapnia, and ultimately death.

Recent neuropathological studies of infants that died of SIDS have found abnormalities in serotonin receptors, the serotonin transporter and the number and morphology of serotonin neurons in the medulla [7]. Genetic studies have also linked SIDS to polymorphisms in the promoter for the serotonin transporter. It is now believed that a large percentage (> 50%) of SIDS cases are due to a developmental defect in 5-HT neurons. This defect can be genetically influenced or induced by environmental factors such as cigarette smoking.

Animal experiments have provided insight into mechanisms by which a defect in the 5-HT system could lead to vulnerability to an exogenous stressor. Selective deletion of 5-HT neurons by genetic methods or neurotoxins in rodents leads to blunted CO_2 chemoreception and impaired thermoregulation in adults. There is also irregular breathing and an increase in mortality in neonatal mice [8]. These abnormalities in mice are reminiscent of defects proposed to exist in SIDS cases. Although the pathological changes in these mouse models are not the same as those in human SIDS, current research is aimed at determining whether the physiological changes are similar, if a test can be developed to identify infants at highest risk, and if preventive treatments are possible.

►Sleep apnea occurs in 4% of adult males in the US, and is most commonly due to obstruction of the upper airway from withdrawal of muscle tone during sleep, particularly during REM. Many patients are apneic more than 15 times per hour, each time becoming hypoxia. This can lead to a variety of consequences including daytime sleepiness, difficulty concentrating, hypertension, right sided heart failure and stroke.

One of the factors that contributes to airway obstruction during sleep is the withdrawal of 5-HT input onto motor neurons that innervate upper airway muscles. Hypoglossal neurons, which have been studied the most intensively, are depolarized *in vitro* by 5-HT, SP and TRH, each of which inhibit leak K^+ channels. During sleep, the firing rate of 5-HT neurons decreases, with almost complete cessation during REM. The decrease in excitatory neuromodulation of motor neurons is thought to play an important role in the decrease in upper airway tone during sleep.

►Multi-System Atrophy (MSA) is a neurodegenerative disorder that involves degeneration of dopamine and autonomic neurons in the brain. Patients have symptoms similar to Parkinson's disease, but also have autonomic dysfunction. It has recently been found that there is also degeneration of 5-HT neurons in some of these patients [9]. This may explain why sleep apnea can be an early manifestation of MSA, because of impairment of central respiratory chemoreception and/or greater reduction in 5-HT tone during sleep.

►Panic attacks are discrete periods of fear or discomfort in which there is rapid development of symptoms such as a feeling of air hunger, choking and/or palpitations. They often include hyperventilation. These episodes can occur spontaneously or can be induced by situational triggers. They can also be induced by breathing CO_2. Selective serotonin reuptake blockers are highly effect for treatment. A widely held theory is that panic attacks are an inappropriate triggering of a reflex that can be activated in normal people by hypercapnia, and which is designed to restore normal blood CO_2 levels. This "false suffocation alarm" has been proposed to be due to a defect in 5-HT neurons [10].

M

References

1. Richerson GB (2004) Serotonin neurons as CO2 sensors that maintain pH homeostasis. Nat Rev Neurosci 5:449–461
2. Manzke T, Guenther U, Ponimaskin EG, Haller M, Dutschmann M, Schwarzacher S, Richter DW (2003) 5-HT4a receptors avert opioid-induced breathing depression without loss of analgesia. Science 301:226–229
3. Feldman JL, Mitchell GS, Nattie EE (2003) Breathing: rhythmicity, plasticity, chemosensitivity. Ann Rev Neurosci 26:239–266
4. Pena F, Ramirez JM (2002) Endogenous activation of serotonin-2A receptors is required for respiratory rhythm generation in vitro. J Neurosci 22:11055–11064
5. Pena F, Ramirez JM (2004) Substance P-mediated modulation of pacemaker properties in the mammalian respiratory network. J Neurosci 24:7549–7556
6. Veasey SC, Fornal CA, Metzler CW, Jacobs BL (1995) Response of serotonergic caudal raphe neurons in relation to specific motor activities in freely moving cats. J Neurosci 15:5346–5359
7. Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC (2006) Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. JAMA 296:2124–2132
8. Erickson JT, Shafer G, Rossetti MD, Wilson CG, Deneris ES (2007) Arrest of 5HT neuron differentiation delays respiratory maturation and impairs neonatal homeostatic responses to environmental challenges. Resp Physiol Neurobiol (in press)

9. Benarroch EE (2007) Brainstem respiratory chemosensitivity: new insights and clinical implications. Neurology 68:2140–2143
10. Klein DF (1993) False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Archiv Gen Psych 50:306–317

MEG

►Magnetoencephalography

Meissner Corpuscle

Definition

Cutaneous mechanoreceptor located in the dermis just below the epidermis, only in glabrous skin.

►Cutaneous Mechanoreceptors, Anatomical Characteristics
►Cutaneous Mechanoreceptors, Functional Behavior

Meissner Corpuscle Regeneration

Chizuka Ide
Department of Anatomy and Neurobiology, Kyoto University Graduate School of Medicine, Yoshidakonoe-cho, Sakyo-ku, Kyoto, Japan; Department of Occupational Therapy, Aino University Faculty of Nursing and Rehabilitation, Ibaragi City, Osaka, Japan

Synonyms

Meissner's corpuscle; Wagner's corpuscle; Corpusculum tactus; Tactile lamellar corpuscle; Digital lamellated corpuscle

Definition

A rapidly-adapting mechanoreceptor for touch sensation, situated at the top of the dermal papillae of the skin. The corpuscle consists of thin sheets of lamellar cells densely piled around axon terminals.

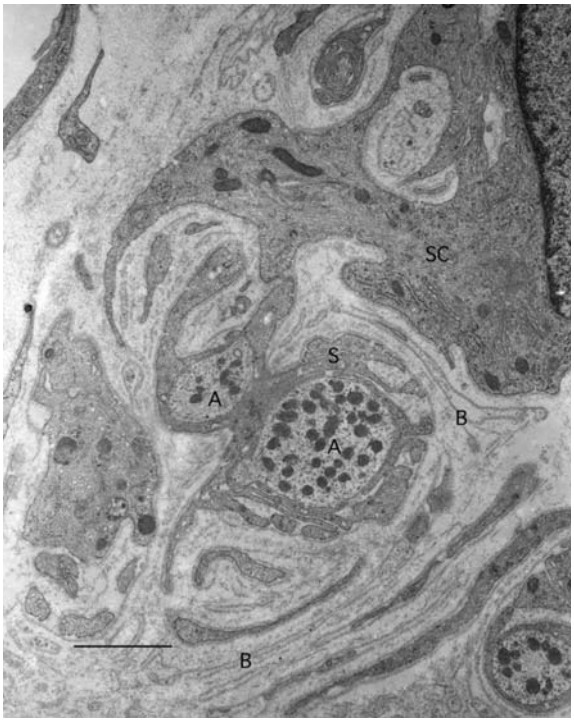
Characteristics

Structure

The corpuscle is oval in shape, with a long axis of ca. 100–300 μm. The corpuscle is usually situated with the apical end pointing towards the base of the epithelium of the dermal papillae. Generally, one or sometimes two to three nerve fibers innervate the corpuscle, ending as enlarged terminals after branching within. The axon terminals are characterized by containing numerous mitochondria and clear vesicles, and are sandwiched by thin lamellar cell processes (ca. 0.5 μm in width) in the basal-apical direction of the corpuscle [1]. Lamellar cells are specialized Schwann cells, extending thin sheet-like cytoplasmic processes with characteristically numerous caveolae on the cell surface membrane [2]. Lamellar cell processes are interposed with neighboring ones by narrow connective tissue spaces, being covered by basal laminae at the connective tissue surface. Lamellar cells secrete the enzyme cholinesterase into the interlamellar spaces [3], and have TGF-beta immunoreactivity [4]. The corpuscle lacks the perineurial sheath.

Regeneration

When an innervating nerve is cut, its axon terminals disappear, and concomitantly the surrounding lamellar cells become atrophic. The atrophic corpuscle then persists for an extended time. When regenerating axons enter the atrophic corpuscle, the lamellar cells retain their original "active" form. Some trophic factors available from axons are needed for lamellar cells to maintain their active form [5]. Meissner corpuscles are reinnervated by host axons in the allograft skin [6], or ectopically grafted digital skin [7]. Meissner corpuscles can regenerate in an acellular environment. When the skin is freeze-treated with liquid nitrogen, all cellular components including lamellar cells are killed and only connective tissues including basal laminae constituting the corpuscle remain in their original condition. Reinnervating axons first enter such an acellular environment, followed by Schwann cells. The Schwann cells then gradually develop into lamellar cells with a small number of thin cytoplasmic processes (Fig. 1). Innervating axons are enlarged at their ends as in the original Meissner corpuscle. Although the patterns of lamellar cells are incomplete compared to the original normal corpuscle, the overall structures are those of normal Meissner corpuscles, and thus can be called an atypical Meissner corpuscle [8]. The extracellular matrix of the Meissner corpuscle has the ability to develop new Meissner corpuscles after re-innervation. A new corpuscle can never develop in an acellular site other than that of the original corpuscle. Similarly, there is no evidence of Meissner corpuscle



Meissner Corpuscle Regeneration. Figure 1 The rat toe skin was freeze-treated to kill the cellular components of tactile digital corpuscles in the toe pad. The extracellular matrix of the corpuscle remained in loco after the cellular components had been removed. About 1 week after treatment, regenerating axons (A) accompanied by immature Schwann cells (SC) entered the acellular matrix of the corpuscle. It is noted that immature Schwann cells with regenerating axons begin to develop into digital corpuscles by extending cellular processes (S) through the basal lamina scaffolds (B), mimicking the formation processes during digital corpuscle development. Axons end in axon terminals associated with layers of Schwann cell lamellae. Thus, the new digital corpuscle, although atypical in cellular organization, can be formed in the acellular matrix of the old corpuscle. Scale bar: 2 μm.

regeneration de novo in nerve fascicular repair [9]. There is no tactile lamellar corpuscle regeneration when developing corpuscles are denervated before postnatal day 5 in the rat [10].

References

1. Ide C (1976) The fine structure of the digital corpuscle of the mouse toe pad, with special reference o nerve fibers. Am J Anat 147:329–356
2. Ide C (1977) Development of Meissner corpuscle of mouse toe pad. Anat Rec 88:49–68
3. Ide C (1982) Histochemical study of lamellar cell development of Meissner corpuscles. Arch Histol Jpn 45:83–97
4. Stark B, Carlstedt T, Risling M (2001) Distribution of TGF-beta, the TGF-beta type I receptor and the R-II receptor in peripheral nerves and mechanoreceptors; observations on changes after traumatic injury. Brain Res 913:47–56
5. Ide C (1982) Regeneration of mouse digital corpuscles. Am J Anat 163:73–85
6. Samulack DD, Munger BL, Dykes RW, Daniel RK (1986) Neuroanatomical evidence of reinnervation in primate allografted (transplanted) skin during cyclosporine immunosuppression. Neurosci Lett 72:1–6
7. Uno H, Montagna W (1982) Reinnervation of hair follicle end organs and Meissner corpuscles in skin grafts of Macaques. J Invest Dermatol 78:210–214
8. Ide C (1986) Basal lamina and Meissner corpuscle regeneration. Brain Res 384:311–322
9. Dellon AL (1976) Reinnervation of denervated Meissner corpuscles: a sequential histologic study in the monkey following fasicular nerve repair. J Hand Surg 1:98–109
10. Zelena J, Jirmanova I, Nitatori T, Ide C (1990) Effacement and regeneration of tactile lamellar corpuscles of rat after postnatal nerve crush. Neuroscience 39:513–522

Mel

►Melatonin

Mel1a

►Melatonin Receptors

Melancholia

►Major Depressive Disorder

Melancholic Features

Definition

These involve the inability to find pleasure in positive things combined with physical agitation, insomnia or

decreased appetite. Roughly 10% of people with depression suffer from melancholic depression.

►Major Depressive Disorder

Melanin and Neuromelanin in the Nervous System

William H. Tolleson
Division of Biochemical Toxicology,
National Center for Toxicological Research,
US Food and Drug Administration, Jefferson,
AR, USA

Synonyms

Neuromelanin; Melanin; Eumelanin; Pheomelanin

Definition

►Melanins are naturally occurring polymeric pigments produced from L-tyrosine and L-cysteine by catecholaminergic neurons and ►melanocytes. Melanin subcategories occurring in humans include ►neuromelanin, ►eumelanin and ►pheomelanin.

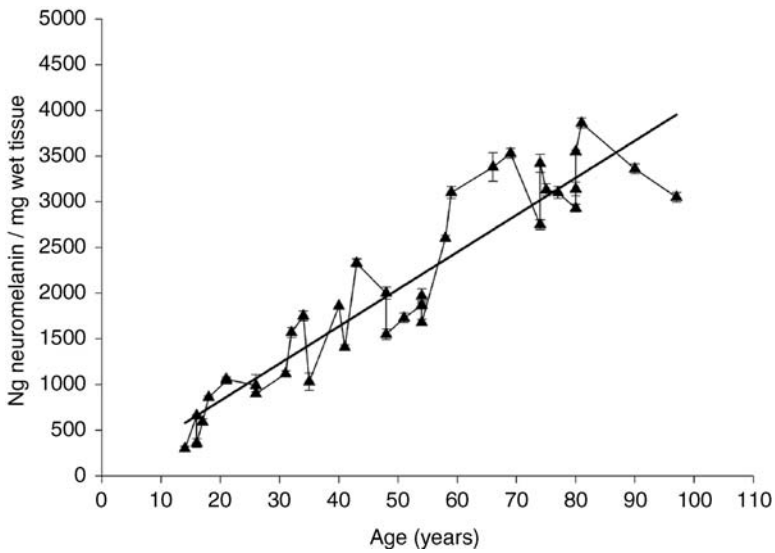
Characteristics

Quantitative Description

In humans, melanin pigments are distributed among anatomic sites harboring melanocytic cells or dopaminergic and noradrenergic neurons. Melanocytes residing in hair follicles and the interfollicular epidermis produce eumelanin and pheomelanin pigments that are responsible for natural individual variations in external pigmentation. Other major populations of melanocytes are present in the: (i) uveal tract in the posterior portion of the eye, (ii) stria vascularis within the scala media of the cochlea, and (iii) meninges covering the brain [1].

Neuromelanin is produced by dopamine- and norepinephrine-synthesizing neurons, but not those producing epinephrine. It is generally believed that ►catecholamine neurotransmitters are the major biochemical precursors of human neuromelanin, although definitive chemical analysis of neuromelanin has been impeded by its low abundance. Elucidating the chemical structure and origin of neuromelanin is a matter of active research.

Dopaminergic neurons of the substantia nigra lack neuromelanin at birth; it is detectable as intracellular granules within the substantia nigra pars compacta by 3 years of age and becomes increasingly abundant throughout life [2]. The substantia nigra pars compacta of normal brains (mean age 61 years) contain approximately 1 mg of neuromelanin, or about 2.5 μg neuromelanin per mg wet tissue (Fig. 1).



Melanin and Neuromelanin in the Nervous System. Figure 1 Neuromelanin content within the substantia nigra increases steadily throughout life. Regression analysis of the relationship between neuromelanin content in the substantia nigra (ng/mg tissue) and age of normal male and female subjects, ages 14–97 years. (By permission, Zecca et al. [2]; copyright (2004) National Academy of Sciences, USA.) Similar concentrations of neuromelanin accumulate within the locus coeruleus.

The major population of noradrenergic neurons located in the locus coeruleus of the brain stem also contains neuromelanin granules. Although greater inter-individual variation is apparent, neuromelanin levels in the locus coeruleus also increase with age and are comparable to the amounts found in the substantia nigra of the same individuals (~2.5 μg/mg wet tissue at 61 years) [2].

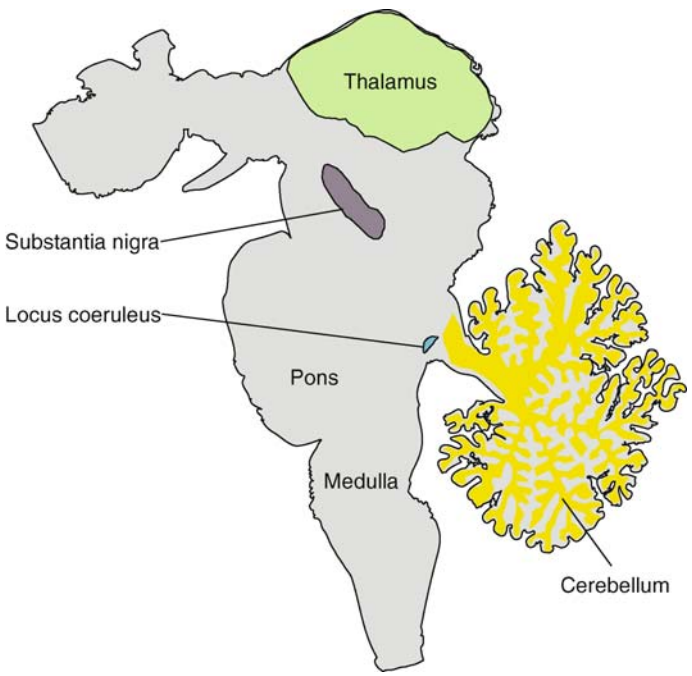
Higher Level Structures

Pigmented Dopaminergic Neurons of the Substantia Nigra Pars Compacta

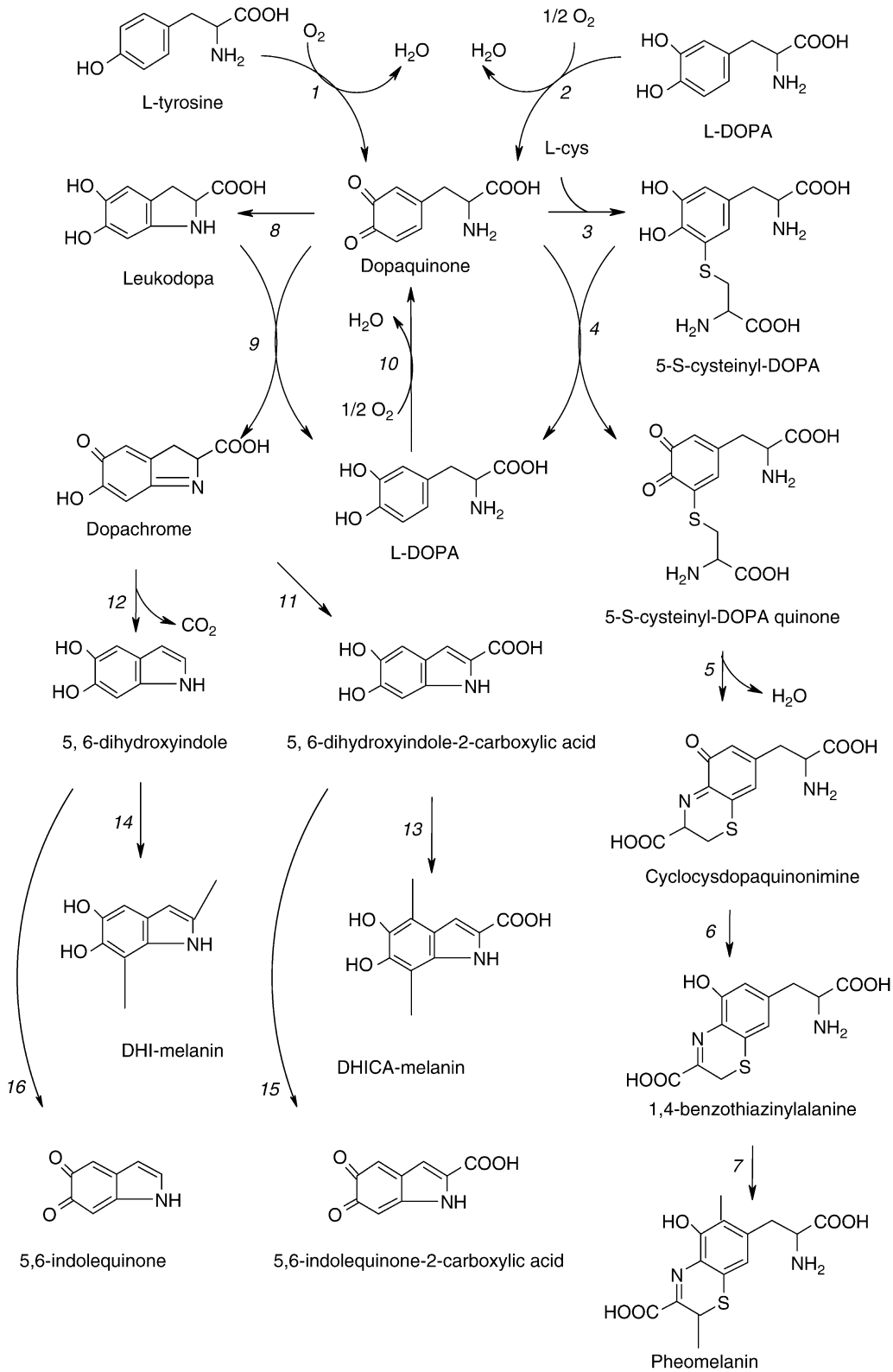
The largest nuclear mass of the mesencephalon is the substantia nigra (Fig. 2), divided into two sections by the interpeduncular fossa and interpeduncular nucleus [3]. The substantia nigra extends caudally from the rostral mesencephalon to the pons. The substantia nigra can be subdivided into its dorsal neuromelanin pigmented portion, designated the substantia nigra pars compacta, and the ventral substantia nigra pars reticularis. The substantia nigra pars compacta includes closely packed, pyramidal or polymorphic neurons containing neuromelanin. The substantia nigra pars reticularis, also called the stratum intermedium, containing polymorphic GABAnergic neurons, is positioned ventrally to the substantia nigra pars compacta and dorsally to the crus cerebri. Cells of the substantia nigra pars reticulum lack neuromelanin but contain abundant iron, which imparts a reddish color to this region. Dopaminergic axons from the substantia nigra pars compacta project anteriorly to the striatum, constituting the nigrostriatal neural pathway that regulates muscle control. A minor number of pigmented dopaminergic neurons innervate the nucleus accumbens and cerebrum. These neurons originate from the ventral tegmentum area, which is ventral to the red nucleus, medial to the substantia nigra and dorsal to the interpeduncular nucleus.

Pigmented Noradrenergic Neurons of the Locus Coeruleus

Noradrenergic neurons are aggregated in the locus coeruleus (Fig. 2) [3,4]. The tightly packed, pigmented, polygonal cells of the locus coeruleus communicate with diverse regions of the CNS. The locus coeruleus receives inputs from the hypothalamus, amygdala, cingulate gyrus, raphe nuclei, and cerebellum. Efferent fibers from the locus coeruleus innervate the spinal cord, cerebellum, hypothalamus, amygdala, cerebral cortex, and the basal telencephalon.



Melanin and Neuromelanin in the Nervous System. Figure 2 Primary neuromelanin-containing regions of the human brain. The majority of neuromelanin-containing dopaminergic neurons are found in the substantia nigra located in the mesencephalon. Another major cluster of neuromelanin-containing cells are found within the locus coeruleus in the anterior pons adjacent to the superior cerebellar peduncle. Dopaminergic axons from the substantia nigra pars compacta, ventral tegmentum area, and arcuate nucleus of the mediobasal hypothalamus project to the striatum, nucleus accumbens, cerebrum, and the hypothalamic median eminence. Noradrenergic neurons innervate the spinal cord, cerebellum, hypothalamus, amygdala, cerebral cortex, and the basal telencephalon.



Melanin and Neuromelanin in the Nervous System. Figure 3 Synthesis of eumelanins and pheomelanins. Tyrosinase (EC 1.14.18.1), a copper-containing monooxygenase, catalyzes the first steps of melanogenesis (reactions 1, 2, and 10) – the formation of dopaquinone by hydroxylation and oxidation of L-tyrosine. Dopaquinone is a key intermediate essential for synthesis of both pheomelanins and eumelanins. Pheomelanin synthesis is initiated

Dopamine Neural Pathways

Four dopamine neural pathways exist: (i) nigrostriatal, (ii) mesocortical, (iii) mesolimbic, and (iv) tuberoinfundibular. The nigrostriatal is the largest of the four dopamine pathways and it connects the substantia nigra pars compacta and striatum to facilitate muscle control. The mesocortical pathway regulates emotional responses and connects the ventral tegmentum area of the midbrain to the cerebrum. The mesolimbic pathway connects the ventral tegmentum area to the nucleus accumbens, the reward/desire center of the brain. The tuberoinfundubular pathway connects the arcuate nucleus of the mediobasal hypothalamus to the hypothalamic median eminence, and regulates the release of prolactin. Neuromelanin granules have been detected within dopaminergic neurons in each of the four pathways, but are the most abundant and consistently evident in the substantia nigra pars compacta of the nigrostriatal pathway.

Melanocytes Associated with the Nervous System

Three major populations of extracutaneous melanocytes provide accessory functions for the nervous system [1]. A large number of highly pigmented melanocytes can be found within the posterior choroid and cilliary body of the uveal tract, separated from the neural retina by the retinal pigment epithelium and Bruch's membrane. Melanin of the pigment epithelium and uveal tract prevents photodynamic damage in the very highly perfused choriocapillaris of the uveal tract and improves visual acuity by absorbing stray light. Specialized melanocytes, termed intermediate cells, are found in the stria vascularis of the scala media in the inner ear. These cells play a critical role in maintenance of the endocochlear potential, essential for hearing, by regulating potassium transport into the endolymph. Scattered melanocytes can be found throughout the meninges but are most apparent within the ventrolateral leptomeninges overlying the pons and medulla. Melanin produced by these melanocyte populations is believed to scavenge toxic materials, including organic and inorganic cations and reactive oxygen species, providing a defense/protective function.

Lower Level Components

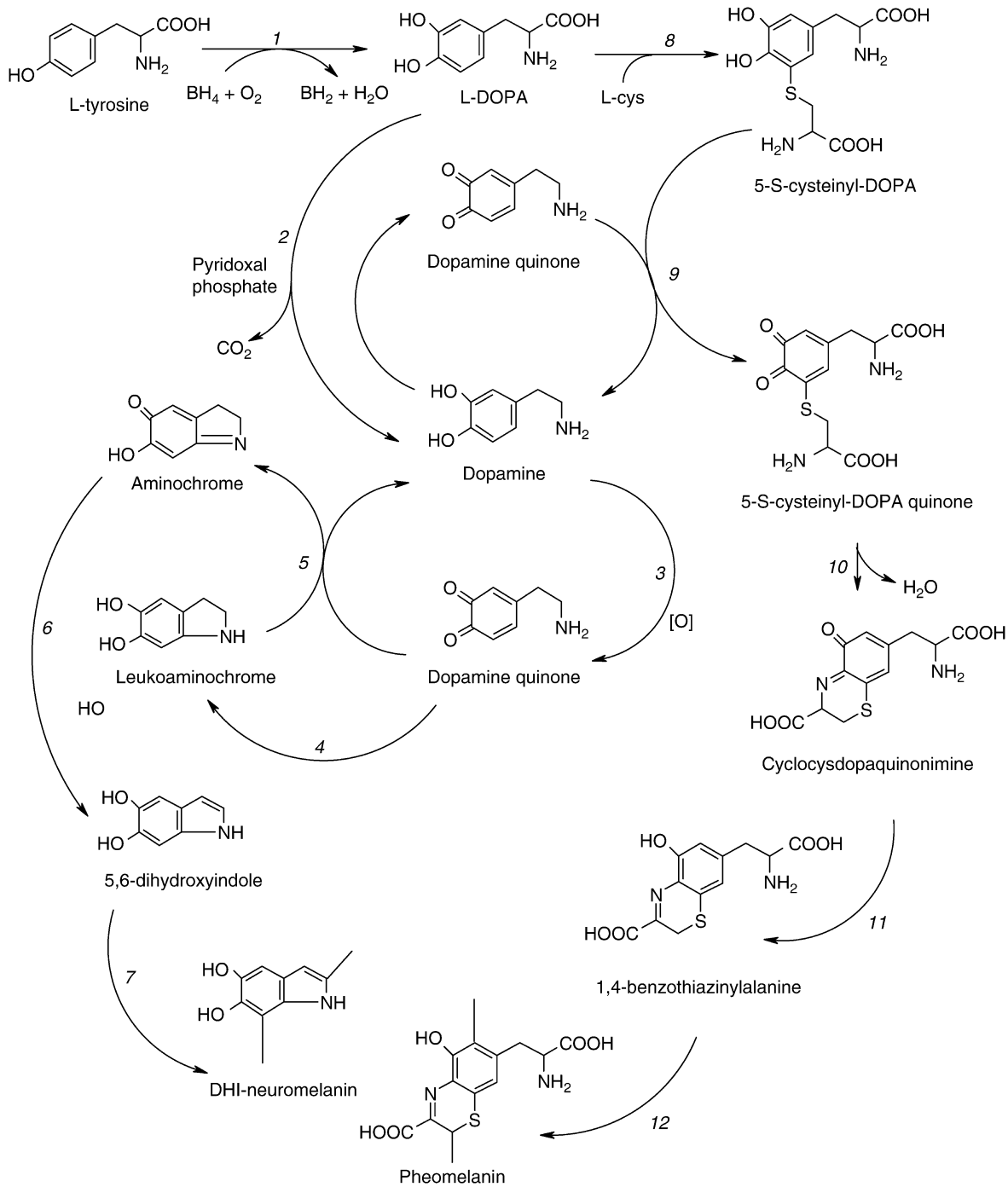
Synthesis of Melanin, Pheomelanin, and Neuromelanin

Eumelanin and pheomelanin biosynthesis from L-tyrosine and L-cysteine sequestered within melanosomes, the specialized cytoplasmic organelles related to lysosomes and unique to melanocytes, is well understood (see Fig. 3) [1]. The levels of these two amino acids within melanosomes, along with intramelanosomal pH and the relative expression of melanin-producing enzymes, influence the forms of melanin ultimately produced. By contrast, less is known concerning neuromelanin synthesis (see Fig. 4). Within melanosomes, tyrosine is converted to L-DOPA by tyrosinase followed by oxidation to dopaquinone (Fig. 3, reactions 1, 2). Dopaquinone may react spontaneously with L-cysteine in the first committed step towards pheomelanogenesis (Fig. 3, reaction 3) or experience intramolecular cyclization to form leukodopa, which leads to the eumelanogenesis pathway (Fig. 3, reaction 8). The cytoplasmic enzyme tyrosine hydroxylase catalyzes formation of L-DOPA from L-tyrosine in neurons (Fig. 4, reaction 1) followed by decarboxylation to form dopamine in a reaction catalyzed by aromatic amino acid decarboxylase (Fig. 4, reaction 2). Dopamine is readily oxidized to the neuromelanin precursor dopamine quinone within dopaminergic neurons (Fig. 4, reaction 3). In noradrenergic neurons, dopamine is converted to norepinephrine by dopamine β-hydroxylase, which is also subject to oxidation to its analogous quinone, noradrenoquinone, believed to be another neuromelanin precursor.

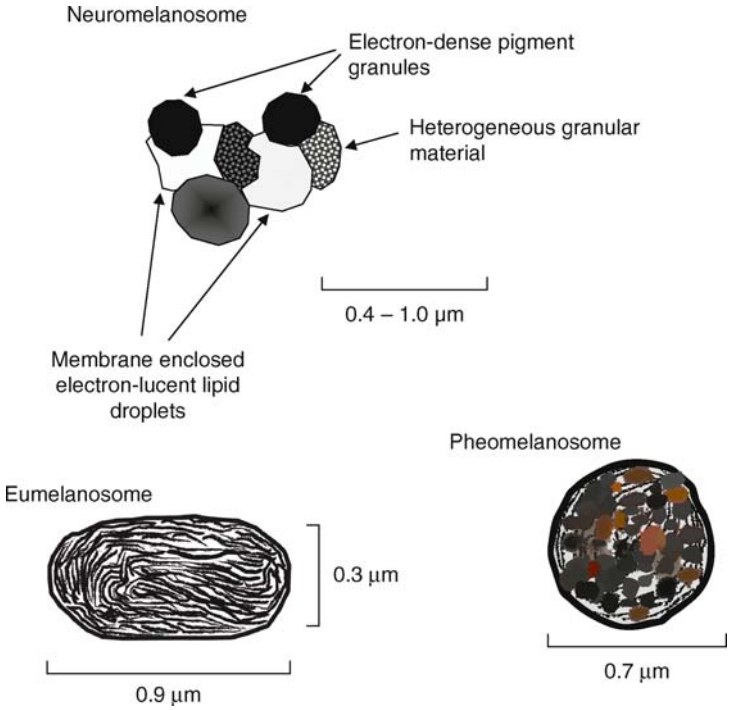
Melanosome Structure

The processes of melanin synthesis and melanosome assembly (divided into Stages I–IV) are coordinated in human melanocytes. Mature human Stage IV ►eumelanosomes are membrane-enclosed ellipsoidal

when L-cysteine reacts spontaneously with dopaquinone to form 5-*S*-cysteinyl DOPA (reaction 3). Excess dopaquinone or other oxidants convert 5-*S*-cysteinyl-DOPA to 5-*S*-cysteinyl-dopaquinone nonenzymatically (reaction 4). Elimination of water from 5-cysteinyl-dopaquinone yields cyclocysdopaquinonimine (reaction 5), which isomerizes spontaneously to form 1,4-benzothiazinylalanine (reaction 6). Polymerization of 1,4-benzothiazinylalanine monomers yields pheomelanin (reaction 7). Synthesis of eumelanins begin with the spontaneous cyclization of dopaquinone to produce leukodopa (cyclodopa; reaction 8) followed by its oxidation to form dopachrome via a recycling reaction that regenerates L-DOPA from excess dopaquinone (reactions 9, 10). Dopachrome tautomerase (tyrosinase-related protein-2, TRP-2, EC 5.3.3.12) converts dopachrome to 5,6-dihydroxyindole-2-carboxylic acid (reaction 11). Spontaneous decarboxylation of dopachrome may occur at a reduced rate in the absence of TRP2 enzyme activity to yield 5,6-dihydroxyindole (reaction 12). Polymerization of 5,6-dihydroxyindole-2-carboxylic acid (reaction 13) yields a lighter colored pigment than does polymerization of 5,6-dihydroxyindole (reaction 14). Tyrosinase (in humans) or tyrosinase-related protein 1 (TRP-1, catalase B) catalyze oxidation of 5,6-dihydroxyindole-2-carboxylic acid or 5,6-dihydroxyindole to their respective *o*-quinones (reactions 15 and 16, respectively), which polymerize spontaneously to form eumelanins.



Melanin and Neuromelanin in the Nervous System. Figure 4 Neuromelanin synthesis. Neuromelanin synthesis begins with hydroxylation of L-tyrosine to produce L-DOPA (reaction 1), catalyzed in catecholaminergic neurons by tyrosine hydroxylase (EC 1.14.16.2), a nonheme Fe-containing monooxygenase that utilizes tetrahydrobiopterin (BH_4) as a cofactor. Aromatic amino acid decarboxylase (EC 4.1.1.28) utilizes pyridoxal phosphate as a coenzyme to produce dopamine via L-DOPA decarboxylation (reaction 2). Dopamine is easily oxidized nonenzymatically at physiological pH to generate dopamine *o*-quinone (reaction 3). Cyclization of dopamine *o*-quinone (reaction 4) to form leukoaminochrome occurs more slowly at physiological pH than in acidic conditions. Leukoaminochrome can be oxidized to aminochrome by dopamine *o*-quinone (reaction 5). Aminochrome rearranges to generate 5,6-dihydroxyindole (reaction 6) that polymerizes to form neuromelanin (reaction 7). Tyrosine hydroxylase also possesses an L-DOPA: L-cysteine conjugating activity that generates 5-*S*-cysteinyl-DOPA (reaction 8). Excess dopa (amine) quinone converts 5-*S*-cysteinyl-DOPA to its *o*-quinone (reaction 9), which can form pheomelanin by the



Melanin and Neuromelanin in the Nervous System. Figure 5 Melanosome structure. Mature Neuromelanosomes found within catecholaminergic neurons may exhibit a distinct lipid bilayer enclosing aggregates of electron dense pigment granules associated with electron lucent lipid and heterogeneous granular material. Eumelanosomes and pheomelanosomes are found within melanocytes – or may be taken up by adjacent cells. A eumelanosome (Stage III) and a pheomelanosome (Stage IV) are depicted here. Stage II–III melanosomes exhibit a striated proteinaceous network that imparts a characteristic "fingerprint" appearance that is often obscured by pigment deposits in Stage IV melanosomes.

M

structures 0.3 µm × 0.9 µm that contain eumelanin pigment deposited in, or on, a fibrillar proteinaceous network that may be partially visible or completely obscured by pigment. Human Stage IV ►pheomelanosomes are spherical membrane-bound organelles 0.7 µm in diameter that contain pheomelanin pigment (Fig. 5).

Melanosome development begins with budding of spherical Stage I melanosomes from the endoplasmic reticulum. Stage I melanosomes (premelanosomes) accumulate their major melanosomal scaffolding protein, Pmel17, which is organized to form the characteristic "fingerprint" network pattern via proteolytic processing. Stage II eumelanosomes begin to adopt their typical ellipsoidal shape and acquire tyrosinase via endosome sorting vesicles. Pigment synthesis begins in Stage III melanosomes and Stage IV melanosomes are fully pigmented.

Neuromelanosome Structure

Mature ►neuromelanosomes examined by electron microscopy vary in size from 0.5 µm to 2.5 µm and appear as aggregates of electron dense pigment granules combined with electron lucent lipid bodies and heterogeneous granular material [5]. A lipid bilayer can sometimes be detected. Proteomic analysis of purified human neuromelanosomes identified 72 proteins and over half were characteristic of lysosomes (29), endosomes or sorting vesicles (9), or endoplasmic reticulum (4), supporting the hypothesis that these

same mechanism as in melanocytes (Fig. 3, reactions 5–7 and Fig. 4, reactions 10–12). Neuromelanogenesis in noradrenergic neurons begins similarly with 3-hydroxylation of L-tyrosine via tyrosine hydroxylase to form L-DOPA, followed by decarboxylation catalyzed by aromatic amino acid decarboxylase to produce dopamine. Norepinephrine is formed from dopamine via dopamine β-hydroxylase (EC 1.14.17.1), a Cu-containing oxidoreductase that utilizes ascorbate and molecular oxygen as cosubstrates. In a process analogous to that described for incorporation of dopamine into neuromelanin, norepinephrine is oxidized to noradrenoquinone, which then cyclizes and rearranges to generate noradrenochrome. Tautomerization converts noradrenochrome to 3,4,6-trihydroxyindole, a neuromelanin monomer.

structures are derived from a lysosomal-endosomal lineage [6].

Process Regulation

Melanin synthesis by melanocytes is stimulated by α-melanocyte stimulating hormone, stem cell factor, endothelins, histamine, eicosanoids, estrogen, and vitamin D [7]. Neuromelanin synthesis is driven by cytoplasmic dopamine or norepinephrine levels that exceed their capacity for removal. In addition to consumption to form neuromelanin, the other principal mechanisms for cytoplasmic clearance of neurotransmitters include: (i) vesicular monoamine transporter (VMAT2)-dependent packaging into secretory vesicles, (ii) conversion to DOPAC by monoamine oxidase, and (iii) methylation via catechol *O*-methyltransferase.

Function

Excessive cytoplasmic catecholamine levels generate dangerous quinone and semiquinone species [1,2,5,8,9]. Polymerization of reactive intermediates to form neuromelanin provides an effective cellular defense mechanism.

Hydrogen peroxide can be converted to much more reactive and dangerous hydroxyl radicals via the ►Fenton reaction. Melanins bind copious amounts of metal ions via abundant hydroxyl and amine functional groups which block these metal ions from participating in hydroxyl radical formation [1,8]. Chemical analysis of eu- and pheomelanosomes isolated from human hair reveal that metal ions represent 4.0% and 1.6% of the total mass, respectively [10]. Similar metal ion binding properties have been determined for neuromelanin [8]. The toxicity of a variety of chemicals and drugs, such as paraquat, chlorpromazine, haloperidol, amphetamine, and imipramine, can be modulated through sequestration by melanins [1,8].

Melanins are characterized as sinks for reactive oxygen species and diffusible alkoxy (RO·) and peroxy (ROO·) radicals. Electron spin resonance spectroscopy shows that melanins (including neuromelanins) exist as stable free radicals; a typical free radical content is one radical per 2,000 polymer unit [2,9]. The uniquely stable combination of quinone, hydroquinone, and radical groups present in melanin allows it to participate as electron donor or acceptor in one- and two-electron transfer reactions. Thus, melanins contribute to cellular antioxidant defenses by consuming a spectrum of toxic oxidizing agents.

FDA Disclaimer

No official support or endorsement of this article by the Food and Drug Administration is intended or should be inferred. The views presented in this article do not necessarily reflect those of the Food and Drug Administration.

References

1. Tolleson WH (2005) Human melanocyte biology, toxicology, and pathology. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 23:105–161
2. Zecca L, Stroppolo A, Gatti A, Tampellini D, Toscani M, Gallorini M, Giaveri G, Arosio P, Santambrogio P, Fariello RG, Karatekin E, Kleinman MH, Turro N, Hornykiewicz O, Zucca FA (2004) The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. Proc Natl Acad Sci USA 101:9843–9848
3. Truex RC, Carpenter MB (1969) Human neuroanatomy, 6th edn. Williams and Wilkins, Baltimore, MD
4. DeArmond SJ, Fusco MM, Dewey MM (1989) Structure of the human brain, 3rd edn. Oxford University Press, Oxford
5. Fedorow H, Tribl F, Halliday G, Gerlach M, Riederer P, Double KL (2005) Neuromelanin in human dopamine neurons: comparison with peripheral melanins and relevance to Parkinson's disease. Prog Neurobiol 75:109–124
6. Tribl F, Gerlach M, Marcus K, Asan E, Tatschner T, Arzberger T, Meyer HE, Bringmann G, Riederer P (2005) "Subcellular proteomics" of neuromelanin granules isolated from the human brain. Mol Cell Proteomics 4:945–957
7. Slominski A, Tobin DJ, Shibahara S, Wortsman J (2004) Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev 84:1155–1228
8. Zecca L, Zucca FA, Wilms H, Sulzer D (2003) Neuromelanin of the substantia nigra: a neuronal black hole with protective and toxic characteristics. Trends Neurosci 26:578–580
9. Borovansky J (1996) Free radical activity of melanins and related substances: biochemical and pathobiochemical aspects. Sb Lek 97:49–70
10. Liu Y, Hong L, Wakamatsu K, Ito S, Adhyaru B, Cheng CY, Bowers CR, Simon JD (2005) Comparison of structural and chemical properties of black and red human hair melanosomes. Photochem Photobiol 81:135–144

Melanocyte

Definition

Melanocyte is a cell located in the bottom layer of the skin's epidermis and in the middle layer of the eye, the uvea. Through a process called melanogenesis, these cells produce melanin, a pigment in the skin, eyes, and hair. There are both basal and activated levels of melanogenesis; lighter-skinned people generally have low basal levels of melanogenesis, and exposure to ultraviolet (UV) radiation generally causes increased melanogenesis (see MSH).

►Melanin and Neuromelanin in the Nervous System

Melanoma-associated Retinopathy

Definition

►Inherited Retinal Degenerations

Melanopsin

Ignacio Provencio
Department of Biology, University of Virginia, Charlottesville, VA, USA

Synonyms

Opn4; OPN4

Definition

The opsin-based ►photopigment that confers photosensitivity upon ►intrinsically photosensitive retinal ganglion cells (ipRGCs). In non-mammalian vertebrates, it is also present in other photoreceptive cells such as melanophores and pinealocytes.

Characteristics

Discovery

Melanopsin was originally identified in the dermal melanophores of the African clawed frog *Xenopus laevis*. Melanophores darken in response to light and this photosensitivity is maintained in culture. Darkening is dependent upon the presence of retinoids, thereby suggesting that an opsin-based photopigment initiates this response. The search for such a photopigment in these cells eventually led to the discovery of melanopsin which was achieved through low-stringency screening of a melanophore cDNA library using probes based on the nucleotide sequences of the known opsin-based photopigments of *Xenopus*. Overexpression of melanopsin in these cells causes hyperphotosensitivity indicating a prominent role for this photopigment in darkening [1].

Melanopsin's deduced amino acid sequence shows highest homology to members of the opsin superfamily of G protein-coupled receptors. A lysine residue is present in the predicted seventh transmembrane domain, a hallmark of all opsins and a required site for retinoid chromophore attachment. Melanopsin possesses an unusually long intracellular carboxy-terminus tail containing many putative phosphorylation sites. Despite being identified in a vertebrate, melanopsin shares greater sequence homology to the rhabdomeric opsins that are typically found in invertebrate ►photoreceptors rather than the ciliary opsins of vertebrate ►rods and ►cones [2].

In addition to amphibians, melanopsin homologs have been characterized in cephalochordates, fish, reptiles, birds, and mammals. Non-mammalian vertebrates possess at least two melanopsin genes designated "x" and "m." The "x" genes are orthologs of the original gene identified in *Xenopus*, and the "m" genes are orthologs of the original homolog identified in mouse. The "x" melanopsin gene was lost in mammals prior to the eutherian/metatherian split [3].

Localization

Like all opsin-based photopigments, mature melanopsin resides in the plasma membrane. However, unlike ciliary or rhabdomeric photoreceptors, the cells that contain melanopsin do not possess a photopigment-dense organelle specialized for light capture such as the outer segments of rods and cones or the rhabdomeres of invertebrate photoreceptors. Rather, melanopsin is found throughout the plasma membrane of most of the cell including the membranes of the cell soma, dendrites, and proximal axon [1].

In mammals, melanopsin is only expressed in a small subset of ►retinal ganglion cells that are intrinsically photosensitive (ipRGCs) [4]. At least three morphologically distinct subclasses of ipRGCs exist. The first subclass has dendrites that reside within the OFF sublamina of the inner plexiform layer (IPL) of the ►retina. The second subclass has dendrites that stratify within the ON sublamina of the IPL. The third subclass ramifies dendrites in the ON and OFF sublaminae of the IPL [5]. The primary central projections of these cells are to the ►suprachiasmatic nucleus (SCN), ►intergeniculate leaflet, ►olivary pretectal nucleus, and lateral habenula. Other areas of the forebrain and midbrain receive less prominent projections [6].

In non-mammalian vertebrates, melanopsin is expressed in a range of cell types previously believed to be photoreceptive. For example, in *Xenopus* a high level of melanopsin is expressed in iridial myocytes, suggesting that melanopsin is likely to be responsible for the photosensitivity observed in the isolated amphibian iris. Non-mammalian vertebrates also exhibit melanopsin expression in the pineal gland and areas of the brain believed to harbor encephalic photoreceptors. In lower vertebrates and birds, inner retinal cells, in addition to a small number of retinal ganglion cells, also express melanopsin. The pattern of retinal expression varies across the classes of vertebrates, with birds demonstrating the most expansive pattern of retinal melanopsin expression. Finally, melanopsin has been identified in amphioxus (*Branchiostoma* spp.), the closest living relative to modern-day vertebrates. In these animals, melanopsin is found in the rhabdomeric Joseph and Hesse photoreceptor cells but not the frontal eye that contains ciliary photoreceptors [1].

Spectral Sensitivity

The pupillary light reflex and ►entrainment of behavioral ►circadian rhythms to the ambient ►light:dark cycle are both examples of light-regulated physiology that does not require the construction of images. Accordingly, they can be considered non-visual responses to light. Previous action spectra studies on such responses in mice lacking functional rods and cones revealed a sensitivity in the blue wavelengths that peaked around 480 nm. At the time of these studies, the photoreceptor cells and their respective photopigments responsible for this blue sensitivity were not known. It is now firmly established that melanopsin-expressing ipRGCs mediate these non-visual photoresponses in blind mice. Consistent with this is the finding that the peak spectral sensitivity of light-induced membrane depolarization in ipRGCs is 484 nm. This value correlates well with photoresponses measured in *Xenopus* oocytes and HEK293 cells heterologously expressing mouse melanopsin. The peak sensitivities observed in these systems were 480 and 479 nm, respectively. Heterologously expressed amphioxus melanopsin absorbs maximally at 485 nm and behaves as a bistable photopigment much like Rh1 opsin of *Drosophila* [1,3,4,6–8].

Signal Transduction

Metazoan opsin-based photopigments can be classified as rhabdomeric (r-opsins) or ciliary (c-opsins) according to the photoreceptor type in which they reside. Typically, ciliary photoreceptors electrically hyperpolarize their cell membrane in response to illumination while rhabdomeric photoreceptors depolarize the membrane. The characteristic that correlates most closely with the rhabdomeric/ciliary classification scheme of opsins is the second messenger system that these photopigments initiate; r-opsins activate a $G_q\alpha$-mediated transduction cascade while c-opsins activate a $G_t\alpha$-mediated pathway. As mentioned, melanopsin, at the amino acid level, shows greater sequence homology to r-opsins than c-opsins [2]. Additionally, all melanopsin-bearing cells studied to date depolarize in response to light. These features strongly suggest that melanopsin initiates a $G_q\alpha$-based cascade [4].

Studies in cultured amphibian melanophores have shown that inhibitors of phospholipase C (PLC) and protein kinase C (PKC) block photoresponses. Furthermore, chelation of intracellular calcium renders melanophores photically insensitive. Moreover, a small cohort of proteins is phosphorylated in a PKC-dependent manner after melanophores are exposed to light. Taken together, these data also suggest that a $G_q\alpha$-based transduction cascade is initiated by melanopsin [1]. Several studies employing heterologous expression in cells not typically photoreceptive have concluded that melanopsin likely signals through a rhabdomeric $G_q\alpha$-mediated pathway [6]. The details of such a transduction mechanism remain unknown. For example, the terminal effector of this cascade that directly results in membrane depolarization is yet to be elucidated. Because of the similarities between melanopsin-based signaling and the canonical insect ►phototransduction cascade, it has been proposed that the melanopsin-initiated cascade is likely to regulate the gating of an ion channel in the *transient receptor potential* channel superfamily [4]. The kinases potentially involved in regulating or modulating the terminal effector also remain to be determined. Interestingly, PKCζ colocalizes with melanopsin in ipRGCs, and mice null for PKCζ are behavioral phenocopies of mice null for melanopsin [3,7].

Function

In mammals, non-visual responses to light persist in the absence of rod and cone photoreceptors. Surgical removal of the eyes, however, abolishes these responses. These findings suggested the presence of an ocular non-rod, non-cone class of photoreceptor. The identification of melanopsin and the subsequent discovery of the ipRGCs that express this photopigment provided an explanation for the paradox that mammals lacking visual photoreceptors continue to respond to light. Mice null for melanopsin show some attenuated non-visual responses to light. Interestingly, they retain residual photoresponses that are mediated by rods and/or cones. Consequently, mice null for melanopsin and lacking rods and cones display no responses to light; they behave as animals do when bilaterally enucleated [1,3,7,9].

Among the non-visual photoresponses shown to be at least partially dependent upon melanopsin-based signaling are the photoentrainment of circadian locomotor rhythms, the acute photic regulation of pineal melatonin synthesis, the acute light-induced suppression of nocturnal activity, and the pupillary light reflex. The central targets of ipRGCs also provide insight into other potential forms of non-visual photophysiology that may be influenced by this newly discovered photosensory system. For example, a projection to the ventrolateral preoptic area suggests a role in the photic regulation of sleep. Likewise, a minor projection to the supraoptic nucleus of the hypothalamus implicates ipRGCs in the light-mediated regulation of neuroendrocrine output. The previously described sparse retinal inputs to the lateral hypothalamus now appear to be derived almost exclusively from ipRGCs, suggesting that information from these cells may converge with olfactory inputs to regulate the reproductive axis. Other targets too numerous to detail here indicate a broad role for the melanopsin-expressing ipRGCs in the photic regulation of physiology [10].

Several human responses to light are maximally sensitive to blue wavelengths, consistent with the involvement of melanopsin. Acute photosuppression of serum melatonin, photic control of alertness and vigilance, light regulation of sleep architecture, and light mediated changes in heart rate all show maximal

sensitivity in the blue wavelengths thereby implicating the melanopsin-based photoreceptive system. In addition, some humans, despite being cognitively blind, continue to suppress serum melatonin levels in response to illumination. Taken together, these responses should give pause to clinicians who recommend enucleation of blind patients to minimize ocular complications such as recurrent infections. Although these patients may not be capable of forming images (vision), their eyes may still be serving them to regulate the multiple emerging examples of physiology regulated by light via the melanopsin-based ipRGC photoreceptors.

References

1. Provencio I (2007) Melanopsin Cells. 1.20:423–431 In: Basbaum AI, Bushnell M, Smith D, Beauchamp G, Firestein S, Dallos P, Oertel D, Masland R, Albright T, Kaas J, Gardner E (eds) The Senses: A Comprehensive Reference. Elsevier, Amsterdam, 4640 pp
2. Arendt D (2003) Evolution of eyes and photoreceptor cell types. Int J Dev Biol 47:563–571
3. Hankins MW, Peirson SN, Foster RG (2007) Melanopsin: an exciting photopigment. Trends Neurosci 31:27–36
4. Berson DM (2007) Phototransduction in ganglion-cell photoreceptors. Pflugers Arch 454:849–855
5. Viney TJ, Balint K, Hillier D, Siegert S, Boldogkoi Z, Enquist LW, Meister M, Cepko CL, Roska B (2007) Local retinal circuits of melanopsin-containing ganglion cells identified by transsynaptic viral tracing. Curr Biol 17:981–988
6. Fu Y, Liao HW, Do MT, Yau KW (2005) Non-image-forming ocular photoreception in vertebrates. Curr Opin Neurobiol 15:415–422
7. Peirson S, Foster RG (2006) Melanopsin: another way of signaling light. Neuron 49:331–339
8. Van Gelder RN (2005) Nonvisual ocular photoreception in the mammal. Meth Enzymol 393:746–755
9. Foster RG, Hankins MW (2007) Circadian vision. Curr Biol 17:R746–R751
10. Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM (2006) Central projections of melanopsin-expressing retinal ganglion cells in the mouse. J Comp Neurol 497:326–349

Melatonin

Josephine Arendt
Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey, UK

Synonyms

N-acetyl-5-methoxytryptamine; mel (abbreviation); MT (abbreviation); Pineal hormone; Darkness hormone

Definition

An indolic hormone derived from the amino-acid tryptophan, via the tryptophan metabolite serotonin (5-hydroxytryptamine).

Characteristics

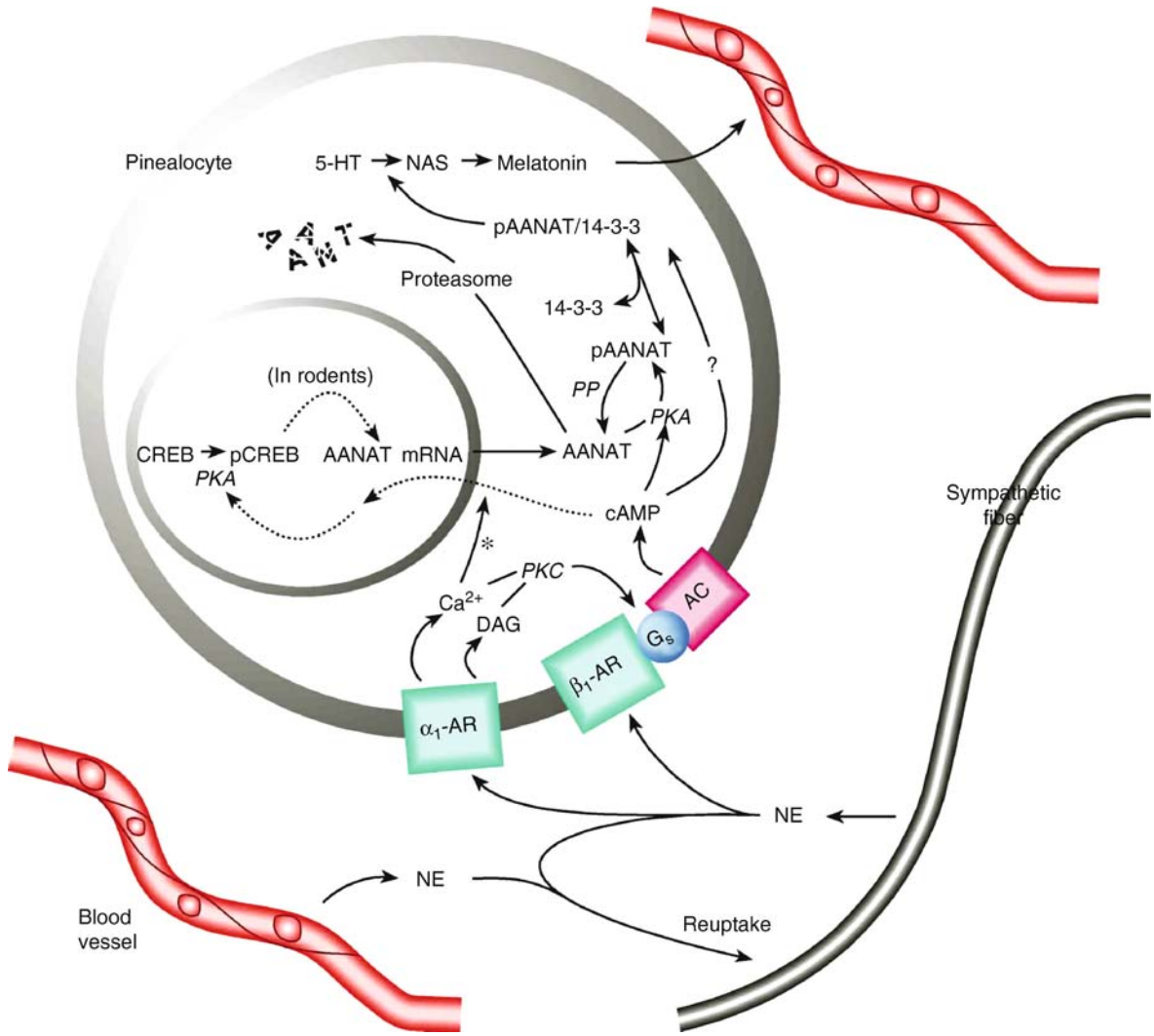
Synthesis

The primary site of melatonin synthesis is the ►pineal gland (*epiphysis cerebri*), a small, unpaired central structure, essentially an appendage of the brain. In humans the pineal weighs around 100–150 mg. Melatonin is synthesized within pinealocytes – cell types derived from ►photoreceptors – via the pathway shown in Fig. 1. In virtually all species studied to date, whether ►nocturnal or diurnal, melatonin is synthesised and secreted during the dark phase of the day. Melatonin production is clearly a highly evolutionarily conserved phenomenon. In most circumstances the rate-limiting enzyme is serotonin-*N*-acetyltransferase (arylalkylamine N-acetyltransferase [AA-NAT] commonly abbreviated as NAT). Control in mammals is via sympathetic innervation from the superior cervical ganglia terminating in adrenergic receptors within the pineal gland. The rhythm of production is endogenous in that, like other circadian rhythms, it is generated in the ►suprachiasmatic nucleus (SCN), the major central rhythm-generating system in mammals (the pineal itself is a self-sustaining "clock" in some, if not all, lower vertebrates) [1]. Other sites of synthesis exist, notably the ►retina, however pinealectomy abolishes the rhythm of circulating melatonin in mammals. Within the rodent retina a self-sustaining "clock" maintains rhythmic production of melatonin *in vitro* as it does in some lower vertebrates [2]. Whether this pattern is true in humans remains to be seen.

Melatonin synthesis is both entrained and suppressed by light of suitable intensity and spectral composition such that the duration of night time secretion reflects the length of the night [3]. The most effective wavelengths for melatonin suppression and ►phase shifting lie in the 460–480 nm area [4]. Rapid decline in activity with light treatment at night appears to depend on proteasomal proteolysis of NAT following dephosphorylation and removal of a protective 14–3–3 protein [5].

Metabolism

Melatonin is metabolized primarily within the liver by 6-hydroxylation, followed by sulphate and/or glucuronide conjugation. 6-sulphatoxymelatonin (aMT6s) is the principle metabolite in humans, accounting for 50–80% of melatonin produced. A number of minor metabolites are also formed through ring splitting, cyclization of the side chain, or demethylation. In humans and rodents, exogenous oral or intravenous melatonin has a short metabolic half-life (20–60 min, depending on the author and species), with a large



Melatonin. Figure 1 Diagram of the sympathetic control of melatonin synthesis in the rodent pineal gland. *5HT*, 5-hydroxytryptamine; *NAS*, N-acetyl serotonin; *AANAT*, serotonin-N-acetyltransferase; *NE*, noradrenalin (norepinephrine); *cAMP*, cyclic adenosine monophosphate; *AC*, adenylate cyclase; *pKA*, protein kinase A; *pKC*, protein kinase C; *DAG*, diacylglycerol; *AR*, adrenergic receptor; *CREB*, cAMP-responsive element–binding protein; *pCREB*, phosphorylated cAMP-responsive element–binding protein; *pAANAT/14–3–3*, phosporylated serotonin-N-acetyltransferase /14–3–3 protein complex; *pAANAT*, phosphorylated serotonin N-acetyl transferase. From Ganguly, S., Coon, S.L. & Klein D,C. Control of melatonin synthesis in the mammalian pineal gland: the critical role of serotonin acetylation. *Cell Tissue Res*, 2002, 309:127–137.

hepatic first-pass effect and a biphasic elimination pattern. In ruminants, longer half-lives are seen after oral administration [3].

A Photoneuroendocrine Transducer

When seasonal functions are primarily timed by day length, species are referred to as being photoperiodic. Moreover photoperiod is often critical for the timing of pubertal development. In photoperiodic mammals and marsupials, an intact innervated pineal gland is essential for the perception of photoperiodic change. The critical signal is the changing duration of melatonin secretion in response to daylength. Long-duration melatonin is equivalent to short days, and short-duration melatonin is equivalent to long days. Interpretation of the signal, as with day length, depends on the physiology (for example, long- or short-day breeder) of the species in question [6]. The mechanism of action of melatonin with regard to seasonal variation in reproductive competence and the timing of puberty in animals is thought to involve an influence of melatonin on steroid feedback mechanisms in the brain, together with a direct influence on the pituitary gland via melatonin receptors. There is recent evidence that melatonin

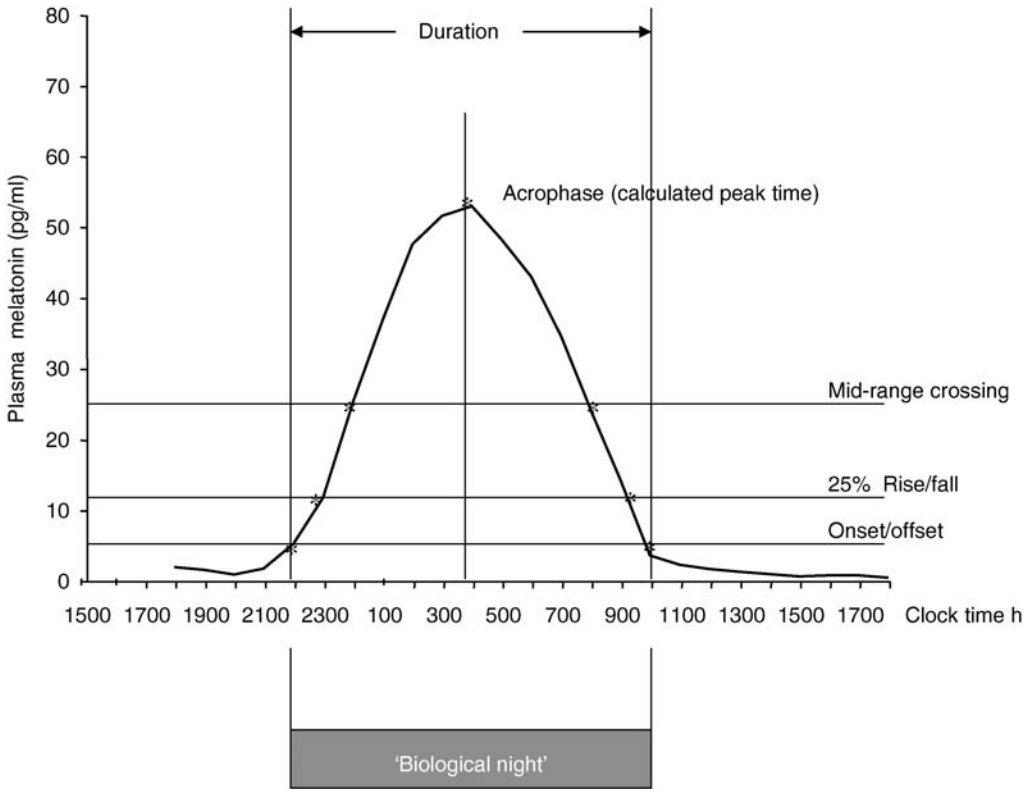
acts directly on peripheral ►clock genes to convey information about photoperiod. Melatonin treatment has been commercialised for the purpose of changing the time of the breeding season (and other seasonal functions) in domestic species such as sheep and goats. In appropriate experimental conditions humans show a duration change in response to daylength changes, like animals [4].

A Hand of the Clock

The secretion of melatonin from the pineal is probably the most direct peripheral link to the central circadian clock. In healthy individuals, the timing, amplitude, and even the details of the profile can be highly reproducible from day to day and from week to week, rather like a hormonal fingerprint even without strictly controlled sampling conditions. The very large interindividual variations have been ascribed to the size of the pineal gland rather than to variations in enzymic activity. No consistent gender differences have been found and a small number of apparently normal individuals have no detectable melatonin in plasma at all times of day. Diurnal preference (morningness) and short ►free-running circadian ►period are associated with earlier melatonin phase. There are seasonal variations in human melatonin (and aMT6s), with an earlier phase in summer and, according to some reports, increased levels and duration of secretion in winter in high latitudes. Plasma melatonin declines during development and with age [4].

For clinical assessments of possible circadian abnormality, the use of melatonin "onset" – the start of the evening rise – in plasma or saliva has been used as a phase marker of the internal clock, as it avoids overnight sampling [4]. There is some evidence that two ►oscillators usually known as M and E (for ►morning/evening oscillators) are concerned with the generation of the melatonin rhythm. The rise is theoretically associated with E, and the fall with M [4]. Differential effects on the rise and fall, and even on the details of the overnight profile, may well be clinically important (Fig. 2). There is extensive evidence for good correlations in both timing and amplitude between the rhythms of plasma and saliva melatonin and the urinary metabolite aMT6s.

A variety of observations in disease states indicate that the amplitude and sometimes the timing of the rhythm may be modified. It is hard to draw any general



Melatonin. Figure 2 Diagram of the markers used to characterize melatonin and aMT6s (6-sulphatoxymelatonin) rhythms. Area under the curve or total 24-h excretion (aMT6s) is used to assess total secretion. At present, there is no standard definition of onset-offset (and hence duration). Redrawn from: Arendt, J. & Skene, D. J. Melatonin as a chronobiotic. *Sleep Med Rev*, 2005, 9:25–39.

conclusions, and it is rare for such clinical studies to control for all known masking factors.

The timing and duration of melatonin secretion are its critical features with regard to physiological functions. The relevance of small changes in melatonin amplitude remains obscure, particularly in view of the enormous individual variation between normal healthy subjects.

Role of Melatonin in the Circadian System

In some lower vertebrates and birds melatonin has a major role in the organisation of circadian rhythms. In mammals this role is hierarchically less important and until quite recently, opinion was that the pineal did not have an important role in the mammalian circadian system. Some strains of (healthy, prolific) laboratory mice have virtually no detectable melatonin. Pinealectomised rats show no obvious circadian abnormalities unless 'challenged'. However, in rats, pinealectomy increases the rate of re-►entrainment to forced phase shifts of the light-dark cycle, and pinealectomy of hamsters in constant light leads to major disruption of the circadian system [3]. In rodents, maternal melatonin can influence the circadian timing of the foetus [7]. In humans it is likely that the phase shifting effects of light do not depend on melatonin suppression, but that the presence of endogenous or exogenous melatonin can in some circumstances modulate the effects of light on the circadian system. Melatonin has received much attention as a 'sleep hormone'. However it is quite possible to sleep out of phase with melatonin (although sleep is somewhat compromised). Essentially the presence of melatonin secretion appropriately timed, at night, reinforces physiological events that occur at night, for example sleep and the decline in core body temperature. Most evidence for a circadian role of melatonin derives from timed administration.

Effects of Exogenous Melatonin on Sleep and Circadian Rhythms

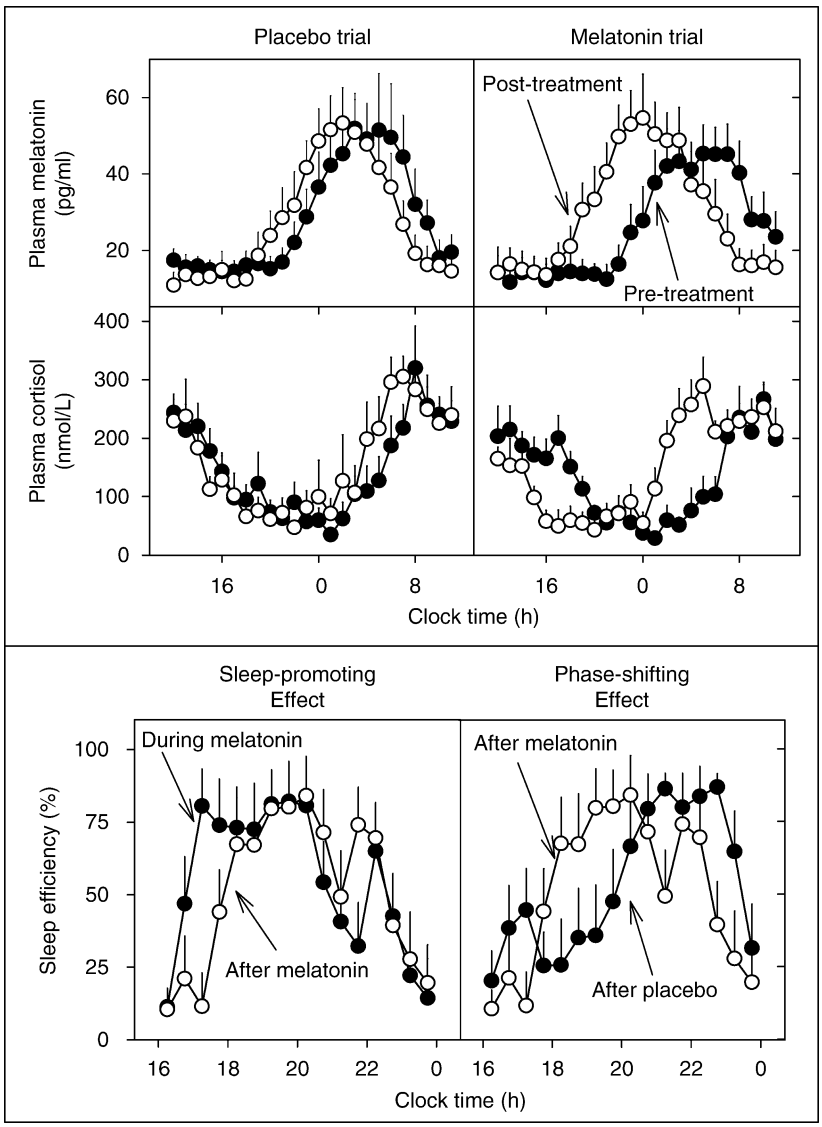
Aaron Lerner discovered melatonin. He was the first person to show, 40 years ago, that melatonin had sleep-inducing effects. Now it is clear that low (0.1–10 mg) doses of melatonin during the "biological day," that is, when endogenous melatonin levels are low, can induce transient sleepiness or sleep, and lower core body temperature, in suitably controlled circumstances (posture is important; the greatest effects are seen with recumbent subjects in very dim light). These effects are opposite to the acute effects of bright light given at night. A substantial body of literature has described effects on sleep and sleep structure comparable to but not identical with benzodiazepines [8]. There is little evidence to suggest that it has important effects in normal sleepers if given at habitual bedtime.

Melatonin can shift the timing of SCN activity in vitro: clear evidence that it affects the central circadian clock [9]. In the dose range 0.05–10 mg melatonin is able to shift circadian timing to both later and earlier times when administration is appropriately timed. ►Phase advances (and possibly ►phase delays) are dose-dependent using a single dose in the range 0.05 to 5 mg. As for light, appropriate timing of treatment to delay or advance the circadian system can in principle be predicted from a ►phase-response curvea (PRC) in subjects whose body clock phase is known [10]. The reported PRCs to melatonin are essentially the reverse of that to light. In controlled experiments melatonin can shift all circadian rhythms observed to date. It is possible to differentiate the acute sleep-inducing and circadian phase shifting effects and in these circumstances it is evident that melatonin changes the timing and distribution of sleep but not total sleep time in healthy subjects (Fig. 3). In subjects whose sleep is suboptimal due to misalignment of circadian rhythms the ability of melatonin to optimise circadian phase relative to sleep and to induce sleep during biological day mean that it has therapeutic properties in circadian rhythm sleep disorder.

The phase shifting properties of melatonin mean that in principle it can entrain free running rhythms. This property was initially demonstrated in rats. However it was only 15–20 years later that full entrainment was shown in humans. There is no doubt that timed melatonin administration (0.5–5 mg at 24-h intervals, usually at desired bedtime) can entrain (or synchronize) the free-running circadian rhythms of most blind subjects, with a consequent improvement in sleep and daytime alertness (even without entrainment, sleep is improved). Interestingly, if entrainment does not occur, shortening of circadian period is seen in the blind. It is possible that one action of melatonin is to shorten period, to the extent that entrainment is possible by other time cues if present [10].

Treatment of Circadian Rhythm Sleep Disorders

Melatonin has been employed to treat various circadian rhythm disorders, including ►delayed sleep phase syndrome (DSPS), free run (non-24 h sleep wake cycles, common in blind people with no light perception at all), and desynchrony due to ►jet lag and ►shift work. Most success has been obtained in DSPS and in blind free-run [10]. Various factors may influence the ability of melatonin to entrain and or phase shift both blind and sighted humans including dose, formulation, individual pharmacokinetics, free-running period, receptor sensitivity, and behavior. In sighted subjects, unknown circadian phase, unpredictable light exposure, and self-selected sleep times are probably the reason for some inconsistency in the clinical trials of melatonin in shift work and jet lag.



Melatonin. Figure 3 The direct and circadian effects of melatonin. (a) Melatonin administration (at 16h) phase-advances endogenous melatonin and cortisol rhythms in healthy volunteers (n = 8) exposed to a phase-advanced, extended sleep opportunity (16.00 h, daily for 8 days). Data are mean ± SEM) for placebo trial (*left*) and melatonin (*right*), pre-treatment (*closed circles*) and post-treatment (*open circles*). Melatonin reinforced the phases advances seen with placebo ($P < 0.05$). Redrawn from Rajaratnam, S. W., Dijk, D. J., Middleton, B., Stone, B. M. & Arendt, J. Artificially prolonged melatonin profile phase-shifts human circadian rhythms without altering the duration of endogenous melatonin secretion, daytime sleepiness, mood or the 24h production of reproductive hormones. *J Clin Endocrinol Metab*, 2003, 88:4303–9. (b) Sleep-promoting and phase-shifting effects of melatonin. Sleep efficiency (% per hour, mean ± SEM, polysomnography) from the study in Fig. 3a. The direct, sleep-promoting effect of melatonin (*left panel*) is seen by comparison of the last day of melatonin treatment (*closed circles*) and the first post-treatment day, open circles). Increased sleep efficiency is observed for the first 2 to 3 h during melatonin treatment (*grey shaded*). The phase-shifting effect of melatonin on sleep (*right panel*) is seen when comparing data (melatonin, closed circles, placebo open circles) from the first post-treatment day. A shift in the distribution of sleep can be observed after melatonin treatment. Redrawn with permission from Rajaratnam, SM.W., Middleton, B., Stone, B.M., Arendt, J. & Dijk, D-J. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities. *J Physiol*, 2004, 561:339–351.

Melatonin and Cancer

This subject is included here since there is evidence that pinealectomy, photoperiod per se and forced phase shifts of the light dark cycle can influence growth of tumors. In vivo, it has also been reported that melatonin may increase or decrease tumor growth, depending on ►photoperiod, in hamsters. It has been proposed that light at night during night shift work suppresses melatonin and that this loss of melatonin "activity" is responsible for the possible increased cancer risk. However, to attribute any detrimental effects directly to loss of melatonin is overspeculative. Light at night has numerous other effects. The mere fact of frequent disruption of all circadian rhythms, not just melatonin, is effectively a physiological insult [4].

Summary

The rhythm of melatonin production provides information on daylength for the organisation of biological rhythms. It appears to be the only solidly established humoral method of signaling time of day and time of year to other physiological systems. The rhythm in plasma or saliva provides the best available measure of the timing of the internal circadian clock. Melatonin is not only a "hand of the clock"; endogenous melatonin acts to reinforce the functioning of the mammalian circadian system. Most is known in humans about its relationship to sleep and the decline in core body temperature and ►alertness at night. Melatonin clearly has the ability to induce sleepiness and lower core body temperature during "biological day" and to change the timing of human rhythms when treatment is appropriately timed. It can entrain free-running rhythms and maintain entrainment in most blind and some sighted people. Used therapeutically it has proved a successful treatment for circadian rhythm disorder, particularly the non-24-h sleep wake disorder of the blind. Numerous other clinical applications are under investigation. In normal subjects endogenous melatonin and light may act in concert to help maintain synchrony with the 24 h day. Threads of evidence indicate an involvement in timing mechanisms throughout life. For therapeutic purposes a combination of timed melatonin and exposure to bright light promises much for the future.

References

1. Klein DC, Coon SL, Roseboom PH, Weller JL, Bernard M, Gastel JA, Zatz M, Iuvone PM, Rodriguez IR, Begay V, Falcon J, Cahill GM, Cassone VM, Baler R (1997) The melatonin rhythm-generating enzyme: molecular regulation of serotonin N-acetyltransferase in the pineal gland. Recent Prog Horm Res 52:307–357; discussion 357–358
2. Iuvone PM, Tosini G, Pozdeyev N, Haque R, Klein DC, Chaurasia SS (2005) Circadian clocks, clock networks, arylalkylamine N-acetyltransferase, and melatonin in the retina. Prog Retin Eye Res 24:433–456
3. Arendt J (1995) Melatonin and the mammalian pineal gland, Chapman Hall, London
4. Arendt J (2005) Melatonin: characteristics, concerns, and prospects. J Biol Rhythms 20:291–303
5. Klein DC (2007) Arylalkylamine N-acetyltransferase: "the Timezyme". J Biol Chem 282:4233–4237
6. Goldman BD (2001) Mammalian photoperiodic system: formal properties and neuroendocrine mechanisms of photoperiodic time measurement. J Biol Rhythms 16:283–301
7. Goldman BD (2003) Pattern of melatonin secretion mediates transfer of photoperiod information from mother to fetus in mammals. Sci STKE:PE29
8. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, Ford I (2005) Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev 9:41–50
9. Gillette MU, Tischkau SA (1999) Suprachiasmatic nucleus: the brain's circadian clock. Recent Prog Horm Res 54:33–58; discussion 58–59
10. Arendt J, Skene DJ (2005) Melatonin as a chronobiotic. Sleep Med Rev 9:25–39

Melatonin Receptors

Josephine Arendt
Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey, UK

Synonyms

MT1, Mel1a, MTNR1A; MT2, Mel1b, MTNR1B

Definition

A seven transmembrane domain, G protein-coupled receptor (GPCR) which binds melatonin.

Characteristics

Melatonin Binding Sites

Melatonin G protein-coupled membrane receptors are considered to mediate the effects of this hormone on numerous physiological systems and notably its influence on seasonal and circadian rhythms. The development of 2-^{125}I-iodomelatonin as a high-specific activity ligand permitted the identification of high-affinity, saturable, specific, and reversible ►melatonin binding to cell membranes in the central nervous system, initially in the central circadian clock, the ►suprachiasmatic nucleus (►SCN), and the *pars tuberalis* (PT) of the pituitary, [1–4] and subsequently in many brain and other areas, including cells of the immune system, a number of cancer cell lines, the gonads, the kidney, and the cardiovascular system. The SCN shows clear binding in human postmortem tissue [3]. Species

variation of melatonin-binding sites in the brain is apparent. The most consistent (but not universal) binding site between mammalian species is the *pars tuberalis*, primarily implicated in transduction of the effects of ►photoperiod, via melatonin, on seasonal variations in prolactin secretion in ruminants [5].

A functional melatonin receptor exists in rabbit and chicken ►retina (inhibition of calcium-dependent dopamine release) and is localized in dopamine-containing amacrine cells in the inner plexiform, in the outer and inner segments in mice, and possibly in the pigmented layer in some mammals [4].

The interaction of melatonin with nuclear receptors (RZR/ROR alpha and RZR beta) and intracellular proteins, such as calmodulin or tubulin-associated proteins has also been reported. The transcription factor RZR/ROR alpha may mediate a direct gene regulatory action of the hormone. It has been hypothesized that while the effects of melatonin on circadian and seasonal rhythms appear to use the membrane receptors, peripheral effects of melatonin (such as immunomodulatory effects) may largely be mediated by RZR/ROR alpha [6].

Melatonin Receptor Pharmacology

Melatonin-induced pigment aggregation in amphibian melanophores provided an early model for investigation of melatonin receptor pharmacology. It is a pertussis toxin-sensitive system and melatonin inhibits forskolin-activated cAMP formation. Inhibition of cAMP production may be a general feature of melatonin receptors. Intensive investigation of the properties of the *pars tuberalis*-binding site has revealed that physiologic doses of melatonin inhibit forskolin-activated cAMP production *in vitro* in a time- and dose-related manner [2]. Guanosine triphosphate analogues, which interfere with the regeneration of G_1-coupled receptors, decrease the affinity and sometimes the capacity of ^{125}I-melatonin binding in reptiles, birds, and mammals.

Melatonin receptors have been cloned, and three subtypes were initially named Mel-1a, Mel-1b, and Mel-1c [3]. The Mel 1a receptor gene has been mapped to human chromosome 4q35.1. Its primary expression is in the *pars tuberalis* of the pituitary and the SCN. Mel 1b has been mapped to chromosome 11q21–22 and its main expression is in the retina and the brain. Mel 1c is not found in mammals. Two cloned mammalian receptors (Mel 1a, Mel 1b) have now been renamed MT1 and MT2 [4]. They are a new family of G protein coupled receptors (GPCRs), have high affinity (Kd 20–175 picomolar) and inhibit forskolin-stimulated cyclic AMP formation. The so-called MT3 receptor is an enzyme, quinone reductase, concerned with detoxification mechanisms. This may be at least a partial explanation for some of the free-radical scavenging/antioxidant properties of high dose melatonin (not to be considered here).

The two cloned receptors, MT1 and MT2, are of particular importance with regard to rhythm physiology and pharmacology. Using gene knockout technology in mice and pharmacological manipulations, initially the MT1 receptor, most studied in the SCN and the *pars tuberalis* of the pituitary, and the MT2 receptor (also found in the SCN) were thought to have different functions, with ►phase shifting rhythms attributed to MT2 and suppression of SCN activity (countering the "wake" signal of the SCN) attributed to MT1. However more recently it appears that there is redundancy between these two receptors [7]. They can also form heterodimers which differ in properties from the monomeric forms [8].

MT1 has important actions within the *pars tuberalis* controlling seasonal prolactin variations in ruminants [5]. The hypothalamic receptor(s) concerned with seasonal and circadian variations in gonadotrophins has not been unequivocally identified, however melatonin regulation of reproductive functions in sheep is mediated by action in the premammillary hypothalamus [9].

Genetic polymorphism has been identified within melatonin membrane receptors, and further investigation of these polymorphisms in relation to photoperioidism, human disease, sensitivity to melatonin, and so on, is ongoing.

Probably the most interesting development in the effects of melatonin concerns its influence on peripheral gene expression in the *pars tuberalis* [5]. In rodent *pars tuberalis* cells, rhythmic expression of the ►clock gene *per1* appears to be dependent on sensitization of adenosine A2b receptors, which in turn depend on melatonin activation of MT1 receptors [10]. Clearly it is possible that the melatonin signal is a widespread humoral mechanism related to biological timing, acting through modification of peripheral clock gene expression. The effects of melatonin on peripheral, as well as central, clock gene expression are likely to be a rich field of enquiry.

Melatonin Analogues

In view of the properties of melatonin (see section "Melatonin") there has been much effort directed to the synthesis and evaluation of indolic and non-indolic analogues specific for either or both of the MT1 and MT2 receptors. Both agonists and antagonists with varying specificity have been described. Human trials of sleep promoting, circadian phase-shifting and anti-depressant effects are ongoing. Most information is available for three agonists (agomelatine/valdoxan/S20098, *N*-[2-(7-methoxynaphthalen-1yl)ethyl]acetamide, ramelteon TAK-375 rozerem (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and VEC-162 (1R-*trans*)-*N*-[[2-(2,3-dihydro-4-benzofuranyl) cyclopropyl] methyl] propanamide). All appear to be selective for the MT1 and MT2 receptors with little

M

affinity for other receptors. Agomelatine in addition has 5-HT2c antagonist activity and in view of this the emphasis of clinical work has shifted to its anxiolytic and anti-depressant activity. It effectively targets both depressive disorders, in particular major depressive disease, and circadian rhythm sleep disorders. Ramelteon has received marketing authorization for insomnia. VEC-162 shows promise with respect to its ability to phase shift the circadian system and to regulate sleep [11].

Development of melatonin agonists and antagonists, with varying affinities to MT1 and MT2, and possibly to other, yet to be reported, melatonin receptors, may elucidate the mechanisms of melatonin action, and further enhance the therapeutic potential of "melatoninergic" drugs.

References

1. Vanecek J, Watanabe K (1999) Mechanisms of melatonin action in the pituitary and SCN. Adv Exp Med Biol 460:191–198
2. Morgan PJ, Williams LM (1989) Central melatonin receptors: implications for a mode of action. Experientia 45:955–965
3. Reppert SM (1997) Melatonin receptors: molecular biology of a new family of G protein-coupled receptors. J Biol Rhythms 12:528–531
4. Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI (2003) Molecular pharmacology, regulation and function of mammalian melatonin receptors. Front Biosci 8:d1093–d108
5. Hazlerigg DG, Morgan PJ, Messager S (2001) Decoding photoperiodic time and melatonin in mammals: what can we learn from the pars tuberalis? J Biol Rhythms 16:326–335
6. Carlberg C (2000) Gene regulation by melatonin. Ann N Y Acad Sci 917:387–396
7. Jin X, Von Gall C, Pieschl RL, Gribkoff VK, Stehle JH, Reppert SM, Weaver DR (2003) Targeted disruption of the mouse Mel(1b) melatonin receptor. Mol Cell Biol 23:1054–1060
8. Ayoub MA, Levoye A, Delagrange P, Jockers R (2004) Preferential formation of MT1/MT2 melatonin receptor heterodimers with distinct ligand interaction properties compared with MT2 homodimers. Mol Pharmacol 66:312–321
9. Malpaux B, Tricoire H, Mailliet F, Daveau A, Migaud M, Skinner DC, Pelletier J, Chemineau P (2002) Melatonin and seasonal reproduction: understanding the neuroendocrine mechanisms using the sheep as a model. Reprod Suppl 59:167–179
10. Von Gall C, Garabette ML, Kell CA, Frenzel S, Dehghani F, Schumm-Draeger PM, Weaver DR, Korf HW, Hastings MH, Stehle JH (2002) Rhythmic gene expression in pituitary depends on heterologous sensitization by the neurohormone melatonin. Nat Neurosci 5:234–238
11. Arendt J, Rajaratnam SW (2008) Melatonin and its agonists for treatment of sleep and circadian rhythm disorders – an update. Brit J Psychiat (in press)

Membrane Biophysics

P. M. Lalley[1], U. Windhorst[2]
[1]Department of Physiology,
The University of Wisconsin School of Medicine,
Medical Science center, Madison,
Wisconsin, USA
[2]Göttingen, Germany

Synonyms

Membrane physico-chemical relationships

Definition

Application of the laws and methods of physics to the study of cell membrane properties and functions.

Introduction

At a cellular level, information transmission and processing must occur within the cell, between its different parts, and with the extracellular environment at the cell surface. Internal membranes that delineate compartments, and the surface cell membrane (►plasmalemma or ►sarcolemma) play prominent roles in organizing cellular life. They serve to preserve the semi-autonomy of the cell, with two competing aspects: cell ►homeostasis (maintenance and preservation of a fairly constant internal milieu) by incapsulation on the one hand, and exchange with the environment through a continual flux of matter, energy and information on the other. Membranes provide and organize means to subserve both aspects. In particular, information transmission must be securely put on a molecular basis. The cell membrane should thus provide the following:

- Mobility of cell wall constituents
- Selective permeability for compounds, implying a reconnaissance function
- Asymmetry between internal and external sides
- Electrical insulator function because the cell membrane must also separate ions and, hence, electric charges (see below)

The information exchange process has two aspects: acquisition and delivery of information. Acquisition involves reception of signals related to many different facets of the environment. Delivery implies executive acts, be they motor, excretory or the like. In single-celled organisms (protozoa) such as *Paramecia*, the same cell carries out both processes and for the most part they take place at cell surface membranes. In highly developed metazoa, cells have specialized functions, certain groups being "receivers" and others "executors" of information, but most in fact are both. Executors include muscle, glandular and other cells because motor

acts and glandular functions transmit information to the environment or other cells.

In the following sections, we will be primarily concerned with information transmission in metazoa. To receive information, metazoa have developed specialized "►receptor cells" (or often, for brevity, ►receptors). As is intuitively clear, metazoa need to collect information about many different aspects of their internal and external environments (►Sensory systems).

Information is an abstract entity that needs to be encoded in a signal to be transmitted and processed. Signals in turn are generated by some material substrate or carrier that may engage one or the other mechanism to produce a signal. This chapter will deal with the following questions:

- What are the signals used by the nervous system to encode information?
- What are the structures carrying them?
- How are the signals generated, by what mechanisms?
- How are the signals transmitted over some distance?
- How is information encoded and decoded again?
- How can information be quantified?

The first problem to be solved by evolving cellular organisms is to find a suitable signal and a carrier. The signal should be:

- Easily implemented with biological structures at hand: molecules and their aggregates
- Reproduced into what can be called a resting state
- Able to propagate over long distances
- Fast (within the scope of biological "time")
- Energy-efficient
- Versatile
- Modifiable

In processing information, protozoa and multi-celled organisms have the same interest. It is therefore intuitively appealing to think that the basic structures and mechanisms involved in information transfer have evolved early on and been preserved fairly well throughout evolution. The signal and its supporting physical structure should then be common to most animals. Communication of a unicellular organism and of an individual cell within a metazoon must occur at their cell surfaces, hence signals must be generated, propagated and processed at cell membranes.

Historical Notes. The study of cell physiology was launched in the seventeenth century with the use of microscopes by M. Malpighi (1627–1694) and A. von Leeuwenhoek (1632–1723). Neurophysiology took off in the eighteenth century after electricity had become amenable to experimentation (Leyden flask). Seminal experiments were performed by A. Galvani (1737–1798) who noted that frog muscles contracted whenever a contact was made with a Leyden flask. He demonstrated that no external source was needed if different metals were used in the frog experiments: contractions also occurred when the brass wire in contact with the spinal cord touched the iron support on which the frog was lying. He concluded that electricity was an intrinsic property of the muscle. Galvani's interpretations were criticized by A. Volta (1745–1827) because he was able to produce electrical batteries from different metals and salt solutions. Volta was correct in saying that Galvani had used external electrical stimulation. Nonetheless, Galvani's idea of the existence of intrinsic electricity turned out to be right in the end. Further important contributions came from, among others, J. Müller (1801–1858), T. Schwann (1810–1882), C. Matteucci (1811–1868), E. du Bois-Reymond (1818–1896), H. von Helmholtz (1821–1894), A. Fick (1829–1901), L. A. Ranvier (1835–1922), W. Kühne (1835–1900), L. Hermann (1838–1914), J. Bernstein (1839–1917), J. von Kries (1853–1928) [1]. In the twentieth century, the field exploded, and a number of achievements were rewarded with the Noble Prize (NP) for Medicine or Physiology, among the prize winners being: E. D. Adrian (1889–1977; NP 1932), J. Erlanger (1874–1965; NP 1944), H. S. Gasser (1888–1963; NP 1944), J. C. Eccles (1903–1997; NP 1963), A. H. Hodgkin (1914–1998; NP 1963), A. F. Huxley (*1917; NP 1963); B. Katz (1911–2003; NP 1970), E. Neher (*1944; NP 1991), B. Sakmann (*1942; NP 1991).

Nerve Cell Membrane

Membrane Structure

The nerve cell membrane (►Cell membrane – components and functions) is a microscopically thin membrane that separates the cell cytoplasm and intracellular organelles from the extracellular milieu. Its chemical composition and structural features allow free passage of most lipids, and selective passage of ions, sugars and amino acids. The membrane, in addition, contains the molecular machinery for cell-to-cell chemical and electrical communication (below) and immune responsiveness (►Neuroimmunology).

Anatomy and Chemical Makeup of the Nerve Cell Membrane

The unit membrane of the nerve cell is, on average, about 50 nm thick and comprised of various types of phospholipids, proteins and carbohydrates. Proteins, being the largest molecules, make up the greatest membrane mass but the smaller phospholipids are the largest in number and carbohydrate molecules are the fewest. The molecules making up the membrane proper, or attached to it, are mobile, interactive and in many cases functionally interdependent. They are replaced by intracellular biosynthesis, and turned over by a process called membrane trafficking.

Membrane Phospholipids

Membrane lipids are arranged in a bilayer with the glycerol phosphates facing the extracellular and intracellular fluids, and the fatty acid chains arranged in rows side by side in the membrane. Phospholipid molecules have a high degree of lateral mobility in the bilayer, which facilitates movement of small non-polar molecules across the cell membrane. Fluidity of cell membrane phospholipids also facilitates ►transport processes and enzyme activities. Less frequently, phospholipid molecules will "flip-flop," i.e., migrate from a monolayer on one side to that on the other.

Functions of membrane phospholipids include:

- Insulation and barrier properties
- Intracellular signaling
- Electrical properties

The extremely thin, expansive lipid bilayer of the nerve cell membrane has a ►membrane capacitance on the order of 1 μF/cm^2 that produces a charge of about 8×10^{-9} coulombs/cm^2 at a resting membrane potential (below; ►Membrane potential – basics) of –80 mV, or approximately 5×10^{11} monovalent ions/cm^2.

Cholesterol. The nerve cell membrane contains large amounts of ►cholesterol, which enhances the permeability-barrier property of the lipid bilayer. This renders the lipid bilayer less permeable to small water-soluble molecules.

Glycolipids. These lipids contain carbohydrate groups and are found only on the extracellular side of the cell membrane. ►Glycolipids are believed to be involved in cell-cell interactions. Five to ten percent of the total lipid mass consists of a particular type of glycolipid called a ►ganglioside. Gangliosides are thought to alter the electrical field across the cell membrane, as well as the concentration of Ca^{2+} ions along the external surface of the cell membrane. They may also be involved in cell–cell recognition at the extracellular matrix that promotes cell aggregation.

Membrane Proteins

The membrane contains a large group of membrane proteins, not all of which have been identified. ►Integral proteins completely traverse the cell membrane, whereas ►peripheral proteins are anchored to either the cytoplasmic or extracellular side. Membrane proteins exhibit function-dependent polarity. Cell membrane proteins are also stored in membranous cisterns in dendrites and axons, where they play important roles in ►synaptic plasticity and ►axon growth.

The locations of different types of proteins in the cell membrane serve as general predictors of how they function in the nerve cell.

Integral membrane proteins serve as:

- ►Ion pumps (below), moving ions against a concentration gradient, using energy derived from adenosine triphosphate (ATP)
- ►Ion channels (below), allowing flow of ions and water across the cell membrane down an electrochemical gradient
- ►Transporters of sugars and amino acids
- Cell–cell recognition sites

Peripheral proteins function as:

- Receptors for ►neurotransmitters, ►neuromodulators, ►hormones and other chemical messengers that trigger membrane ion permeability changes
- Enzymes that catalyze intracellular signal cascades
- Immunoreactive elements (Neuroimmunology)
- Membrane structural support proteins
- Mediators of neurite outgrowth and axon bundling
- Intermediaries in membrane trafficking

Membrane Potential

Membrane potential denotes the electrical potential difference (►voltage, V) across the cell membrane of all living cells, which is produced by an unequal net distribution of positive and negative charges on either side of the cell membrane. The potential in the intracellular milieu is normally negative with respect to the extracellular milieu, reference set to zero (Membrane potential – basics).

Resting membrane potentials can be measured in all living cells. They vary in magnitude, but are negative inside vs. outside. It is assumed, on well-established physico-chemical grounds, that they originate from concentration differences across the cell membrane of ions that carry electric charges. Generally, the concentrations of Na^+ and Cl^- are high extracellularly and low intracellularly, thus establishing a strong inward concentration gradient across the cell membrane. The situation is opposite for K^+. Another ion that is unequally distributed is Ca^{2+}, with a high extracellular and a normally very low intracellular concentration.

Membrane Potential and Ion Concentration Gradients

In 1902, Julius Bernstein [2] hypothetized that the resting membrane potential, V, is a diffusion potential determined exclusively by K^+. According to the ►Nernst equation, V should then be the K^+ equilibrium potential, E_K:

$$V = E_K = \frac{R.T}{F} \times \ln \frac{[K^+]_0}{[K^+]_i}$$

where $[K^+]_o$ is the external and $[K^+]_i$ the internal K^+ concentration.

However, later measurements showed that Bernstein's hypothesis could not fully account for the real

situation because, in addition to K^+, other ions can permeate the membrane even under resting conditions, giving rise to deviations of the membrane potential from E_K. A most important ion is Na^+, whose equilibrium potential is opposite in sign to that of K^+. In most cells, the resting membrane potential is much closer to E_K than to E_{Na}, however, because under resting conditions the membrane permeability for K^+ is much larger than that for Na^+. Also, Ca^{2+} with its positive charge and inwardly directed concentration gradient has, like Na^+, a positive equilibrium potential. Chloride with its negative charge and inwardly directed concentration gradient has a negative equilibrium potential (Membrane potential – basics).

Ion Pumps

As outlined above, even under steady-state or resting conditions, membrane channels, including some K^+ and Na^+ channels, stay open and generate a "►leak conductance" [3]. In effect, what results is a leaky RC circuit, with a specific membrane resistance of about 1,000 Ωcm^2 [4]. The RC circuit properties have functional consequences. In the resting state, the net movement of K^+ ions down its concentration gradient through leak channels will leave behind impermeant cytoplasmic organic anions that accumulate on the inner side of the cell membrane and an accumulation of cations on the extracellular side [5], which accounts for the potential difference (V) of about −80 mV across the cell membrane (Membrane potential – basics).

Because the membrane is permeable to several ions that flow passively down electrochemical gradients, unrestricted ion flow would eventually abolish concentration differences between the inside and outside of the cell and, in consequence, the equilibrium and membrane potentials. In order to prevent this, the cell invests much energy in so-called ion pumps that transport the leaking ions back to where they come from, against their respective gradients (►Ion transport). Such pumps need

- Metabolic energy, ultimately supplied by adenosine triphosphate (ATP)
- Regulation mechanisms, including the sensitivity for particular ions and their concentrations (e.g., inside for Na^+)

The action of the Na^+ pump that expels Na^+ from a cell was first demonstrated by Hodgkin and Keynes [6], who showed that the metabolic poison dinitrophenol (DNP), which deprives energy sources for the Na^+/K^+ pump, depresses cellular extrusion of Na^+. Since then, other laboratories have demonstrated the active role of ion pumps that maintain steady state membrane potential by regulating intracellular Na^+, Cl^-, K^+ and Ca^{2+} concentration.

Spread of Local Potentials

Local potential changes (►receptor potential, ►synaptic potential) originating anywhere on the cell surface must ultimately be conveyed to other regions of the cell or, more generally, the nervous system, where a response to the stimulus begins to be formulated. However, passive electrical properties, resistive and capacitive, reduce the size and alter the shape of the receptor potential as it moves transversely through the cell's soma and fibrous, cable-like processes (►Cable theory). Passive cable properties that affect the receptor potential are also present in dendrites and axons of nerve cells, and thin elongated muscle fibers such as frog sartorius muscle [5]. In the latter preparation, a rectangular current pulse depolarizes membrane potential with a near-exponential time course, declines in amplitude with distance along the fiber and changes shape due to temporal filtering. The pulse-evoked response is an approximate simulation of the receptor potential, and attributable to the cable properties of an ►equivalent electrical circuit that consists of a membrane ►capacitor (C_m) and a resistor (R_m) arranged in parallel. In the RC circuit of a biological membrane, C_m is a leaky capacitor that allows ionic charge to accumulate and dissipate through R_m. The time-related change of voltage during discharging of an RC circuit is described by the relationship:

$$V(t) = V_0[\exp(-t/\tau)] \quad (1)$$

Where V_0 is the membrane potential at the cessation of applied current, V(t) is the membrane potential at a corresponding time after termination of the applied current, and τ is the time constant, where $\tau = R_m C_m$. In neurons, time constants τ are of the order of 0.5–5 ms [7].

Current flowing from the receptor region through the longitudinal resistances of the cytoplasm and extracellular fluid form current circuit loops. Current gets progressively smaller with distance. A constant fraction per unit length is diverted through ion leak channels, and falls off exponentially with distance from the region where the stimulus has originated:

$$\Delta V(d) = \Delta V_0.\exp(-d/\lambda), \quad (2)$$

where the length (space) constant λ is $\sqrt{(R_m/R_i)}$, defining the distance at which the original voltage change drops to a fraction of $1/e \approx 0.37$.

The principles illustrated in these simple reduced preparations provide only a relatively primitive explanation for some of the basic properties of sensory transduction. Nonetheless, two important conclusions are evident:

- The passive or ►electrotonic spread of local membrane potential changes (receptor and synaptic potentials) across a cell membrane is no means for transmitting information over long distances.

M

- A process of ►encoding, is necessary to transform the receptor potential from a wave form to a discharge of ►*action potentials* that reach sites of sensory integration, and that reflects the magnitude and duration of the waveform and thus the applied stimulus.

Action Potential

The action potential is the active electrical response of an excitable cell membrane to a stimulus, reflected in a fairly stereotyped change in membrane potential from a resting value (negative inside) to a depolarized (positive inside) value and back (Action potential). The durations of action potentials range from a few milliseconds in neurons to hundreds of milliseconds in cardiac and smooth muscle cells. The underlying mechanisms include time- and voltage-dependent changes in ion conductances.

Ion Currents Underlying the Squid-Axon Action Potential

Early, simple experiments by a number of investigators led Bernstein [2] to propose that the action potential represented a sudden transition from a selective K^+ permeability at rest to a generalized, i.e. non-selective increase of membrane ion permeability. On this basis, one would predict a value of 0 mV at the peak of an action potential. However, Bernard Katz's measurements with conventional ►intracellular recording in the 1940's (reviewed in [4,8]) showed that membrane potential at the peak of a shock-evoked action potential was on the order of +50 mV. From Nernstian considerations, this implicates a cation species such as Na^+, which Katz proved by showing that the amplitude of the action potential changed by about 58 mV for a 10-fold change of extracellular Na^+ concentration. But the peak depolarization was rapidly followed by repolarization and ►hyperpolarization that momentarily exceeded the resting value, indicating that a secondary, selective ion permeability change had occurred. It was previously shown that in frog muscle fibers, resting membrane potential changed in approximate conformation with the Nernst equation when external K^+ concentration was varied. Moreover, Keynes [9] was able to measure shock-evoked efflux of radioactive K^+ from Sepia giant axons.

The superposition of various time-varying currents was difficult to disentangle using the more conventional methods of the time. The invention of the ►voltage-clamp technique (Action potential; Intracellular recording), a by-product of advances in electronics pioneered by K. S. Cole in 1949 [10] and used by A. F. Hodgkin and A. L. Huxley in the 1950's [11], made it possible to separate and analyze voltage-and time-dependent properties of the action potential (Action potential). The giant axon of the squid turned out to be a favorable structure because its size (diameter 0.5–1 mm) and robustness allowed it to be removed from the animal, placed in a bath and subjected to varying extracellular compositions. Its size allowed insertion of relatively bulky longitudinal electrodes, and because of membrane durability it was possible to squeeze out the intracellular content and replace it with solutions of varying composition (Intracellular recording).

The squid-axon experiments showed that the action potential is brought about by voltage-dependent opening of Na^+, Ca^{2+} and K^+ channels. The action potential is initially depolarizing due to opening of Na^+ (►Sodium channels) and/or Ca^{2+} channels (►Calcium channels – an overview), and subsequently repolarizing due to delayed opening of K^+ channels (►Neuronal potassium channels).

Na^+ Inactivation. The fall of the action potential from its peak is promoted not only by K^+-channel opening, but also by inactivation of the Na^+ conductance, which has a slower time course than activation. The Na^+ system recovers from inactivation with an approximately exponential time course and a time constant on the order of 5 ms, with the time constant depending on the holding potential imposed experimentally [2]. The period of reduced Na^+ channel reactivity characterizes the ►refractory period. The impact of membrane depolarization on both activation and inactivation of Na^+ conductance has profound functional consequences. The sequence of Na^+ activation and inactivation (i) limits action potential rate (below); (ii) controls the direction of ►action potential propagation (Action potential propagation); (iii) leads to accommodation; (iv) has clinical implications (Action potential).

Single-Channel Currents. In 1976, Neher and Sakmann [12] introduced the breakthrough ►patch-clamp technique, through which it became possible to voltage-clamp small patches of cell membrane and record ►single-channel currents (Intracellular recording).

Action Potentials in Central Neurons

The squid axon is a simple system devoted to conducting action potentials along the axon (Action potential propagation). Individual central neurons, however, typically express several subtypes of voltage-dependent ►Na^+ channels, voltage-dependent Ca^{2+} channels (Calcium channels – an overview), voltage-dependent K^+ channels (Neuronal ►potassium channels), Ca^{2+}-activated K^+ channels (Neuronal potassium channels), ►hyperpolarization-activated, ►non-selective cation channels (►HCN channels), and more. The different combinations of channels enable diverse action potential amplitudes, shapes and firing patterns [13].

Sodium (Na^+) Currents. In central neurons, the rising phase of the action potential is generated by very fast activation and inactivation of ►voltage-dependent Na^+ channels [13] (Action potential propagation).

Calcium (Ca^{2+}) Currents. Inward Ca^{2+} currents (Calcium channels – an overview) contribute little to

the action potential upstroke, but initiate intracellular signaling pathways, influence action-potential shape and firing patterns, and – at presynaptic terminals the amount of neurotransmitter released [13] (Action potential propagation).

Potassium (K^+) Currents. Central neurons express a wide range of ►Voltage-gated (or –dependent) K^+ channels (Kv; Neuronal potassium channels), only a fraction of which activate appreciably during the action potential. Significant contributions to action potential repolarization are commonly made by Kv3 family and Kv4 family channels mediating the ►A-type K^+ current (I_A). Large-conductance Ca^{2+}-activated K^+ channels (►BK channels) promote membrane repolarization. Small-conductance Ca^{2+}-activated K^+ channels (SK channels) contribute to the following ►afterhyperpolarization [13] (Action potential propagation; Neuronal potassium channels). Furthermore, ►$Na^{\pm}$-activated $K^{\pm}$ channels (K(Na) channels) may modulate action-potential shape, and contribute to slow afterhyperpolarization after repetitive firing [14] (Action potential).

Afterdepolarization. In many neurons, the fast phase of action potential repolarization is followed by a delayed depolarization, whose origins may be passive and/or active, i.e., mediated by an electrotonic mechanism or amplified and supported by active Na^+, Ca^{2+} and ►non-selective cation currents (Action potential propagation).

Afterhyperpolarization (AHP). Afterhyperpolarizations in mammalian central neurons may be complex, often showing different phases and being due to different K^+ currents. BK-channel-mediated afterhyperpolarizations are usually brief, while SK-channel-mediated ones can last up to seconds [13] (Action potential propagation). ►Na^+-activated K^+ channels (K(Na) channels) may contribute to slow afterhyperpolarization after repetitive firing [14] (Action potential).

Repetitive Firing. Many central neurons discharge over a wide range of rates and with various patterns, to which many factors may contribute, including various Na^+, K^+, Ca^{2+} and HCN channel currents. Many central neurons fire spontaneously and fairly regularly, and are called "►pacemakers" [13] (Action potential propagation).

Fast-Spiking Neurons. Neurons capable of firing at high rates for prolonged periods often possess voltage-gated K^+ channels or special "resurgent" Na^+ current, which activates transiently upon repolarization after inactivation due to strong depolarization and is sensitive to ►tetrodotoxin (TTX) [13] (Action potential propagation).

Action Potential Propagation

Propagation along Muscle and Nerve Fibers

The action potential propagates over long distances. Propagation along a nerve or muscle fiber occurs automatically as a consequence of the axonal cable structure (Cable theory; Action potential propagation).

In a muscle or nerve fiber, the ring of membrane that is just being depolarized during the action potential's rise experiences a strong influx of positive charges (Na^+) that distribute internally in both forward and backward directions. The local currents reaching out in the action potential's propagation direction unload the capacitor of the advanced membrane regions and depolarize them. This depolarization increases the Na^+ conductance and elicits the inward Na^+ current in the adjacent membrane segment until threshold is reached for action potential generation at this site. Since charging or discharging of a capacitor takes some time, expressed in the time constant, the substantial depolarization-induced ionic (Na^+) currents are delayed.

In a muscle fiber or an unmyelinated axon, action potentials propagate in feed-forward fashion, regenerating progressively with passage in small increments of membrane. In myelinated nerve fibers, the conduction mechanism is different. The ►myelin sheath is a good insulator. When a ►node of Ranvier between internodes (stretches of myelin sheath) is depolarized during an action potential, local circuit currents depolarize the next one ahead, without discharging the internodal region. The excitation thus leaps from node to node, a process called ►saltatory conduction. This type of conduction confers several advantages: (i) economy of space; (ii) economy of energy expenditure; (iii) high safety factor for conduction (Action potential propagation).

Myelination has notable disadvantages, namely limits to ►regeneration after injury and involvement in various neurological diseases. Functional recovery following injury differs dramatically in the peripheral and the central nervous system (Regeneration).

Demyelination disorders are numerous and are exemplified by the ►Guillain-Barré syndrome and ►Multiple sclerosis.

Back-propagation of Action Potentials

In many neurons, action potentials originate close to the axon's juncture with the cell soma (the initial segment), from where they travel down the efferent axon, but may also "back-propagate" into the dendritic tree (Action potential propagation). These back-propagating action potentials are supported by active, tetrodotoxin-sensitive, voltage-dependent Na+ channels and possibly ►$Ca^{2\pm}$ channels. The extent of this decremental back-progagation varies widely between different types of central neurons, different specimens of the same sort, and possibly different dendritic branches of individual cells. Back-propagation depends on cell morphology and densities of dendritic ion channels, as well as adaptive influences provided by excitatory and inhibitory inputs and neuromodulators. Back-propagating action potentials have been implicated in

short-term and long-term changes in ►synaptic efficacy involving increases in Ca^{2+} influx [15] (Action potential propagation).

More Ion Channels and their Functions

A wide range of channels affect additional cellular functions in addition to control of excitability.

Cyclic Nucleotide-regulated Cation Channels

►Cyclic nucleotide-regulated cation channels are activated by intracellular binding of cyclic AMP (cAMP) or cyclic GMP (cGMP) to a cyclic nucleotide-binding domain (CNBD) in the channel protein, thereby translating intracellular changes in signaling molecules to changes in membrane potential. Two families of channels, both exhibiting a high sequence similarity to voltage-gated K^+ (Kv) channels (Neuronal potassium channels) and regulated by cyclic nucleotides, have been identified, the *cyclic nucleotide-gated (CNG) channels* and the *hyperpolarization-activated ►cyclic nucleotide-gated channels (HCN) channels*. CNG channels require the obligatory binding of a cyclic nucleotide in order to be activated. In contrast, HCN channels are activated by membrane hyperpolarization and modulated by cyclic nucleotides [16]. Cyclic nucleotides enhance HCN channel activity by affecting the voltage-dependence of channel activation.

Hyperpolarization-activated Cyclic Nucleotide-regulated Channels

The HCN1–4 channel gene family encodes HCN channels. They are slowly activated by membrane hyperpolarization and by intracellular cAMP or cGMP, and give rise to depolarizing inward ionic currents termed *Ih*, *If* ("f" for "funny") or *Iq*. They were first discovered in cardiac pacemaker cells, but are widely distributed in various excitable cells including CNS neurons, retinal ►photoreceptors and ►taste buds. HCN channels are structurally similar to voltage-gated K^+ (Kv) channels (Neuronal potassium channels), but much (> or = 25 times) less selective than Kv channels [17]. They are involved in a range of functions, including the setting of resting membrane potential (Membrane potential – basics), ►input conductance and ►length constants, dendritic integration, cardiac and neuronal pacemaker activity, and the regulation of presynaptic release of neurotransmitter [18]. Deficits in the HCN1 gene impair motor learning but enhance spatial learning and memory. Deletion of HCN2 plays a role in ►absence epilepsy, ►ataxia and sinus node dysfunction [19].

Non-selective Cation Channels

Non-selective cation channels are macromolecular pores in the cell membrane that form an aqueous pathway. In distinction to selective ion channels, non-selective cation channels enable cations such as Na^+, K^+ or Ca^{2+} to flow rapidly, as determined by their electrochemical driving force, at roughly equal rates ($>10^7$ cations per channel pore and per second). One of them is the ►nicotinic acetylcholine receptor (►nAChR); others include the ►ionotropic glutamate receptors, ►capsaicin receptors, cyclic nucleotide-gated (CNG) cation channels, and ►TRP channels.

Transient Receptor Potential (TRP) Channels

Non-selective cation channels of the *transient receptor potential* (TRP) superfamily (TRP channels) display a great variety of activation mechanisms and sensitivities and are thus involved in multifarious functions. TRP proteins are assigned to distinct subfamilies based on sequence similarities to *Drosophila* TRP or structural and functional features. The ion-permeating pores mostly allow the permeation of monovalent and divalent cations through all channels and of Ca^{2+} ions through all but two channels [20]. TRP channels make significant contributions to ►olfaction, taste, ►hearing, ►vision, ►thermosensation, ►touch, ►osmosensation, and ►nociception [21]. As to thermosensation, at least six different TRP channels cover the spectrum of relevant temperatures for our body. As mechanosensors, TRP channels are involved in functions ranging from *Drosophila* hearing to nematode touch to mouse mechanical pain [22]). Other TRP channels are essential for the Ca^{2+} and Mg^{2+} homeostasis in our body.

Anion Channels

Chloride channels (►Chloride channels and transporters) are membrane proteins that allow for the passive flow of anions across biological membranes. As Cl^- is the most abundant anion under physiological conditions, these channels are often called "Cl^- channels" instead of "anion channels", although other anions (such as iodide or nitrate) may permeate more easily. In mammals, the CLC gene family encodes nine different Cl^- channels in the plasma membrane or intracelluar organelles such as vesicles. These diverse channels are involved in the control of membrane potential in muscle and nerve cells, in the regulation of cell volume, in the acidification and ionic homeostasis of endosomes and synaptic vesicles, in the transepithelial transport of salt and water, and in the degradation of bone by osteoclasts. Mutations of human CLC channels cause diseases such as myotonia, neurodegeneration and possibly epilepsy, cystic fibrosis, Bartter syndrome (renal salt loss) with or without deafness, Dent's disease (kidney stones and proteinuria), osteopetrosis. The CLC from Escherichia coli functions as a $Cl^-/H+$ exchanger [23]. Some Cl^- channels are activated by intracellular Ca^{2+} (Ca^{2+}-activated Cl^--channels) [24].

Ion Channel Development

The distribution patterns and properties of ligand- and voltage-gated ion channels in developing nerve and muscle cells differ profoundly from those of mature cells (►Ion channel development). At early developmental stages, these specific patterns determine the timing and waveform of spontaneous electrical activity, which is required for the normal maturation of excitability and synaptic connections and for Ca^{2+} influx triggering activity-dependent developmental programs [25].

Channelopathies

Rapid advances in genetics, molecular biology and neurophysiology have enabled unraveling and characterization of the molecular bases of a number of neurological and other diseases, among which ►channelopathies comprise a class of diseases caused by ion channel dysfunctions. They can be due to autoimmune and paraneoplastic [26] processes and drug, toxic or genetic mechanisms that affect all kinds of channels: Ca^{2+}, Cl^{-}, K^{+}, Na^{+}, HCN, TRP channels etc. Mutations in genes encoding ion channel proteins that alter channel function are common mechanisms underlying channelopathies. Examples are plentiful (see Calcium channels – an overview; ►Calcium channelopathies; ►Epilepsy [27]; ►Episodic ataxia [28]; ►Familial periodic paralyses and ►Non-dystrophic myotonias [29]; ►Migraine; ►Neuromyelitis optica; Non-dystrophic myotonias). Channelopathies may also affect internal cell membranes, e.g., of the mitochondria [30].

Prospects

There has been a rapid progression of new concepts related to membrane structure and function, so much so that we seem to have merely touched the surface in our understanding of cell membranes. As we go forward with new techniques that provide more accurate spatial and temporal resolution of membrane dynamics, it seems likely that molecular conformational changes involving channel proteins and lipids will be visualized with optical methods and other techniques as they occur. Gene-gene interactions and the impact of environmental perturbations may also be fruitfully investigated, leading to treatments directed at channelopathies, synaptic dysfunction and correction of myelin disorders.

References

1. Greger R, Windhorst U (1996) Physiology past and future. In: Greger R, Windhorst U (eds) Comprehensive human physiology. From cellular mechanisms to integration. Springer, Berlin Heidelberg New York, pp 1–17
2. Bernstein J (1902) Untersuchungen zur thermodynamik der bioelektrischen Ströme. Pflügers Arch ges Physiol 92:521–562
3. Snutch TP, Monteil A (2007) The sodium "leak" has finally been plugged. Neuron 54:505–507
4. Aidley DJ (1998) The physiology of excitable membranes, Chapter 3, 4th edn. Cambridge University Press, UK
5. Woodbury JW (1965) In: Ruch TR, Paton HD, Woodbury JW, Towe (eds) AL Neurophysiology, Chapter 1, 2nd edn. WB Saunders, Philadelphia.
6. Hodgkin AL, Keynes RD (1955) Active transport of cations in giant axons from Sepia and Loligo. J Physiol (Lond) 128:28–60
7. Kuffler SW, Nicholls JG (1976) From neuron to brain. Sinauer Associates, Sunderland (Mass)
8. Katz B (1966) Nerve, Muscle and Synapse. McGraw-Hill, New York
9. Keynes RD (1951) The ionic movements during nervous activity. J Physiol (Lond) 114:119–150
10. Cole KS (1949) Dynamic electrical characteristics of the squid axon membrane. Arch Sci Physiol 3:253–258
11. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol (Lond) 117:500–544
12. Neher E, Sakmann B (1976) Single-channel currents recorded from membrane of denervated frog muscle cells. Nature (Lond) 260:799–802
13. Bean BP (2007) The action potential in mammalian central neurons. Nat Rev Neurosci 8:451–465
14. Bhattacharjee A, Kaczmarek LK (2005) For K^{+} channels, Na^{+} is the new Ca^{2+}. Trends Neurosci 28:422–428
15. Waters J, Schaefer A, Sakmann B (2005) Backpropagating action potentials in neurones: measurement, mechanisms and potential functions. Prog Biophys Mol Biol 87:145–170
16. Craven KB, Zagotta WN (2006) CNG and HCN channels: two peas, one pod. Annu Rev Physiol 68:375–401
17. Siu CW, Lieu DK, Li RA (2006) HCN-encoded pacemaker channels: from physiology and biophysics to bioengineering. J Membr Biol 214:115–122
18. Robinson RB, Siegelbaum SA (2003) Hyperpolarization-activated cation currents: from molecules to physiological function. Annu Rev Physiol 65:543–480
19. Hermann S, Stieber J, Ludwig A (2007) Pathophysiology of HCN channels. Pflugers Arch 454:517–522
20. Nilius B, Owsianik G, Voets T, Peters JA (2007) Transient receptor potential cation channels in disease. Physiol Rev 87:165–217
21. Venkatachalam K, Montell C (2007) TRP channels. Annu Rev Biochem 76:387–417
22. Christensen AP, Corey DP (2007) TRP channels in mechanosensation: direct or indirect activation? Nat Rev Neurosci 8:510–521
23. Jentsch TJ, Poët M, Fuhrmann JC, Zdebik AA (2005) Physiological functions of CLC Cl-channels gleaned from human genetic disease and mouse models. Annu Rev Physiol 67:779–807
24. Hartzell C, Putzier I, Arreola J (2005) Calcium-activated chloride channels. Annu Rev Physiol 67:719–758
25. Moody WJ, Bosma MM (2005) Ion channel development, spontaneous activity, and activity-dependent development in nerve and muscle cells. Physiol Rev 85:883–941

26. Vernino S (2007) Autoimmune and paraneoplastic channelopathies. Neurotherapeutics 4:305–314
27. Heron SE, Scheffer IE, Berkovic SF, Dibbens LM, Mulley JC (2007) Channelopathies in idiopathic epilepsy. Neurotherapeutics 4:295–304
28. Rajakulendran S, Schorge S, Kullmann DM, Hanna MG (2007) Episodic ataxia type 1: a neuronal potassium channelopathy. Neurotherapeutics 4:258–266
29. Ryan AM, Matthews E, Hanna MG (2007) Skeletal-muscle channelopathies: periodic paralysis and nondystrophic myotonias. Curr Opin Neurol 20:558–563
30. Pi Y, Goldenthal MJ, Marín-García J (2007) Mitochondrial channelopathies in aging. J Mol Med 85:937–951

Membrane Capacitance

Definition

The membrane capacitance is the stored charge of ions across the cell membrane. The cell membrane serves as an insulator of the membrane potential generated by the disequilibrium of ionic charge on either side of the membrane. The membrane capacitance (C) is a function of the stored charge divided by the potential difference across the membrane. As a result, any potential difference change generates a capacitance transient. Membrane capacitance is directly proportional to surface area, so biophysicists often use membrane capacitance as a measure of the changes to membrane surface area.

►Action Potential
►Cable Theory
►Membrane Potential: Basics

Membrane Conductance

Definition

Easiness of passing ion or electricity across membrane. When membrane is activated, membrane conductance increases probably because certain ionic channels are open.

►Action Potential
►Action Potential Propagation
►Cable Theory
►Membrane Potential: Basics

Membrane-delimited Modulatory Mechanism

Definition

Molecular events confined to the membrane surface and triggered by the activation of a G-protein coupled receptor (GPCR). The activated G-protein subunit diffuses along the membrane and activates (or inhibits) surrounding ion channels or metabotropic receptors.

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

Membrane-patch Excision

Definition

Mechanical manipulation of the cell using glass micropipettes that leads to the extraction of a narrow region of cell membrane. The excision can lead to an isolated membrane patch in which the side of the membrane is preserved (outside-out) or inverted (inside-out).

►Intracellular Recording

Membrane Potential: Basics

Uwe Windhorst[1], Peter M. Lalley[2]
[1]Göttingen, Germany
[2]Department of Physiology, The University of Wisconsin School of Medicine, Medical Science center, Madison, Wisconsin, USA

Synonyms

Transmembrane voltage

Definition

The electrical potential difference (►voltage) across the cell membrane (►plasmalemma or ►sarcolemma) of all living cells that is produced by an unequal net distribution of positive and negative charges on either

side of the cell membrane. The potential in the intracellular milieu is normally negative with respect to the extracellular milieu, reference set to zero.

Characteristics

Even phylogenetically ancient unicellular organisms such as Paramecium need to exchange matter and information with their environment. In multicellular organisms, the exchange must be organized across different cellular and body parts. Information is an abstract entity that needs to be encoded in a signal to be generated, transmitted and processed. Signals in turn are generated by mechanisms bound to some material substrate or carrier. The basic structure for information exchange is the cell membrane, and the signals required are generated by physico-chemical mechanisms. Here, we describe a fundamental type of signal: the membrane potential. To understand how it is generated, it is instructive to start from two basic principles.

Ion Concentrations Differ in the Internal and External Solutions of Cells

The first principle is that the concentrations of some basic sorts of ions, which characteristically are abundant on the earth's surface, are different in the internal and external milieus of cells. Table 1 lists concentrations of some pertinent ions in the frog muscle fiber and in the giant axon of the squid.

The respective ion concentrations are higher in the squid axon than in the frog muscle fiber, because the squid lives in seawater with higher ion concentrations. For both types of cells, the concentrations of Na^+ and Cl^- are high extracellularly and low intracellularly, thus establishing a strong inward ►concentration gradient across the cell membrane. The situation is opposite for K^+. Another ion that is unequally distributed is Ca^{2+}, with a high extracellular and a normally very low intracellular free concentration.

Membrane Potential: Basics. Table 1 Extra vs. intracellular concentrations of several types of ion in mM/l (Data from [1])

Ion	Extra	Intra	Ratio extra/intra
(A) Frog muscle fiber			
K^+	2.5	140	0.018
Organic anions	40	86	0.465
Na^+	120	10	12
Cl^-	77.5	1.5	51.667
(B) Giant axon of squid			
K^+	10	400	0.025
Organic anions		360	
Na^+	460	50	9.2
Cl^-	540	40–100	5.4–13.5

Cells Exhibit a Resting Membrane Potential

This second principle is apparent from the experimental measurement illustrated in Fig. 1a. A long skeletal muscle fiber is isolated and put in a medium representing the extracellular milieu. Two sets of electrodes measure the electrical potential differences and apply electrical stimuli. To do the former, a large electrode (so-called indifferent, or reference electrode) is placed in the extracellular milieu, and another movable electrode with a very fine tip is also situated initially in the extracellular fluid. Both electrodes are connected to an amplifier that leads the potential difference to a voltmeter (►Intracellular recording). As long as the movable electrode remains in the homogeneous extracellular milieu, there is no potential difference (Fig. 1b, left), but once the fine electrode penetrates the membrane and enters the interior, a potential difference of about −90 mV is measured (Fig. 1b, right). This steady-state voltage is called the ►*resting membrane potential*. A value of roughly 0.1 V across a membrane 50–100 Å thick corresponds to an electrical field strength of $1–2 \times 10^5$ V cm^{-1} [2].

Resting membrane potentials can be measured in all living cells. They vary in magnitude, but are negative inside vs. outside. It is assumed, on well-established physico-chemical grounds, that they originate from concentration differences across the cell membrane of ions that carry electric charges.

Relation Between Ion Concentration Gradients and Membrane Potential

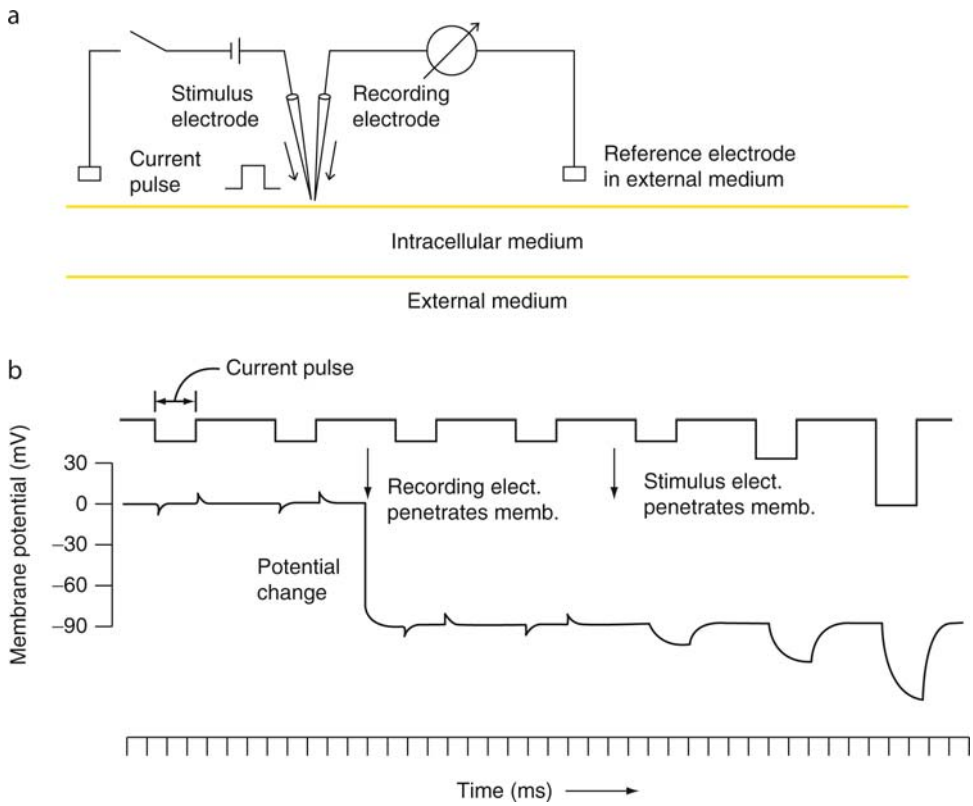
In order to understand this relation, consider some fundamental phenomena in aqueous salt solutions.

Diffusion

Imagine a container made up of two compartments separated by a thin membrane. Both compartments contain a solution of two types of electrically uncharged molecules, one of relatively high molecular weight and the other small. The concentrations are low in the left compartment (c_2) and high in the right compartment ($c_1 = 10.c_2$). If a step-like change in concentration occurs right at the membrane and the membrane is removed, diffusion occurs because of the statistical thermal movement of the particles. The diffusion process follows the following physico-chemical rules:

1. Net flux of both particles proceeds from higher (right) to lower (left) concentrations because, on the average, there are more particles on the right moving leftward than particles on the left moving rightward.
2. Concentration gradients, initially step-like, flatten with progressing diffusion until equilibrium (homogeneous particle concentration) is reached.

M



Membrane Potential: Basics. Figure 1 (a–b) Recording from, and stimulation of, an isolated skeletal muscle fiber (*yellow lines*). (a): Two microelectrodes (micro-pipettes filled with an electrolyte solution) are connected to a battery (*left*) or voltmeter (*right*), and are referenced to large indifferent electrodes in the external medium. (b): As long as the recording electrode tip remains in the external medium, it measures a zero potential difference relative to the large indifferent electrode (*left lower trace*). When the recording electrode tip enters the internal medium of the muscle fiber (*first vertical arrow*), the potential difference jumps to a negative value of ca. −90 mV, corresponding to the so-called resting membrane potential. As long as the stimulus electrode tip remains in the external medium, rectangular current pulses passed through it (*upper trace*) elicit only small smoothed voltage changes picked up by the recording electrode whether extra- or intracellular (*left upper trace*). When the stimulus electrode tip enters the muscle fiber (*second vertical arrow*), the recording electrode measures deviations from the resting potential corresponding to low-pass filtered versions of the current pulses (Adapted from [7]).

3. Velocity of diffusion depends quantitatively on: Concentration gradient at any time and site: the shallower the gradient, the slower the diffusion. Velocity is faster for the small than the large particles because the former meet less friction in solution than do the latter, therefore the diffusion fronts of both particles will separate over time (this difference being eliminated in equilibrium). The higher the temperature, the faster are the particles' motions, thus diffusion is faster.

Diffusion Potential

The above model considers uncharged particles. What happens when we are dealing with ions? Assume, for example, that the small particles are potassium ions (K^+) and the large particles are organic anions (A^-) such as isethionate, glutamate, aspartate and organic phosphates with a net negative charge. Initially, when the membrane is still in place, there are equal numbers of oppositely charged particles in each compartment, providing electro-neutrality.

After removal of the membrane, diffusion will again set in from right to left, with the small (positive) particles tending to rush away from the large (negative) particles, as long as there is a concentration gradient. However, the two types of particle are not moving independently of each other because positive and negative charges attract each other. There is thus a competition between opposing forces. The concentration gradient tends to separate small from large particles, while the ensuing charge separation tends to re-unite particles in the opposite direction. These two forces create an ►electrochemical equilibrium. (In case the two opposite forces are not of equal magnitude, they create an ►electrochemical gradient).

The two particle types will therefore separate only partially, building up a potential difference between their diffusion fronts; specifically, a ►diffusion potential. It is a vector force, with a direction and a magnitude. The direction is from left (positive) to right (negative), because K^+ ions rush away leftward from the anions.

The diffusion potential has the following characteristics:

1. ►Equilibrium potential. It is an equilibrium potential because it equalizes the chemical force originating in the concentration gradient and acting in opposite direction.
2. Dependence on concentration gradient. The equilibrium potential's magnitude naturally depends on the concentration gradients, it thus disappears when diffusion stops (in thermodynamic equilibrium).
3. Dependence on the difference of ion mobilities. The equilibrium potential's magnitude depends on the difference of ion mobilities in watery solution, u_+ and u_-. If there is no mobility difference, as is the case with K^+ and Cl^-, there is no diffusion potential.

Quantitatively, the last two dependencies are formalized as follows. The magnitude of the diffusion potential, E_D, depends on the concentration gradient as expressed in the ratio c_1/c_2, and on the difference of ion mobilities, u_+-u_-, according to the formula [2]:

$$E_D = \frac{R.T}{z.F} \times \frac{u_+ - u_-}{u_+ + u_-} \times \ln(c_1/c_2), \qquad (1)$$

where R is the general gas constant (1.987 cal K^{-1} mol^{-1} = 8.315 J K^{-1} mol^{-1}), T the absolute temperature in Kelvin (K), z the number of elementary electric charges per molecule (e.g., z = 1 for K^+), and F the Faraday constant (9.648 × 10^4 C mol^{-1}).

In the special case where one ion, say the large anion, cannot diffuse at all, i.e., that its mobility is zero and $u_- = 0$, (1) simplifies to:

$$E_D = \frac{R.T}{z.F} \times \ln(c_1/c_2) \qquad (2)$$

This is the famous *Nernst equation* (named after Walther Nernst, Nobel Prize in Chemistry 1920), which describes the situation of a single sort of ion in free solution. (For a derivation from thermodynamic principles see, e.g., [2,3]. Could it describe a real situation?

Semi-Permeable Membranes

In the container model (above), the two compartments are initially separated by a membrane that cannot be passed by either sort of ion. Now assume that the membrane contains pores, through which only the small K^+ ions, but not the large anions can pass. The K^+ ions will then diffuse through the pores from right to left, but separate from the anions left behind only as much as the evolving diffusion potential allows them to do. This diffusion potential is the equilibrium potential for K^+, E_K. This is a physical situation described by the Nernst equation (2).

The membrane described above is semi-permeable, which has important consequences:

1. The concentration differences are maintained because the large anions cannot diffuse through the membrane and thus, through the diffusion potential, also prevent the small permeable ions from equalizing their concentrations.
2. The diffusion potential is maintained because the concentration differences stay the same.

Semi-permeability can be generated by several mechanisms: Pores (more often called channels) with different diameters let ions pass or not pass, according to their (hydratized) diameters. Electric charges within in the channels prevent the passage of ions of the same charge.

Bernstein's Hypothesis

In 1902, Julius Bernstein [4] proposed that the resting membrane potential, V (Fig. 1b), is a diffusion potential that is determined exclusively by K^+. According to the Nernst equation, V should then be equal to the K^+ equilibrium potential, E_K:

$$V = E_K = \frac{R.T}{F} \times \ln \frac{[K^+]_o}{[K^+]_i}, \qquad (3)$$

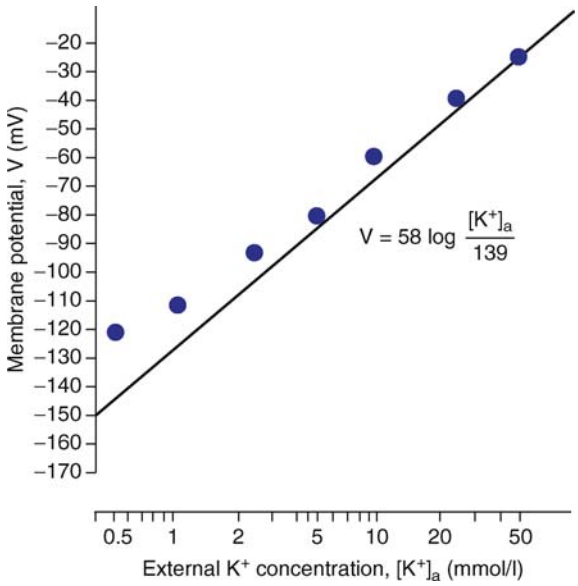
where $[K^+]_o$ is the external and $[K^+]_i$ the internal K^+ concentration.

Bernstein was not able to test his hypothesis experimentally because the required techniques including ►intracellular recording and the related electronics were not yet available. A more recent test [5] is shown in Fig. 2. It was conducted at the frog muscle fiber at a temperature of T = 20° C = 293 K. Inserting values for R and F, and with ln a = 2.3 $\log_{10}$ a, (3) becomes

$$V = E_K = 58 \log_{10} [K_o/K_i] (\text{in mV}). \qquad (4)$$

While the internal K^+ concentration $[K^+]_i$ remains constant at about 140 mM l^{-1}, the external K^+ concentration $[K^+]_o$ can easily be changed, and the resultant theoretical dependence of V on $[K^+]_o$ according to (4) is depicted in Fig. 2 as the solid straight line. The values actually measured experimentally are given as dots. Note that, since the external K^+ concentrations are lower than the internal concentrations, the resultant membrane potentials are negative. At high external K^+ concentrations, the measured resting membrane potentials are fairly well fitted by the solid line, in agreement with Bernstein's hypothesis, but the measurements deviate from the prediction to more positive values at low K^+ concentrations.

M



Membrane Potential: Basics. Figure 2 Dependence of resting membrane potential on extracellular K^+ concentration. Frog sartorius muscle fiber. The resting membrane potential is plotted on the ordinate (in linear coordinates) as a function of extracellular K^+ concentration in logarithmic units on the abscissa. The *straight solid line* shows the theoretical relation according to the Nernst equation, assuming that only K^+ passes through the membrane; the *blue dots* are experimental measurements (Adapted from [5]).

Resting Membrane Potential: Weighted Average of Equilibrium Potentials

The discrepancies between theory and measurement in Fig. 2 suggest that Bernstein's hypothesis cannot fully account for the real situation, and invite an inquiry into the underlying reasons. The starting point of course is to question the central assumption in the hypothesis, which is that K^+ is the only ion able to diffuse through the membrane.

What happens if – in addition to K^+ ions – other ions can diffuse through the membrane as well? First consider another major cation, namely Na^+. The resulting situation can be captured by two limiting cases:

1. Limiting case 1: Membrane permeable solely to K^+ ions $\Rightarrow V = E_K$, as assumed by Bernstein: This makes the cell interior negative with respect to the outside, according to the Nernst equation; in nerve cells E_K is around −70 mV, in muscle cells around −90 mV.
2. Limiting case 2: Membrane permeable solely to Na^+ ions $\Rightarrow V = E_{Na}$; this makes the cell interior positive with respect to the exterior because Na^+ ions would tend to diffuse inward and thus impose their positive charge onto the inside: E_{Na} is around +50 mV.

If, however, the membrane is permeable to both K^+ and Na^+ ions, membrane potential V must lie somewhere between E_K and E_{Na}, which as extreme cases constitute the limits for V: $E_K < V < E_{Na}$. This could account for the positive deviation of the experimentally measured V values (circles) from the theoretical E_Ks (straight line) in Fig. 2.

If the membrane is permeable to both K^+ and Na^+ ions, no cation is at its equilibrium. This has important consequences, as illustrated in Fig. 3. The left column (a–b) explains the situation for K^+ ions and the right column (c–d) for Na^+ ions.

Figure 3a depicts limiting case 1, where $V = E_K$. K^+ is at its equilibrium, and there is thus no net K^+ flow through the membrane. In Fig. 3b, $E_K < V$, implying that the electrical potential does not compensate for the K^+ concentration gradient. Hence, K^+ ions flow out of the cell, following the surplus electrochemical gradient directed outward.

Figure 3c depicts limiting case 2, where $V = E_{Na}$. Na^+ is at its equilibrium, and there is thus no net Na^+ flow through the membrane. In Fig. 3d, $V < E_{Na}$, implying that the electrical potential does not compensate for the Na^+ concentration gradient. Hence, Na^+ ions flow into the cell, following the electrochemical gradient directed inward.

In general, therefore, when $E_K < V < E_{Na}$, there will be net ion currents flowing through the membrane, outward K^+ and inward Na^+ currents.

These qualitative points can be formulated quantitatively. According to ►Ohm's law, the amount of current I carried by each ion through the membrane is proportional to the electric ►conductance g (in units of Ω^{-1} cm^{-2}) of each ion and the ►driving potential, which is the difference between the actual membrane potential V and the equilibrium potential for each ion, as follows:

$$I_{Na} = g_{Na}(V - E_{Na}), \tag{5a}$$

$$I_K = g_K(V - E_K). \tag{5b}$$

Whenever the membrane potential V remains constant during steady state, no net current flows through the membrane. Hence, the two currents I_{Na} and I_K must cancel each other:

$$I_{Na} = -I_K \text{ or } I_{Na} + I_K = 0$$

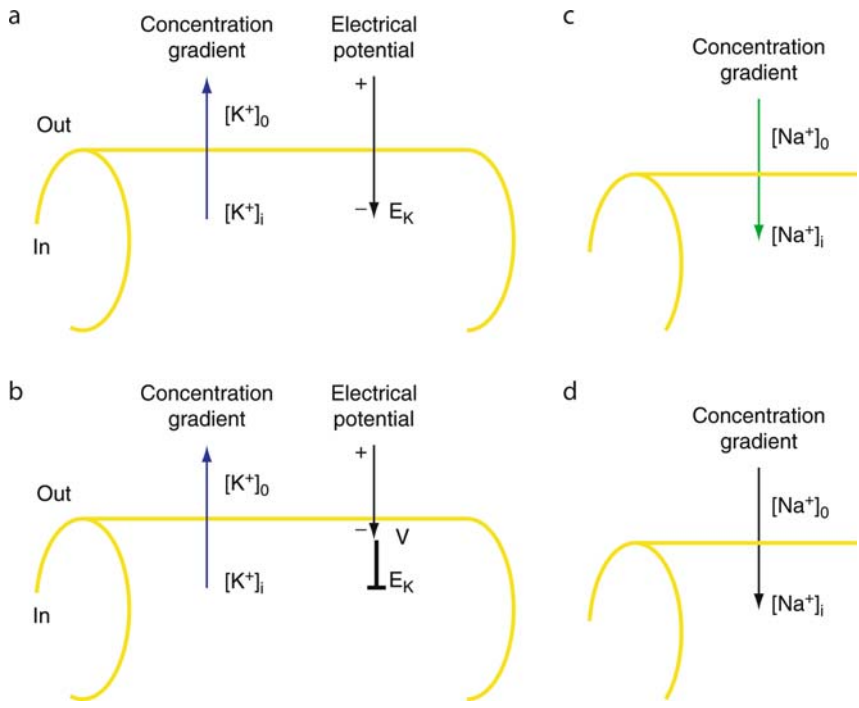
$$g_{Na}(V - E_{Na}) + g_K(V - E_K) = 0$$

Solving for V yields

$$V = \frac{g_{Na}\, E_{Na} + g_K\, E_K}{g_{Na} + g_K} \tag{6}$$

In the extreme,

1. Limiting case 1: for $g_{Na} = 0 \Rightarrow V = E_K$



Membrane Potential: Basics. Figure 3 (a–d) Origin of passive net K^+ and Na^+ ion flows across the cell membrane. The left column (a–b) explains the situation for K^+ ions and the right column (c–d) for Na^+ ions. (a): Situation at $V = E_K$: There is no net K^+ flow because the outward concentration gradient (*left blue arrow headed upward*) is balanced by the inward electrical potential (*right arrow headed downward*) corresponding to the K^+ equilibrium potential, E_K. (b): Situation for $E_K < V$: K^+ ions flow out of the cell, following the surplus electrochemical gradient directed outward. (c): Situation at $V = E_{Na}$. There is no net Na^+ flow because the inward concentration gradient for Na^+ (*left green arrow headed downward*) is balanced by the outward electrical potential difference (*right arrow headed upward*). (d): Situation for $V < E_{Na}$. Na^+ ions flow into the cell, following the huge electrochemical gradient directed inward (Adapted from [6]).

2. Limiting case 2: for $g_K = 0 \Rightarrow V = E_{Na}$

In this Na^+-K^+ system (with conductances for all other ions being zero), the two equilibrium potentials determine the limits, within which the membrane potential V can move.

Other Ions

Equation 6 can be extended to other sets of ions, e.g., by including additional conductances, such as, e.g., for Ca^{2+} and Cl^-. Ca^{2+} with its positive charge and inwardly directed concentration gradient has, like Na^+, a positive equilibrium potential. Chloride with its negative charge and inwardly directed concentration gradient has a negative equilibrium potential. Including Cl^- with Na^+ and K^+ in (6) would yield:

$$V = \frac{g_{Na}\,E_{Na} + g_K E_K + g_{Cl}\,E_{Cl}}{g_{Na} + g_K + g_{Cl}} \qquad (7)$$

Constant Field Equation

The formulations in (6) and (7) use electrical variables, i.e., conductances and potentials, which are related to chemical variables, albeit not in a simple way. The equilibrium potentials are related to concentration gradients via the Nernst equation, and the conductances to permeabilities (in units of cm/s) of the membrane to certain ions [2].

These relationships are expressed in the ▶Goldman-Hodgkin-Katz equation (Alan Hodgkin and Bernard Katz, Nobel Prizes in Physiology or Medicine 1963 and 1970, respectively) or ▶constant field equation, which has the form of a generalized Nernst equation (generalized to several permeant ions) (see, e.g., refs. [2,3,7,8]):

$$V = \frac{R.T}{F} \times \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}, \qquad (8)$$

where P_K is the membrane permeability for K^+ etc. Note that, in the strict sense, the common habit of using the terms conductance and permeability as synonyms is not correct [2].

Conductances as Weighting Factors

Equations (6) and (7) reveal the role of the different ion conductances as weighting factors: Increasing any one

of them drags the membrane potential V closer to the equilibrium potential of the respective ion, and vice versa. V is thus an average of the relevant equilibrium potentials weighted by the conductances.

In most cells, the resting membrane potential is much closer to E_K than to E_{Na} because under resting conditions g_K is much larger than g_{Na} (by a factor of 10–75 in different cells, the latter value applying to frog muscle fibers; see ref. [2]).

Ion Pumps

Because the membrane is permeable to several ions that flow passively down electrochemical gradients, unrestricted ion flow would eventually abolish concentration differences between the inside and outside of the cell and, in consequence, the equilibrium and membrane potentials. In order to prevent this, the cell invests much energy in so-called ►ion pumps that transport the leaking ions back to where they come from, against their respective gradients (►Ion Transport). Such pumps need:

1. Metabolic energy, ultimately supplied by adenosine triphosphate (ATP).
2. Regulation mechanisms, including the sensitivity for particular ions and their concentrations (e.g., inside for Na^+).

The action of the Na^+ pump that expels Na^+ from a cell was first demonstrated by Hodgkin and Keynes [9], who showed that the metabolic poison dinitrophenol (DNP), which deprives energy sources for the Na^+/K^+ pump, depresses cellular extrusion of Na^+. Since then, other laboratories have demonstrated the active role of ion pumps that maintain steady state membrane potential by regulating intracellular Na^+, Cl^-, K^+ and Ca^{2+} concentrations [10].

Sub threshold Membrane Potential Transients are Shaped by cable Properties

Membrane potential changes is response to transmembrane current flow are low-pass filtered as illustrated in Fig. 1, (right side). As long as the stimulus electrode tip remains in the external medium, rectangular current pulses passed through it (upper trace) elicit only small smoothed voltage changes picked up by the recording electrode whether extra- or intracellular (left upper trace). When the stimulus electrode tip enters the axon (second vertical arrow), the recording electrode measures deviations from the resting potential corresponding to low-pass filtered versions of the current pulses. The low-pass filtering is due to cable properties of the nerve or muscle fiber (►Cable Theory).

References

1. Sargent PB (1992) Electrical signaling. In: Hall ZW (ed) An introduction to molecular neurobiology. Sinauer Associates, Sunderland (Mass), pp 33–80
2. Katz B (1966) Nerve, muscle and synapse. McGraw-Hill, New York
3. DeVoe RD, Maloney PC (1981) Principles of cell homeostasis. In: Mountcastle (ed) Medical physiology. Mostby, St Louis, pp 3–45
4. Bernstein J (1902) Untersuchungen zur Thermodynamik der bioelektrischen Ströme. Pflügers Arch ges Physiol 92:521–562
5. Adrian RH (1956) The effect of internal and external potassium concentration on the membrane potential of frog muscle. J Physiol (Lond) 133:631–658
6. Kuffler SW, Nicholls JG (1976) From neuron to brain. Sinauer Associates, Sunderland (Mass)
7. Hille B (1992) Ionic channels of excitable membranes, 2nd edn. Sinauer Associates, Sunderland (Mass)
8. Keener J, Sneyd J (1998) Mathematical physiology. Springer, Berlin Heidelberg New York
9. Hodgkin AL, Keynes RD (1955) Active transport of cations in giant axons from Sepia and Loligo. J Physiol (Lond) 128:28–60
10. DiPolo R, Beauge L (2006) Sodium/calcium exchanger: influence of metabolic regulation on ion carrier interactions. Physiol Rev 86:155–203

Membrane Properties

►Intrinsic Properties of Auditory Neurons

Membrane Resistance

Definition

The membrane resistance is a measure of the impediment to the transmembrane flow of ions. The membrane resistance is infinite in the absence of ionic channels and transporters in the membrane. The membrane resistance decreases as the number of ion channels and transporters increase in the membrane, which permit the transmembrane flux of ions under the driving force of electrochemical gradients.

►Action Potential
►Action Potential Propagation
►Cable Theory
►Membrane Potential: Basics

Memory

►Learning and Motivation

Memory, Long-term

Definition

►Long-term Memory

Memory, Molecular Mechanisms

Toshiya Manabe
Division of Neuronal Network, Department of Basic Medical Sciences, Institute of Medical Science, University of Tokyo, Tokyo, Japan

Definition

Formation of certain kinds of memory (declarative memory) requires functional activation of the hippocampus. Synaptic plasticity of excitatory synaptic transmission, represented by long-term potentiation (LTP), has been regarded as a cellular and molecular model of learning and memory. LTP in the hippocampal CA1 region is induced by the activation of the ►NMDA receptor, which is one type of the ►ionotropic glutamate receptors, and is expressed by the enhancement of basal synaptic transmission mediated by the ►AMPA receptor, which is another type of the ionotropic glutamate receptors. NMDA receptor activation regulates intracellular biochemical processes, resulting in long-lasting modification of synaptic transmission, which has been thought to be a molecular mechanism of memory.

Characteristics

Hippocampal LTP

Fast excitatory synaptic transmission in the central nervous system is mediated mainly by the two ionotropic glutamate receptors, the AMPA receptor and NMDA receptor [1]. Basal synaptic transmission in the pyramidal cell at a membrane potential around the resting membrane potential is mostly mediated by AMPA receptors. When the neurotransmitter glutamate is released from the presynaptic terminal and binds to the AMPA receptor, the receptor channel opens regardless of the membrane potential and permeates monovalent cations. Because the ionic concentration of Na^+ is higher outside the cell, the ionic concentration of K^+ is higher inside the cell, and the membrane potential of the cell is negative at rest, mainly Na^+ ions enter the cell through AMPA receptors, resulting in the depolarization of the cell.

On the other hand, NMDA receptors fail to open at a membrane potential around the resting membrane potential even if glutamate binds to the receptor, because external Mg^{2+} ions block the ionic channel of the receptor (Mg^{2+} block). However, when the synapse is repetitively activated at high frequencies and the postsynaptic cell sufficiently depolarizes, the Mg^{2+} block is released and Ca^{2+} ions as well as Na^+ ions enter the postsynaptic cell through the NMDA receptor channel [1]. Thus, the NMDA receptor functions as a coincidence detector for presynaptic and postsynaptic activities.

The increased intracellular Ca^{2+} then activates Ca^{2+}-dependent biochemical processes such as the calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C cascades, which further promotes the process of LTP expression. The final expression mechanism for LTP is thought to involve an insertion of active intracellular AMPA receptors into the synaptic site and/or a long-lasting increase in the conductance of AMPA receptor channels [2].

LTP and Memory

LTP has been thought to be involved in memory formation. In Morris water maze task, in which the ability of spatial memory in rats and mice can be assessed, the blockade of LTP by intraventricular injection of an NMDA receptor antagonist impairs the spatial learning in the rat [3]. It has also been reported that the genetic deletion of the NR2A subunit of NMDA receptors in the mouse causes the reduction of hippocampal LTP and the impairment of learning abilities in Morris water maze task [4]. Furthermore, overexpression of the NR2B subunit has been reported to enhance learning and memory in the mouse [5]. Thus, the NMDA receptor, which is essential for LTP induction, plays a pivotal role in memory formation.

There are many reports showing the involvement of various intracellular signaling molecules downstream of NMDA receptor activation in learning and memory. The first papers in which LTP of knockout mice is examined suggest that CaMKII is essential for LTP induction in the hippocampal CA1 region [6] and that spatial memory of the mutant mice is severely impaired [7]. So far, many intracellular signaling molecules, such as protein kinase C, mitogen-activated protein kinase and protein kinase A, have been shown to be involved in both LTP and memory formation.

References

1. Ozawa S, Kamiya H, Tsuzuki K (1998) Glutamate receptors in the mammalian central nervous system. Prog Neurobiol 54:581–618
2. Lynch MA (2004) Long-term potentiation and memory. Physiol Rev 84:87–136
3. Morris RGM, Anderson E, Lynch GS, Baudry M (1986) Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319:774–776

4. Sakimura K, Kutsuwada T, Ito I, Manabe T, Takayama C, Kushiya E, Yagi T, Aizawa S, Inoue Y, Sugiyama H, Mishina M (1995) Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor ε1 subunit. Nature 373:151–155
5. Tang YP, Shimizu E, Dubé GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ (1999) Genetic enhancement of learning and memory in mice. Nature 401:63–69
6. Silva AJ, Stevens CF, Tonegawa S, Wang Y (1992) Deficient hippocampal long-term potentiation in α-calcium-calmodulin kinase II mutant mice. Science 257:201–206
7. Silva AJ, Paylor R, Wehner JM, Tonegawa S (1992) Impaired spatial learning in α-calcium-calmodulin kinase II mutant mice. Science 257:206–211

Memory, Short-term

Definition

►Short-term Memory

Memory: Eidetic, Photographic

Definition

The ability to store perceived events. Eidetic memory refers to motor programs that help to orient in familiar environments even when no sensory input is present (people may find light switches in familiar dark rooms). If the storage results in a representation of space similar as in a photograph, the term photographic memory is used.

Memory and Dementia

Murray Grossman
Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Definition

Memory is the acquisition and mental representation of information. ►Dementia is a progressive neurodegenerative disease that compromises neurologic functioning in individuals who have attained adult levels of intact cognition. There are many kinds of memory, and each of these has a different fate in patients with the most common form of dementia, ►Alzheimer's disease (AD). The distinct ways in which these different forms of memory are compromised depends in large part on the neuroanatomic distribution of disease in AD.

Characteristics

►Episodic memory is the ability to learn a new event consciously and then to recall this specific event purposefully and at will [1]. This form of memory depends on the hippocampus and intimately related structures in the medial temporal lobe. The earliest evidence of histopathologic disease in AD is the accumulation of neuritic plaques composed of amyloid and neurofibrillary tangles consisting of paired helical filaments of tau in the hippocampus, and the earliest clinical feature of AD thus is impaired episodic memory. Indeed, a prodromal Alzheimer's condition known as amnestic Mild Cognitive Impairment (aMCI) is defined clinically as an isolated deficit of episodic memory.

Impaired episodic memory is commonly demonstrated by a list-learning task. On this task, a supraspan list of words (a list of 10–15 words that is longer than can be repeated in one try) is presented for learning, and as many words as possible are repeated by the patient. This sequence of list presentation and repetition is repeated for several learning trials. Subsequently, a brief period filled with another task is administered to prevent rehearsal of the words, then the list is recalled. Although we do not fully understand how the hippocampus and medial temporal structures accomplish this task, one important theory proposes that a to-be-remembered event is bound to its context or other associated attributes of the event. On a list-learning task, this is the specific list of words bound to its recent presentation as part of the memory test. Healthy adults typically demonstrate learning by repeating a longer list on each successive learning trial. Moreover, despite the filled period that prevents rehearsing the list, healthy adults can recall most of the stimulus words. In AD, by comparison, there is impaired learning and impaired recall. AD patients may repeat only three or four words during a learning trial, and they do not show learning by repeating more words on subsequent trials. Moreover, AD patients typically recall no words following the brief delay. Patients with aMCI and mild AD may be able to recognize some of the words in a multiple-choice format. A similar pattern of findings is evident regardless of the stimulus modality (e.g. aural or visual) or material (e.g. words or geometric designs). Imaging studies directly relate this episodic memory deficit to hippocampal atrophy or reduced hippocampal metabolism in AD through correlation studies, while functional imaging that monitors brain activity during episodic memory shows reduced hippocampal activation in AD patients compared to healthy adults [2].

►Remote Memory is the long-term representation of information that was learned months to years earlier [3]. This may include factual knowledge or personal autobiographical knowledge. It often seems that remote memory is relatively preserved in AD, since these patients frequently enjoy reminiscing about events that occurred in their early years. However, careful examination demonstrates that remote memory also may be impaired in AD [4]. These are at least two possible explanations for this deficit. One account, paralleling the mechanism for episodic memory mediated by the hippocampus, suggests that impaired remote memory involves difficulty retrieving facts bound to a specific, remote period of time. However, functional neuroimaging studies of healthy adults suggest that the hippocampus may not be activated to retrieve information from remote memory. An alternate possibility is that the neural representation of remote memories is degraded as the disease in AD spreads from the hippocampus to other cortical areas in the temporal lobe and the frontal lobe.

►Semantic Memory is the representation of the meaning of words, objects, actions, thoughts, and the like [5]. Semantic memory is also impaired in up to 50% of patients with AD. Like episodic memory and remote memory, one theory of semantic memory difficulty in AD is that hippocampal disease interferes with this form of memory. This may be because the hippocampus is necessary for binding features into a meaningful category of knowledge, or the hippocampus mediates retrieving semantic information form its long-term cortical representation. However, these accounts would not explain the dissociation between episodic memory difficulties present in virtually all patients with AD, and the semantic memory deficit that is present only in a subset of these patients. An alternate possibility is related to the frequent correlation of impaired semantic memory with cortical atrophy in the posterolateral temporal and dorsolateral frontal lobe. It is unlikely that temporal and frontal regions are the neural repository for all semantic knowledge. Instead, the semantic memory deficit associated with temporal and frontal disease may be related to a categorization process that assembles information that is widely represented throughout the cortex into a meaningful concept. Consistent with this possibility, the temporal and frontal regions consist of multimodal association cortex, where there is a connectivity pattern involving reciprocal projections with all unimodal association cortices. Functional neuroimaging studies of semantic categorization in healthy adults show activation of these areas, and this activation is reduced in AD [6].

►Working Memory is a form of short-term memory that may supplement many of the other forms of memory described above [7]. For example, retrieval from episodic, remote or semantic memory may benefit from working memory that maintains the to-be-remembered target in an active mental state during searches and decision-making components of these forms of memory. Working memory also may contribute to other processes such as understanding a long and grammatically complex sentence, or weighing all relevant facts during mental reasoning tasks. Much evidence indicates that working memory is impaired in AD. This appears to be related to disease in prefrontal cortex and inferior parietal cortex, according to correlation studies of cortical atrophy in AD.

►Implicit Memory is another form of memory for acquiring new information [8]. Unlike the kinds of memory described above, implicit memory occurs without conscious awareness. This may take the form of a habit that is acquired through repeated performance of a particular activity, or repeated exposure to a category of similar materials that subsequently biases an individual towards accepting similar appearing materials as members of the same category. Implicit memory appears to be relatively preserved in AD [9]. Thus, patients with AD are able to learn a new habit and a new perceptual category such as a dot array when presented implicitly. Recent work also suggests that AD patients can learn a meaningful category when presented implicitly. Functional neuroimaging studies in healthy adults suggest that implicit memory tasks involve the caudate as well as other cortical association regions. Functional neuroimaging studies of patients with AD during implicit memory challenges show some activation of caudate and cortical association regions. The hippocampus is not activated in AD, ad this may account for the minor deficit in implicit memory tasks in AD relative to age-matched controls.

Memory difficulty in non-Alzheimer's forms of dementia is also well documented [10]. In semantic dementia, for example, there is profound impairment of semantic memory. In this condition, comprehension of words, objects, actions and abstract concepts is significantly compromised. This is related to their temporal lobe disease. In frontotemporal dementia presenting with a disorder of social comportment and personality, working memory is regularly compromised. This appears to be due to their prefrontal disease. In Parkinson's dementia, habit learning is impaired due to disease affecting the caudate.

Multiple forms of memory difficulty are evident in AD. While we typically think of an episodic memory deficit as the *sine qua non* of AD, difficulty with remote memory, semantic memory, and working memory also are regularly compromised in AD. More surprisingly, it appears that some forms of memory are relatively preserved in patients with AD, including habit learning and implicit memory.

Acknowledgement

This work was supported in part by NIH (AG15116, AG17586; NS44266; NS53488) and the Dana Foundation.

References

1. Eichenbaum H (2004) Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron 44:109–120
2. Golby A et al. (2005) Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. Brain 128:773–787
3. Nadel L, Samsonovich A, Ryan L, Moscovitch M (2000) Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10:352–368
4. Fama R et al. (2001) Remote memory for public figures in Alzheimer's disease: relationships to regional cortical and limbic brain volumes. J Int Neuropsychol Soc 7:384–390
5. Koenig P, Grossman M (2007) Neural basis of semantic memory. Cambridge University Press, Cambridge, UK
6. Grossman M et al. (2003) Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. Brain 126:292–311
7. Baddeley AD, Sala Della S (1996) Working memory and executive control. Philos Trans R Soc Lond B Biol Sci 351:1397–1403
8. Squire LR, Knowlton BJ (1995) Learning about categories in the absence of memory. Proc Natl Acad Sci USA 92:12470–12474
9. Fleischman DA et al. (2005) Implicit memory and Alzheimer's disease neuropathology. Brain 128:2006–2015
10. Libon DJ et al. (2007) Patterns of neuropsychological impairment in frontotemporal dementia. Neurology 68:369–375

Memory and Sleep

Shigenobu Shibata
Division of Physiology and Pharmacology, School of Science and Engineering, Waseda University, Tokyo, Japan

Definition

Memory and sleep refer to the role of sleep in memory processing

Characteristics

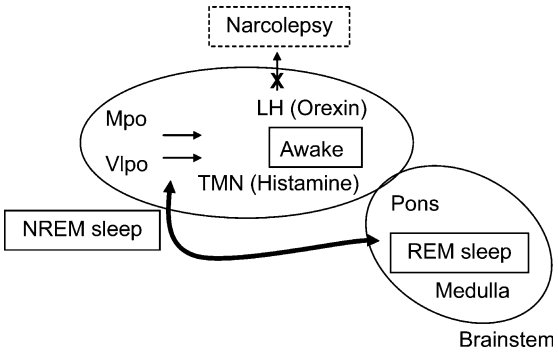
A large number of studies offer substantial evidence supporting the role of sleep in what is becoming known as sleep-dependent memory processing [1]. Many reports, ranging from studies on cellular and molecular processes in animals to behavioral studies in humans, have provided a wealth of converging evidence that sleep-dependent mechanisms of neural plasticity lead to the consolidation of learning and memory across a range of animal species. There are a number of stages of memory consolidation, and each stage uses distinct brain processes to perform separate functions. When combined with multiple memory systems such as procedural or declarative memory and the different stages of sleep such as ►REM or ►NREM sleep, one is faced with a truly staggering number of possible ways that ►sleep cycle might affect memory consolidation. Recent findings show that sleep deprivation can impair learning and memory for both motor procedural and declarative memory systems. It is only by asking whether a specific stage of sleep affects a particular aspect of memory processing for a given type of memory that one can begin to ask scientifically answerable questions concerning sleep-dependent memory processing. There remain numerous important and unanswered questions regarding sleep-dependent memory consolidation. While procedural learning, both perceptual and motor, is clearly enhanced by post-training sleep, the forms of declarative memory that are similarly affected are uncertain. Contribution of sleep to the processes of memory stabilization, enhancement, reconsolidation, integration, translocation, and active erasure require further elucidation. The actual processes within sleep that effect consolidation are almost completely unknown; however, many papers allow us to draw conclusions. Both REM and NREM sleep seem necessary for learning and memory: thus, for efficient consolidation of both (declarative) knowledge and (procedural) skills, the biggest risk can come from sleep loss or fragmentation.

Different Sleep Stages: REM and NREM Sleep

Sleep can be defined as a state of immobility and greatly reduced responsiveness distinguishable from coma or anesthesia by its rapid reversibility. An additional defining characteristic of sleep is that when it is prevented, the body tries to recover the lost amount, termed "rebound." Sleep is the state of natural rest observed in humans and throughout the animal kingdom in all mammals and birds, and in many reptiles, amphibians, and fish. Two types of sleep have been defined based on the measurement of eye movement during slumber: rapid eye movement (REM) and non-rapid eye movement (NREM). Each type has a distinct set of associated physiological, neurological, and psychological features.

In NREM sleep, the body is active and the brain inactive, and there is relatively little dreaming. NREM is comprised of four stages according to the "The American Academy of Sleep Medicine (AASM)"; stages1 and 2 are considered the light sleep stages, and 3 and 4 the deep sleep stages, differentiated solely by electroencephalography (EEG). NREM accounts for 75–80% of total sleep time in normal human adults.

Sleep-activated neurons, which have been discovered in the preoptic and basal forebrain regions [2], are maximally active during NREM sleep. When



Memory and Sleep. Figure 1 Schema of sleep-regulating neuronal populations. Mpo, median preoptic area; Vlpo, ventrolateral preoptic area; LH, lateral hypothalamus; PH, posterior hypothalamus; NREM sleep, non-rapid eye movement sleep; REM sleep, rapid eye movement sleep.

stimulated, these cells will induce the NREM state. In contrast, damage to these regions greatly reduces sleep. The neurons in these brain regions give inhibitory projections to aminergic, cholinergic, and orexinergic neurons in the forebrain and brainstem. GABAergic inhibitory projections from preoptic regions might be important in inhibiting orexin neurons, which are thought to be involved in sleep regulation, during sleep (Fig. 1).

In humans, the duration of REM sleep episodes progressively increases throughout the sleep period and is maximal just prior to the expected time of awakening. For example, the initial REM sleep period may last only 5–10 min, whereas the last REM period before awakening may last for more than 25 min. REM amounts are maximal near the nadir of the brain and the core body temperature cycles. REM sleep phenomena can be generated by the isolated brainstem region, in particular the pons and adjacent midbrain [2]. Although an animal in REM sleep is behaviorally asleep, brain metabolic and neuronal activity are high, respiration and heart rate are variable, rapid eye movement and twitches of the extremities occur, and males frequently develop erections. Several theories have suggested that REM state, and its associated ►periodic brain activation, plays a role in localized recuperative processes and in emotional regulation during sleep. The brain areas where REM sleep neural activity is higher than wakefulness consist of the anterior cingulated cortex, the amygdala and the limbic-paralimbic regions, and the associated visual areas [3].

Each sleep cycle (NREM sleep + REM sleep) lasts about 90 min. Most people repeat this cycle four times a night, for a total of approximately 6–8 h of sleep. REM sleep time elongates with each repeating cycle, and a comfortable wake-up is best just after the end of a REM sleep period. The alternation between NREM and REM sleep is the outcome of a balanced action based on the cyclic function of the brainstem and forebrain structures.

Sleep and the Different Memory Systems: Declarative and Non-Declarative Procedural Memory

Human memory has been subjected to several different classification schemes, the most popular being based on the distinction between declarative and non-declarative (procedural) memory. Non-declarative memory includes procedural memory ("knowing how") learning of actions, habits, and skills, as well as implicit learning. This type of memory system appears to be less dependent on medial temporal lobe structures. Declarative memory is comprised of the consciously accessible memories of fact-based information. Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, including the hippocampus, a structure that is thought to form a temporally ordered retrieval code for neocortically-stored information.

The evidence for sleep-dependent consolidation of declarative memories is less consistent. Many earlier experiments investigated the effects of classic tests of declarative memory (verbal learning tasks) on REM sleep changes following training. More recently, verbal (recall of paired–associated word lists) and non-verbal declarative memory were investigated through a subject's ability to recall spatial locations in memory rotation tasks, and findings showed improved recall spanning the early sleep interval, rather than late sleep interval, and the corresponding intervals of wakefulness. While the results were taken to mean that in addition to REM sleep, NREM also exerted a selective facilitation of declarative memory consolidation in humans, they may actually just reflect the nature of the word pairs used: unrelated word pairs such as dog-leaf for earlier and related pairs such as dog-bone for later. Other findings on declarative memory suggest that following initial practice of a numeric sequence problem-solving task, a night of sleep can trigger insight into a hidden rule(?) and thus improve performance strategy the following morning.

In contrast to the declarative memory system, there have been robust and consistent findings that across a wide variety of functional domains, including visual, auditory and motor systems, procedural memory relies on sleep. The results from many reports seem to support the hypothesis of sequential processing of memories during sleep stages, suggesting that memory formation is promoted by NREM and then consolidated by REM sleep. Accordingly, the amount of sleep-dependent improvement on a perceptual learning task is linearly correlated with the amount of NREM during the first quarter of the night and with the amount of REM sleep in the last quarter.

The beneficial effect of sleep on procedural memory has also been investigated through motor skill learning tasks. A night of sleep can trigger significant performance improvements in speed and accuracy on a sequential finger-tapping task, while equivalent periods of awake time provide no significant benefit. These sleep-dependent benefits appear to be specific to both the motor sequence learned and the hand used to perform the task. Furthermore, overnight learning gains seem to correlate with the amount of stage 2 NREM sleep. A complex procedural motor adaptation task requiring hand–eye coordination was introduced. The extent of the local parietal lobe increase in slow-wave activity in the first 90 min of sleep strongly correlated with subsequent performance enhancement (learning) observed the next day, showing a close relationship between local EEG activity and subsequent regional slow-wave activity homeostasis.

It has been shown that periods of awake time following training on a synthetic speech recognition task result in a degradation of task performance, while a subsequent night of sleep can restore performance to post-training levels. Hence, it appears that there is a process of sleep-dependent consolidation capable of reestablishing previously learned complex auditory skill memories. Faced with such consistent and reproducible findings on sleep-dependent visual, auditory, and motor skill learning, it seems difficult to refute the claim that sleep is necessary for the consolidation of human procedural skills, the restoring of previously decayed memory traces, and the triggering of additional learning.

On the whole, recent findings have generally been interpreted as supportive of the notion that early night NREM and late night REM play a fundamental role in the consolidation of procedural memories in humans, while NREM-rich sleep seems to have facilitating effects for declarative memories.

Studies with monoamine oxidase inhibitors and other REM suppressing antidepressants have proven that REM sleep plays no role in memory consolidation, and thus the argument arose that such REM suppressants could be taken for years with no deleterious effects on memory. However, there are some arguments for the reemergence of REM sleep with chronic drug treatment and REM rebound with drug withdrawal.

Sleep-Dependent Brain Plasticity

Memory formation depends on brain plasticity-lasting structural and/or functional neuronal changes in response to stimuli from an individual's experiences. If sleep is to be considered a critical mediator of memory consolidation, then evidence of sleep-dependent plasticity would greatly strengthen this claim. Indeed, there is now a wealth of data describing sleep-dependent brain plasticity at a variety of different levels thanks to neuron-imaging studies, electrophysiological studies, and cellular molecular studies in both animals and humans, complementing evidence of sleep-dependent changes in behavior. Findings of sleep-dependent plasticity in the visual cortex of the rat suggest that REM sleep, in conjunction with visual stimuli, modulates the initial course of visual cortex maturation. At the molecular level, administration of protein synthesis inhibitors to rats during REM sleep windows, a time thought to be critical to consolidation, prevents behavioral improvement following the sleep period. Thus, learning and memory are dependent on processes of brain plasticity, the same processes that must also mediate sleep-dependent learning and memory consolidation. Many examples of such plasticity during sleep have now been reported, several of which were specifically induced by experiences that took place during awake time.

Sleep and Academic Performance

As sleep has a relevant role in facilitating learning and memory processes, and since sleep deprivation and/or fragmentation usually impair these functions, the effect of sleep patterns and schedules on academic performance is an area of interest. In terms of an indirect link between sleep and academic performance, it was shown that students with more regular sleep-wake patterns (shorter sleep latency, fewer night awakenings, later school rise times, earlier rise times on weekends) reported a higher grade point average, whereas students with lower grades reported increased daytime sleepiness, also as a consequence of less sleep at night [4].

Orexins, Narcolepsy and Memory

Endogenous ►orexin, also referred to as hypocretin, may be involved in multiple functions including arousal, the sleep-wake cycle, sleep disorders, and learning and memory. Orexin is the common name given to a pair of highly excitatory neuropeptide hormones. The two related peptides (orexin A and B), are produced by cleavage of a single precursor protein. Although these peptides are produced by a very small population of cells in the lateral hypothalamus [5], they send projections throughout almost the entire brain. The orexin system was initially suggested to be involved in the stimulation of food intake, and later in sleep regulation because of dysfunctional orexin and its association with the sleep disorder ►narcolepsy. Orexin neurons strongly excite various brain nuclei with roles in wakefulness and the dopamine, norepinephrine, histamine, and acetylcholine systems.

Orexin A enhances normal long-term potentials (LTP) in medial perforant path – dentate granule cell synapse in the hippocampus. Given the well-documented involvement of monoaminergic and cholinergic neurotransmitter systems over a wide range of memory processes,

memory impairments might accompany the sleep symptoms seen in narcolepsy.

The main characteristic of narcolepsy is an overwhelming excessive daytime sleepiness, even after an adequate night of sleep. A person with narcolepsy is likely to become drowsy or fall asleep, often at inappropriate times and places. Daytime naps can occur several times a day. Drowsiness may persist for prolonged periods of time, and nighttime sleep may be fragmented by frequent awakening.

In narcolepsy, the order and length of NREM and REM sleep periods are disturbed, with REM sleep occurring at sleep onset instead of after a period of NREM sleep. Thus, narcolepsy is a disorder in which REM sleep appears at an abnormal time. When narcolepsy patients were compared to matched control subjects on a range of tasks that measured attention, memory and executive control, impairments were only observed during the attention and executive function tasks, which involved higher demands on inhibition or task management abilities. The relatively routine memory and attention tasks yielded intact performances in the narcolepsy patients. Thus, the overall pattern of results indicates an executive control deficit that occurs with narcolepsy that might be related to a reduction of available cognitive processing resources because of the need for continuous allocation of resources toward monitoring and maintaining vigilance.

References

1. Stickgold R, Walker MP (2007) Sleep-dependent memory consolidation and reconsolidation. Sleep Med 8:331–343
2. Siegel (2005) Clues to the functions of mammalian sleep. Nature 437:1264–1271
3. Halasz P, Terzano M, Parrino L, Bodizs R (2004) The nature of arousal in sleep. J Sleep Res 13:1–23
4. Curcio G, Ferrara M, De Gennaro (2006) Sleep loss, learning capacity and academic performance. Sleep Med 10:323–337
5. Ohno K, Sakurai T (2008) Orexin neuronal circuitry: role in the regulation of sleep and wakefulness. Front Neuroendocrinol 29(1):70–87

Memory Capacity

Definition

Maximum ratio between the number of patterns stored in an associative memory network and the number of units of that network, above which the stored patterns are not stable states of the network.

►Associative Memory
►Neural Networks

Memory Consolidation

Definition

The time-dependent process of fixation of new memory traces into stable long-term memory.

►Emotional Learning/Memory

Memory Distortion

Daniel M. Bernstein[1], Elizabeth F. Loftus[2]
[1]Department of Psychology, Kwantlen University College, Surrey, BC, Canada
[2]Departments of Psychology and Social Behavior, Criminology, Law and Society, Cognitive Sciences, University of California, Irvine, Irvine, CA, USA

Synonyms

False memory; Memory illusions

Definition

Memory distortion refers to a memory report that differs from what actually occurred.

Characteristics

Memory's fate is determined by factors present at encoding (when the memory is first recorded), storage (how and where the memory is represented in the brain), and retrieval (when the memory is reported). The level of attention paid to the original event, the time that passes after the original encoding, the match between encoding and retrieval contexts, and the presence of competing and interfering information in memory are but a few of the factors that determine memory accuracy. Memory records experiences. The recording includes sensory information like sight, sound and touch, as well as emotions, thoughts, and feelings about the experience. These details are stored in a distributed fashion throughout the brain, making it difficult if not impossible to localize any particular memory trace in the brain [1].

The British psychologist, Sir Fredrick Bartlett [2] demonstrated the constructive nature of memory. Bartlett examined the fate of memory, and concluded that memory undergoes typical transformation over time including omissions, deletions and distortions. In one of Bartlett's most famous experiments, British subjects read a Native American folktale called the War of the Ghosts in which a battle occurs between two warring tribes. Using a

method called serial reproduction (akin to the child game called "telephone"), one subject would recall the story in as much detail as possible. Another subject would read the first subject's account of the story and then try to recall it, followed by additional subjects reading the account of their immediate predecessor and trying to recall it. This method revealed that memory for the original story undergoes massive distortion after very few repetitions.

Memory Distortion Techniques

Many techniques have been shown to distort memory. A partial list of techniques includes misinformation, outcome information, semantic relatedness, suggestion, imagination, and more subtle manipulations such as subliminal repetition and unscrambling. Each of these techniques reveals the inherent fallibility of memory.

In the early 1970s, researchers began to explore the effects of misleading post-event information on memory for events. In one study, subjects viewed a simulated vehicle-pedestrian accident. Some subjects watched as a car approached an intersection and stopped at a stop sign. The car then turned right and hit a pedestrian who was crossing the street. After viewing the accident, some subjects were asked a question that suggested it was a yield sign. Later subjects had to report on the sign they had actually seen, and many subjects who received the misinformation incorrectly recalled seeing the opposite sign. In related work, researchers showed how the wording of a question during an eyewitness interview affects memory for what was seen. For example, subjects who viewed an accident on film and were asked, "About how fast were the cars going when they smashed into each other?" reported greater speed than did subjects who were asked, "About how fast were the cars going when they hit each other?" Additionally, those who were asked the "smashed" question were more likely to report having seen broken glass than subjects who were asked the "hit" question, even though no broken glass had appeared. Thus, simple word choices can distort memory for details of an event [3].

In a related paradigm involving post-event information, subjects predicted the outcome of an event that had not yet occurred. After finding out the true outcome, they were asked to remember what they originally predicted. For example, prior to Nixon's 1972 visit to China and the Soviet Union, subjects were asked to provide probability estimates for various outcomes: President Nixon will meet Chairman Mao; President Nixon will declare the trip a success. Even when told to ignore the true outcome, most subjects adjusted their original estimates to concur with the actual outcome, thereby claiming that they "knew it all along." This hindsight bias has been demonstrated using a variety of materials and sensory modalities, including verbal, visual, and even gustatory judgments [4]. Like the misinformation effect, hindsight bias is a form of memory distortion that is influenced by outcome information that conflicts directly with one's original memory.

Other techniques show how easy it is to distort memory for details of prior experience. For example, consider the following set of words: bed, rest, awake, tired, dream, wake, night, blanket, pillow. Most people who hear or read a similar list will mistakenly recall hearing or seeing the word, "sleep" in the original list. The fact that the words in the list are all semantically related to the critical word, "sleep" causes the vast majority of people to misremember [5]. Semantic relatedness also underlies another common form of memory distortion called ►conjunction errors. These errors occur when people fuse together in memory aspects of an event or experience. For example, subjects who read the words, blackboard and jailbird often mistakenly remember having read the conjunction word, blackbird. Again, these examples demonstrate how easy it is to distort people's memory for details of a prior experience [6].

But is it possible to distort memory in a larger way, namely by making people believe that they experienced a whole event in the past that never occurred? The answer is, "yes." Simply by suggesting to adults that they had experienced a particular event in their childhood, like being lost in a shopping mall for an extended period of time or being hospitalized overnight for an ear infection, investigators have created ►false memories for whole events in their subjects' minds. In such studies, researchers often use a form of strong suggestion where they might tell a subject that a family member reported the event in question or that the subject's dreams suggest that she had a particular unpleasant experience as a child. For instance, researchers might tell the subject that "most" people under the age of five have been attacked by a dog. The purpose of such suggestive techniques is to increase the plausibility of the false event. Researchers might also ask their subjects to imagine the false event in detail: "Even if you do not recall the event, just try to imagine what it was like. Where were you when the event occurred? Who were you with? What were you doing? How did it make you feel?" Imagination serves to imbue the false memory with sensory details, and often leads people to adopt the false memory as part of their autobiography [3].

In contrast to the more obvious forms of suggestion that distort memory for the past, memory can be distorted by more subtle means. Consider the phenomenon called unconscious plagiarism, in which a person inadvertently claims ownership of an idea that belongs to someone else. There are numerous examples of unconscious plagiarism, including cases of accusations against high-profile individuals like the writer, Helen Keller and the singer, George Harrison. Unconscious plagiarism relates to priming in that the information or idea, once heard or read from another source, may return to one's memory

later without the person realizing that the information was encountered before. Another related form of memory distortion, called unconscious transference, occurs when an eyewitness to a crime adamantly declares that a certain person was the "one" who committed the crime simply because this certain person looks familiar. For example, the memory researcher, Donald Thomson, was accused of rape after appearing on live television in Australia. The victim in this case was raped while watching the television program featuring Dr. Thomson. Thus, the fact that the victim had seen Thomson's face before, albeit in another context that was linked to the rape, was enough to lead her to believe that Thomson was the rapist.

Given the variety of memory distortions that have been observed and created in laboratory experiments, what is the evidence that memory distortion also happens in the real world? Unfortunately, all-too-meaningful therapists, seeking to help a client, may encourage their client to plumb the depths of memory for clues that might help explain the client's problems. Although potentially therapeutic, this tactic sometimes backfires: Therapists have been known to implant false memories in their clients, often using many of the techniques that we have discussed here, like suggestion and imagination. These implanted false memories have resulted in innocent people being sent to prison, and have caused lasting and irrevocable damage to family unity and trust. Related to this issue of false memory, is the issue of repressed memory. ►Repressed memory refers to the hypothesized notion that the mind banishes traumatic experiences from conscious awareness due to the memory's threatening nature. This memory, once repressed, may return to consciousness at some later point in a person's life. The resulting memories are thought to be accurate in detail, and the processes involved different from ordinary forgetting and remembering. Although there is clear experimental evidence that false memories exist, there is at present no direct experimental evidence for repressed memories.

By now, it should be clear that memory is malleable. Given the variety of techniques that can and have been used to distort memory, one might ask how these techniques work.

Proposed Mechanisms

Several theories have been proposed to explain the formation of false memories and memory distortion. We focus here on three of these theories. According to the *Source Monitoring Framework*, people routinely monitor their memory for accuracy. ►True memories tend to elicit more sensory and contextual detail, for example, "It was a rainy afternoon when I saw the accident. I remember that my jacket was drenched and my shoes squished when I walked. The car turned at the intersection and hit the pedestrian in the crosswalk." False memories, however, can also contain sensory detail. This makes it particularly difficult to distinguish between true and false memories. The Source Monitoring Framework argues that techniques such as imagination serve to create memory traces that sometimes can be distinguished from actual experiences stored in memory. The problem is that over time it becomes harder to monitor the origin of information coming from different sources like imagination, perception and action, resulting in source monitoring errors and false memories [7].

Another theory, related to source monitoring, involves what is called *Familiarity Misattribution*. According to this theory, techniques like suggestion, imagination, repetition and unscrambling serve to increase the fluency with which a person processes an event or experience. By fluency, we mean that the experience is processed more quickly. Consider imagination and repetition. Both techniques serve to prime an individual to process an event or experience more quickly. After imagining an event in detail, the event will be processed more quickly and fluently when the person subsequently thinks about it. In this way, the event seems to "spring" to mind. Similarly, repetition speeds subsequent processing. For example, if I present the word "window" to you, and then sometime later ask if you ever broke a window as a child, you will process the word "window" more quickly the second time you see it. This means that you will read and understand the word "window" faster than if you had not seen that word presented earlier. Just like with imagination, we tend to interpret the enhanced processing fluency as familiarity. So, the event, "broke a window" might now feel somehow familiar to you. If you fail to realize that the event feels familiar because you saw the word, "window" earlier, then you may mistakenly claim that you broke a window as a child [8].

One final theory that we discuss, called *Fuzzy-trace theory,* divides memory into two types of traces. Verbatim traces store sensory information, while gist traces store semantic information. Verbatim-based memory relates to detailed recollection of past experience, while gist-based memory relates to familiarity for past experiences [9]. Both types of memory traces can produce true and false memory; however, true memory is more often associated with verbatim traces, while false memory is more often associated with gist traces. Returning to our memory-distortion techniques, the suggestion that one was lost in the mall as a child leads to many different associations with malls. The person receiving this suggestion might begin to think about different, actual experiences that she did have in malls as a child. She might even think about how she would feel if she were lost in the mall. These associations, thoughts, and emotions would be stored as gist-based memory traces. When later asked about the event in question "were you ever lost in the mall as a child," the event will likely feel familiar. If our imaginary subject fails to realize the source of this familiarity – that

last week the experimenter told her that she had been lost in the mall as a child – she will mistakenly come to believe that the event actually occurred.

Thus, source monitoring, familiarity misattribution and fuzzy trace theory all posit that people routinely monitor their memory for accuracy. Failure to distinguish among potential sources (e.g., I imagined the broken glass, I saw the broken glass, I only heard the broken glass) can result in memory distortion.

Memory Distortion and Brain

Much work over the past decade has focused on the neural regions supporting true and false memory. In search of a neural signature of true and false memories, researchers have employed a variety of neuropsychological, neuroimaging, and electrophysiological techniques. These include lesion studies, Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), electroencephalogram (EEG), event-related potentials (ERPs), and more recently transcranial stimulation, and near-infrared spectroscopy. A consensus is beginning to emerge that true and false memories activate different brain regions, leading some investigators to claim that they have located a neural signature of false memories. Specifically, the medial temporal lobe has been implicated in false recognition, while the prefrontal cortex has been implicated in memory monitoring errors [7,10]. Despite these advances, some studies have also found that true and false memories activate similar brain regions, including prefrontal cortex, parietal cortex and medial temporal lobe. There is at present growing excitement in the field of cognitive neuroscience. As this field advances, it should soon be possible to distinguish true from false memories reliably and consistently by observing brain activation. Someday it may even be possible to determine the veridicality of one's memory for an individual event simply by looking at the person's overall pattern of brain activity.

References

1. Thompson RF, Madigan SA (2005) Memory: the key to consciousness. Joseph Henry, Washington DC
2. Bartlett FC (1932) Remembering: a study in experimental and social psychology. Macmillan, New York
3. Loftus EF (2003) Make-believe memories. Am Psychol 58:864–873
4. Blank H, Musch J, Pohl RF (2007) Hindsight bias: on being wise after the event. Soc Cogn 25:1–9
5. Roediger HL, McDermott KB (1995) Creating false memories: remembering words that were not presented in lists. J Exp Psychol Learn Mem Cogn 21:803–814
6. Jones TC, Bartlett JC, Wade KA (2006) Nonverbal conjunction errors in recognition memory: support for familiarity but not for feature bundling. J Mem Lang 55:138–155
7. Johnson MK (2006) Memory and reality. Am Psychol 61:760–771
8. Bernstein DM, Whittlesea BWA, Loftus EF (2002) Increasing confidence in remote autobiographical memory and general knowledge: extensions of the revelation effect. Mem Cognit 30:432–438
9. Brainerd CJ, Reyna VF (2005) The science of false memory. Oxford University Press, New York
10. Schacter DL, Slotnick SD (2004) The cognitive neuroscience of memory distortion. Neuron 44:149–160

Memory Dysfunction

►Amnesia

Memory-guided Saccade Task

Definition

A task in which a target is briefly presented at the same time that the subject continues to look at a fixation point. The subject is not allowed to make a saccade to the target until after the fixation point is extinguished, usually 0.5–3 s after the target disappears. Thus the subject must make a saccade to the remembered location of the target.

►Saccade, Saccadic Eye Movement

Memory-guided Saccades

Definition

A type of saccadic eye movement that is directed to a remembered target. The target position is indicated while the subject is fixating at the center and then the subject is required to make a saccade to the remembered position.

►Saccade, Saccadic Eye Movement

Memory Illusions

►Memory Distortion

Memory Impairment

►Amnesia

Memory Improvement

Kiyofumi Yamada[1], Toshitaka Nabeshima[2]
[1]Laboratory of Neuropsychopharmacology, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa, Japan
[2]Department of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Meijo University, Nagoya, Japan

Synonyms

Cognition enhancement

Definition

Memory improvement refers to the enhancement of cognitive functions such as attention, learning and memory without affecting other physiologic functions in subjects with cognitive deficits as well as in healthy subjects.

Characteristics

Conditions

Learning is the acquisition of new information or knowledge. Memory is the retention of learned information. Certain diseases and injuries to the brain cause a serious impairment of learning and memory, the condition known as amnesia. Amnesia following brain trauma has two different forms; ►anterograde amnesia and ►retrograde amnesia. Transient global amnesia is an inability to form new memories (anterograde amnesia), which lasts less than 24 h, and is not associated with other focal neurological signs or symptoms. This type of amnesia can be induced by brief cerebral ischemia, in which the blood supply to the brain is temporarily reduced, or concussion to the head from trauma such as a car accident. There is also retrograde amnesia for recent events before the attack. ►Anxiolytic agents such as benzodiazepines, muscarinic acetylcholine (ACh) receptor antagonists such as scopolamine, and N-methyl-D-aspartate (NMDA) receptor antagonists are known to induce memory impairment in humans and experimental animals. Some neuropsychiatric diseases, including Alzheimer's disease, mild cognitive impairment, vascular dementia, and schizophrenia, are accompanied by memory impairment or loss.

Alzheimer's Disease

Alzheimer's disease is the most common cause of senile dementia, which is characterized by the presence of numerous senile plaques, neurofibrillary tangels accompanied by neuronal loss. The cholinergic neurons that project from the medial septal nuclei and basal nucleus of Meynert to the hippocampus and cerebral cortex, respectively, play an important role in learning and memory. Degeneration of the basal forebrain cholinergic neurons is correlated with cognitive deficits in Alzheimer's disease. The so-called "cholinergic hypothesis" proposed in the early 1980s essentially states that a loss of cholinergic function in the central nervous system contributes significantly to the cognitive deficits associated with aging and Alzheimer's disease [1]. Based on the hypothesis, agents that can enhance cholinergic function have been developed to improve memory deficits in Alzheimer's disease. An alternative hypothesis regarding the mechanism of Alzheimer's disease is that excessive activation of glutamate receptors may be responsible for the neuronal loss observed in those with the disease. Although it is unlikely that glutamate-mediated excitotoxicity is the primary etiopathological factor in Alzheimer's disease, it may partly contribute to the neurodegeneration. Supporting this idea, memantine, an uncompetitive NMDA receptor antagonist with moderate affinity, has been approved in Europe and USA for the treatment of moderate to severe Alzheimer's disease. In addition, various ►neuroprotective agents with diverse mechanisms of action have been proposed for treating Alzheimer's disease [2]. The dominant hypothesis regarding the etiology and pathogenesis of Alzheimer's disease is the "amyloid cascade hypothesis": Amyloid β produced by the amyloidogenic processing of amyloid β precursor protein triggers a neurotoxic cascade, thereby causing neurodegeneration and Alzheimer's disease [3]. According to the amyloid cascade hypothesis, there are several possible molecular targets for treating Alzheimer's disease [2].

Mild Cognitive Impairment (MCI)

Mild cognitive impairment is regarded as a transition phase between healthy cognitive ageing and dementia. Accordingly, clinical studies of elderly individuals with memory impairment reveal a rapid rate of conversion to Alzheimer's disease, reaching as high as 15% per year. Recognition that MCI may represent a transition phase between normal cognitive decline by ageing and dementia will provide a possible early diagnosis and potential treatment with the aim of delaying the onset or preventing dementia [4].

Vascular Dementia and Stroke

Vascular dementia, the second most common form of dementia, is a term currently used to define any

type of dementia resulting from cerebral blood vessel disease. The classification of vascular dementia is based on the following main diagnostic points: cognitive deficits, a history of stroke and/or focal vascular neurological deficits, neuroimaging showing neurovascular focal or diffuse lesions, and a temporal association between stroke and the onset of dementia. Among the risk factors for vascular dementia, hypertension has a major role. An elevated blood pressure measured in midlife increases the risk of dementia or accelerates age-related cognitive decline. Clinical studies have demonstrated that donepezil, an acetylcholinesterase (AChE) inhibitor, has significant effects on the cognitive deficits of vascular dementia [5]. In stroke victims, the ischemic vascular bed is composed of a core area where cerebral blood flow (CBF) is severely decreased and a more distal penumbra with less severely affected CBF. The penumbra is the focus of new therapeutic targets because it may be salvaged with restored circulation, and prevention of cell death may be possible with neuroprotective agents. Several compounds such as NMDA receptor antagonists, calcium channel blockers, radial scavengers, and antioxidants have shown neuroprotective effects in animal models, but have failed to be effective in human clinical trials [6].

Schizophrenia

Schizophrenia is a chronic mental disorder characterized by psychosis (e.g., hallucinations and delusions), flattened emotions, and impaired cognitive function. There are no drugs that can effectively treat the cognitive dysfunction in patients with schizophrenia. The areas of impaired function are verbal learning and memory, working memory, visual learning and memory, speed of processing, reasoning and problem solving, attention and vigilance, and social learning [7]. The "NMDA receptor hypofunction hypothesis" has been proposed for schizophrenia because NMDA receptor antagonists such as phencyclidine and ketamine induce a schizophrenia-like spectrum of symptoms in healthy subjects and exacerbate symptoms in patients with schizophrenia. Hypofunctioning of NMDA receptors contributes to the pathophysiology of schizophrenia, especially those symptoms associated with the endophenotype such as cognitive impairment and negative symptoms [8]. According to the hypothesis, agents that enhance NMDA receptor function may ameliorate the cognitive impairment and negative symptoms in patients with schizophrenia. Because an excessive activation of NMDA receptors could lead to excitotoxicity and neuronal degeneration, an indirect enhancement of NMDA receptor function with agonists acting at the glycine modulatory site on NMDA receptors would be required for the treatment of schizophrenia [8]. Ampakines that bind to a site on the AMPA receptor and stabilize the receptor in its channel-open state following the binding of glutamate are also promising candidates for agents to treat cognitive dysfunction [9]. Furthermore, there are possible molecular targets for treating cognition in schizophrenia such as dopamine D_1 receptors, serotonin 5-HT_{1A}, 5-$HT_{2A,}$ and 5-HT_6 receptors, muscarinic and nicotinic ACh receptors, and GABA receptors [7].

Cognitive Enhancers

Various agents with different chemical structures and diverse mechanisms of action are currently being investigated as a ►cognitive enhancer or ►anti-amnesic agent to improve cognitive functions such as learning and memory. They include AChE inhibitors, and muscarinic and nicotinic ACh receptor agonists. Alternatively, agents that directly or indirectly activate the glycine modulatory site on the NMDA receptor complex, ampakines, and ►sigma-1 receptor ligands may provide memory improvement in those with cognitive disorders. Furthermore, neuroprotective agents that can protect neurons from various neurotoxic substances including glutamate, amyloid β, and free radicals may afford memory improvement in cases where cognitive deficits are associated with neurodegenerative diseases, such as Alzheimer's disease and cerebral ischemia.

AChE Inhibitors

The cholinergic system in the cerebral cortex and hippocampus plays an important role in learning and memory. Degeneration of the basal forebrain cholinergic neurons is correlated with cognitive deficits in Alzheimer's disease. Therefore, enhancement of cholinergic function would lead to an improvement of memory deficits in those with Alzheimer's disease. One of the pharmacologic strategies used to enhance cholinergic function is to inhibit the decomposition of ACh into choline and acetic acid, which is catalyzed by AChE. Four AChE inhibitors (tacrine, donepezil, rivastigmine and galantamine) have been approved so far for the treatment of Alzheimer's disease [2].

Muscarinic ACh Receptor Agonists

The direct activation of muscarinic ACh receptors is supposed to improve cognitive deficits in Alzheimer's disease as well as other neuropsychiatric diseases. Muscarinic M1 receptors are predominantly present in the frontal cortex and hippocampus, while M2 and M3 receptors predominate peripherally where they mediate effects on cardiovascular, respiratory, and secretory systems. Accordingly, specific M1 receptor agonists are supposed to ameliorate cognition impairment with few peripheral side effects associated with the stimulation of M2 and M3 receptors. However, no muscarinic M1 receptor agonists have been approved so far because of their side effects [2,7].

Nicotinic ACh Receptor Agonists

The activation of nicotinic ACh receptors with selective agonists may have some beneficial effects on the cognitive deficits in patients with Alzheimer's disease and/or schizophrenia. Nicotinic ACh receptors are ligand-gated cation channels, the neuronal subtypes of which (α7 and α4β2) are highly permeable to Ca^{2+}. Thus, nicotinic ACh receptors modulate neurotransmitter release and synaptic plasticity, and thereby improve cognition. Moreover, accumulated evidence demonstrates that nicotine and subtype selective nicotinic ACh receptor agonists have neuroprotective effects in the brain. For instance, nicotine provides neuroprotective effects against glutamate and amyloid β toxicity via α7 nicotinic ACh receptors. Galantamine, a weak AChE inhibitor, allosterically modulates nicotinic ACh receptors and improves Alzheimer's disease [2,7].

Ampakines

Ampakines bind to a site on the AMPA-type glutamate receptor, and stabilize the receptor in its channel-open state following the binding of the neurotransmitter glutamate, with no agonistic or antagonistic effects. Thus, ampakines prolong current flow through AMPA receptors and enhance synaptic responses. Ampakines accelerate learning, reduce age-related memory impairments, and suppress symptoms in models of schizophrenia, attention-deficit hyperactivity disorder, and depression [9].

Glycine Modulatory Site Agonists

NMDA receptors play an important role in the synaptic plasticity associated with learning and memory. The activation of NMDA receptors requires the binding of L-glutamate to the NR2 subunit and a co-agonist (D-serine or glycine) at the glycine modulatory site on the NR1 subunit. D-serine is abundant in the forebrain and the expression is correlated with that of NMDA receptors. The glycine modulatory site is not saturated so that the activation could potentially modulate responses of the NMDA receptors. According to the NMDA receptor hypofunction hypothesis, enhancement of NMDA receptor function with agonists at the glycine modulatory site could have benefits in the treatment of schizophrenia. The results of clinical trials are encouraging with D-serine having a beneficial effect on the positive, negative, and cognitive domains of schizophrenia [8].

Sigma-1 Receptor Ligands

Sigma receptors are widely distributed in the mammalian brain, and recognize a diverse array of compounds, including opiates, antipsychotics, antidepressants, phencyclidine-related compounds, and neurosteroids. Two sigma receptor subtypes have been identified, and the sigma-1 receptors have been cloned. Sigma-1 receptors regulate NMDA receptor function and the release of neurotransmitters such as ACh and dopamine. Accordingly, selective sigma-1 receptor ligands have been suggested to represent a new class of therapeutic agents for neuropsychiatric disorders [10].

References

1. Coyle JT, Price DL, Delong MR (1983) Alzheimer's disease; a disorder of central cholinergic innervation. Science 219:1184–1190
2. Yamada K, Nabeshima T (2002) Animal models of Alzheimer's disease and evaluation of anti-dementia drugs. Pharmacol Ther 88:93–113
3. Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256:184–185
4. DeCarli C (2003) Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2:15–21
5. Chui H, Stoog I (2006) Advances in vascular cognitive impairment 2005. Stroke 37:323–325
6. Weinberger JM (2006) Evolving therapeutic approaches to treating acute ischemic stroke. J Neurol Sci 249:101–109
7. Tamminga CA (2006) The neurobiology of cognition in schizophrenia. J Clin Psychiatry 67:9–13
8. Coyle JT (2006) Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol 26:365–384
9. Lynch G, Gall CM (2006) Ampakines and the threefold path to cognitive enhancement. Trends Neurosci 29:554–562
10. Hayashi T, Su TP (2004) Sigma-1 receptor ligands: potential in the treatment of neuropsychiatric disorders. CNS Drugs 18:269–284

Memory Loss

►Amnesia

Memory Retrieval

Definition

A cognitive process in which information is accessed from memory.

►Emotional Learning/Memory

Menière's Disease

Definition

Disorder of the labyrinth characterized by episodes of vertigo, fluctuating hearing loss, tinnitus and fullness in the ear. The disorder typically begins in one ear but can in some patients progress to involve both ears.

►Disorders of the Vestibular Periphery
►Labyrinth (Vestibular Labyrinth)
►Tinnitus
►Vertigo

Meningeal Cell

Definition

►Leptomeningeal Cell

Meninges and Cisterns

►Dura Mater Of Brain
►Falx Cerebri
►Fourth Ventricle
►Pia Mater
►Third Ventricle
►Ventricular System

Meningism

Definition

A syndrome of headache and neck stiffness with flexion indicative of meningeal irritation. This syndrome may be found with viral or bacterial meningitis or subarachnoid hemorrhage.

►Headache

Meningitis

Definition

An inflammation of the membranes (dura mater, arachnoid mater and pia mater) covering the brain and spinal cord due to infectious, immune-related or paraneoplastic (associated with cancer) causes, injury or medication. Infectious causes of meningitis include bacteria, viruses, fungi, parasites and protozoa. Symptoms typically begin with non-specific flu-like symptoms: fever, headache, eye pain, back pain, malaise, myalgias and sometimes a rash, then proceed to stiffness and pain of the neck (meningismus), change in mental status or coma, and at times weakness, cranial nerve dysfunction, or seizures. Diagnosis is confirmed by demonstration of increased number of white blood cells in the cerebrospinal fluid (pleocytosis) or contrast enhancement of the meninges on computerized tomography or magnetic resonance imaging.

Meningoencephalitis

Definition

Inflammation of the brain and meninges. Also called cerebromeningitis, encephalomeningitis, and meningocerebritis.

.

Meningoencephalomyelitis

Definition

Inflammation of the meninges, brain, and spinal cord.

.

Meningovascular Syphilis

Definition

Meningovascular syphilis manifest itself ca. 2 years after the primary infection and presents with cerebrovascular accidents, cranial nerve palsies, and often convulsions.

Mental Causation

Definition

"*Mental causation*" is a term for the causal interaction between mental and physical phenomena. Although it applies to physical-to-mental causation and mental-tomental causation no less than to mental-to-physical causation, it is customarily reserved for instances of mental-to-physical causation, as when a sharp pain makes one wince, fear makes the heart beat faster, remembering an embarrassing situation makes one blush, and Fred's desire for beer and his belief that there is beer in the fridge cause him to go to the fridge.

►Epiphenomenalism

Mental Development

Definition

Cognitive development. Changes with age in human ontogeny in mental processes and abilities, that is, the development of higher mental processes such as problem solving, reasoning, conceptualizing, classifying, and planning, as well as more basic processes such as perception and language.

►Cognitive Development

Mental Models

Verena Gottschling
Department for Philosophy, York University, Toronto, ON, Canada

Definitions

Kenneth Craik was the first to introduce the term "mental model." He contends that humans translate external events into internal mental models and that ►reasoning takes place by manipulating these models. Then, either the resulting symbols are in turn translated into actions, or recognition of a correspondence between these symbols and an external event occurs. Hence, for Craik a mental model is mainly a simulation of the world; this simulation also has a structure similar to that of the simulated process.

Subsequently, various mental model accounts have been introduced. Apart from their labels, these accounts have little in common other than the fact that internal representations are involved. Indeed, the term "mental model" is sometimes used as a synonym for "►mental representation."

In our days, the term "mental model" is used mainly to refer to Philip Johnson-Laird's mental models account. According to Johnson-Laird, a mental model is a special kind of mental representation – either long-term or short-term knowledge – whose structure is isomorphic to the structure of the situation it represents, and in which no free variables are found.

Characteristics

Description of the Theory

Mental models are thought to be the result of several cognitive processes, and they are assumed to play a role in central cognitive processes like comprehension, reasoning, and discourse. [1] They are internally generated models of situations, scenes, or objects and can play a role in very different situations. But besides this, it turns out to be surprisingly difficult to determine precisely what mental models are. As we will see, mental models can be short-term or long-term representations, conscious or unconscious representations, and they can be voluntarily or spontaneously generated. We can distinguish mental models in discourse, in perception, and in reasoning processes. I will consider them in turn. A further tricky issue is to determine the role mental models play in another cognitive capacity, namely visual imagination and mental imagery.

Mental Models in Discourse

Mental models are considered to be representations that can be constructed during verbal discourse. Descriptions of complex situations lead us to construct a mental model of the situation and read out information that is only implicitly contained in the description. For example, by using a mental model in working memory we envisage the setting of a verbal description. Consider: "Watson enters the kitchen from the right door, at the opposite end Holmes was kneeling beside the crying victim, whereby the glistering sunshine from the window nearby threw light on the scene, even if the rest of the kitchen was relatively dark." This assertion establishes a relation between several entities, Holmes, Watson, and other elements of the scene, the door, and the window. We can infer that the victim is at the left side of the kitchen on the basis of a mental model we construct. This mental model is isomorphic to the situation described, and contains at least three mental tokens, corresponding to Watson, the unnamed victim, and Holmes. Furthermore, these tokens are interrelated

in a way that corresponds to the spatial relation between them. According to Johnson-Laird, these discourse models make explicit the structure of situations as we perceive or imagine them.

Mental Models in Perception

Mental models are also supposed to play a role in perception, especially in vision. Vision is characterized as a multi-stage process. It is accomplished in three separable and successive processing states often referred to as low-level, intermediate-level and high-level vision.[1] Cognitive neuropsychologists distinguish successive states in vision roughly corresponding to David Marr's levels, together with three different levels of perceptual representations mentioned before [2].

Johnson-Laird's mental models have often been identified with high-level representations, that is, with viewpoint independent, three-dimensional models of the spatial relations between objects. Correspondingly, the most appropriate candidates for their neural correlates seem to be regions in the inferior-temporal cortex (IT) in the ventral system.

In contrast to high-level representations, the experienced percept, a viewpoint-dependent representation is typically identified either with low-level or intermediate representations. These representations are not object-centered, but strongly bound to knowledge about visual appearances – information that resides in the 3D representation described above. Therefore, images and percepts are restricted to a particular point of view; they are instances of categories stored in the conceptual system and generated from knowledge contained in 3D models.

Ray Jackendoff [3] proposes a related but different view. He sees the conceptualized world as divided between the "cognitive structure," which is approximately propositional, and the "spatial structure," which is geometric, but is nonetheless not restricted to a particular point of view, and more abstract than experienced images and percepts. In the cognitive structure, knowledge, like category memberships and properties, is encoded. The spatial structure[2], by contrast, is identified with Marr's 3D sketch and Johnson-Laird's mental models. Here, knowledge about visual appearance is encoded; these representations are 3D representations, which are roughly understood as images of prototypic instances of categories. Thus, they are imagistic, but no longer strictly visual. Additionally, they are abstract and support visual object categorization and identification. They are image-schemas, abstract structures from which a variety of different images can be generated and to which a variety of percepts and images can be compared. These representations are conceptual, they specify the configuration of the object's parts relative to one another, and encode possible shape variations of objects. But for Jackendoff, this structure is, to some degree, modality-independent[3]. Thus, elements in the spatial structure including mental models are not perceptual representations, but part of central cognition. The spatial structure is concerned with judgments and inferences having to do with shapes and locations and necessary for visual object categorization and identification. This structure includes all parts of the object, including hidden parts. It is not a simple three-dimensional object but a complex hierarchy of representations, which encode how objects can be regarded as assemblages of parts.

Mental Models and Visual Images

Other authors do not distinguish between theories of visual imagery and mental model theories. They identify mental models and visual mental images. Pictorialist theories of visual imagery understand images as mental representations that function in the way pictures do, whereas the most important relations to be discussed are spatial relations. During the last years, participants in this debate moved away from an emphasis of pictorial representation and more towards perceptual representations. [4] The mental spatial representations they focus on are identical with perceptual representations, and are also thought to play an important role in reasoning and learning. But as in the case of identification with perceptual representations, the relation between mental models and visual images is controversial. Their possible relations can be summarized as follows:

1. Images and mental models are assumed to be different terms for the same entities.
2. Images are a subclass of mental models, very rich mental models within perception. "Mental models" is the more general term, though [5] mental models can take many forms and serve many purposes. A model can be a "physical" model and consist of elements corresponding only to perceptible entities, in which case it may be realized as an image, either perceptual or imaginary. Alternatively it can contain elements corresponding to abstract notions; in this case it would be a "conceptual" model.
3. According to Johnson-Laird's "triple-code" hypothesis [6], mental models are a different and more abstract format of mental representations than images. Images differ from mental models and need distinct processes, although they often function like models. But both sorts of representations are more closely related than the third kind of mental representations, namely propositional representations. Both mental

[1] They can be roughly identified with David Marr's three levels, the primary sketch, the 2.5D-ketch, and the 3D-sketch.
[2] Jackendoff's spatial structure makes use of Marr's 3D sketch and understands Biederman's geons as an extension.
[3] In contrast to Marr, who saw it as a part of vision, as the "perceptual front end."

models and visual images can be used in reasoning processes, but under some circumstances visual imagery can in fact impede reasoning [1,7]. There is a structural isomorphism between the represented situation and the representations in both cases. Both mental models and visual images are isomorphic, but differ with respect to the relations and properties that make up this structural isomorphism. In contrast to images, mental models are pure spatial representations. In mental models, visual characteristics like color, texture, and form can be neglected. Mental models are not restricted to a specific modality, they can contain symbols, and there may be only a minimal degree of analogical structure. Even tokens representing abstract concepts like negation, which are hard to visualize, are accredited. However, mental models can also be used to generate visual images. These images are assumed to be necessarily restricted to two dimensions, are conscious, and contain visual information.

All three views understand mental models as representations in working memory, in contrast to theories described above, which identify them only with the structures used to generate these representations. The situation is even worse: Imagery theorists describe the relation between visual images and mental models differently. The focus in the imagery debate lies in spatial relations as well. With regard to other typically "pictorial" properties the theories are more or less silent; it is not always assumed that images can only be two dimensional. It is controversial how strongly they are bound to concepts, as well as whether they have to be pictorial in a literal sense [4,8,9], and whether they are to be identified with patterns of activation in the visual system, and if so, which level this is. Sometimes image properties (such as color and texture) are assumed to be represented elsewhere in a more abstract format, and are connected by pointers to specific parts of the depictive representation. The main proponent of pictorialism, Steven Kosslyn, is sympathetic to these hybrid accounts. A related claim is that images are symbolic representations, but nonetheless modality-specific; they consist of a subset of neural activity associated with the corresponding visual perception. [10] Thus, images are basically representations using a spatial layout. In addition, images are not to be identified with the experience of having them. The imagery debate is rather about the format of the mental representations that come along with this experience. In other words, it seems we run into a similar problem than the one we already encountered: The term "image" is used in the same broad sense as "mental model."

Reasoning in Mental Models

Mental model theory as a model-theoretical method is an alternative view to formal rule theories. Formal rule theories posit that deduction depends on formal rules of inference. In contrast, the main idea in the mental model theory of deduction uses the idea that instead of rules we use a special kind of mental representation in reasoning. We construct a model, or a set of models, based on such things as relevant background knowledge, meaning of the premises, and perceptual information. We then formulate a conclusion by describing a relation in the models that was not explicitly asserted in the premises. Finally, we check whether there are alternative models that comply with the premises but are incompatible with the conclusion. The conclusion is valid and necessary if the conclusion holds in all models of the premises. In cases of connectives like "if," "and," and "or" we construct a set of models in which each model represents a different possibility. The complete set of mental models describes exactly the cases where the compositional statement is true. Deductions that depend on quantifiers like "all" or "some" call for the construction of models containing sets of tokens, in which each token represents an individual. Again, we generate as many mental models as possible and check whether the conclusion is true. If we fail to find a mental model in which the conclusion is false, the composed statement is taken to be true. The underlying idea in mental model theory is again that the model or set of models represents the relation between the elements by isomorphism. Drawing the inference, then, is reading out the information that is implicitly contained.

An important advantage of mental model theory is that it covers not only deductive reasoning, but also probabilistic and ►modal logic. In probabilistic and modal cases, we need to adjust the description above: We do not talk about true or false statements, but about possible or impossible circumstances, propositions that might be true or false etc. A conclusion is impossible if it holds in no mental model; possible if it holds in at least one mental model; probable if it holds in most mental models; and necessary if it is valid in all mental models.

Furthermore, mental model theory gives us explanations for several systematically invalid conclusions people typically draw, i.e. they explain performance errors reasoners frequently make. These conclusions tend to correspond to just a single model instead of all possible models. Reasoners seem to fail to realize what is common in those multiple models. Mental model theory even predicts that reasoners will commit certain systematic fallacies. In the case of complex models, they construct models that are too simple and neglect some aspects. Content effects are to be expected as well. Logically untrained reasoners do not use formal rules, but rather, rely on their ability to understand the premises. Their models mirror their understanding of the situation, along with their background knowledge. The conclusions they draw are true with respect to their

models. Other systematic invalid conclusions are illusory inferences in probabilistic reasoning. Naïve individuals assume that each constructed model is equally probable, and wrongly infer the probability of an event from the proportion of models in which this event occurs.

For all these reasons, mental model theory in deduction can be seen as a strong alternative to formal rule reasoning.

Mental Models and Central Cognition: Meta-Reasoning, Mindreading, and Theories of Concepts

In addition to reasoning associated with logical conclusions, mental models are assumed to play an important role in other central cognitive capacities such as meta-reasoning, i.e. reasoning about what other individuals have reasoned. Mental models are also thought to play a role in mindreading, our ability to understand and predict the mental states of our conspecifics. More precisely, they are assumed to play a role in developing central concepts for mindreading: In order to attribute mental states or to reason about other people's reasoning, I need to understand how a situation is represented from the perspective of other subjects. It is assumed that we use mental models during these processes.

In addition, the value of mental models for theories of concepts has recently been discussed. According to exemplar theories, concepts are stored instances of individual categories; they are perceptually derived mental representations. These stored representations can be activated in working memory to represent a category. Prototype theories and proxytype theories are related versions, which see concepts either as generated from perceptually derived individual representations (prototypes) or sets of prototypes (proxytypes). Again, mental models are frequently mentioned as paradigm examples for these representations. Since concepts play a role in almost all cognitive processes, these accounts would assign mental models a central role in cognition in general.

Let us take stock. According to the majority of mental model accounts, these representations are short-term representations. They are generated during reasoning processes, during discourse or in mental imagery, or as the result of visual perception. Sometimes the concept "mental model" is used for long-term representations as well, for example if mental models are identified with the underlying information used to generate short-term representations. Even if the term "mental model" is used for representations stored in long-term memory, these representations are assumed to have a similar structure to the representations used in working memory. Examples are accounts that treat mental models as schemas or stored prototypes of spatial representation, or accounts of concepts holding that they are long-term memory networks of perceptual representations. These accounts do justice to Johnson-Laird's central idea that mental models may be a central structure of cognition: "It is now plausible to suppose that mental models play a central and unifying role in representing objects, states of affairs, sequences of events, the way the world is, and the social and psychological actions of daily life." [5, p. 397]

Problems With Mental Models

Mental Models: A Variety of Connected Concepts

The most pressing problem in the debate is that the notion of a mental model is unclear and that proponents do not us the same characterization of "mental model." In other words, the central term is used both vaguely and ambiguously. Moreover, the term "mental model" is often used as an umbrella term covering all sorts of spatial representations. Researchers in Artificial Intelligence, linguistics, and psychology often seem to use mental models in this broad sense as well. Mental models are spatial representations of any kind. Moreover, authors who use the term in a stricter sense use it either for long-term representations or short-term representations. Different authors also explicitly use different characterizations. Unfortunately, these characterizations are probably incompatible. The term is used not only in different ways, but also in mutually exclusive ways.

Ockham's Razor

The postulation of a special format of mental representations characterized by structural isomorphism is frequently accused of being unnecessary. The reason is that alternative explanations exist which postulate symbolic representations only. According to Ockham's Razor, entities must not be multiplied beyond necessity. As a result, the postulation of mental model is not warranted, or so the argument goes.

A standard reply is that the legitimacy of a postulated entity does not only depend on Ockham's Razor. More factors play a role, and Ockham's Razor is only warranted if the alternative explanations and predictions are comparable. Other criteria, such as physiological evidence, optimality, plausibility, and efficiency, give us additional constraints, and they help us to decide between theories that posit different kinds of representations. Consequently, advocates of mental models could argue, for example, by presenting empirical evidence for spatial representations in high-level vision and intermediate-level vision. They can also argue that mental models explain performance errors in reasoning, and systematic invalid conclusions people typically draw, in a more plausible way than rule-based reasoning theories.

Confusing Levels of Explanation? Properties of the Underlying Representations

Related to the former two issues, another group of objections is frequently mentioned: We witness a confusion of levels in mental model theory. Mental models are supposed to be high-level representations, representations at the "representational level" (Marr). At this level we postulate *representations of different formats and algorithms*. We deal with representations of the input and output as well as an algorithm, which transforms one into the other. Another level of analysis is the implementation or *hardware level*, dealing with the physical realization of these algorithms and representations. According to the theory we outlined, mental models are representations which play an important role for explanatory projects at the representational level. It seems hasty to simply identify them with neural representations in the brain, representations postulated as elements within a different explanatory project. A related objection states that we should not identify these representations with the experiences we have during events of reasoning. For it is not clear that the experience during, for example, mental imagery, helps us to learn something about the properties of the representations used in these processes. This takes us to the classical interface problem: how do explanations at different levels (in the different disciplines) relate to one another? This is a question about the connection between the different explanatory projects and of the theoretical postulates at different levels. In other words, what does a successful inter-theoretical reduction look like? What are the requirements a theory has to fulfill in order to give an explanation for phenomena at a higher level? Unfortunately, the term "explanatory level" is not clear, nor do unambiguous criteria exist for distinguishing particular levels, or for specifying the notion of an explanatory (or analytical) level. It is clear though that the personal level and sub-personal levels of analysis should be distinguished. The former level of explanation deals with the explanation and prediction of behavior of the thinking and acting person, whereas lower levels of analysis explain the mind at sub-personal levels. If consciously experienced images (personal level) are identified with mental models (sub-personal level), or even specific retinotopic areas in the brain (a lower sub-personal level), it is tempting to suspect that we witness a confusion of levels. Another question is how the theoretical postulates in different accounts are related. Far from uncontroversial though, according to the classical view, the structure of "higher levels" of a system should not be assumed to be isomorphic, or even similar, to the structure of "lower levels" of a system. The same holds for the explanatory projects at these levels. Since the term "mental model" is used for structures at different levels, it invites confusion, to put it moderately.

But to say that the concept of mental models is an umbrella concept, and that some of the characterizations are even incompatible, does not imply that it is out of the question to develop a consistent explanatory account. Rather, a refinement and improvement of this concept is required.

References

1. Held C, Knauff M, Vosgerau G (ed) (2006) Mental models and the mind. Amsterdam
2. Marr D (1982) Vision. New York
3. Jackendoff R (2002) Foundations of language. Oxford
4. Kosslyn SM (1994) Image and brain: the resolution of the imagery debate. Cambridge, MA
5. Johnson-Laird PN (1983) Mental models. Cambridge, MA
6. Johnson-Laird PN (1996) Images, models, and propositional representations. In: de Vega M, Intons-Peterson MJ, Johnson-Laird PN, Denis M, Marshar M (eds) Models of visuospatial cognition. New York, pp 90–127
7. Knauff M, Johnson-Laird PN (2002) Visual imagery can impede reasoning. Mem Cogn 30:363–371
8. Gottschling V (2003) Bilder im Geiste. Die Imagery-Debatte. Paderborn
9. Tye M (1991) The imagery debate. Cambridge, MA
10. Barsalou L (1999) Perceptual symbol systems Behav Brain Sci 22(4):577–660

Mental Representation

Definition

A theoretical construct of cognitive science. It is a basic concept of the Computational Theory of Mind, according to which cognitive states and processes are constituted by the occurrence, transformation and storage (in the mind/brain) of information-bearing structures (representations) of one kind or another. More broadly construed, a mental representation is a mental object with semantic properties, which need not be understood only in computational terms, but as a vehicle that refers to or denotes something, or as the relation between a thing and the object or state of affairs that it stands for.

►Mental Models

Mental Rotation

Definition

A particular type of mental image transformation abilities. The ability to mentally rotate representations

of two-dimensional or three-dimensional objects is conceived to be analogous to a physical rotation. Research showed that reaction times are linearly proportional to the difference in angle between two items when participants decide whether they are the same or not (i.e. a mirror image).

►Action Representation

Mental States (States of Mind)

Definition

The perceptions, beliefs, desires, hopes, fears and intentions of an individual.

►Theory Theory (Simulation Theory, Theory of Mind)

Mentalizing, Mind-Reading

Definition

The ability to attribute mental states to oneself and others in order to predict and explain thoughts, feelings and behavior.

►Theory Theory (Simulation Theory, Theory of Mind)

Merkel Cell-Neurite Complex Regeneration

Tamiko Tachibana[1], Chizuka Ide[2,3]
[1]Department of Oral Anatomy, Iwate Medical University School of Dentistry, Uchimaru, Morioka, Japan
[2]Department of Anatomy and Neurobiology, Kyoto University Graduate School of Medicine, Yoshidakonoe-cho, Sakyo-ku, Kyoto, Japan
[3]Department of Occupational Therapy, Aino University, Faculty of Nursing and Rehabilitation, Shigashiohta, Ibaragi, Osaka, Japan

Synonyms

Merkel's corpuscle

Definition

The Merkel cell-neurite complex is a slowly adapting type I mechanoreceptor that recognizes punctate pressure stimuli applied to the surface of the skin or oral mucosa.

The corpuscle is composed of a specific epithelial cell, the Merkel cell, discovered by F. S. Merkel in 1875, and an afferent axon terminal.

Characteristics

Structure and Distribution

Merkel cell-neurite complexes are usually localized in the basal layer of the epithelium of the skin and oral mucosa. They are mainly distributed in areas of high touch sensitivity, including the digital pads, the vermilion border of the lip, ►touch domes of hairy skin, hair follicles, ►sinus hair, ►Eimer's organ and the epithelia of masticating oral mucosa [1].

Merkel cells are less electron-dense with scanty tonofilaments than epidermal cells, extending spur-like projections (1–2 μm long and ca. 0.2 μm wide) into the intercellular spaces between neighboring epithelial cells. An axon terminal containing numerous mitochondria and clear vesicles attaches to the Merkel cell like a disc at the basal surface, i.e., the side towards the basal lamina. Merkel cells contain many dense-cored granules of ca. 100 nm in diameter, which deviate in the cytoplasm towards the associated axon terminal. These granules contain bioactive substances such as neuropeptides, ATP, serotonin and glutamate [1]. Although the function of Merkel cells is still unclear, it has been proposed that Merkel cells serve as mechanoreceptors by the exocytotic release of neurotransmitters or neuromodulators from granules [1,2].

Regeneration

Following transection of the nerve innervating Merkel cell-neurite complexes, most Merkel cells (60–80%) disappear, while some survive without any contact with axons for an extended period [3,4]. Regenerating axons, after penetrating the basal lamina, make contact with those surviving Merkel cells. Although the number of Merkel cells decreases immediately after denervation, the original population of Merkel's corpuscles can be retained following re-innervation [4]. There are usually nerve-free Merkel cells in varying proportions in normal skin and oral mucosa. Approximately 4% of the total Merkel cells have no contact with axon terminals in the adult rabbit labial mucosa, in which the population of Merkel cells is estimated to be ca. 1,000 per 1 mm^2 [5]. A touch dome in the adult rat contains between 80–100 Merkel cells, of which only 50% or fewer are innervated [6]. It is considered that Merkel cells are targets of regenerating axons [6].

Merkel cells can newly differentiate in the epithelium of labial mucosa during wound healing in adult rabbits. These Merkel cells make contact with the regenerating

axons, and finally develop into structurally normal Merkel cell-neurite complexes [5].

It appears that Merkel cells probably develop from epithelial cells bordering the wound. On the other hand, a recent study has reported that Merkel cells are derived from the neural crest [7]. Interestingly, Merkel cells do not develop in the absence of neurotrophin-3 [8].

References

1. Tachibana T (1995) The Merkel cell: recent findings and unresolved problems. Arch Histol Cytol 58:379–396
2. Halata Z, Grim M, Bauman KI (2003) Friedrich Sigmund Merkel and his "Merkel cell", morphology, development, and physiology: review and new results. Anat Rec 271:225–239
3. Tachibana T, Sakakura Y, Ishizeki K, Iida S, Nawa T (1983) An experimental study of the influence of sensory nerve fibers on Merkel cell differentiation in the labial mucosa of the rabbits. Arch Histol Jpn 46:469–477
4. Nurse CA, Macintyre L, Diamond J (1984) Reinnervation of the rat touch dome restores the Merkel cell population reduced after denervation. Neuroscience 13:563–571
5. Tachibana T, Ishizeki K (1981) Merkel cell development in the wound healing in the labial mucosa of adult rabbits. Arch Histol Jpn 44:151–165
6. Mills LR, Nurse CA, Diamond J (1989) The neural dependency of Merkel cell development in the rat: the touch domes and foot pads contrasted. Dev Biol 136:61–74
7. Szeder V, Grim M, Halata Z, Sieber-Blum M (2003) Neural crest origin of mammalian Merkel cells. Dev Biol 253:258–263
8. Halata Z, Kucera J, Kucera T, Grim M (2005) Apoptosis of Merkel cells in neurotrophin-3 null mice. Anat Embryol (Berl) 209:335–340

Merkel's Corpuscle

►Merkel Cell-Neurite Complex Regeneration

Merosin (Laminin-2)

Definition

One type of laminin and is closely related to axonal regeneration.

►Laminin
►Regeneration
►Regeneration of Optic Nerve

Mesencephalic

Definition

Related to the midbrain (mesencephalon).

Mesencephalic Locomotor Area

Definition

Mesencephalic nuclear region that can coordinate simple step movements. Corresponds to the pedunculopontine tegmental nucleus, pars compacta.

►Mesencephalon

Mesencephalic Reticular Formation (MRF)

Definition

A neuronal structure located in the core of the brain stem whose caudal boundary is the crossing of the superior cerebellar peduncle (brachium conjunctivum) and extends rostrally to the thalamic reticular nucleus. It is reciprocally interconnected with the superior colliculus. Original function was defined as part of the reticular activating system (RAS). Clear evidence now that there are subgroups of cells that participate in the control of saccadic and vergence eye movements. The MRF has two major subdivisions. The posterior commissure in the subhuman primate serves to separate the MRF into rostral and caudal regions. The cells of the rostral portion of the MRF are associated with the control of vertical eye movements, while neurons in the caudal region also termed the central MRF (cMRF) are more closely associated with the control of horizontal eye movements.

►The Central Mesencephalic Reticular Formation – Role in Eye Movements

Mesencephalon

Definition

Midbrain. The most rostral portion of the brainstem. Three parts:

1. The cerebral peduncles contain large fiber bundles from the cerebrum.
2. The tegmentum area contains substantia nigra, red nucleus, cranial nerve nuclei and parts of the reticular formation.
3. The tectum is formed from the quadrigeminal plate (inferior and superior colliculi). Tasks: eye movement, fine motor control, sensory-motor coupling, effector movement, synaptic center.

Mesenchymal Stem Cell

Definition

Mesenchymal stem cells are derived from various tissues including bone marrow, skin, adipose tissue, synovium, periosteum, skeletal muscle, placenta and thymus. They proliferate *in vitro*, and have the pluripotent capacity of differentiating into a broad range of cells such as osteocytes, chondrocytes, tenocytes, adipocytes, and smooth and cardiac muscle cells. Mesenchymal stem cells express CD 13, CD 29, CD 44, CD 90, CD 105, and HLA-ABC.

►Transplantation of Bone Marrow Stromal Cells for Spinal Cord Regeneration

Mesentery

Definition

Mesentery is a thin transparent membrane containing neurovascular bundles supplying blood and innervation to the viscera. In certain areas, the membranes form an omentum with a similar structure, but without such well defined attachments to viscera.

Mesopallium, Nidopallium, Entopallium

Definition

Three major nuclear components of the pallium of birds (see Reiner et al., 2004, J Comp Neurol 473:377–414).

►Evolution of the Wulst

Mesopontine Tegmentum

Philip Winn
School of Psychology, University of St Andrews, Fife, UK

Definition

The mesopontine tegmentum sits between the midbrain (also called the *mesencephalon* and therefore *meso*) and the anterior pons (and therefore *pontine*). The term *tegmentum* is a generic one that translates directly from Latin as "a cover". The mesopontine tegmentum is therefore the upper area at the junction of pons and midbrain; it is a region of brain rather than a clearly delineated structure. It sits above the underlying pontine tissue (principally the pontine nuclei and the nuclei of the pontine reticular formation) and the fibers of the superior cerebellar peduncle, which marks an approximate border between the mesopontine tegmentum and these nuclei. Laterally, both the pontine nuclei and mesopontine tegmentum are bordered by the fibers of the lemniscal system. Medial to the mesopontine tegmentum is the central gray and in the dorsal part of the area is the inferior colliculus, though this is a structure better understood in conjunction with the superior colliculus in the midbrain proper. In comparative terms, the mesopontine tegmentum differs little across vertebrate species, suggesting that whatever its functions are, they evolved early and have been preserved. What differentiates the region across species most clearly is the density of the fiber systems that cross the area rather than its structural or morphological identity.

Within the mesopontine tegmentum are two small nuclei with uncertain functions, the microcellular tegmental nucleus and the deep mesencephalic nucleus. These are identifiable by the aggregation of neurons of similar morphology, separable from the surrounding structures. In addition there is the cuneiform nucleus and three nuclei – the parabigeminal nucleus, the laterodorsal tegmental nucleus (LDTg) and the pedunculopontine tegmental nucleus (PPTg PPT or PPN). The pedunculopontine tegmental nucleus can also be referred to as the pedunculopontine nucleus, the tegmental pedunculopontine nucleus (TPP) or the nucleus tegmenti pedunculopontinus (NTPP). Pedunculopontine tegmental nucleus (PPTg) is preferred, being used by the major stereotaxic atlases. These nuclei, all of which contain large, deeply pigmented neurons whose principal neurotransmitter is acetylcholine, are undoubtedly the most prominent in the mesopontine tegmentum and are thought to be part of the ascending reticular activating system ARAS), an organized network of neurons in the hind- and mid-brain that regulate neural

functions throughout the entire CNS. However, while the cholinergic neurons of the PPTg and LDTg fulfill the criteria for inclusion in this system, it is important to recognize that different elements of the ARAS have different functions. Using this one generalized term to describe a number of structures collectively carries the danger that one obscures the specific functions of each one.

Characteristics

Neurodevelopment

The neurodevelopmental literature refers to a structure not recognized in the adult brain, called the isthmus. It sits between the midbrain and hindbrain – the area that in the adult brain includes the mesopontine tegmentum. This primordial tissue contains what is known as the "isthmic organizer", responsible for the proper development of midbrain and hindbrain tissue from the tectum to the cerebellum. The critical molecule involved in this, as demonstrated by a range of transplantation techniques, appears to be Fgf8, though a variety of other transcription factors are also involved [1].

The developmental history of the large cholinergic neurons that are the most prominent cells of the mesopontine tegmentum has been specifically studied. In rats, similar histories have been described for both PPTg and LDTg cholinergic neurons. The final adult number and morphology are achieved by postnatal day 21, but their development is not linear. The numbers of what will become cholinergic neurons (identifiable by morphology, location and the use of antibodies for choline acetyltransferase [ChAT] and the vesicular acetylcholine transporter [VAChT]) *declines* over postnatal days 1–3 but *increases* progressively thereafter, with ChAT and VAChT activity developing during postnatal days 7–14. Neuronal size is relatively large during this time, with later shrinkage to the adult form. This developmental time course appears to parallel changes in sleep, from the juvenile active sleep (which does not involve muscle atonia) through to the adult rapid eye movement (or paradoxical) sleep, in which muscle atonia is a prominent feature [2].

Principal Structures

The cuneiform nuclei – so called because of their wedge (cuneiform) shape – receive inputs from the superior colliculus and send projections to the medulla and spinal cord. They function as relay stations for collicular motor output and have been suggested to be involved in rapid "fight or flight" activities. For example, local chemical manipulation of the cuneiform nuclei produces behavioral freezing or darting movements. The cuneiform nuclei are also part of the mesencephalic locomotor region (MLR), a region defined functionally rather than anatomically. In pre-collicular – post-mamillary transected animals, electrical stimulation of the MLR elicits co-ordinated walking. This is a robust and reliable effect, but one whose significance can be misinterpreted. In otherwise intact animals, bilateral ▶excitotoxic lesions of the cuneiform do not impair locomotion and similar lesions of the PPTg (similarly suggested to be in the MLR) also leave locomotion intact. The MLR's existence should not be taken as showing that the primary function of this part of the brain is locomotor control. Rather, it might better be taken to demonstrate that in the absence of descending inhibitory control from the forebrain, these low level systems are capable of generating organized responses.

The pedunculopontine tegmental, laterodorsal tegmental and parabigeminal nuclei are nuclei that each contain a population of cholinergic neurons, designated (using the classification of Marek Marsel-Mesulam) Ch5, Ch6 and Ch8 respectively. The Ch8 neurons of the parabigeminal nuclei sit in an isolated cluster and innervate principally the geniculate nuclei of the thalamus. Ch5 and Ch6 however are closely coupled, forming a continuous chain of cholinergic neurons – called the caudal cholinergic column when first identified – that stretches (in rodents) from the caudal pole of the substantia nigra back as far as the locus coeruleus. These cholinergic neurons are thought in addition to contain a variety of other neurotransmitters (including neuropeptides and neuroactive amino acids) and neuromodulators (including nitric oxide – nitric oxide synthase is present in virtually all mesopontine cholinergic neurons). Receptors for a very wide variety of signaling molecules are present on these neurons, including those for acetylcholine; there appears to be strong intercommunication between PPTg and LDTg. Both also contain populations of non-cholinergic neurons, identified by morphology, electrophysiology and the absence of cholinergic markers. Precisely which neurotransmitters characterize these neurons is not clear, though recent evidence from immunohistochemical and *in situ* hybridization studies strongly suggests that many of them contain GABA.

Mesopontine Connections with the Limbic System, Basal Ganglia, Sensory and Motor Systems

The mesopontine tegmentum is a point of convergence for a variety of information. Visual, auditory and somatosensory data are all processed through here and some of this processing is very fast, PPTg neurons for example fire in response to auditory signals with a mean latency of only ~8 ms. Complementing this sensory input, several structures in the mesopontine tegmentum have output to sites of motor control in (for example) the pontine and medullary reticular formation, the trigeminal complex and spinal cord. As well as these sensory inputs and motor outputs, there is substantial descending (mostly inhibitory) control from the forebrain, with convergence of information from both basal ganglia and limbic system. Indeed, the description

"►limbic-motor interface" which was applied to the nucleus accumbens in the forebrain might better be used in relation to the mesopontine tegmentum. All of this connectivity is well illustrated by considering in particular the most closely studied mesopontine structures, the PPTg and LDTg.

The Pedunculopontine and Laterodorsal Tegmental Nuclei

The cholinergic neurons of the PPTg and LDTg project widely through the brain. These neurons are both heavily collateralized and, in many instances, have ascending and descending connections. They innervate the thalamus *en masse*, as well as midbrain dopamine (DA)-containing neurons (which they excite) and elements of the basal ganglia, the colliculi, hypothalamic and basal forebrain sites of non-specific cortical input and multiple motor structures in the brainstem and spinal cord. As well as these cholinergic neurons, both PPTg and LDTg contain non-cholinergic neurons that project widely, though not to quite the same extent as the cholinergic neurons. What controls the activity of these neurons appears to be two types of information: (i) basic sensory information from midbrain and brainstem visual, auditory and somatosensory systems and (ii) descending control from limbic structures (such as the amygdala, extended amygdala and hypothalamus) and from various parts of the basal ganglia (including the prefrontal and motor cortex). These various connections can be made sense of if brain systems are considered to be organized hierarchically in a form of layered architecture. The PPTg and LDTg receive primary sensory data and can generate output aimed at motor systems – this represents a simple system aimed at producing rapid responses to imperative signals. In addition to this, it can activate systems at a higher level, aiding more detailed processing. However, descending forebrain output, nearly all of which is GABA-mediated inhibition, allows for modification of both the ascending signals from PPTg and the rapid motor response generation to be effectively regulated by neural systems at higher levels of the architecture [3]. Note that this organization is consistent with the effects described above in relation to the MLR; loss of descending inhibition does not impair the ability of the PPTg to organize locomotion.

At the single unit level, the characteristic firing patterns of individual neurons in the PPTg and LDTg have been used to discriminate putative cholinergic and non-cholinergic neurons (see [4] for a brief review). More globally, mesopontine cholinergic neurons have been known for many years to be involved in regulating the electrical activity of the thalamus and through this, the cerebral cortex. Cholinergic activity in the thalamus has a complex action on the thalamic reticular nucleus and thalamic relay nuclei, with the outcome that increased cholinergic activity is associated with effective corticothalamic transmission, while decreased cholinergic activity inhibits traffic. These two states are differentiated in ►behavioral state control processes – increased cholinergic activity is associated with the waking state and REM sleep, while decreased activity is associated with slow wave (or paradoxical) sleep [5].

The traditional view has been very much that structures at this level of the brain are associated with basic mechanisms of behavioral state control and the regulation of locomotion. However, recent studies have revealed that more complex processing is represented here as well. There is no doubt that PPTg and LDTg neurons are differentially active at different stages of the sleep wake cycle, and as such play a role in behavioral state control. However, bilateral excitotoxic lesions of the PPTg do not prevent rats from exhibiting normal patterns of sleep and wakefulness, indicating that while the PPTg is important in the sleep wake cycle, it is not critical; it is not some form of master switch for sleep. As noted above, the PPTg is a part of the brain described previously as part of the MLR. Likewise, bilateral excitotoxic lesions do not impair locomotion, indicating that the essential function of this area is not just the production of movement. Indeed, a variety of studies from many labs worldwide have shown that bilateral excitotoxic lesions of the entire PPTg do not impair locomotion, feeding, drinking, grooming or any other basic activity; in their home cages, such lesioned rats are indistinguishable from controls. However, when challenged in a variety of tests involving more complex processes relating to ►reward and reinforcement, attention, learning and memory, lesioned rats are strikingly impaired [4]. In a recent attempt to aggregate these various deficits into a theoretical framework, Alderson and Winn [6] argued that the essential deficit present in PPTg lesioned rats is an inability to properly associate actions and outcomes. It is a significant move away from considering tissue at this level of the neuraxis as being only involved in automatic regulatory processes, one that moves toward a different account of the relationships between processes such as learning and memory and widely distributed brain systems.

One final point of interest is that the PPTg has been linked to neurodegenerative brainstem disorders such as Parkinson's disease and progressive supranuclear palsy [4]. In this context it is important to note that outflow from the basal ganglia to a focused part of the PPTg (termed the midbrain extrapyramidal region by David Rye and his colleagues) is disturbed in Parkinsonism. Very recently, several groups have shown that deep brain stimulation in the region of the PPTg can provide relief from some of the motor symptoms of this disorder. What the longer-term consequences of

this are – and whether there are any non-motor effects – remains unclear, but this is nevertheless an exciting new therapeutic development.

New ideas about the role of this part of the brain in both neurological disorders and more complex psychological processing than had previously been expected suggest that it might be exposed to more detailed study in the near future.

References

1. Nakamura H, Katahira T, Matsunaga E, Sato T (2005) Isthmus organizer for midbrain and hindbrain development. Brain Res Rev 49:120–126
2. Ninomiya Y, Kayama Y, Koyama Y (2005) Postnatal development of cholinergic neurons in the mesopontine tegmentum revealed by histochemistry. Int J Dev Neurosci 23:711–721
3. Prescott TJ, Redgrave P, Gurney K (1999) Layered control architectures in robots and vertebrates. J Adaptive Behav 7:99–127
4. Winn P (2006) How best to consider the structure and function of the pedunculopontine tegmental nucleus: evidence from animal studies. J Neurolog Sci 248:234–250
5. Steriade M (2006) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137:1087–1106
6. Alderson HL, Winn P (2005) The pedunculopontine and reinforcement. In: Bolam JP, Ingham CA, Magill PJ (eds) The basal ganglia VIII. Springer, Berlin Heidelberg New York, pp 523–532

Messenger RNA (mRNA)

Definition

Messenger RNA (mRNA) is the mature RNA, processed from the single stranded pre-mRNA transcribed from DNA, which is translated into protein.

Metabolic Coupling

Definition

The term metabolic coupling refers to the ability of many gap junctions to coordinate the metabolic and/or signaling state of multiple cells trough the exchange of small intracellular messenger molecules and metabolites.

►Electrical Synapses
►Gap Junctions

Metabolic Encephalopathy

Definition

One form of encephalopathy.

►Encephalopathy (or Acute Organic Brain Syndrome)

Metabotropic

Definition

An influence on ion channel activity mediated indirectly by the binding of a neurotransmitter or hormone to its receptor. Commonly, receptor binding activates one or more second messenger systems within the target cell, which ultimately causes relatively long-lasting changes in the activity of voltage-dependent ion channels. This is a relatively long-latency, long-lasting event.

Metabotropic Glutamate Receptors (mGluRs)

Definition

G-protein-coupled receptors activated by glutamate made up of three groups: I, II, and III. Group I mGluRs trigger phospholipase C (PLC) hydrolysis of phosphatidyl inositol (4,5)-bisphosphate (PIP_2), whereas groups II and III trigger adenylyl cyclase synthesis of cyclic adenosine monophosphate (cAMP).

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

Metabotropic Receptors

Definition

Neurotransmitter receptors that activate or inhibit intracellular biochemical processes when the neurotransmitter

binds to the receptor. They are membrane protein with a seven-transmembrane domain.

►G-Protein Coupled Receptors in Sensory Neuron Function and Pain
►Memory, ►Molecular Mechanisms
►Associative Long-Term Potentiation (LTP)
►Long-Term Potentiation (LTP)

Metachromatic Leukodystrophy (MLD)

Definition

Rare, autosomal recessive, lysosomal storage disorder characterized by severe and progressive ►demyelination. It is caused by a deficiency of the lysosomal enzyme arylsulfatase A (ARSA), which leads to the accumulation of galactosylceramide-3-O-sulfate (sulfatide) in the central and peripheral nervous systems. In the late-infantile form (50% of the patients), which manifests in the second year of life and for which no efficient therapy exists, death occurs within a few years. There are also juvenile forms (onset between 4 and 12 years) and adult forms (onset after 12 years). Allogeneic hematopoietic cell transplantation may ameliorate the condition of selected patients with juvenile or adult forms.

►Lysosomal Storage Disease

Metacognition

Shunichi Maruno, Kazuo Kato
Department of Psychology, Kyushu University, Fukuoka, Japan

Synonyms

Metalearning

Definition

Metacognition is, in a narrow sense, defined as cognition about and emotion for one's own cognitive states and processes, but in a broader sense, the self-regulatory process of cognitive processes while engaging in the task, or even more simply cognition and cognition (which is based upon the view underlying those definitions that "humans are reflective thinking agents who are actively monitoring, regulating, and reflecting upon their own cognitive processes while engaging, in order to achieve certain set goals").

Characteristics

In the accompanying essay, we shall discuss (i) components, (ii) characteristics of research, and (iii) new directions.

Two Components of Metacognition

The first component includes declarative, procedural, and conditional (if-then) knowledge and strategies, and beliefs on human cognitive processes and states (e.g., ►self-appraisal). It could be called as a set of beliefs or as naïve theories of human cognitive functioning.

The second component constitutes the online control process that monitors and guides underlying cognitive processes, or the dynamic executive system (e.g., ►self-management) that actively guides the processes generating cognitions. It consists of the four functions: (i) to know what the problem is, (ii) to plan and activate strategies appropriate for engaging in and solving the problem, (iii) to predict and direct performance, and (iv) to monitor and regulate ongoing cognitive activities [1,2]. Those functions are closely intertwined and are recurrently deployed until achieving set goals satisfactorily.

Five Research Areas: What Aspects of Metacognition have been Focused upon?

Metacognition has been investigated in various areas of psychology (developmental, educational, cognitive, social, brain/neuroscience, etc.). What functions and mechanisms of metacognition researchers believe is essential to elucidate and unveil and probably what methodology to employ, however, depends upon what theoretical approach they would take [3]. For example, cognitive psychologists analyze accuracy and bases of metacognitive judgments in memory and learning – where ►prospective monitoring and ►retrospective monitoring is involved (e.g., feeling of knowing (FOK), judgments of task difficulty and ease of learning (EOL), and judgments of learning (JOL)), and regulatory mechanisms of the cognitive processes that occur based upon those judgments. Educational psychologists investigate the role of metacognition as a tool for self-regulated learning of reading, writing, mathematics, and problem-solving in academic contexts (i.e., in what way metacognition is related with age, motivation, IQ, and academic achievement, and how

it can be cultivated so as to facilitate instruction and learning) [4,5]. Developmental psychologists study ontogeny of metacognition in a variety of areas, by examining individual- and group-differences in metacognitive knowledge, ability, strategies, etc. Brain scientists and cognitive neuropsychologists determine, with elders and patients suffering from brain function disorders, the area(s) that control(s) metacognition, and how those different areas interact.

Finally, the solution to the endlessly debated question of whether metacognition is conscious/explicit versus unconscious/implicit depends upon what metatheory researchers hold. We believe that "metacognition operates implicitly as long as problem-solving proceeds smoothly, but once problems emerge, it begins to function explicitly and solves them; the beneficial functions of metacognition, therefore, come into play whenever trouble-shooting is necessitated."

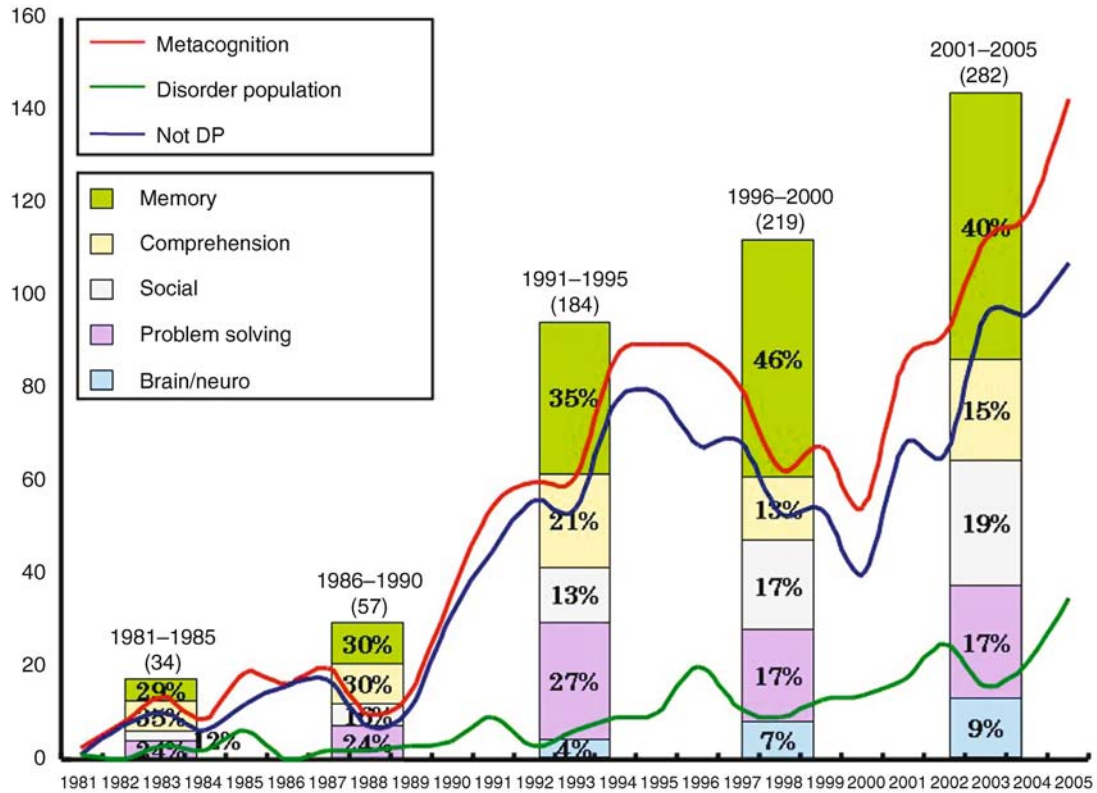
New Directions in Metacognition Research

Figure 1 shows differentially increasing trends (the number of papers) in the five research areas from 1981 to 2005.

The following characteristics can be pointed out: (i) in the 1980s, most research focused on memory, comprehension, and problem-solving with normal children and adults; (ii) in the late 1980s, social metacognition research began to increase; (iii) in 1992, brain/neuroscience research began (the journal of "Consciousness and Cognition" started), and (iv) research with the populations suffering from psychiatric and brain function disorders increased, corresponding closely to the increment of brain/neuroscience research. In addition to those general trends, the following changes are particularly noteworthy.

Metacognition in Social Contexts

A review on the previous research led to the realizations: (i) although online, or moment-to-moment, monitoring, control, and emotional reactions have been well investigated, implicit theories underlying society and culture were not paid much attention, and (ii) most research has put too much emphasis on metacognitive judgments within the individual, and, therefore, failed to put into perspective the role of metacognition on others and situations [4]. On the basis of those realizations,



Metacognition. Figure 1 Trends in the five areas of metacognition research from 1981 to 2005. (a) 1358 articles in peer-reviewed journals were retrieved, by searching PsycInfo database with the keyword "metacognition." (b) Five bar graphs indicate the percentages for the total number of articles published during 5 years in the five areas. (c) Line graphs delineate the increasing trend of research in each area from 1981 to 2005.

M

social cognition researchers recently began to address the importance of metacognitive perspectives and accordingly to investigate theories of mind, stereotypes, naïve psychology, and even further critical thinking in discussion situations as well as decision-making processes. Especially, the processes in which creative thinking is generated through discussions with others deserve special attention because they require situational monitoring of grasping the situation and social metacognitive abilities of flexibly collaborating with others.

Expertise and Metacognition

Metacognition facilitates the progress in expertise. Expertise can be categorized into routine and adaptive expertise [6]. Routine experts carry out a predetermined (or routinized) sequence of procedures accurately and quickly. Adaptive experts, on the other hand, not only carry out such procedures (or strategies) effectively, but because they deeply understand the utility and limitations of those procedures, they can also flexibly and appropriately adjust and modify them so as better to cope with incessantly changing demands of the situation. To become an adaptive expert, therefore, it is not sufficient just to be able to apply previously acquired declarative and procedural knowledge to the task, but one needs to expand expertise constantly, to attempt self-improvement, and to gain many experiences of reflective practice with conditional knowledge and strategies.

To facilitate the acquisition of adaptive expertise in students' learning, metacognitive tool (e.g., computers – which allow to externalize tacit thinking processes and monitor metacognitive strategies) and teachers' adaptive metacognition (e.g., knowledge of how to create social environments to support reflective discourse) are drawing attention from researchers [6,7].

Frontal Lobe Dysfunction and Metacognition

In the last decade, researchers have attempted to identify the brain regions that control metacognitive functions, especially the executive function involving monitoring and control, using neuroimaging techniques (e.g., positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG)), by examining higher-level mental activities in the brain [8,9].

Patients who are in the pathological states involving the frontal lobes (e.g., traumatic brain injury, frontal strokes, dementia, schizophrenia, attention deficit disorder, Alzheimer's disease, Korsakoff's syndrome) suffer from disorders in cognitive monitoring (e.g., error detection, ►source monitoring in memory retrieval) and cognitive control (conflict resolution, error correction, inhibitory control, emotional regulation). They also suffer from disorders not only in executive functions but also in self-appraisal. However, they do not show disorders in implicit memory (e.g., routinized procedural knowledge), because it requires no active and conscious metacognitive monitoring functions.

The regions that control the error monitoring system are located in the medial areas of the frontal lobe. The fact that the task requiring cognitive and emotional controls activates its mid-frontal areas suggests that a common neuroanatomy underlying those executive controls might exist. For the time being, however, it is still unknown whether this neuroanatomy is a set of independent modules or an integrated cognitive-emotional system that is located in the midfrontal areas.

Social Neuroscience and Metacognition

To live a social life, human beings need to figure out what the other person thinks, wants, and intends to do, and, at the same time, to make appropriate judgments on what actions should be taken accordingly.

Amodio and Frith [10] conducted meta-analyses on neuroscientific findings to determine in what regions of the brain are located the following functions of social cognition: (i) mentalizing, or theory of mind (TOM) (e.g., self-reflection, person perception, making inference about the other's thought and intent), (ii) outcome monitoring linked to the reward system (reward and punishment), and (iii) action monitoring. The analyses revealed that these functions are located in the medial prefrontal cortex (MPFC).

References

1. Chambres P, Izaute M, Marescaux PJ (2002) Metacognition: Process, function and use. Kluwer Academic, Norwell, MA
2. Paris SG, Paris AH (2001) Classroom applications of research on self-regulated learning. Educ Psychol 36:89–101
3. Kuhn D (2000) Metacognitive development. Curr Dir Psychol Sci 9:178–181
4. Hacker DJ, Dunlosky J, Graesser AC (1998) Metacognition in educational theory and practice. LEA, New Jersey
5. Perfect T, Schwartz B (2002) Applied metacognition. Cambridge University Press, Cambridge, MA
6. Lin X, Schwart DL, Hatano G (2005) Toward teachers' adaptive metacognition. Educ Psychol 40:245–255
7. Azeved R (2005) Using hypermedia as metacognitive tool for enhancing student learning?: The role of self-regulated learning. Educ Psychol 40:199–210
8. Fernandez-Duque D, Baird JA, Posner MI (2000) Executive attention and metacognitive regulation. Conscious Cogn 9:288–307
9. Pannu JK, Kaszniak AW (2005) Metamemory experiments in neurological population: a review. Neuropsychol Rev 15:105–130
10. Amodio DM, Frith CD (2006) Meeting of minds: The medial frontal cortex and social cognition. Nat Rev 7:268–277

Metalearning

►Metacognition

Metalloproteinases

Definition

Metalloproteinases are a family of proteolytic enzymes, known as the metzincin superfamily, that depend on Zn as a co-factor for endopeptidase activity. Several different subfamilies exist, including matrix metalloproteinases (MMPs), A disintegrin and metalloproteinases (ADAMs) and astacins. They can proteolytically degrade extracellular matrix proteins as well as a number of bioactive molecules (e.g. cell surface receptors). In the nervous system, metalloproteinases are implicated in cancer biology and other pathologies, and more recently during development. Secreted, transmembrane and membrane associated forms exist.

Metamorphosis

Definition

A radical change in body form and lifestyle between larval and adult stages of an organism

►The Phylogeny and Evolution of Amniotes

Metarepresentation

Definition

A representation of a representation, e.g. a thought about a thought or a belief about a belief.

►Theory Theory (Simulation Theory, Theory of Mind)

Metencephalon

Definition

Pons and cerebellum.

►General CNS

Method of Adjustment

Definition

A psychophysical procedure in which an observer adjusts stimulus intensity: Increasing intensity until s/he just perceives (ascending trials), or decreasing a clearly perceptible intensity until s/he just fails to perceive the stimulus (descending trials).

►Psychophysics

M

Method of Constant Stimuli

Definition

A psychophysical procedure in which each of a fixed set of stimuli (ranging near the threshold) is presented repeatedly in random order; the stimulus value yielding a detection response in 50 percent of the time is taken as the threshold.

►Psychophysics

Method of Limits

Definition

A psychophysical procedure in which stimulus intensity is varied independently of the observer (by the experimenter or computer program) until the observer

just perceives (ascending trials), or just fails to perceive the stimulus (descending trials).

►Psychophysics

Methylphenidate

Definition

Methylphenidate is a stimulant drug that inhibits the noradrenaline and dopamine transporters. The drug is used in the treatment of patients with attention deficit hyperactivity disorder (ADHD).

►Attentional Disorder
►Stimulants

1-Methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MTPT)

Definition

MTPT is a meperidine derivative that is used for experimental studies in a non-human primate model of ►Parkinson disease.

►Parkinson Disease

Metric, Metric Space

Definition

A coordinate system for measuring arbitrary spaces. Measurements and judgments about the similarity or relatedness of objects require an explicitly or implicitly defined metric by which to compare them. For example, a blue ball on the ground and another blue ball on the roof are similar if the metric is color or some quantification of shape, but are relatively dissimilar in terms of spatial location. Scale is of course a critical factor in such judgments – on a continental scale, for example, the two balls are in nearly identical locations. Objects can be located as points or regions within metric spaces according to their properties; e.g. with a color metric, our ball would be located at a point in the blue spectrum. The distance between two objects in the relevant metric space is a measure of their similarity; e.g. blue is more similar to green than it is to red.

Meynert Cells

Definition

Meynert (nineteenth century Austrian psychiatrist) cells make up the nucleus basalis neurons in the basal part of the forebrain. They are cholinergic and project widely to the cerebral cortex. The term Meynert cell is also an old term for large pyramidal cells found in occipital cortex near the calcarine fissure. Meynert also gave the first description of “association neurons.”

Microaerobic

Definition

Living, active, or occurring only in the presence of low concentrations of oxygen.

Microampullary Organ

►Electroreceptor Organs

Microarray, DNA Chip

Definition

A technology that allows simultaneous measurement of the expression levels for up to tens of thousands of genes (genome-wide expression profiling) in various cells and tissues and under different conditions.

Microarray Analysis of Molecular-Genetic Controls over Development of Neuronal Subtypes

Noriyuki Kishi[1], U. Shivraj Sohur[1], Bradley J. Molyneaux[1], Paola Arlotta[2], Jeffrey D. Macklis[1]
[1]MGH-HMS Center for Nervous System Repair, Departments of Neurosurgery and Neurology, and Program in Neuroscience, Harvard Medical School; Nayef Al-Rodhan Laboratories, Massachusetts General Hospital; Department of Stem Cell and Regenerative Biology, and Harvard Stem Cell Institute, Harvard University, Boston, MA, USA
[2]Center for Regenerative Medicine, Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Synonyms

Characterization of neuronal subtypes by microarrays; Microarray analysis using pure neuronal subpopulations; Identification of neuronal subtype-specific genes by microarrays

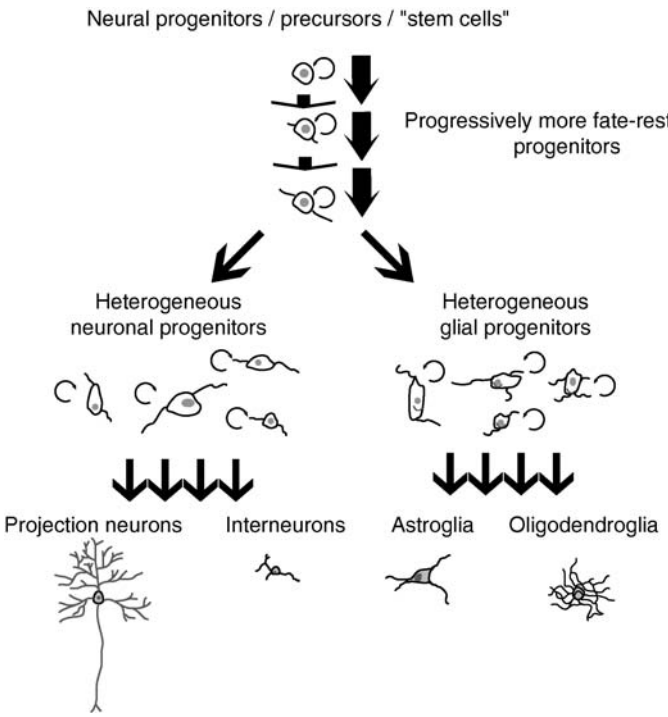
Definition

Emergence of microarray technology is now enabling molecular-genetic analysis of developmental controls for neuronal subpopulations in the cellularly heterogeneous brain.

Characteristics

Cellular Heterogeneity in the CNS

The central nervous system (CNS) is composed of three major cell-types: neurons, astroglia, and oligodendroglia (Fig. 1), and these cell types are differentiated from neural progenitors/precursors/"stem cells," which have self-renewal capacity and multipotency (diverse populations of neural precursors are often termed "neural stem cells," though many types of data indicate that these are quite heterogeneous by region and developmental stage) [1]. Neurogenesis is a very involved process: unlike other tissues, there are hundreds of intermixed neuronal subtypes in the mammalian brain [2–4]. The mechanisms by which such a rich neuronal diversity is produced in the CNS are poorly



Microarray Analysis of Molecular-Genetic Controls over Development of Neuronal Subtypes.
Figure 1 Diversity of neural lineage. There is progressive differentiation of early neural progenitors/precursors/"stem cells," by which they become more fate-restricted by regional type, neuron subtype, and neuronal-glial lineage. Subsequently, neural progenitors include heterogeneous neuronal and glial progenitors. Heterogeneous neuronal progenitors produce related groups of distinct mature neuronal subtypes. Morphologically and functionally, neurons are subdivided into two major classes, excitatory projection neurons that send axons long distances, and inhibitory and local interneurons.

understood. During the development of the CNS, neuronal progenitors undergo precise stepwise differentiation to ultimately produce the complex variety of neuronal subtypes that populate the mature brain. Morphologically, neurons are divided into two broad categories: (i) projection neurons, which extend axons to distant target areas, and (ii) interneurons, which make local connections. Projection neurons and interneurons are further subclassified by location, neurotransmitter production or sensitivity, electrophysiological characteristics, and axonal connectivity and neuronal circuits within which they send projections. Gene expression analysis in the brain is generally complicated by the coexistence of many different cell types, resulting in high background noise and the masking of small differences in cell type-specific gene expression.

The relative lack of approaches for efficient isolation of pure neuronal populations, and the difficulties involved with analysis of minute amounts of mRNA, have previously hampered progress toward understanding the molecular development of neuronal subtypes. However, the rapid emergence of microarray technologies, as well as development of approaches for isolation of neuronal subtypes have provided for a synergistic advance in the field. ►DNA microarrays (also known as gene chips or gene arrays) are a collection of DNA spots representing individual genes, arranged on a chip, and used for monitoring expression levels of thousands of genes simultaneously, thus allowing comparison of thousands of genes between different populations.

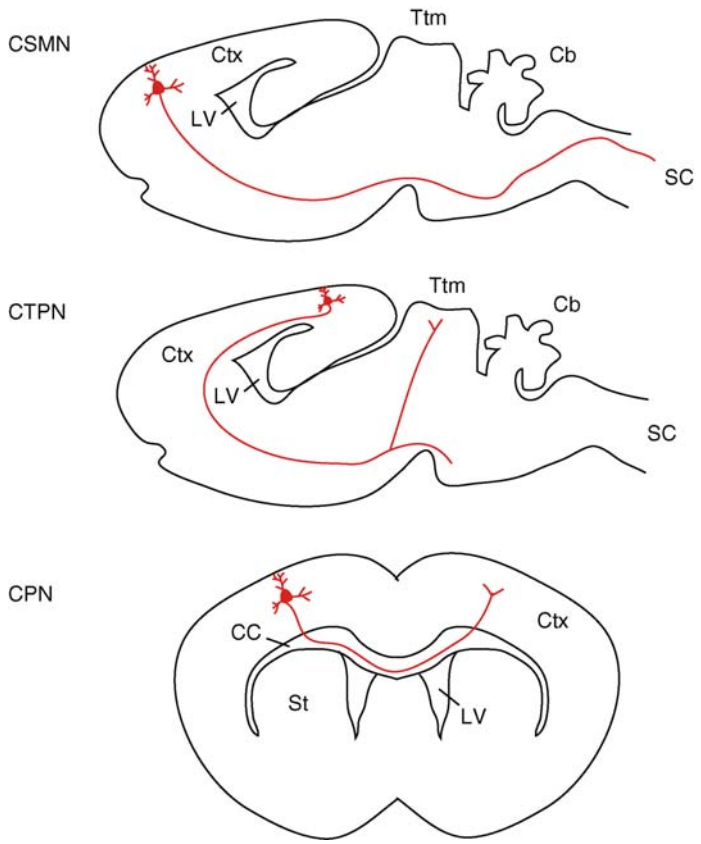
In this essay, we review three recent approaches using microarray analysis to investigate the molecular developmental controls and/or identity of specific brain neuronal subtypes.

Molecular Controls over Development of Corticospinal Motor Neurons (CSMN) and Other Forebrain Neuronal Populations

Our laboratory has begun to uncover molecular controls over the development of corticospinal motor neurons (CSMN; upper motor neurons; residents of layer V of the cerebral cortex) and other forebrain projection neurons (Fig. 2). CSMN degeneration is a key component of motor neuron degenerative diseases, including amyotrophic lateral sclerosis (ALS), and CSMN injury contributes critically to the loss of motor function in spinal cord injury. The anatomical and morphological development of CSMN have been extensively characterized, but the genetic mechanisms that control their development were previously unknown. Importantly, understanding the molecular controls over CSMN circuitry development might enable future strategies for therapeutic repair or modulation in disease.

To uncover the gene regulation programs of mouse CSMN development and other forebrain projection neurons, our lab has developed and established approaches using comparative microarray analysis of stage-specific gene expression by CSMN purified by ►fluorescence-activated cell sorting (FACS) [5]. Like other forebrain projection neurons, there are no specific markers for CSMN that could be utilized to isolate them. However, CSMN extend axons to the spinal cord, so they can be retrogradely labeled by injecting an appropriate retrograde label in the spinal cord. We developed an approach to retrogradely label CSMN with fluorescent latex microspheres; dissociate labeled cortex; and isolate the labeled CSMN by FACS. In addition to CSMN, we also purified two distinct cortical projection neuron subtypes, callosal projection neurons (CPN) and corticotectal projection neurons (CTPN) (Fig. 2). CPN are interhemispheric callosal projection neurons, a subset of which share lamina V location with CSMN, offering insight into genes that are involved in cell type specification rather than lamina specification by comparing between CSMN and CPN. CTPN are subcerebral layer V projection neurons extending axons to the tectum instead of the spinal cord, likely sharing some overlapping early developmental gene regulation programs with CSMN. Comparison between CSMN and CTPN can allow the identification of genes unique to CSMN among other highly related layer V subcerebral projection neurons. Using these FACS-purified pure cell populations at multiple developmental stages, we performed microarray analyses, and identified genes specifically expressed in CSMN as well as genes that are expressed in other projection neurons, but not in CSMN. We classified those genes into one of six groups based on expression profiles suggestive of specific role in distinct aspects of CSMN development: (i) genes that are expressed at higher levels in CSMN at all stages of development and might be important for the establishment and maintenance of CSMN identity; (ii) genes that are highly expressed in CSMN early in development and may be important for early CSMN specification; (iii and iv) genes that exhibit increasing levels of expression as CSMN develop and might control intermediate (iii) or later aspects (iv) of CSMN differentiation; (v) genes that are expressed at higher levels in CSMN compared to the highly related population of CTPN and are representative of the small class of genes that differentiate CSMN from other subcerebral projection neurons of layer V; (vi) genes that are negative markers of CSMN but that are expressed in CPN or CTPN.

Thus, we identified a number of CSMN-specific genes, including *COUP-TF1 interacting protein 2* (*Ctip2*, also known as *Bcl11b*). *Ctip2* had very recently been identified by Kominami and colleagues to have a critical role in the immune system, controlling T cell subtype specification and survival in the developing thymus, but had not been investigated in the CNS. Ctip2 is expressed at high levels in layer V of cortex, and



Microarray Analysis of Molecular-Genetic Controls over Development of Neuronal Subtypes.
Figure 2 Subtypes of cortical projection neurons. Arlotta et al. analyzed three distinct populations of cortical projection neurons [5]. CSMN (corticospinal projection neurons) are located in the sensorimotor area of the neocortex and maintain primary projections to the spinal cord. CTPN (corticotectal projection neurons) are located in the visual area of the neocortex and maintain primary projections to the superior colliculus of the tectum. CPN (callosal projection neurons) are primarily located in layers II/III, V and VI, and extend their axons across the corpus callosum to the contralateral hemisphere. Cb; cerebellum, CC; corpus callosum, Ctx: neocortex, LV: lateral ventricle, SC: spinal cord, St: Striatum, Ttm: tectum. (Adapted from Molyneaux, Arlotta et al. *Nat Rev Neurosci*, 2007 [2].)

expressed both in CSMN and CTPN, but not in CPN, indicating that Ctip2 is expressed at high levels in subcerebral projection neurons which extend axons to outside of the cortex. In *Ctip2* mutant mice, CSMN axons exhibit defects in fasciculation, outgrowth, and pathfinding, resulting in failure of CSMN to connect to the spinal cord [5]. Interestingly, Arlotta, Molyneaux and others in our lab have recently identified that *Ctip2* in the *Gsh2* developmental domain plays a totally different and critical role in the proper differentiation of striatal medium spiny neurons and the patch-matrix cytoarchitectural organization of the striatum.

Another CSMN-specific gene, *Forebrain embryonic zinc finger-like* (*Fezl*, recently renamed *Fezf2*) [6], is also expressed in CSMN and CTPN, like *Ctip2*. However, unlike *Ctip2*, *Fezl* is expressed in ventricular zone and subventricular zone progenitors of subcerebral neurons, in addition to subcerebral neurons themselves. *Fezl* is centrally involved in the birth and specification of CSMN. Importantly, in *Fezl* mutant mice, the entire population of both CSMN and CTPN is never born in the cortex. In addition, both anterograde and retrograde labels confirm the total absence of the corticospinal tract in *Fezl* mutant mice, indicating that no other neurons compensate to form such circuitry. Gain-of-function analysis using *in vivo* electroporation showed that overexpression of *Fezl* in cells that give rise to superficial layer neurons results in an accessory layer of *Ctip2*-expressing subcerebral neurons that send axons toward the spinal cord, further reinforcing that *Fezl* plays a critical role in the specification of subcerebral projection neurons.

As a third example of critical regulators of the development of CSMN and other corticofugal neurons, Lai, Jabaudon and others in our lab recently identified *Sox5* as regulating the sequential generation

of cortical projection neuron diversity [7]. It represses the onset of differentiation of CSMN, thereby allowing generation of the other corticofugal neuron types. *Ctip2*, *Fezl*, *Sox5*, and a larger program of molecular-genetic controls over CSMN differentiation all were identified by the original microarray analysis.

Molecular Analysis of Excitatory and Inhibitory Neurons in the Adult Forebrain

Nelson and colleagues used microarray analysis to propose a molecular taxonomy of major neuronal classes in the adult forebrain [8]. They identified various neuronal subtypes by retrograde labeling with a fluorescent tracer, or using fluorescently labeled neurons from transgenic mice. In these transgenic mice, specific neuronal subtypes are visualized with green/yellow fluorescent protein (GFP and YFP, respectively) driven by the promoters *Thy1*, *Gad1*, and *Gad2*. Thy1 is an immunoglobulin superfamily member that is expressed by excitatory projection neurons in many parts of the nervous system, as well as by several nonneuronal cell types, including thymocytes. Gad1/2 are glutamic acid decarboxylase 1 or 2, and are expressed in distinct subpopulations of inhibitory GABAergic interneurons. Using these transgenic mice, they defined 12 neuronal populations characterized by neurotransmitters and electrophysiological properties, and analyzed gene expression profiles by microarray. Based on similarity of the gene expression, they classified these 12 populations, showing that this molecular taxonomy largely parallels the traditional classification criteria (e.g. GABAergic neurons vs. glutamatergic pyramidal neurons, neocortex vs. hippocampus vs. amygdala).

Molecular Analysis of Striatal Projection Neuron Subtypes

Yang and colleagues analyzed differential gene expression between striatal projection neuron subtypes using FACS-purified cell populations from ►GENSAT project (Gene Expression Nervous System Atlas) BAC transgenic mice [9,10]. In the striatum, 95% of the neurons are projection neurons called medium spiny neurons (MSNs), and these neurons are subdivided into two morphologically indistinguishable neuronal subtypes: striatonigral MSNs and striatopallidial MSNs. Current understanding suggests that these two projection neuron pathways provide balanced but antagonistic influences on the basal ganglia output and behavior. It is thought that their functional imbalance is involved in movement disorders, such as Parkinson's and Huntington diseases, and psychiatric disorders including schizophrenia and depression.

Using FACS, Yang and colleagues isolated striatonigral MSNs and striatopallidial MSNs for microarray studies from mice containing cell type-specific regulatory elements that express enhanced green fluorescent protein (EGFP) specifically in MSN subtypes. Their analysis identified a new set of differentially expressed genes in addition to known MSN subtype-specific genes, such as *Penk1* and *Drd2*. They identified the transcription factors *Zfp521* and *Ebf1* as new striatonigral MSN-specific genes, which functionally interact with each other. Importantly, they showed that the number of striatonigral MSNs and their axonal projections to the substantia nigra are affected in *Ebf1* mutant mice, whereas striatopallidal MSNs are preserved, demonstrating that these striatonigral MSN-specific genes play a critical role in the development of striatonigral MSNs.

Molecular Analysis of Neuronal Subtypes in the Future

Although developmental, precursor, and stem cell biology may enable future therapeutic approaches to some diseases of the nervous system, including neurodegenerative diseases, little is known about individual molecular and genetic characteristics of individual neuronal subtypes. Understanding regarding molecular controls over development of specific neuronal subtypes is still in its infancy. Recent microarray technologies have enabled analysis of broad gene expression profiles using smaller amounts of RNA (nanogram levels). New markers and control genes now enable dissection of neuronal diversity more and more deeply. Additionally, availability of genetic labeling using fluorescent proteins under neuronal subtype specific promoters has dramatically increased. These approaches will promote understanding of the molecular development and molecular anatomy, and functional analysis of individual neuronal subtypes, and reveal gene regulation underlying precise development and potentially regeneration of specific neuronal subtypes.

Acknowledgments

This work was partially supported by grants from the National Institutes of Health (NS45523, NS49553, NS41590), the Harvard Stem Cell Institute, the Spastic Paraplegia Foundation, the ALS Association, and the International Rett Syndrome Foundation to J.D.M.. P.A. was partially supported by a Claflin Distinguished Scholar Award, the Harvard Stem Cell Institute, the Spastic Paraplegia Foundation, and a grant from the ALS Association. B.J.M. was supported by the Harvard M.S.T.P. and the United Sydney Association. U.S.S. was partially supported by fellowships from the CP Repair Research Fund, and the Edward R. and Anne G. Lefler Center. N.K. was supported by a fellowship from the Japan Society for the Promotion of Science.

References

1. Gage FH (2000) Mammalian neural stem cells. Science 287:1433–1438

2. Molyneaux BJ, Arlotta P, Menezes JR, Macklis JD (2007) Neuronal subtype specification in the cerebral cortex. Nat Rev Neurosci 8:427–437
3. Rallu M, Corbin JG, Fishell G (2002) Parsing the prosencephalon. Nat Rev Neurosci 3:943–951
4. Sohur US, Emsley JG, Mitchell BD, Macklis JD (2006) Adult neurogenesis and cellular brain repair with neural progenitors, precursors and stem cells. Philos Trans R Soc Lond B Biol Sci 361:1477–1497
5. Arlotta P, Molyneaux BJ, Chen J, Inoue J, Kominami R, Macklis JD (2005) Neuronal subtype-specific genes that control corticospinal motor neuron development in vivo. Neuron 45:207–221
6. Molyneaux BJ, Arlotta P, Hirata T, Hibi M, Macklis JD (2005) Fezl is required for the birth and specification of corticospinal motor neurons. Neuron 47:817–831
7. Lai T, Jabaudon D, Molyneaux BJ, Azim E, Arlotta P, Menezes JR, Macklis JD (2008) SOX5 controls the sequential generation of distinct corticofugal neuron subtypes. Neuron 57:232–247
8. Sugino K, Hempel CM, Miller MN, Hattox AM, Shapiro P, Wu C, Huang ZJ, Nelson SB (2006) Molecular taxonomy of major neuronal classes in the adult mouse forebrain. Nat Neurosci 9:99–107
9. Gong S, Zheng C, Doughty ML, Losos K, Didkovsky N, Schambra UB, Nowak NJ, Joyner A, Leblanc G, Hatten ME, Heintz N (2003) A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. Nature 425:917–925
10. Lobo MK, Karsten SL, Gray M, Geschwind DH, Yang XW (2006) FACS-array profiling of striatal projection neuron subtypes in juvenile and adult mouse brains. Nat Neurosci 9:443–452

Microarrays

Definition

Microarrays consist of thousands of cDNAs printed on a glass slide. Alternatively, the GeneChip® arrays (Affymetrix, Santa Clara, CA, USA) consist of quartz chips on which up to 500,000 oligonucleotide probes can exist on an area of 1.28 cm2. Both are used to bind labelled cDNA derived from tissues or cells of interest. Differences in the intensity of binding between cDNA samples can be used to assess differences in RNA expression levels between experimental samples. This technology can pinpoint differences between normal and diseased tissues, identify genes crucial to certain disease processes, and generate gene expression profiles unique to individual tissue samples. Such "fingerprints" are proving useful in assignment of identity to samples and revealing relationships between them.

►Bioinformatics

Microcephaly

Definition

Developmental brain disorder characterized by a small-sized brain and skull, often associated with mental retardation.

►Endocrine Disorders of Development and Growth

Microcircuits

Patterns of interaction between nerve cells which process information such as the odor patterns.

►The Proust Effect

Microdialysis

Definition

A technique for measuring extracellular concentrations of substances (e.g. neurotransmitters) in tissues, usually in vivo, by means of a small probe equipped with a semi-permeable membrane. Substances may also be introduced into the extracellular space through the membrane.

Micro-electrode Array (MEA)

Definition

Device for *in-vivo* or *in-vitro* multi-site, long-term recordings of the electrical activity of neuronal populations. MEAs may be passive (arrays of metal or silicon electrodes), or active (electrodes and amplifiers are integrated in the same chip). Since their introduction in the early 80's due to advancements in micro-fabrication technologies, these devices have enabled the experimental investigation of the collective dynamics and computational properties of large populations of neurons.

►Extracellular Recording

Microelectrophoresis

►Microiontophoresis and Micropressure Ejection

Microfilament

Definition

A thin (approximately 7 nm in diameter) cytoskeletal filament composed of a linear polymer of actin subunits.

Microglia

Definition

(Greek mikros, small; glia, glue) Small supporting cells of the central nervous system (CNS), serving as brain-resident phagocytes and antigen-presenting cells. They normally exist in a resting state, but a trigger (injury, illness) can activate them to support injured tissue. If their activation is not properly regulated, it can have devastating side effects, including neuroxicity.

►Microglia: Functions in Immune Mechanisms in the Central Nervous System

Microglia: Functions in Immune Mechanisms in the Central Nervous System

Akio Suzumura
Department of Neuroimmunology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan

Definition

Immune mechanisms are implicated in various pathological conditions in the central nervous system (CNS). Microglia are resident immune cells functioning as either antigen presenting cells or effector cells that destroy myelin or neurons. In contrast, they also produce a variety of neurotrophins to support neuronal survival. Microglia-derived cytokines induce proliferation of astrocytes, also suggesting their possible role in gliosis formation.

Characteristics

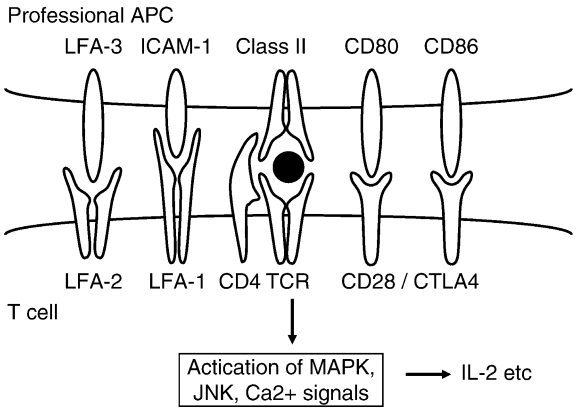
Quantitative Description

Since ►microglia first appear in the early postnatal period in the brain parenchyma, they may play a role in the development of neural cells and/or neuronal network. Another important role of microglia is the function as immune cells in the CNS. Microglia provide a first line defense in either infection or injury of the brain. They express ►CD14 and a variety of ►toll-like receptors (TLR). Microglia express TLR1,2,3,4,6, which are upregulated in inflammatory lesions in the CNS. Microglia recognize lipopolysaccaride (LPS) or peptidoglycan on the bacterial membrane non-specifically via these receptors to produce ►cytokines, such as IL-1β, IL-6, TNFα, and other inflammatory mediators like nitric oxide (NO) or reactive oxygen species (ROS). Microglia are also activated through complement receptors and Fc receptors. This classical innate immunity had been considered to be only a defense mechanism in the CNS. The brain had long been considered as an immunological privileged site where specific immune responses do not occur. However, studies in the last three decades have clearly disclosed that this is no more the case. In acquired immunity, microglia play a critical role, either as antigen presenting cells (APC), or effector cells. Microglia, as other neural cells, do not usually express class II ►major histocompatibility complex (MHC) antigen that is essential for antigen presentation to T cells. However, in some pathological conditions, microglia are induced to express class II MHC antigens. Although astrocytes and endothelial cells can be class II MHC antigen-positive, the functional APC that express all other co-stimulatory molecules are microglia.

Microglia also function as effector cells in inflammation, demyelination, and gliosis via production of various inflammatory mediators. In addition, the recent studies have shown the involvement of immune and/or inflammatory mechanisms in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington disease (HD). Activated microglia are accumulated in or around degenerating neurons in these diseases, and have been shown to play a principal role in neuronal degeneration and regeneration.

Microglia as Antigen Presenting Cells

The immune response is initiated when protein antigen is presented to T cells by APC. The APC process



Microglia: Functions in Immune Mechanisms in the Central Nervous System. Figure 1 Molecules and signals in antigen presentation. Antigens (*black circle*) processed and expressed on class II MHC antigens by professional antigen presenting cells (APC) are recognized by T cell receptors (TCR), which activates MAP kinase (MAPK), JNK and Ca^{2+}-NFAT system. These signal cascades activate transcriptional regulation region to produce T cell activating factors including interleukin-2 (IL-2).

antigen, either foreign or self, by internalizing and digesting it into peptide fragments. The processed peptide fragments are then expressed on the surface of APC as a form of MHC-peptide complex. When the MHC-peptide complex interacts with T cell receptors (TCR), subsequent T cell activation occurs (Fig. 1). Class II MHC molecules present antigen to CD4-positive T cells, while class I MHC molecules present antigen to CD8-positive T cells. Binding of the MHC-peptide complex to the TCR is critical, but not sufficient, for activation of T cells. There should be several co-stimulatory molecules that interact with the ligands on T cells for sufficient activation. These co-stimulatory molecules include B7.1 (CD80), B7.2 (CD86), leukocyte function associated molecule-3 (LFA-3), intercellular adhesion molecule-1 (ICAM-1), ICAM-2 and ICAM-3. They bind to ligands on T cells to form ligand pairs such as B7.1-CD28/CTLA4, B7.2-CD28/CTLA4, LFA-3-CD2, ICAM-1, 2 or 3-LFA-1. Interaction of T cells and APC occurs in a MHC-restricted manner. The T cells recognize a foreign antigen only when the antigen forms a complex with self MHC molecules on APC. Therefore, the cells expressing class II MHC and co-stimulatory molecules constitutively are considered to be professional APC. Those include macrophages, B cells, dendritic cells, and Langerhans cells. Non-professional APC differs from the professional APC by expressing little or no MHC class II molecules constitutively, and by not having a complete set of co-stimulatory molecules. The candidates for the non-professional APC in the CNS are microglia, astrocytes and endothelial cells. They do not usually express class II MHC antigen constitutively. These cells, however, are induced to express class II MHC molecules with certain inflammatory cytokines, especially IFNγ [1], and also express some of the co-stimulatory molecules [2]. There are evidences that endothelial cells, astrocytes, and pericytes can process and present protein antigens to primed CD4-positive T cells in vitro, but the specific role of these cells as APC in vivo is still unclear. At least, astrocytes do not usually express class II MHC antigens in vivo, even in the presence of inflammatory cells. Since microglia have very similar characteristics to macrophages and are induced to express class II MHC antigens as discussed above, microglia are the most possible candidates for APC in the CNS. Microglia express co-stimulatory molecules, such as B7, ICAM, LFA3, but only some in astrocytes. It has been shown that human microglia, but not astrocytes, express both B7-1 and B7-2, suggesting that microglia is a much more suitable candidate for local APC in the CNS. In fact, microglia when stimulated with IFNγ can present antigen to antigen-specific T cells in vitro. Microglia have been shown to function as APC in pathological conditions in vivo [3]. In bone marrow chimera of experimental autoimmune encephalomyelitis (EAE)-susceptible and resistant animals, EAE lesions developed only when the perivascular microglia were replaced with an EAE-susceptible strain, suggesting that antigen presentation by perivascular microglia is critical for the development of EAE lesions.

Professional APC such as dendritic cells or macrophages produce IL-12 and IL-18. IL-12 and IL-18 are key cytokines in the development of autoimmune processes, regulating differentiation of naïve T cells into T helper 1 (Th1). To exert its activity, IL-12 needs to form a heterodimer of P35 and P40; homodimer of P40 suppresses the functional heterodimer. Immature IL-18 is cleaved by caspase-1 to become functionally mature IL-18 that induces differentiation of Th1 and cytotoxic activity of NK and T cells. Microglia produce a functional heterodimer of IL-12 upon stimulation. LPS-stimulated microglia have bioactivity of IL-18 to induce INFγ production by T cells in synergism with IL-12. This suggested that microglia also express caspase-1.

Another IL-12 family cytokine, IL-23, is a heterodimer of IL-12 p40 and p19. It has been shown recently that p35 knockout mice that cannot produce IL-12 develop EAE, while p40 knockout mice that cannot produce IL-12 and IL-23 do not, suggesting that IL-23, but not IL-12, is a critical cytokine for the Th-1 development [4]. IL-27 is also an IL-12 family member, and plays a role in the early stage of Th-1 development. Both IL-23 and IL-27 are produced by microglia upon activation [5]. Since all Th-1 inducing cytokines are produced by microglia in the CNS, while IL-4 that induces Th-2 response is not

produced, a Th-1 response occurs much more easily in the CNS than a Th-2 response.

The most potent stimulus to induce MHC class II antigen on neural cells is IFNγ. IFNγ has been considered to be produced exclusively by lymphoid cells, such as T cells or NK cells. However, microglia can produce IFNγ upon stimulation with IL-12 and/or IL-18 [6]. Thus, induction of MHC antigen expression on neural cells may occur without immune cell infiltration in the CNS.

Immune Mechanisms in Neurodegenerative Disorders

Recent evidence suggests the presence of immune and/or inflammatory mechanisms in neurodegenerative disorders [7]. In AD, PD and HD, there is no obvious accumulation of activated immune cells. Nevertheless, potent inflammatory molecules such as cytokines, chemokines, free radicals and complement are detected in the cerebrospinal fluid and CNS lesions. Amyloid-β (Aβ) or tau protein reportedly activates microglia to produce neurotoxic substances to kill neurons. Visualizing microglial activation in vivo using positron emission tomography (PET) with activated microglial marker, PK11195, clearly demonstrated accumulation of activated microglia in the early stage of AD and HD. Therefore, microglia may play a critical role in neurodegeneration and prevention of the active inflammation may suppress disease process. A non steroidal anti-inflammatory drug (NSAID) was used for this purpose to prevent the progression of AD, and gave favorable results.

In contrast, microglia can also produce neurotrophic factors, such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin-3, 4 (NT-3,4), suggesting neuroprotective functions of microglia. Taken altogether, immune and inflammatory mechanisms may be involved in neurodegeneration, where microglia play a critical role on both neuronal degeneration and regeneration. The mechanisms of how microglia exert the opposite effects on neurons are currently unknown. There may be distinct subpopulations of microglia, toxic versus protective. Alternatively, some specific ligand-receptor complex may decide the functions of microglia.

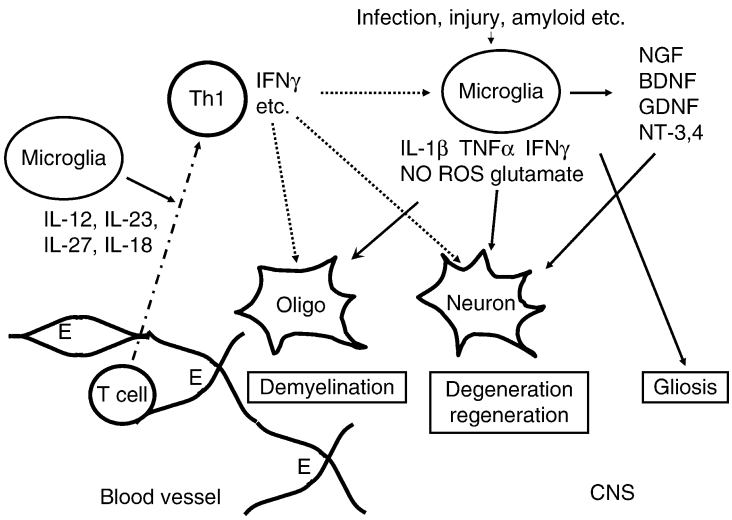
Microglia as Effector Cells in Inflammation and Neuronal Degeneration

Microglia produce a variety of cytokines, such as IL-1, IL-5, IL-6, IL-8, IL-10, IL-12 family, TNFα, and M-CSF, in response to LPS and/or IFNγ. These stimuli also induce chemokines, nitric oxide (NO), superoxide (O_2^-) and glutamate. TNFα, NO, O_2^- have been shown to destroy mylein and neuronal cells to induce demyelination and neuronal degeneration. Recently, it has been shown that the most neurotoxic factor from activated microglia is glutamate, which disturbs the mitochondrial respiratory chain to cause energy depletion in neurons [8]. TNFα was a candidate for neurotoxic factor from activated microglia. However, in our experimental conditions, TNFα did not kill neurons. Although TNFα by itself is not a potent neurotoxic factor, it induces glutamate production in microglia via upregulation of glutaminase. Interestingly, thus produced glutamate is released through the hemichannel of gap junctions but not through glutamate transporters [9]. Thus, microglia can act as effector cells in either inflammatory demyelination and neuronal degeneration. In addition, since IL-1β, TNFα and IFNγ induce proliferation of astrocytes in vitro, these microglia-derived cytokines may contribute to the formation of gliosis, a scar formation in the CNS (Fig. 2).

Recently, a great deal of attention has been focused on the relation between activated microglia through adenosine 5′-triphosphate (ATP) receptors and neuropathic pain [10]. Neuropathic pain is often a consequence of nerve injury through surgery, bone compression, diabetes, or infection. There is abundant evidence that extracellular ATP and microglia have an important role in neuropathic pain. The expression of the P2X4 receptor, a subtype of ATP receptors, is enhanced in spinal microglia after peripheral nerve injury model, and blocking pharmacologically and suppressing molecularly P2X4 receptors produces a reduction of the neuropathic pain. Several cytokines such as IL-1β, IL-6, and TNFα in the dorsal horn are increased after nerve lesion and have been implicated in contributing to nerve-injury pain, presumably by altering synaptic transmission in the CNS, including the spinal cord. Nerve injury also leads to persistent activation of p38 mitogen-activated protein kinase (MAPK) in microglia. An inhibitor of this enzyme reverses mechanical allodynia following spinal nerve ligation. ATP is able to activate MAPK, leading to the release of bioactive substances, including cytokines, from microglia. Thus, diffusible factors released from activated microglia by the stimulation of purinergic receptors may have an important role in the development of neuropathic pain.

Suppression of Microglial Functions as Therapeutic Strategy

Inhibitory cytokines such as TGFβ and IL-10 suppress the IFNγ-induced class II MHC antigen expression and LPS-induced cytokine production by microglia. Therefore, suppression of microglial functions by TGFβ or IL-10 may result in suppression of the disease process. As expected, these inhibitory cytokines successfully suppressed the development of EAE. The cAMP-elevating agents, either phosphodiesterase inhibitor or adenylate cyclase activator, suppress TNFα and NO production by microglia. These drugs have also effectively suppressed the development of EAE and clinical relapse of multiple sclerosis (MS). Analysis of



Microglia: Functions in Immune Mechanisms in the Central Nervous System. Figure 2 Functions of microglia in immune and inflammatory mechanisms in the CNS.Microglia produce a variety of neuroprotective and neurotoxic factors. These factors play a role on the development of demyelination, neuronal degeneration, regeneration, and gliosis. Infiltrating T cells, especially Th1 cells, activate microglia to function as effector cells in neuroinflammation. *Arrows* indicate functions of soluble factors from microglia, and *dotted lines* indicate functions of Th1-derived factors. E: endothelial cells, oligo: oligodendrocytes, other abbreviations are indicated in the text.

the cytokine profile in CD4-positive T cells during the treatment of MS shows that phosphodiesterase inhibitors induce a Th1 to Th2 shift. Since phosphodiesterase inhibitors upregulate IL-10 and down-regulate IL-12 production by microglia, this mechanism may be involved in the Th1 to Th2 shift to suppress MS relapse.

HMG Co-A reductase inhibitors (statins) may also be useful to suppress EAE via suppressing microglial activation, cytokine production and induction of MHC antigen. Statins are now the candidates for the treatment of MS, ischemic brain disease and neuronal degeneration.

As discussed above, neurotoxic glutamate is released from microglia via gap junctions. In addition, microglia produce glutamate by glutaminase using extracellular glutamine as a substrate. Thus, inhibitors for gap junction or glutaminase may be able to suppress glutamate from activating microglia without affecting physiological glutamate. These drugs are another candidate for the treatment of neurodegenerative disorders.

References

1. Suzumura A, Mezitis SGE, Gonatus N, Silberberg DH (1987) MHC antigen expression on bulk isolated macrophage-microglia from newborn mouse brain: induction of Ia antigen expression by gamma-interferon. J Neuroimmunol 15:263–278
2. De Simone R, Giampaolo A, Giometto B, Gallo P, Levi G, Peschle C, Aloisi F (1995) The costimulatory molecule B7 is expressed in human microglia in culture and multiple sclerosis acute lesions. J Neuropathol Exp Neurol 54:175–187
3. Hickey WF, Kimura H (1988) Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239:290–292
4. Gran B, Zhang GX, Yu S, Li J, Chen XH, Ventura ES, Kamoun M, Rostami A (2002) IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination. J Immunol 169:7104–7110
5. Sonobe Y, Yawata I, Kawanokuchi J, Takeuchi H, Mizuno T, Suzumura A (2005) Production of IL-27 and other IL-12 family cytokines by microglia and their subpopulations. Brain Res 1040(1–2):202–207
6. Kawanokuchi J, Mizuno T, Takeuchi H, Kato H, Wang J, Mitsuma N, Suzumura A (2006) Production of interferon-γ by microglia. Mult Scler 12:558–564
7. Zipp F, Aktas O (2006) The brain as a target of inflammation: common pathway link inflammatory and neurodegenerative diseases. Trends in Neurosci 29(9):518–527
8. Takeuchi H, Mizuno T, Zhang G, Wang J, Kawanokuchi J, Kuno R, Suzumura A (2005) Neuritic beading induced by activated microglia is an early feature of neuronal dysfunction toward neuronal death by inhibition of mitochondrial respiration and axonal transport. J Biol Chem 280:10444–10454
9. Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, Sonobe Y, Mizuno T, Suzumura A (2006) Tumor necrosis factor-a induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem 281:21362–21368
10. Inoue K (2002) Microglial activation by purines and pyrimidines. Glia 40(2):156–163

Microglial Cell

Definition

The microglial cell is the smallest of the neuroglial cells. It is of mesodermal origin and some can act as phagocytes absorbing and digesting up neuronal waste products and debris.

Microglial Signaling Regulation by Neuropeptides

KYOUNGHO SUK
Department of Pharmacology, School of Medicine, Kyungpook National University, Daegu, Korea

Definition

Neuropeptides are short-chain peptides found in brain tissue, with some functioning as neurotransmitters and others functioning as hormones. Recent studies indicated that neuropeptides may directly or indirectly regulate glial functions in the central nervous system (CNS). Described here are the effects of neuropeptides pituitary adenylate cyclase-activating polypeptide (PACAP) and corticotropin-releasing hormone (CRH) on inflammatory activation of microglia and intracellular signal transduction pathways associated with the microglial activation. As microglia are believed to function as the resident immune defense system of the brain and to participate in neuroinflammation in response to intrinsic or extrinsic stimuli, the neuropeptides may modulate immune and inflammatory responses in the CNS by influencing microglial signaling.

Characteristics

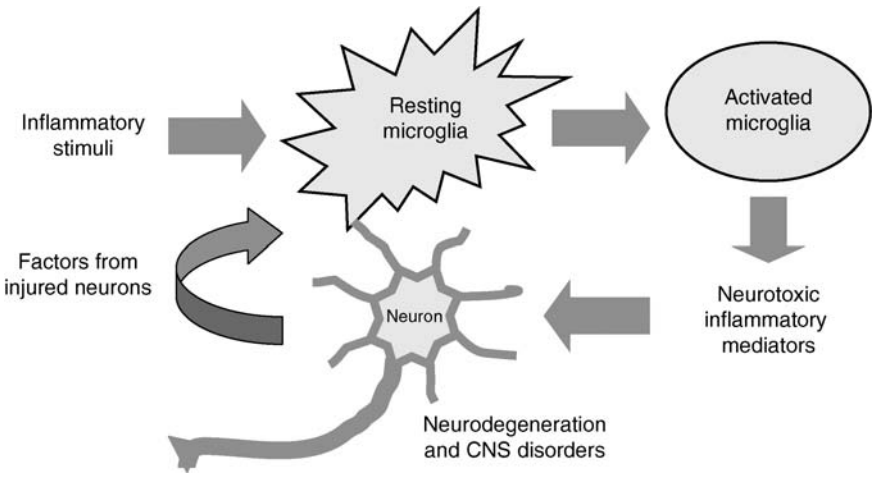
Description of the Structure/Process/Conditions

Microglia and Neuroinflammation

The central nervous system (CNS) consists of neuron and neuroglia. Neuroglia were once merely thought of as a structural support for neurons in the CNS. Increasing evidence now indicates that neuroglial cells actively participate in brain functions by nurturing neurons and facilitating neuronal activity. Four different types of neuroglial cells – oligodendrocytes, ependymal cells, astrocytes, and ►microglia – fulfill distinct tasks. Oligodendrocytes are the myelin-forming cells of the CNS and they ensure rapid signal conduction in the white matter. Ependymal cells constitute the lining of cerebral ventricles. Astrocytes provide guiding structures during development and they represent important elements for controlling the composition of the extracellular space mediating signals between the brain endothelium and the neuronal membrane. Microglial cells are immunocompetent cells in the brain and their functional role is best defined as the first responsive elements during pathologic events in the CNS [1]. Microglial cells are ubiquitously distributed in the CNS and comprise of up to 20% of the total glial cell population in the brain [2]. Microglial cells function in a manner similar to monocytes/macrophages in the periphery. Microglia, as the CNS resident phagocytes, migrate to the area of injured nervous tissue, and they engulf and destroy microbes and cellular debris. In response to brain injury or infection, microglia are mobilized to secrete various soluble immune mediators such as cytokines and chemokines, and they function as immunocompetent cells expressing MHC class I and II molecules. Activated microglia also secrete neurotoxic inflammatory cytokines and mediators such as tumor necrosis factor (TNF)α and nitric oxide (NO), which may initiate or amplify the neuroinflammatory responses [3,4] (Fig. 1). The activation of microglial cells may initially be aimed at protecting neurons. Activation of microglial cells and inflammatory products derived from them, however, have also been implicated in neuronal destruction commonly observed in various neurodegenerative diseases [4] (Fig. 1). Recent studies indicated that brain inflammation is closely associated with the pathogenesis of neurodegenerative diseases. Compared with inflammation in peripheral tissue, inflammation in the brain appears to follow distinct pathways and time courses. The major immune cells that respond to and produce inflammatory stimuli in the brain are microglia. The inflammatory responses in microglia are coordinately regulated by the production of cytokines, chemokines, proteases, and reactive oxygen or nitrogen species. These molecules function in a synergistic and/or antagonistic manner, eventually leading to neurodegeneration via inflammatory cascades. The activation of microglia is regulated by signals from neurons and astrocytes as well as various systemic signals.

Intracellular Signal Transductions of Microglial Activation

Microglia exert both positive and negative effects on the nervous system. As the first line of defense, microglia protect neurons against toxic insults, while the chronic and excessive activation of microglia may play direct or indirect roles in various neuropathologies [5]. The signals that activate microglia or that are produced by activated microglia could be neutralized in order to suppress the negative effects of microglia. Alternatively, intracellular signal transduction pathways that are involved in microglial activation could be interrupted to block microglial activation. Many endogenous and



Microglial Signaling Regulation by Neuropeptides. Figure 1 A role of microglial activation in neurodegeneration. Resting microglia (ramified type) can be activated by inflammatory stimuli such as LPS, IFNγ, and hypoxia. Activated microglia (amoeboid type) produce a variety of inflammatory mediators including nitric oxide, TNFα, and IL-1β, which in turn cause neuronal injury and neurodegeneration (and possibly other CNS disorders). Damaged neurons also act as a stimulus that induces neuroinflammation. This constitutes a vicious cycle by which the process of inflammation-mediated neurodegeneration is perpetuated.

exogenous agents have been demonstrated to influence the microglial signal transduction. Signal transduction pathways that have been shown to be associated with microglial activation include NF-κB, MAPKs, STAT/IRFs, and TLRs.

NF-κB constitutes a canonical pathway of microglial activation in neuroinflammation. NF-κB regulates a wide variety of inflammatory gene expressions in microglia, and its signaling pathways are well characterized. Upon the stimulation of microglia with a wide variety of inflammatory mediators, IκB kinase (IKK) is activated to phosphorylate IκB. Phosphorylated IκB triggers its degradation through the ubiquitin system, where the target molecule is masked by a chain of ubiquitins for degradation by the 26S proteasome. The free NF-κB can then translocate to the nucleus and activate the transcription of numerous inflammatory genes. NF-κB has been shown to mediate the transcriptional activation of CD40, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, chemokines, TNFα, interleukin (IL)-1 and other cytokines upon the stimulation of microglia with lipopolysaccharide (LPS; endotoxin), transglutaminase 2, S100B, thrombin, gangliosides, plasminogen, advanced glycation endproducts (AGEs), and neuromelanin. NF-κB also plays an important role in a number of neuropathology occurring in neurodegenerative processes and neuronal cell death [6, 7]. NF-κB activation can prevent the death of neurons by inducing the production of anti-apoptotic proteins. Molecular pathways upstream and downstream of NF-κB in neurons are being elucidated and may provide novel targets for therapeutic intervention in various neurological disorders. MAPK pathways have been implicated in the inflammatory activation of glial cells. MAPKs consist of three subgroups: ▶p38 MAPK, extracellular signal regulated kinase (ERK), and c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK). These kinases are activated by the phosphorylation of both tyrosine and threonine residues that is catalyzed by specific upstream MAPK kinase (MAPKK). Activated MAPKs phosphorylate their specific substrates on serine and/or threonine residues, thus ultimately leading to the activation of specific subsets of transcription factors. While ERKs are stimulated mainly by growth factors and tumor promoters, p38 MAPK and JNK/SAPK are activated by inflammatory stimuli and environmental stresses such as osmotic shock. In the CNS, ERKs and p38 MAPK have been shown to regulate the iNOS and TNFα gene expression in endotoxin-stimulated primary glial cultures. In addition, MAPKs play a crucial role in regulating the neurochemistry of N-methyl-D-aspartate receptors, their physiologic and biochemical/biophysical properties, and their potential role in pathophysiology [8]. JAK/STAT1 and IRF-1 constitute the main component of IFNγ signaling in microglia. IFNγ phosphorylates STAT1 through JAK and subsequently the IRF-1 expression is induced. As a transcription factor, these two gene products regulate the expression of numerous IFNγ-inducible genes, thereby playing a critical role in the cellular response to IFNγ. The specific inhibition of JAK by AG490 attenuated the IFNγ-induced NO production in microglia as well as in mixed glial cultures, thus demonstrating the critical role of JAK in IFNγ signaling in the glia. In contrast to the downstream

M

signaling events of microglial activation that have been partly elucidated, little is known about the early signaling events proximal to the plasma membrane. Toll-like receptors (TLRs) play a critical role in early innate immunity to invading pathogens by sensing microorganisms. TLRs are evolutionary conserved homologues of the Drosophila Toll gene, which recognize structural motifs that are only expressed on microbial pathogens called pathogen-associated molecular patterns (PAMPs). PAMPs include bacterial DNA, flagellin, and their cell wall components such as LPS, peptidoglycan, and lipopeptides. The stimulation of TLRs by these PAMPs initiates a signaling cascade that involves a number of Toll/IL-1 receptor (TIR) domain-containing adaptor proteins (MyD88, TIRAP/Mal, TRIF, TRAM), protein kinases (IRAK-1, IRAK-M, MAPK), and other signaling intermediates (TRAF6, Tollip). The TLR-initiated signaling pathways ultimately lead to the activation of NF-κB, PKR, STAT1, and IRFs. Some of these signaling pathways are involved in the microglial activation.

Regulation of the Structure/Process/Conditions

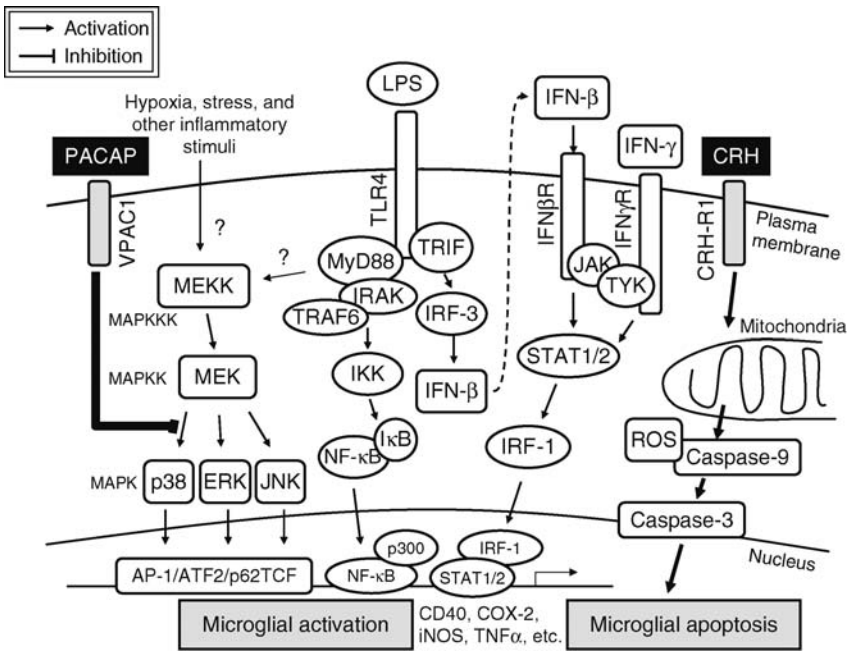
Regulation of Microglial Signal Transductions by Neuropeptides

►Neuropeptides are short-chain peptides found in brain tissue, with some functioning as neurotransmitters and others functioning as hormones. Recent studies indicated that neuropeptides may directly or indirectly regulate glial functions in the CNS. Among many neuropeptides, this essay focused on the effects of PACAP and CRH on inflammatory activation of microglia and intracellular signal transduction pathways associated with microglial activation.

Effect of PACAP

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide that was first identified as an activator of adenylate cyclase in rat anterior pituitary cells. PACAP is widely distributed in the brain and peripheral organs, notably in the endocrine pancreas, gonads, and respiratory and urogenital tracts. Consistent with its widespread distribution, PACAP exerts multiple actions in the CNS and periphery through three distinct receptor subtypes – PAC1, VPAC1, and VPAC2. In the CNS, PACAP is thought to act as a neurotrophic factor during development, whereas the neuropeptide seems to function as a neuroprotector against various insults in the adult brain [9]. PACAP also elicits a broad spectrum of biological effects on natural and acquired immunity [10]. PACAP has been shown to inhibit cytokine production and the proliferation of T cell, and to inhibit several macrophage functions, including phagocytosis, respiratory burst, chemotaxis, and cytokine production. It has also been shown that PACAP inhibits inflammatory activation of microglia through VPAC1 receptor. PACAP inhibited production of chemokines and CD40 expression from LPS-stimulated microglia. However, little information is available regarding the effect of PACAP on microglial signal transduction pathways. In one report, PACAP inhibited the JNK signaling pathway in endotoxin-activated microglia. PACAP inhibited TNFα production from rat microglia following spinal cord injury via a cAMP-dependent pathway. PACAP has also been reported to inhibit LPS-stimulated production of inflammatory mediators by inhibiting NF-κB activation. Moreover, PACAP inhibition of NF-κB-controlled gene expression was mediated via inhibition of CBP-NF-κB interaction. A recent study systematically evaluated the effect of PACAP on signal transduction of microglia initiated by various inflammatory stimuli, in an attempt to better understand how the neuropeptide PACAP influences CNS inflammation [11] (Fig. 2). In that study, the BV-2 mouse microglia cell line was utilized as a model system to determine the effect of PACAP on microglial signal transduction. The BV-2 cell line was originally established by oncogenic viral transformation of primary microglial cells derived from mouse brain. The cell line is known to exhibit morphological and functional properties that are similar to freshly isolated microglia, and has been widely used for the investigation of microglial activation. It has been shown that PACAP suppresses the inflammatory activation of BV-2 microglia via specific inhibition of LPS-induced p38 MAPK pathway (Fig. 2): (i) pretreatment of BV-2 cells with PACAP resulted in a significant decrease in LPS- or IFNγ-induced NO production as well as iNOS and IL-1β mRNA levels; (ii) the inhibitory effect of PACAP appeared to be mediated through an increase in intracellular cAMP; (iii) PACAP inhibition of LPS-induced NO production was accompanied by inhibition of p38 MAPK activation, but not ERK, JNK, or NF-κB; and (iv) IFNγ-induced STAT-1 activation or IRF-1 induction was not significantly influenced by PACAP [11].

As it has previously been shown that hypoxia induces inflammatory activation of cultured microglia and their inducible nitric oxide synthase induction via the p38 MAPK pathway [12], it was hypothesized that the neuropeptide may inhibit the hypoxic activation of microglia, and this may provide a neuroprotection against inflammation-induced neuronal injury. When this possibility was tested using cultured microglia and PC12 cells, it was found that PACAP attenuates inflammatory activation of microglia under hypoxic condition, and protects co-cultured PC12 cells from microglial neurotoxicity [13]. In addition, the neuropeptide reduced the hypoxia-induced activation of p38



Microglial Signaling Regulation by Neuropeptides. Figure 2 Schematic diagram of microglial signal transduction following exposure to LPS, IFNγ, and other inflammatory or stress signals: the action sites of PACAP and CRH. After treatment of microglia with LPS, TLR4 signaling is initiated with the ensuing NF-κB activation and IFNβ production, which feeds back to evoke the secondary signaling. IFNγ induces STAT1 activation followed by IRF-1 induction. Hypoxia and stress signals initiate three subgroups of MAPK pathways. NF-κB, STAT/IRF, and MAPKs commonly induce the transcription of a wide variety of inflammatory genes. PACAP specifically inhibits p38 MAPK, while CRH induces apoptosis of microglia via mitochondrial pathway (ROS production and caspase-9 activation with subsequent caspase-3 activation).

MAPK, indicating that the p38 MAPK is also a molecular target of the PACAP action in microglia under the hypoxic condition. The neuroprotective effects of PACAP in animal models of cerebral hypoxia/ischemia may be partly due to its direct actions on brain microglia and neurotoxic inflammation.

Effect of CRH

Corticotropin-releasing hormone (CRH) plays a pivotal role in stress responses as a key mediator of hypothalamic-pituitary-adrenocortical system [14]. CRH is released from the hypothalamus, and then carried to the pituitary gland, where it causes secretion of the adrenocorticotropic hormone (ACTH) that triggers cortisol secretion from the adrenal glands. The peptide hormone has also been implicated in the regulation of neuronal cell survival, exerting either neurotoxic or neuroprotective effects. Peripheral secretion of CRH is involved in the modulation of peripheral immune responses by acting at specific receptors on multiple populations of immune cells to produce a wide range of effects. Earlier works support a proinflammatory role of CRH: it induced activation of monocytes/macrophages, T cells, and mast cells. In the CNS, primary microglia cultures, microglial cell lines, and microglia in vivo have been shown to be a direct target of CRH action. Microglia express CRH receptor 1 (CRH-R1), and the ligation of this receptor by CRH induced TNFα release in cultured rat microglia, IL-18 and β-endorphin production in microglial cells, and cAMP accumulation in mouse microglia, respectively.

Proapoptotic activity of CRH has previously been reported in the PC12 rat pheochromocytoma cell line with neuronal characteristics, where CRH induced Fas ligand expression and ►apoptosis. CRH also increased the apoptosis of activated T cells through Fas ligand induction, suggesting a role for CRH in immunotolerance. Based on these proapoptotic activities of CRH, the effects of the neuropeptide on the survival or death of purified microglia have been investigated [15]. While vasoactive intestinal peptide, substance P, cholecystokinin, or neuropeptide Y did not affect microglial cell viability, CRH induced a classical apoptosis of mouse microglia in culture as evidenced by nuclear condensation and fragmentation, TUNEL staining, and cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP) protein (Fig. 2). CRH, however, did not influence nitric

oxide production or inflammatory gene expression including cytokines and chemokines, indicating that CRH did not affect the inflammatory activation of microglia. The CRH-induced microglial apoptosis appeared to involve a mitochondrial pathway and reactive oxygen species (Fig. 2). Taken together, these results indicate that the stress neuropeptide CRH may regulate neuroinflammation by inducing the apoptosis of microglia, the major cellular source of inflammatory mediators in the CNS.

Function

Regulation of Microglial Signaling by PACAP

PACAP has been proposed as a deactivator of innate immune responses. In the CNS, PACAP suppressed neuroinflammation by inhibiting inflammatory activation of microglia. Therefore, PACAP may act as a neuroprotector by inhibiting microglial activation under the conditions where inflammatory responses associated with microglial activation play an important pathogenic role in neuronal injury. In fact, the neuroprotective effect of PACAP has been well documented in a variety of experimental models in vivo as well as in vitro. PACAP has been reported to reduce brain damage after global and focal ischemia in vivo. Also, PACAP has been found to prevent neuronal cell death under various neurotoxic conditions in vitro: PACAP protected cerebellar granule neurons against oxidative stress- or ethanol-induced apoptosis; it reduced LPS-induced neurotoxicity in mixed cortical neuron/glia cultures; and it attenuated β-amyloid-induced toxicity in PC12 cells. Although some of these previous works have shown that PACAP may act on neurons directly to exert its neurotrophic or neuroprotective activities, it has also been suggested that inhibition of pathological activation of microglia may be another way that PACAP exerts its neuroprotective effects in vivo. The findings that PACAP specifically inhibits p38 MAPK activation thereby resulting in down-regulation of inflammatory activation of microglia enhance our understanding of the mechanistic basis of the neuroprotective action of PACAP. The cellular target of PACAP action in the CNS may be either microglia or neurons, and the molecular target of PACAP in microglia appears to be p38 MAPK.

During cerebral ischemia, hypoxia may not only impose the damage on neurons directly, but also promote neuronal injury indirectly via microglial activation. The neuroprotective PACAP also inhibited microglial activation under hypoxic conditions, thereby suggesting that PACAP may directly act on microglia to exert its neuroprotective effects against hypoxia/ischemia. In addition, using a co-culture of microglia and PC12 cells, it has been shown that PACAP is protective against microglial neurotoxicity. In the co-culture system, it was demonstrated that: (i) hypoxia could stimulate microglia to secrete neurotoxic molecules, which actually mediated PC12 cell death; and (ii) PACAP acted on microglia to block their activation under hypoxic condition, mitigating PC12 cell death [13]. The results corroborated the hypothesis that the PACAP inhibition of hypoxic activation of microglia is neuroprotective.

Induction of Microglial Apoptosis by CRH

Activated microglia are believed to contribute to neuronal damages in neurodegenerative diseases or stroke through the excess release of proinflammatory and/or cytotoxic factors [4]. An apoptotic elimination of activated microglia has recently been suggested as one way of regulating the microglial activation in vitro as well as in vivo [15]. It has recently been reported that a stress neuropeptide CRH induces apoptosis of microglia, and reactive oxygen species (ROS) generation and mitochondrial pathways are involved in the CRH-induced microglial apoptosis. Ase microglia play a central role in inflammatory responses in the CNS, the current results indicate an important link between the stress response and the neuroinflammation, and may have a relevance to CNS pathologies under stress conditions. An abnormal production of CRH under stress conditions may deregulate the self-regulatory microglial apoptosis, thereby contributing to CNS diseases.

CRH may exert dual effects on microglia depending on their proliferative state. CRH seems to enhance proliferation of serum-starved microglia to some extent, while it may induce apoptosis of normally growing microglia (at the inflammatory sites in vivo). The CRH-induced proliferation was also observed in astrocytes cultured under serum-free conditions, while CRH inhibited proliferation of mouse melanoma cells that were actively progressing through the cell cycle. CRH did not affect the viability, proliferation, or apoptosis in astrocyte cultures that were maintained with 5% serum. Astrocytes have previously been reported to express CRH receptor. These results suggest that CRH exerts differential effects on cell proliferation or viability depending on the conditions under which the cells reside.

CRH mediates immunological, autonomic, and behavioral responses to stress. In the CNS, CRH has been shown to act on glia to exert either neurotoxic or neuroprotective effects depending on the experimental systems employed. In addition, the neuropeptide induced apoptosis of microglia, a cellular population that plays a pivotal role in neuroinflammation. As neuroinflammation is closely associated with neuronal injury and neurodegenerative diseases, the CRH induction of microglial apoptosis suggests an existence of the interconnection among stress responses, neuroinflammation, and CNS disorders. However, further study is required to precisely understand the in vivo relevance of the CRH-induced microglial apoptosis, and to determine the molecular mechanisms underlying the CRH-induced microglial apoptosis.

Acknowledgements

The author's laboratory was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-005-J04202; KRF-2006-311-E00045) and by the Brain Korea 21 Project in 2006–2007. This work was also supported by the Neurobiology Research Program from the Korea Ministry of Science and Technology. Studies on the microglial signal transduction were supported by grant No. R01-2006-000-10314-0 from the Basic Research Program of the Korea Science & Engineering Foundation.

References

1. Streit WJ, Conde JR, Fendrick SE, Flanary BE, Mariani CL (2005) Role of microglia in the central nervous system's immune response. Neurol Res 27:685–691
2. Gehrmann J, Matsumoto Y, Kreutzberg GW (1995) Microglia: intrinsic immuneffector cell of the brain. Brain Res Brain Res Rev 20:269–287
3. Minghetti L, Levi G (1998) Microglia as effector cells in brain damage and repair: focus on prostanoids and nitric oxide. Prog Neurobiol 54:99–125
4. Gonzalez-Scarano F, Baltuch G (1999) Microglia as mediators of inflammatory and degenerative diseases. Annu Rev Neurosci 22:219–240
5. van Rossum D, Hanisch UK (2004) Microglia. Metab Brain Dis 19:393–411
6. Lezoualc'h F, Behl C (1998) Transcription factor NF-κB: friend or foe of neurons? Mol Psychiatry 3:15–20
7. Mattson MP, Meffert MK (2006) Roles for NF-κB in nerve cell survival, plasticity, and disease. Cell Death Differ 13:852–860
8. Haddad JJ (2005) N-methyl-D-aspartate (NMDA) and the regulation of mitogen-activated protein kinase (MAPK) signaling pathways: a revolving neurochemical axis for therapeutic intervention? Prog Neurobiol 77:252–282
9. Vaudry D, Gonzalez BJ, Basille M, Yon L, Fournier A, Vaudry H (2000) Pituitary adenylate cyclase-activating polypeptide and its receptors: from structure to functions. Pharmacol Rev 52:269–324
10. Delgado M, Abad C, Martinez C, Juarranz MG, Leceta J, Ganea D, Gomariz RP (2003) PACAP in immunity and inflammation. Ann N Y Acad Sci 992:141–157
11. Lee H, Suk K (2004) Selective modulation of microglial signal transduction by PACAP. Neuroreport 15:1469–1474
12. Park SY, Lee H, Hur J, Kim SY, Kim H, Park JH, Cha S, Kang SS, Cho GJ, Choi WS, Suk K (2002) Hypoxia induces nitric oxide production in mouse microglia via p38 mitogen-activated protein kinase pathway. Brain Res Mol Brain Res 107:9–16
13. Suk K, Park JH, Lee WH (2004) Neuropeptide PACAP inhibits hypoxic activation of brain microglia: a protective mechanism against microglial neurotoxicity in ischemia. Brain Res 1026:151–156
14. Charmandari E, Tsigos C, Chrousos G (2005) Endocrinology of the stress response. Annu Rev Physiol 67:259–284
15. Jones LL, Banati RB, Graeber MB, Bonfanti L, Raivich G, Kreutzberg GW (1997) Population control of microglia: does apoptosis play a role? J Neurocytol 26:755–770

Microgliosis

Definition

Aggregation of microglia in the brain in response to hypoxia/ischemia or infection. Microglial activation involves increased recruitment of cells through mitosis of resident microglia and probably also from bone marrow derived precursors that infiltrate the central nervous system (CNS). Microglia phagocytose debris occurring as a result of injury, programmed cell death and possibly axonal and dendritic remodelling. Prolonged microglial activation in inflammation can release toxic substances including cytokines and cause cell death.

►Cytokines

Micrographia

Definition

Small handwriting, usually a sign of bradykinesia in Parkinson disease. Micrographia is best brought out by asking the patient to write continuously in cursive letters without resting or taking the pen off the paper.

►Parkinson Disease

Microgravity

Definition

A condition of cancelled terrestrial gravitational force (weightlessness) during orbital flight in space.

►Autonomic Function in Space

Microiontophoresis and Micropressure Ejection

Peter M. Lalley
Department of Physiology, The University of Wisconsin School of Medicine and Public Health, Medical Sciences Center, Madison, WI, USA

Synonyms

Microelectrophoresis; Iontophoretic application; Pressure micro-ejection

Definition

Microelectrophoresis: Ejection of charged molecules from a capillary microelectrode close to or within a nerve or muscle cell by electrical current.

Micro-pressure ejection: Ejection by pressure of a small liquid volume containing a chemical or drug from a micropipette in the vicinity of a cell or group of cells.

Purpose

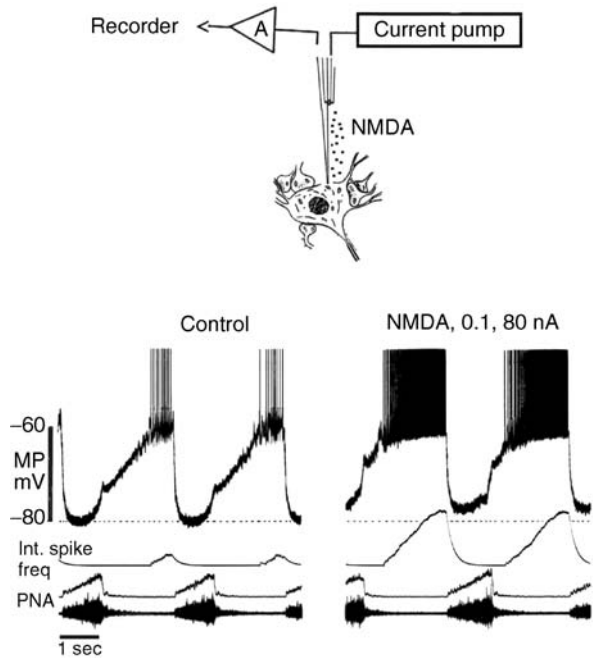
►Microiontophoresis and Micro-pressure Ejection are used to apply drugs or chemicals to nerve cells. The ejected agents bind to cell membrane binding sites (►receptors) or cross the cell membrane, altering the cell's excitability. The methods are also used to mark the location of cells in a region of the central nervous system.

Principles

Microiontophoresis

Microiontophoresis involves the ejection of charged drugs or chemicals from a conductive electrolyte solution in a glass capillary micropipette into the extracellular milieu of cells or into a cell's cytoplasm. Direct current (d.c.), either negative or positive and ranging from nanoamperes to microamperes (10^9–10^6 amperes), is passed from a "current pump" through a fine silver wire to a micropipette solution containing positively- or negatively-charged molecules to be ejected. To eject the substance, current of a polarity identical to its charge is applied. Between ejections, applying current of opposite polarity retains the substance. Thus, for example, acetylcholine (ACh^+) would be ejected with positive current and retained by negative current.

Extracellular microiontophoresis is commonly used to test several substances on a neuron by ejecting them sequentially or simultaneously from a ►multibarrel microelectrode assembly (Fig. 1). Several ►neurotransmitters or analogs that bind to cell receptors and alter action potential discharges as well as substances that block the neurotransmitter's receptor sites can be tested on the same cell. After testing, a dye can be ejected to mark the location of the cell.



Microiontophoresis and Micropressure Ejection. Figure 1 Intracellular recording of responses evoked from a respiratory neuron during extracellular s of an excitatory neurotransmitter analog. Upper panel: Recording and microiontophoresis arrangement The sharp tip of the recording micropipette penetrates the cell membrane and records membrane potential changes evoked during extracellular iontophoresis of *N*-methyl-D-aspartate (NMDA), an amino acid that binds to a subtype of receptor for the excitatory neurotransmitter glutamate. Iontophoresis of NMDA is accomplished by applying negative d.c. current from a current pump connected to a silver wire inserted in a pipette containing 0.1 M Sodium NMDA, a negatively charged compound. Lower panels: Responses to NMDA recorded intracellularly from a respiratory neuron in an anesthetized cat. Traces, top to bottom in each panel, are: Membrane potential (MP), the time integral of neuron action potential frequency, the time integral of action potential frequency recorded from the phrenic nerve and the electroneurogram of phrenic nerve activity (PNA) (Lalley and Bischoff, unpublished data).

Present day microiontophoresis units typically consist of 6–7 constant current pumps, or channels. Each pump provides a separate, independent source of ejecting or retaining current that is passed through a silver wire to a current-conducting electrolyte solution, typically 165 mM NaCl solution containing the charged chemical. The current pump incorporates a high voltage

►field effect transistor (FET) amplifier with plus or minus outputs in the nanoampere range (typically, up to ± 200 × 10^9 amperes). Some units may have pumps capable of generating microampere currents for dye ejection. Channel output is measured and recorded by a ►galvanometer and can be operated manually, programmed for automatic sequential operation or controlled externally, e.g. by computer. A summing, or neutralizing channel applies a current that is the sum of all applied currents but of opposite polarity to a separate barrel of the array. The neutralizing current balances out ejecting and retaining currents that might otherwise pass through the extracellular fluid to alter excitability by direct electrical field effects on the cell membrane.

Intracellular microiontophoresis of a chemical allows nerve cells to be labeled for subsequent histological identification, or it can be used to study the actions of a substance that alters excitability through actions on intracellular signaling proteins. The ejecting current is most often delivered while recording with a conventional capillary microelectrode, or with ►theta glass capillary tubing (►theta tubing). On one side of the ►theta glass septum is the electrolyte and a fine Ag/AgCl wire connected to an amplifier to record bioelectric signals, and on the other side is the solution of molecules to be ejected and a silver wire connected to the current pump.

Extracellular microiontophoresis can be combined with intracellular recording to more thoroughly analyze effects of ejected substances on membrane potential (Fig. 1). A single glass capillary micropipette for intracellular recording is either glued side by side to a multibarrel microiontophoresis assembly, or a recording micropipette is inserted into the enlarged central orifice of a customized multibarrel array. In either case the tip of the recording pipette projects beyond the multibarrel tips, usually by 40–50 µM.

Advantages and Disadvantages

Advantages and Disadvantages of Microiontophoresis

Microiontophoresis has three principal advantages over other methods of drug and chemical delivery. (i) Diffusion barriers and breakdown by enzymes that impede access to neurons by parenteral administration can be avoided. (ii) Effects of neurotransmitters, their congeners, second messengers and receptor blockers can be analyzed on a single cell. (iii) Many cells can be tested in an experiment.

There are two major disadvantages. (i) Neuronal responses can be evoked with the applied electric current and interpreted as drug or chemical effects, however there are well-established control procedures [1] that minimize the potential for such current artifacts. (ii) The concentration of the ejected substance at the site of action is unknown, however there are procedures to determine relative potencies of test substances [2,3].

Micro-Pressure Ejection

Pressure ejection is used to deliver uncharged or poorly charged substances to the vicinity of neurons. The technique is useful for in vivo and in vitro studies. In the in vitro slice preparation, separate recording and pressure-ejection pipettes are positioned close to the target neuron. In the in vivo preparation, ►micropressure ejection has been used in two general ways:

1. Single micropipettes with relatively large tips (10 µm or greater) have been used to inject nanoliter volumes for the purpose of altering the excitability of groups of neurons in a small area.
2. Volumes less than 1nl of neuroactive drugs and neuromodulators have been applied to single neurons from ►multibarrel assemblies during extracellular or intracellular recording [4].

Volumes of neuroactive substances are ejected from micropipettes connected by soft catheter tubing and high-pressure tubing to a source of compressed gas, usually nitrogen. A switch- or ►TTL pulse-controlled ►solonoid valve is used to deliver pulses of known pressure and duration.

The general procedure is to microscopically measure with a reticule the length (L) of fluid ejected under pressure from a pipette of known internal radius (r). Volume (V) can then be calculated from $V = \pi r^2 L$. From the known concentration of the pipette solution, the amount of substance ejected can be calculated. The volume ejected is linearly proportional to either the applied pressure with ejection duration held constant, or to ejection duration when pressure is constant [4].

Micropipettes with tip resistances between 1.0 and 1.4 MΩ resistance will usually eject uniform volumes for a given pressure and duration over long test periods. Pipettes with finer tips tend to plug in brain or spinal cord tissue, whereas larger tips (resistance less than 1.0 MΩ) produce variable results, and larger volumes are ejected that are more likely to produce volume-related response artifacts [4,5].

Advantages and Disadvantages of Micro-Pressure Ejection

Pressure ejection has several advantages. (i) Uncharged drugs and chemicals that can be made soluble in an aqueous medium can be tested on neurons. (ii) As with microiontophoresis, diffusion barriers and enzymatic degradation outside the central nervous system are circumvented. (iii) There is no possibility for current artifacts, as with iontophoretic drug delivery. (iv) The essential equipment is relatively inexpensive.

Disadvantages include (i) Potential effects on neurons related to pH when substances are made soluble by pH values <5.5 and >8. (ii) Solution volume can produce injury discharges and changes of membrane potential, and can move nerve cells away from the recording and drug delivery assembly. (iii) Solvents other than water, such as ethanol or dimethylsulfoxide, can also alter neuron behavior. (iv) Solutions of high osmolarity can affect neuron responses through redistribution of cytoplasmic and extracellular water.

References

1. Lalley P (2004) Dopamine$_1$ receptor agonists reverse opioid respiratory network depression, increase CO_2 reactivity. Resp Physiol Neurobiol 139:247–262
2. Curtis DR (1964) Microelectrophoresis. In: Nastuk WL (ed) Physical techniques in biological research, vol 5. Electrophysiological methods, Part A, Academic Press, NewYork, pp 144–190
3. Hill RG, Simmonds MA (1973) A method for comparing the potencies of γ-aminobutyric acid antagonists on single neurones using micro-iontophoretic techniques. Br J Pharmacol 48:1–11
4. Palmer MR, Fossom LH, Gerhardt GA (1986) Micro pressure-ejection techniques for mammalian neuropharmacological investigations. In: Geller HM (ed) Electrophysiological techniques in pharmacology. Alan R. Liss, New York, pp 169–187
5. Sakai M, Swartz BE, Woody CD (1979) Controlled microrelease of pharmacological agents: measurements of volumes ejected in vitro through fine-tipped glass microelectrodes by pressure. Neuropharmacology 18: 209–213

Microneurography

Definition

Technique developed by Karl–Erik Habarth and Åke Vallbo in Upsalla, Sweden, in which an insulated tungsten microelectrode is inserted percutaneously into an accessible peripheral (or cranial) nerve to record electrical signals from nerve fibers (axons) in awake human subjects. The technique is used to record from groups of axons or, usually, single type-identified axons such as muscle spindles, tendon organs and tactile afferents. Microneurography also allows one to record from single unmyelinated axons, such as afferent C fibers or sympathetic axons. The technique has contributed significantly to our understanding of sensorimotor control, pain and cardiovascular control.

►Cutaneous Mechanoreceptors, Functional Behavior
►Muscle Spindle
►Tendon Organs

Microoxic

Definition

Conditions characterized by low concentrations of oxygen.

microRNA

►miRNAs in Neurobiology

Microsaccades

Definition

A saccade which ranges from about 0.01°–0.3° in amplitude and is unconsciously generated at a rate of 1–2 Hz during fixation but is suppressed during tasks requiring fine visual discrimination. The functional role of micro-saccades is unclear as yet; to some degree they appear to correct for fixation errors from slow eye drifts, and they may contribute to avoid fading of the visual scene (which occurs if its image is stabilized on the retina), although other involuntary micro-movements of the eyes could serve the same purpose.

►Saccade, Saccadic Eye Movement

Microsatellite Markers

Definition

Highly polymorphic di-, tri- or tetranucleotide repeat sequences which are scattered over the genome. Mapped microsatellites are used in linkage analysis to locate disease genes. Furthermore, their highly polymorphic nature makes them useful for forensic analysis and paternity testing, for example.

►Bioinformatics

Microstimulation

Definition

Low intensity (less than about 100 μA) electrical activation of a region of the brain through a microelectrode.

Microtubule

Definition

Microtubules form a major part of the cell's cytoskeleton and are found in most eukaryotic cells. Structurally, microtubules are hollow cylinders that are ~24 nm in diameter with a wall thickness of about 5 nm and with 13 protofilaments that consist of the dimeric protein α- and β-tubulin. Microtubules exhibit a structural and functional polarity with a minus (−) end and a plus (+) end. Microtubule-organizing centers nucleate the assembly of microtubules from their -end. In a process known as dynamic instability, microtubule plus ends undergo alternating phases of growth and shrinkage. Microtubules associate with a wide range of proteins (e.g., microtubule-associated proteins (MAPs) which contribute to the dynamism of the microtubule networks, and motor proteins involved with transport such as kinesin). Microtubules are involved in a number of cellular processes such as cell elongation, migration and maintenance of cell shape. Microtubules also serve as tracks for the movement of molecular cargo in cells; in neurons this is particularly important where material needs to be transported down the length of the axon (axonal transport).

►Cytoskeleton
►Kinesin
►Microtubule-sssociated Proteins (MAPs)

Microtubule-associated Proteins (MAPs)

Definition

Proteins that interact with microtubules of the cytoskeleton. Neurotrophin binding and activation of the mitogen-activated protein kinase (MAPK) pathway results in MAP phosphorylation, leading to increased stabilization of microtubule structure.

►Cytoskeleton
►Mitogen Activated Protein Kinase (MAPK)
►Microtubule

Microvilli

Definition

Small processes found on the receptive surface of sensory cells, such as taste cells, olfactory cells, or Merkel cells.

Micturition, Neurogenic Control

William C. de Groat
Department of Pharmacology, University of Pittsburgh Medical School, Pittsburgh, PA, USA

M

Synonyms

Neural control of voiding; Neural control of the lower urinary tract; Urination

Definition

Micturition

Storage and periodic elimination of urine are dependent on a complex neural control system that coordinates the activity of two functional units in the lower urinary tract: (i) a reservoir (the urinary bladder) and (ii) an outlet (consisting of the bladder neck, urethra, and striated muscles of the ►pelvic floor) [1–3]. During urine storage the bladder outlet is closed and the bladder is quiescent, thereby maintaining a low intravesical pressure over a wide range of bladder volumes. A low intravesical pressure is essential to allow urine flow from the kidney into the bladder. During micturition (►Bladder control (neural)), outlet resistance is reduced as a consequence of relaxation of the pelvic floor and periurethral striated muscles in conjunction with mechanical shortening of the urethra and opening of the bladder neck. These changes are followed in a few seconds by a bladder contraction and a rise in intravesical pressure, which is maintained until the bladder is empty. This reciprocal relationship between bladder and outlet is controlled by neural pathways

(►Urogenital reflex) that are organized in the brain and lumbosacral spinal cord.

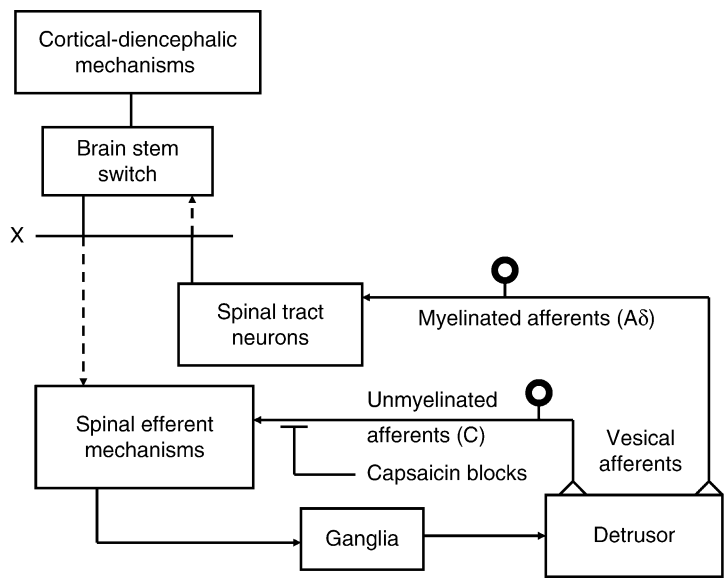
Characteristics

During urine storage intravesical pressure is usually below 10 cm H_2O and maximal pressure in the urethral outlet is high (70–100 cm H_2O) [1]. Cystometric studies in normal healthy women revealed that the first sensation of bladder filling and the first desire to void occur on average at mean bladder volumes of 160 and 320 ml, respectively. Voiding occurs at intravesical pressures ranging between 50 and 70 cm H_2O and normal maximal urine flow rates range between 20 and 30 ml/min. Healthy women normally void 5–7 times per day at a mean volume of 300 ml.

Peripheral Nervous System

The lower urinary tract is innervated by three sets of nerves arising at the lumbosacral level of the spinal cord [1–3]. Like other visceral organs, the bladder and urethra receive an innervation from both divisions of the autonomic nervous system. Parasympathetic preganglionic pathways, which arise from neurons in the intermediolateral region of the sacral spinal cord (S_2–S_4) travel in the ►pelvic nerve and provide an excitatory input to parasympathetic ganglion cells located in the pelvic plexus and in the wall of the organs. These cells in turn innervate the bladder and urethral smooth muscle. Sympathetic preganglionic pathways to the lower urinary tract which arise in the lumbar spinal segments (L_1–L_4) provide excitatory input to ganglion cells in the sympathetic chain ganglia as well as prevertebral ganglion cells in the hypogastric and pelvic plexus that in turn innervate bladder and urethral smooth muscle [3]. Periurethral striated muscles, which form the external urethral sphincter, and pelvic floor striated muscles are innervated by sacral motoneurons (S_2–S_3) that send axons into the ►pudendal nerves and levator ani nerves, respectively.

Afferent activity arising in the bladder is conveyed to the central nervous system via both sets of autonomic nerves [2,3]. The most important afferents for initiating micturition are those, which arise from neurons in the lumbosacral dorsal root ganglia and travel in the pelvic nerve to the sacral spinal cord. These afferents consist of small myelinated (A-δ) and unmyelinated (C) fibers (Fig. 1), which convey impulses from tension receptors and nociceptors in the bladder wall. Afferent activity arising in the urethra passes through the pelvic, hypogastric and pudendal nerves.



Micturition, Neurogenic Control. Figure 1 Diagram showing the organization of the parasympathetic excitatory reflex pathway to the detrusor muscle. Scheme is based on electrophysiologic studies in cats. In animals with an intact spinal cord, micturition is initiated by a supraspinal reflex pathway passing through a center in the brain stem. The pathway is triggered by myelinated afferents (A δ fibers) that are connected to the tension receptors in the bladder wall. Injury to the spinal cord (indicated by X) above the sacral segments interrupts the connections between the brain and spinal autonomic centers and initially blocks micturition. However, over a period of several weeks following cord injury, a spinal reflex mechanism emerges, which is triggered by unmyelinated vesical afferents (C-fibers); the A-fiber afferent inputs are ineffective. The C-fiber reflex pathway is usually weak or undetectable in animals with an intact nervous system. Capsaicin (20–30 mg, subcutaneously) blocks the C-fiber reflex in chronic spinal cats, but does not block micturition reflexes in intact cats. Intravesical capsaicin also suppresses detrusor hyper-reflexia in patients with neurogenic bladder dysfunction.

Central Nervous System

The central neural control of micturition depends on reflex pathways in the spinal cord and brain stem as well as circuitry in the forebrain that mediate the voluntary control of micturition [3,4]. Anatomical tracing and electrophysiological studies in animals have revealed that spinal reflex pathways are primarily polysynaptic and consist of at least three elements. Afferent neurons from the bladder and urethra send projections into Lissauer's tract from which collaterals extend laterally and medially around the surface of the dorsal horn into the region of the autonomic nuclei and the dorsal commissure. Afferent fibers terminate on interneurons. Interneurons in turn make synaptic connections with preganglionic neurons that send their axons into the periphery via the ventral roots. A similar circuitry controls the motoneurons innervating the urethral sphincter.

Electrophysiological and tracing studies in animals [2,3,5] and brain imaging experiments in humans [4,6] have been identified various populations of neurons at sites in the brain stem (periaqueductal grey, ►pontine micturition center (Barrington's nucleus), medullary raphe nucleus, locus ceruleus, A5 noradrenergic nucleus) and in the forebrain (paraventricular nucleus, medial preoptic nucleus, cingulate gyrus, prefrontal cortex, basal ganglia) that have a role in the regulation of micturition.

Lower Level Components

The parasympathetic postganglionic innervation of the bladder is distributed throughout the base and dome of the bladder and each smooth muscle cell receives a neural input [2,3]. However the sympathetic innervation is concentrated in the base of the bladder and in the urethra. Afferent nerves are also heavily concentrated in the bladder base. A-δ afferent nerves are located in the smooth muscle layers; whereas C-fiber afferents (►C-fiber afferent nerves) are distributed within and below the epithelial layer (the urothelium) [1,3,7].

Peripheral Nervous System

Parasympathetic nerves excite bladder smooth muscle via the release of acetylcholine and a noncholinergic transmitter (adenosine triphosphate, ATP). Acetylcholine acts on ►muscarinic receptors (M_2 and M_3); whereas ATP acts on P2X ►purinergic receptors [8–10]. Parasympathetic nerves also inhibit urethral smooth muscle via the release of nitric oxide. Sympathetic postganglionic nerves which release norepinephrine provide an excitatory input to the smooth muscle of the bladder neck and urethra and an inhibitory input to smooth muscle of the bladder dome. The excitatory effects of adrenergic nerves in the bladder and urethra are mediated by α_1-adrenergic receptors, whereas the inhibitory effects in the bladder dome are mediated by β_3 adrenergic receptors [8,10]. Sympathetic nerves also inhibit transmission in bladder parasympathetic ganglia.

A-δ afferents respond to bladder distension and normally trigger the sensation of bladder fullness and initiate voiding [3]. C-fiber afferents are activated by bladder irritation or infection and can induce bladder hyperactivity. C-fiber afferents synthesize and release various transmitters including substance P, calcitonin-gene-related peptide, and ►glutamic acid and express multiple receptors, e.g., purinergic ($P2X_{2/3}$), neurokinin and capsaicin receptors (TRPV1) [3,9]. Although afferent nerves can respond directly to bladder distension or to chemicals present in the urine, it is also likely that they are affected indirectly by chemical transmitters released from the urothelial cells which line the bladder lumen and which receive an afferent innervation. Recent studies have revealed that urothelial cells release ATP and nitric oxide in response to stretch or chemical stimulation. Urothelial cells express ►TRPV1 receptors [7] as well as receptors for various transmitters including, muscarinic, nicotinic, adrenergic, purinergic and serotoninergic receptors [1,3]. It has been proposed that ATP and nitric oxide released by urothelial cells act on afferent nerves adjacent to and within the urothelium to influence afferent nerve firing. Thus urothelial cells exhibit "neuronal-like" properties and seem to play a role in sensory mechanisms in the bladder [7].

Central Nervous System

Electrophysiological studies in animals indicate that the micturition reflex is mediated by a spinobulbospinal (SBS) reflex pathway that passes through a coordinating center (the pontine micturition center, PMC) in the rostral brain stem (Fig. 1). This pathway is activated by A-δ bladder afferents and is in turn subject to modulating influences from higher centers in the cerebral cortex and diencephalon, which are essential for the voluntary control of micturition. Axonal tracing studies in cats indicate that the ascending limb of the SBS micturition pathway consists of projections of spinal tract neurons in the sacral spinal cord to neurons in the periaqueductal gray that in turn send inputs to neurons in the PMC [4]. Projections from the PMC back to the sacral parasympathetic nucleus in the spinal cord complete the reflex circuit [3,4].

Pharmacological experiments in animals have revealed that glutamic acid is the principal excitatory transmitter in the spinal and supraspinal components of the micturition reflex pathway [2,3]. The effects of glutamic acid are mediated by NMDA and non-NMDA ►glutamatergic receptors. Other excitatory transmitters (substance P, dopamine, nitric oxide, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating peptide and norepinephrine) appear to act by modulating glutamatergic transmission. Transmitters that are involved in inhibition of the micturition reflex include: gamma aminobutyric acid, glycine, opioid peptides, serotonin and dopamine [2,3].

Function

Micturition is a visceral function that is under voluntary control. Storage and elimination of urine requires the coordinated activity of a number of smooth and striated muscles and is dependent upon the integrative properties of neural pathways at various levels of the neuraxis ranging from the cerebral cortex to the lumbosacral spinal cord and the peripheral autonomic ganglia. The central reflex mechanisms controlling lower urinary tract function seem to be organized as simple on-off switching circuits which maintain a reciprocal relationship between the bladder and urethral outlet. During urine storage a low level of activity in the sacral afferent pathways initiates reflex firing in the sympathetic and somatic efferent pathways to the urethral outlet, thereby contributing to the maintenance of urinary continence. At the same time, parasympathetic efferent pathways to the bladder are quiescent. The storage reflexes are organized in the lumbosacral spinal cord. During micturition a high level of sacral afferent activity from tension receptors in the bladder wall reverses the pattern of efferent outflow, resulting in firing in the parasympathetic excitatory pathways to the bladder and inhibition of the sympathetic and somatic inputs to the outlet. These reflexes occur in their simplest form in infants where micturition is purely an involuntary act. In adults the basic reflexes are integrated into a more complex voluntary control of micturition.

Pathology

Damage to forebrain structures due to injury, tumors, cerebrovascular disease or neurological disorders such as Parkinson's disease or multiple sclerosis usually leads to an enhancement of micturition reflexes and symptoms of urinary urgency, frequency and incontinence; indicating that forebrain mechanisms mediate a predominant inhibitory control [2–4]. In these conditions the bladder usually exhibits involuntary contractions during storage leading to activation of mechano-sensitive afferent nerves and irritative sensations; however bladder-sphincter coordination is usually maintained. Similar symptoms (the overactive bladder syndrome) can also occur by unknown mechanisms in the absence of overt neural dysfunction particularly in the elderly population.

Damage to the bulbospinal pathways in patients with spinal cord injuries leads initially to urinary retention and complete loss of bladder function due to interruption of the supraspinal micturition reflex pathway. In most paraplegic patients, bladder reflexes slowly recover as a result of a reorganization of synaptic connections in the spinal cord and the emergence of sacral reflex mechanisms that initiate involuntary bladder contractions [3,5]. However, micturition in these patients is usually compromised due to a lack of coordination between bladder and sphincter activity (a condition termed detrusor-sphincter dyssynergia). This condition is characterized by simultaneous contractions of the bladder and the striated urethral sphincter causing incomplete emptying and urinary retention.

Experimental studies in animals and humans indicate that the emergence of involuntary voiding reflexes following spinal cord injury is due in part to plasticity in bladder afferent pathways and the unmasking of reflexes triggered by capsaicin-sensitive, C-fiber bladder afferent neurons (Fig. 1) [2,3,5]. C-fiber afferents have also been implicated in the bladder hyperactivity associated with other neurological disorders such as multiple sclerosis.

Damage to peripheral neural pathways to the lower urinary tract or to the lumbosacral spinal cord (i.e. a lower motoneuron lesion) causes a loss of bladder sensations as well as loss of voluntary and reflex voiding. Injury to muscles or the motor nerves of the urethral sphincter and pelvic floor can often occur during pregnancy and/or childbirth. This results in decreased urethral closure mechanisms and involuntary loss of urine (stress urinary incontinence) during increases in abdominal pressure that are associated with straining, sneezing or coughing.

Therapy

Urinary frequency, urgency and urgency incontinence occurring in the absence of a neurological disorder (the overactive bladder syndrome) or as a result of central nervous system lesions are usually treated with antimuscarinic agents that reduce involuntary bladder contractions [1,3,10]. These drugs increase bladder capacity and reduce urgency sensations as well as incontinent episodes. However these agents are not effective against stress urinary incontinence which is caused by reduced urethral outlet resistance. A new drug (duloxetine) that blocks serotonin and norepinephrine reuptake mechanisms in the central nervous system and that enhances reflex activation of the urethral sphincter is effective in the treatment of stress urinary incontinence. Botulinum toxin is injected into the external urethral sphincter to suppress detrusor-sphincter-dyssynergia or injected into the wall of the urinary bladder to treat neurogenic or idiopathic overactive bladder conditions. Intravesical administration of capsaicin or resiniferatoxin, neurotoxins that desensitize C-fiber afferents, is also used to treat neurogenic bladder hyperactivity and incontinence [3,10].

References

1. Chancellor MB, Yoshimura N (2002) Physiology and pharmacology of the bladder and urethra. In: Walsh PC, Retik AB, Vaughn ED, Wein AJ (eds) Campbell's urology. W.B. Saunders, Philadelphia, pp 831–886

2. de Groat WC, Booth AM, Yoshimura N (1993) Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA (ed) The autonomic nervous system, vol 3: nervous control of the urogenital system. Harwood Academic Publishers, London, pp 227–289
3. Morrison J, Steers WD, Brading A, Blok B, Fry C, de Groat WC, Kakizaki H, Levin R, Thor K (2002) Neurophysiology and neuropharmacology. In: Abrams P, Cardozo L, Khoury S, Wein A (eds) Incontinence. Health Publication Ltd, Paris, pp 83–164
4. Blok BFM (2002) Brain control of the lower urinary tract. Scand J Urol Nephrol Suppl 36 210:11–15
5. de Groat WC, Araki I, Vizzard MA, Yoshiyama M, Yoshimura N, Sugaya K, Tai C, Roppolo JR (1998) Developmental and injury induced plasticity in the micturition reflex pathway. Behav Brain Res 92:127–140
6. Athwal BS, Berkley KJ, Hussain I, Brennan A, Craggs M, Sakakibara R, Frackowiak RSJ, Fowler CJ (2001) Brain responses to changes in bladder volume and urge to void in healthy men. Brain 124:369–377
7. Birder LA, Nakamura Y, Kiss S, Nealen ML, Barrick S, Kanai AJ, Wang E, Ruiz G, de Groat WC, Apodaca G, Watkins S, Caterina MJ (2002) Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 5:856–860
8. Andersson KE, Arner A (2004) Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev 84:935–986
9. Burnstock G (2001) Purinergic signaling in the lower urinary tract. In: Abbracchio MP, Williams M (eds) Handbook of experimental pharmacology. Springer Verlag, Berlin, pp 423–515
10. de Groat WC, Yoshimura N (2001) Pharmacology of the lower urinary tract. Ann Rev Pharmacol Toxicol 41:691–721

Midbrain

Definition

Also known as the mesencephalon. The region of the brain between the hindbrain and the diencephalon. Its dorsal region is the tectum and its ventral region is the tegementum. Among its functions are aspects of vision and the control of eye movements and reflexes.

►Evolution of the Spinal Cord

Middle Cerebellar Peduncle

Synonyms

Pedunculus cerebellaris med

Definition

Composed exclusively of afferent fibers which all come from the pontine nuclei, and account for the majority of cerebellar afferents and are designated collectively as the pontocerebellar tract. The fibers decussate before entering the peduncle of the contralateral side, giving off collaterals to the dentate nucleus and projecting to the cerebral cortex of the cerebellar hemispheres.

►Cerebellum

Midline and Intralaminar Thalamic Nuclei

Definition

A group of nuclei extending from the rostral to caudal pole of the thalamus in the midline and embedded within the internal medullary lamina. Midline nuclei include the parataenial, paraventricular, intermediodorsal, reuniens and rhomboid. Intralaminar nuclei are the central medial, paracentral, central lateral, parafascicular and subparafascicular. These nuclei are extensively connected to brainstem and diencephalic structures associated with the reticular formation, such as the pedunculopontine and laterodorsal tegmental nuclei and the lateral hypothalamus and also receive inputs from brainstem visceroceptive nuclei such as the nucleus of the tractus solitarius and parabrachial complex. Collectively, they project to the entire cerebral cortex and most of the deep telencephalic nuclei and are thought to be involved in processes associated with arousal and awareness.

►Thalamus

Migraine

Definition

A moderate to severe primary headache disorder which is usually unilateral with a pulsating quality, accompanied by nausea and/or vomiting, photophobia and phonophobia.

►Headache

Migrating Motor Complex

Definition

During fasting, several hours after the previous meal, the stomach and the small intestine exhibit a distinct pattern of behaviour characterized with bursts of intense activity, electrically and mechanically, with long silent intervals of 75–90 min in humans. This pattern is termed the migrating motor complex (MMC) or migrating myoelectric complex. Other terms used by different investigators are the intestinal housekeeper, the interdigestive migrating electric complex, and the interdigestive migrating motor complex.

Miller Fisher's Syndrome

Definition

A clinical syndrome consisting of ophtalmoplegia, areflexia and ataxia without significant limb weakness.

Mind Body Problem

Definition

The question of how mental states, such as beliefs and desires, are related to physical, actual brain states.

►Mental Models

Mineralocorticoid Receptor (MR)

Definition

Nuclear receptor with a 10 fold higher affinity than the GR for glucocorticoids and a high affinity for aldosteron. It is involved in mineral metabolism and is more restricted in its distribution than the GR, and e. g. found selectively in the hippocampus and the kidney.

►Hypothalamo-Pituitary-Adrenal Axis, ►Stress and Depression

Minimum Convex Polygon

Definition

A minimum polygon with no obtuse internal angles, drawn to enclose the points in a data-set.

►Evolution and Brain-Body Allometry

Minimum-jerk Model

Definition

This model makes the assumption that movement trajectories are smooth, i.e. that the square of jerk, which is the third derivative of position (or equivalently, jerk is the first derivative of acceleration), integrated over movement time, is minimal.

►Motor Control Models

Minimum Torque-change Model

Definition

This model makes the assumption that movements from one position to another with a particular movement time, are made under the constraint that the integral over movement time of the square of changes in torque is minimal.

►Motor Control Models

Mint

Definition

Together with CASK and Velis, a component of a conserved heterotrimeric synaptic scaffolding protein complex; also known to interact with Munc18. Also know as the X11 protein family.

►Synaptic Proteins and Regulated Exocytosis

Miosis

Definition

Pupillary constriction, particularly when the pupil is strongly constricted to approach its minimum diameter.

►Neural Regulation of the Pupil

miRNA Profiling

Definition

Refers to an in depth analysis of the miRNAs present in a biological sample, for example from a particular cell type or a developmental stage. A variety of experimental assays are now available for miRNA profiling (e.g. microarray technology, Real-Time PCR, deep sequencing, bead-based flow cytometry).

►miRNAs in Neurobiology

miRNAs in Neurobiology

F. Gregory Wulczyn
Center for Anatomy, Institute for Cell and Neurobiology, Charité University Hospital, Berlin, Germany

Synonyms

microRNA

Definition

miRNA are ~21–22 nucleotide single-stranded RNAs that are encoded in the genome. The transcription units lie either in mRNA-poor genomic regions, or frequently within the introns of protein-encoding genes. In either case, they are generally transcribed by the same RNA polymerase as mRNAs, RNA polymerase II, and carry the standard features of a protein-encoding mRNA (5′ cap and a polyadenosine tail). The transcribed product undergoes nuclear and cytoplasmic processing events to generate the ~21–22 nucleotide single-stranded miRNA. The single-stranded miRNA is incorporated into a regulatory multi-protein complex, the miRNA-specific RNA induced silencing complex (miRISC), which scans mRNAs for short stretches of sequence complementarity to the miRNA. Although exceptions to the rule have recently been identified, in most cases recognition of the mRNA by the miRISC leads to a decrease in the translation of the mRNA. While a great deal remains to be learned about the miRNA/mRNA interaction, it is well established that miRNAs represent a widespread and fundamental level of control over the protein repertoires of individual cells.

Characteristics

Putting miRNAs in Context

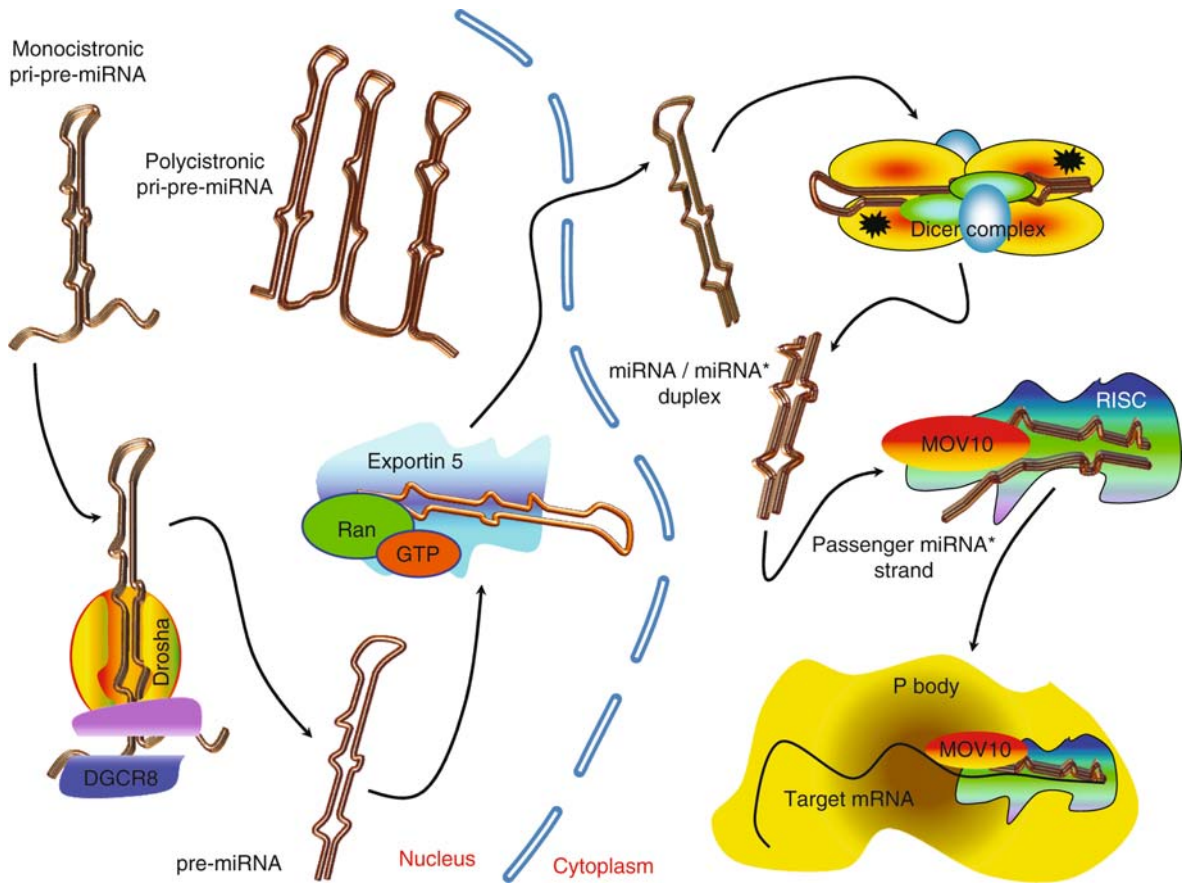
Most people are familiar with the allegory of the butterfly in Mexico beating its wings, and how the initial motion is successively amplified, and initiates a chain of events that ends in a typhoon sweeping ashore on a distant continent. The discovery of the first miRNA in 1993 is akin to the butterfly, and presently the winds in the scientific world are gathering. Indeed, in a recent review of progress in genomic biology in the scientific journal Nature, the discovery of miRNA was placed alongside the elucidation of the DNA double helix structure by Watson and Crick as one of the seminal discoveries. These analogies may, of course, prove overblown, and the purpose of this review is to summarize recent advances in our knowledge of miRNAs as they relate to nervous system development and function. But we will also attempt to provide some ideas about where this very new and promising field may be heading.

One of the reasons that miRNA are generating so much interest is because they are an unexpected challenge to one of the underpinnings of molecular genetics, the formulation of the one gene – one protein hypothesis by Beadle and Tatum in 1941. miRNA share many of the features of a conventional regulatory gene: they are encoded in the genome, are transcribed (most frequently) by the same RNA polymerase as mRNAs, RNA polymerase II, and often carry the standard features of a protein-encoding mRNA (5′ cap and a polyadenosine tail). Like mRNA for protein-coding genes, the primary miRNA transcript is first subjected to nuclear processing events that ready the transcript for export to the cytoplasm. However, the nuclear and cytoplasmic processing pathways for miRNA and mRNA differ, as will be discussed later. For miRNAs, the end result is an ~21–22 nucleotide single-stranded RNA. To date, the sole known function of miRNAs is to influence the efficiency of protein-encoding mRNA utilization. As such, miRNAs represent an additional level of control over the protein repertoire of individual cells that was essentially unrecognized until the year 2000. Indications are that the influence of miRNAs, in particular during development, is pervasive, as efforts to elucidate their myriad functions intensify.

Scientific reviews of the discovery of miRNAs can be found in [1], of miRNA biology in [2] and current knowledge of miRNA in neurobiology in [3–5]. There are many excellent reviews discussing miRNA, and more are published almost weekly, but these should give an overview and links to the entire miRNA literature.

miRNA Biogenesis

Because one of the approaches to study the significance of miRNAs for neural development and function is to interfere with the pathway in which miRNAs are generated and then utilized, it is useful to briefly describe miRNA biogenesis. An overview of the pathway is also provided in Figure 1. miRNA genes can be transcribed either as independent transcription units from mRNA-poor genomic regions, or as part of mRNA transcripts with the mRNA positioned in an intron. One consistent feature shared by miRNA genes is that sequences immediately surrounding the mature miRNA form stable ►stem-loop structures of approximately ~60–70 nucleotides. In most cases, this structure serves as a recognition element for a nuclear processing complex comprised, at a minimum, of the ►ribonuclease (RNase) Drosha and its partner the DGCR8 (DiGeorge Candidate Region 8) protein (Some intronic miRNAs have recently been shown to bypass Drosha cleavage). Drosha cleavage releases the hairpin from surrounding sequences, generating the so-called miRNA precursor. The miRNA precursor is actively transported to the cytoplasm, where it is recognized by a second protein complex centered on the ribonuclease Dicer. The Dicer complex orients itself on the precursor stem and cleaves off a 21–22 nucleotide duplex RNA. What happens next is not understood in detail, but the



miRNAs in Neurobiology. Figure 1 Overview of the miRNA pathway. Starting at the upper left, primary miRNA transcripts (either mono- or polycistronic) are seen. Pri-miRNA are engaged by the Microprocessor, a protein complex containing DGCR8 and Drosha. Drosha cleavage releases the miRNA precursor (Pre-miRNA). Exportin 5 mediates the energy dependent export of the pre-miRNA to the cytoplasm. Cytoplasmic processing is performed by thr Dicer ribonuclease, accompanied miniually by an Argonaute protein and TARBP2. Cleavage of the pre-miRNA yields a 22nt duplex RNA. One strand becomes integrated within a third protein complex, the miRISC, which mediates regulatory interactions between the miRNA and its target mRNAs. miRNAs, the miRISC as well as translationally suppressed mRNAs accumulate in P-bodies, cytoplasmic centers of RNA storage and metabolism.

duplex is subsequently unwound, with one strand destined for incorporation into a regulatory multiprotein complex we will refer to as the miRISC (for miRNA-specific RNA induced silencing complex). The miRNA-primed miRISC is a regulatory machine that scans mRNAs for short stretches of sequence complementarity to the miRNA. In almost all studies performed so far, recognition of an appropriate miRNA interaction site in an mRNA, referred to as a target mRNA, results in suppression of the target mRNA. Very recently, the group of Joan Steitz at Yale University found that under certain conditions (cell cycle arrest), the outcome may be reversed: that miRNA binding may activate translation. It is not yet clear how widespread miRNA-mediated activation may be, but this is a very exciting new insight.

At the moment, there is considerable controversy regarding the precise mechanism miRNA use to inhibit translation, and different targets may in fact interact with the miRISC in different ways. In general, however, the miRNA-miRISC-mRNA interaction appears to suppress the entry of the targeted mRNA into the translational cycle, leading to an inhibition of protein synthesis. Frequently, but not always, mRNA targeting also results in the destruction of the mRNA due to enhanced degradation.

Although the field is progressing rapidly, the genetic and biochemical analysis of the miRNA pathway is in its infancy. Mutational phenotypes of a number of genes in the pathway have been reported, whether in humans, mice or invertebrate model systems. In general, loss of Drosha, DGCR8, Dicer, or the Argonaute proteins of the miRISC is incompatible with embryonic development; in most cases nervous system development is also severely disrupted. From these results, it seems clear that the miRNA pathway plays a fundamental role in the developmental regulation of gene expression in the nervous system.

Neural miRNA Genes

By intervening between the transcription and translation steps of mRNA utilization, miRNAs act to sculpt the raw information of the transcriptional output of the cell into temporal and tissue specific patterns of protein expression. This raises the inevitable question: "Who regulates the regulators." There is not yet a firm count of the number of miRNA genes, over 400 have been experimentally verified in mammalian genomes, with some estimates of the total number exceeding one thousand. Expression analysis of miRNAs initially relied on Northern blotting of individual sequences, this has now been supplanted by high-throughput sequencing of cloned miRNA libraries, miRNA-specific RT-PCR, chip-based miRNA microarrays, and ►deep sequencing. At the cellular level, the introduction of high affinity locked-nucleotide probes has allowed traditional in situ hybridization methods to be modified for detection of miRNAs (please refer to [2] for a description and references for these important innovations). The CNS has a particularly rich repertoire of miRNAs, with over 30% of the known miRNAs expressed in the brain. An increasing body of work applying these new methods is now providing a detailed look at miRNA expression patterns. One fundamental issue that was addressed early on is whether miRNA expression is specific for individual cells and tissues. As more and more miRNAs were discovered and characterized, it was shown that many miRNAs are expressed nearly ubiquitously with little preference for particular organs or tissues, but others show various degrees of tissue specificity. In a study headed by Todd Golub at the Broad Institute, tissue specificity was found to be characteristic enough to allow the tissue of origin of tumor samples to be predicted based on ►miRNA profiling. A recently published large scale compendium of miRNA expression patterns (headed by Thomas Tuschl at The Rockefeller University), however, identified less than a dozen miRNAs with strong overrepresentation in the human and mouse nervous systems. Within the brain, large scale efforts to define expression patterns in zebrafish, chicken, mouse and in primates have revealed regional as well as temporal specificity in expression patterns (again, refer to [2] for links to specific papers). These efforts provide an invaluable starting point for the investigation of the roles of individual miRNAs in both the development of the nervous system, and in the function of neural cell types in the brain.

miRNA Functions in the CNS

The Sensory Nervous System of Caenorhabditis Elegans Leads the Way

As discussed above, the complexity of neural miRNA populations appears to reflect the cellular and architectural complexity of the nervous system. Approximately 30% of the known miRNA genes are expressed in the CNS, however, their precise roles and functions remain for the most part enigmatic. In this section we will highlight groundbreaking studies that have revealed the involvement of miRNAs in developmental processes such as neuronal specification, and then turn to evidence for miRNAs as mediators of mature brain functions such as synaptic plasticity and memory.

Probably the most thoroughly characterized example of miRNA involvement in cell specification relates to the establishment of asymmetry in the nematode *Caenorhabditis elegans* as elaborated in a series of papers from Oliver Hobert's group at the Columbia University Medical Center. These studies evoke the classical molecular genetic investigations by Jacob and Monod of another binary fate choice, the decision between lysis and lysogeny by the bacteriophage λ. In

both cases, transcriptional and post-transcriptional regulatory mechanisms intertwine to stabilize genetic networks that discriminate between alternative cell states. In the gustatory system of *Caenorhabditis elegans,* two taste receptor neurons termed "ASE left" (ASEL) and "ASE right" (ASER) express distinct sets of ►chemoreceptors, an arrangement that allows the nematode to orient itself in relation to a source of food. The establishment of left/right asymmetry in gene expression from symmetric ►progenitors involves mutually exclusive ►feedback loops driven by miRNAs working in concert with ►transcription factors.

In ASEL cells, the transcription factor *die-1* and the miRNA *lsy-6* are expressed and together promote ASEL genes while suppressing ASER genes. Similarly, in ASER cells the transcription factor and miRNA pair *cog-1* and *miR-273* activate ASER specific genes and antagonize *die-1* and *lsy-6*. Although the initial trigger has not yet been defined, the results so far demonstrate how miRNAs can play integral roles in the establishment, reinforcement and maintenance of cell-specific ►gene expression patterns and therefore represent a model for the possible contribution of miRNAs to the myriad ►cell fate decisions required to construct the vertebrate brain. Whether or not miRNAs are also involved in the ►left/right asymmetry typical for the human brain is not yet clear, but very recently a study by Choi, Giraldez, and Schier implicated the zebrafish miRNA *mir-430* in left/right asymmetry, and the group of Tamas Dalmay at the University of East Anglia demonstrated strong asymmetry in the expression of mouse *mir-500*.

mir-124 – a Significant Actor in Neuronal Cell Identity

Turning to studies of the vertebrate nervous system, *mir-124* has attracted a great deal of interest as a paradigm for tissue specific miRNAs. By sequencing small RNA libraries prepared from various mouse tissues, Thomas Tuschl's group, then at the Max-Planck-Institute in Martinsried, had originally discovered a remarkable property of miRNA expression. Whereas many miRNA were expressed across many tissues, others were highly restricted to individual tissues or organs. *mir-124* is a striking example of this principle, with expression restricted to neurons, where it accounts for over 25% of the total miRNA population. Very recently, Tom Maniatis' group at Harvard University found that *mir-124* promotes neuronal specification by regulating mRNA splicing factors. The end consequence is to allow a greater degree of flexibility in neuronal splicing. Although it is not yet clear what the relative advantage of greater diversity in splicing products for neurons compared to other somatic cell types might be, the conservation of *mir-124* across animal phyla suggests that neurons may have acquired this property early in the evolution of the nervous system.

miRNAs and Synaptic Plasticity and Learning

So far, we have discussed examples of miRNAs that act at early stages in the establishment of neuronal identity. Michael Greenberg's laboratory, also at Harvard University, has shown that miRNAs influence neuronal connectivity. They were able to demonstrate that one neuronal miRNA, *mir-134*, is present in ►dendritic spines, structures that form the receiving end of synaptic communication between neurons. It is known that translational regulation is important in reinforcing connectivity at active synapses. *mir-134* was shown to target a mRNA, *limK1*, that encodes a kinase involved in determining the size of dendritic spines. Interestingly, both the levels of *mir-134* and its efficiency as a translational inhibitor were affected by synaptic activity. In their model, *mir-134* acts as a local inhibitor of dendritic maturation; at least in part by regulating *limK1*. Importantly, the inhibitory effect of *mir-134*, and by extension other synaptic miRNAs, was relieved after neuronal stimulation by brain derived neurotrophic factor (►BDNF). Because BDNF is released at active synapses, the result conforms to expectations for positive regulators of ►synaptic plasticity.

Taking advantage of the genetic power of *Drosophila melanogaster*, another group at Harvard University headed by Sam Kunes was able to go one step further and link the miRNA pathway to ►memory formation. The beauty of this study lies in their ability to monitor local translation at specific synapses as they respond to a learning task. Specifically, they examined the role of miRNA-mediated regulation of a key synaptic translation product: ►Calcium/Calmodulin-dependent Kinase II (CaMKII). Synapses participating in memory formation increase their synthesis of CaMKII. Flies carrying mutations that inactivate the miRISC express much higher levels of CaMKII, implying a regulatory network similar to that described above for LimK1 and *mir-134*. The Kunes group showed that increased synaptic activity resulted in the elimination of miRNA pathway proteins by protein degradation, suggesting a general role for the pathway in dampening responses in quiescent neurons.

The miRNA Pathway and the Maintenance of the Cerebellum

In the near future, transgenic approaches can be expected to rapidly advance our understanding of miRNA functions in the brain. As a recent example, Paul Greengard's group at the Rockefeller University examined the effects of eliminating the Dicer protein in a single cell type within the ►cerebellum, the ►Purkinje neurons. Although the analysis was complicated by the gradual and uneven loss of the Purkinje miRNA population, the affected mice did not display an overt phenotype or detectable changes in the electrophysiological properties of the affected cells for several weeks. Thereafter, profound ►neurodegeneration set

in, beginning with the Purkinje cells and then spreading to the entire cerebellum. Although more work remains to be done, these results underscore a requirement of miRNAs for cellular viability. In contrast, they do not provide evidence for miRNA involvement in short term synaptic activity, at least in Purkinje neurons.

The miRNA Pathway and Neurological Disease

Several protein components of the miRNA biogenesis pathway discussed in the previous sections are critical not only for CNS development but also are associated with neurological diseases. We will discuss some of the initial discoveries, including miRNA involvement in mental retardation syndromes, neurodegeneration, Tourette's Syndrome and cancer (Fig 1).

miRNAs and Mental Retardation

The ►Fragile X Mental Retardation Protein (FMRP) is silenced in patients with Fragile X Syndrome, an inherited form of mental retardation. The gene responsible for Fragile X Syndrome, FMR1, is situated on the X chromosome and consequently contributes to the higher incidence of mental retardation observed in males. As a likely correlate of cognitive impairment, affected individuals also demonstrate altered dendritic spines, focusing attention on alterations of neuronal ►connectivity in the disease state. FMRP is an evolutionarily conserved protein that contains several RNA binding domains that mediate interactions with mRNAs. mRNA binding by FMRP leads to a suppression of protein translation. FMRP can be detected in synapses where it regulates local protein synthesis and thereby plays an important role in synaptic plasticity and dendritic development. The initial link to the miRNA pathway was forged by the groups of Scott Hammond at the Cold Spring Harbor Laboratory and Haruhiko Siomi at the University of Tokushima, who showed that the *Drosophila melanogaster* FMRP homolog, dFMR1, co-purified with miRNA pathway proteins. Stephen Warren's group at the Emory University School of Medicine extended these findings to the human protein, then returned to the *Drosophila melanogaster* system to show that dFMR1 acts together with the miRNA pathway protein dAgo1 in the regulation of synaptic plasticity. These studies provided the first demonstration that the miRNA pathway contributes to normal neuronal function, in addition to advancing our understanding of the Fragile X disease state.

miRNAs and Neurodegeneration

The miRNA pathway has also been implicated in the pathogenesis of a complex of neurodegenerative diseases characterized by ►expansion of the trinucleotide CAG (poly-glutamine, or poly-Q, expansion). Using a genetic model designed in *Drosophila melanogaster*, a group headed by Nancy Bonini at the University of Pennsylvania designed a genetic test which showed that disruption of the miRNA biogenesis pathway exacerbated neurodegeneration induced in the fly retina by poly-Q proteins. The authors then extended the results to a human cell-based system, supporting the potential relevance for human disease. How miRNA's contribute to the observed neuroprotection remains to be determined.

miRNA Dysregulation and Tourette's Syndrome

The Fragile X Mental Retardation and the Poly-Q Expansion Syndromes summarized above may reflect the consequences of widespread disruption of miRNA biogenesis or translational regulation. In the case of ►Tourette's Syndrome, a mutation that disrupts a single miRNA-mRNA interaction is linked to a neurological disorder. A team of scientists centered at the Yale University School of Medicine and headed by Matthew State identified ►*Slit and Trk-like 1* (SLITRK1) as the first candidate gene for Tourette's Syndrome, a prevalent neuropsychiatric disorder characterized by so-called ►tics. The term tic refers to repetitive, stereotyped and irresistible movements or vocalizations with considerable individual variability, ranging from sneezing or blinking to outbursts of profanity or complex series of movements. In two independent cases, point mutations were identified in the 3′UTR of the SLITRK1 gene. Remarkably, the mutations were shown to lie in a binding site for the miRNA *mir-189*, and had the affect of increasing the affinity of the miRNA for the mRNA, thus enhancing inhibition of SLITRK1. SLITRK1 is one of a family of transmembrane proteins with similarities to both the SLIT family of ►axon guidance factors and, with the exception of SLITRK1, ►neurotrophin receptors. So far, the SLITRK's have not been well-characterized functionally, but the State group was able to support the initial characterization of SLITRK1, by Aruga and Mikoshiba at the Riken Brain Science Institute, as a protein involved in dendritic ►outgrowth and morphology. Although the work to date depends primarily on correlation, it represents a breakthrough as the first example in which mutations in a miRNA binding site were shown to be causative for a human disease.

miRNAs and Cancer

One of the most active current directions in miRNA research relates to their role in cellular growth control and apoptosis. A thorough discussion of this rapidly expanding field is beyond the scope of this review. In general terms, miRNAs have been implicated in the control of stem cell differentiation in a variety of contexts, and in the regulation of a number of well-studied genes and pathways commonly affected in human cancers (for example *bcl-2*, *c-myc*, *N-ras*, *p27* and *p53*). Given the likelihood that cancer stem cells are

the catalysts for each of the main forms of brain tumors (►medulloblastoma, ►glioblastoma and ►ependymoma), interest in the contribution of miRNA misregulation is high. In the case of glioblastoma, a number of investigators have catalogued characteristic changes in miRNA profiles, and begun to relate those changes to potential oncogenic target genes. miRNAs are attractive targets for pharmaceutical interventions, as they can at least in principle be specifically blocked or mimicked by small molecules, such as chemically modified antisense inhibitors.

Conclusions and Outlook

It is impossible to introduce all of the interesting findings from dozens of new miRNA articles that appear each month. In this short overview, we have instead focused on a few of the groundbreaking discoveries that have illuminated the whole field. Going forward, it seems likely that miRNA research will be increasingly integrated into traditional research programs as outlined above (oncogenesis, ►cell specification, cortical development, learning and memory, etc). Continuing refinement in target mRNA predictions are facilitating the identification of gene networks under miRNA control, which can then be studied with a variety of new tools for manipulating miRNA expression. Genetic analysis will dissect the functions of miRNA pathway proteins and individual miRNAs at an increasingly fine scale, despite the challenge imposed by the considerable redundancy of miRNA genes. The pace of discovery in the field over the past 5 years has been bracing, we hope we have been able to communicate a sense of that excitement.

References

1. Ruvkun G, Wightman B, Ha I (2004) The 20 years it took to recognize the importance of tiny RNAs. Cell 116:S93–6
2. Bushati N, Cohen SM (2007) microRNA Functions. Annu Rev Cell Dev Biol 23:175–205
3. Klein ME, Impey S, Goodman RH (2005) Role reversal: the regulation of neuronal gene expression by microRNAs. Curr Opin Neurobiol 15:507–513
4. Kosik KS, Krichevsky AM (2005) The elegance of the MicroRNAs: a neuronal perspective. Neuron 47:779–782
5. Cao X, Yeo G, Muotri AR, Kuwabara T, Gage FH (2006) Noncoding RNAs in the mammalian central nervous system. Annu Rev Neurosci 29:77–103

Mirror Neuron

Definition

A particular class of neurons, originally discovered in the ventral premotor cortex of macaque monkeys (area F5) and then observed in the inferior parietal lobule (PF/PFG), which code goal-related motor acts like grasping. They become activated both when the subject performs a particular action, e.g. a precision grip, and when the subject observes another individual performing a similar goal-related action. There is evidence for a similar system in the human brain.

►Action Representation
►Visual Space Representation for Reaching

Mismatch Negativity (MMN)

Definition

A sound-evoked event-related potential. A response to an acoustical change in two sounds. It is evoked by an occasional subtle stimulus change in a long train of repetitive stimuli. The difference may be in frequency, intensity, complexity, etc. A difference in the evoked response between the two stimulus types indicates that a detection of the difference has taken place.

►Auditory Evoked Potentials

Missense Mutation

Definition

A nucleotide substitution that causes the replacement of one amino acid by another in the polypeptide typically leading to a change in the function of the protein.

Mitochondrial Disease

Definition

Mitochondrial disease refers to a group of medical disorders in which the primary metabolic defect affects the respiratory train/electron transfer system producing ATP in the intracellular organelles called mitochondria.

Genetic disorders of mitochondrial dysfunction can be inherited as either single gene mendelian or primary mitochondrial traits. This is because the mitochondrial respiratory train enzymes are encoded by both nuclear and mitochondria DNA. The clinical syndromes often

include seizures, cognitive deficits, visual loss, hearing loss, myopathy and peripheral neuropathy.

►Seizures

Mitochondrial Myopathies

Definition

Consequences of ►mitochondrial diseases resulting from defects in the mitochondrial respiratory chain (in particular defects in nuclear DNA and mutations in tRNA genes of mitochondrial DNA), which compromise energy production. This may cause myalgia, cramps, exercise intolerance, recurrent ►myoglobinuria, or weakness, particularly in extraocular muscles leading to ptosis (drooping of eyelids) and progressive external ►ophthalmoplegia.

Mitochondrial Uniporter

Definition

A channel on the inner membrane of the mitochondria that transports cytosolic Ca^{2+} into the mitochondrial matrix.

►Influence of Ca^{2+} Homeostasis on Neurosecretion

Mitogen-activated Protein Kinase (MAPK)

Definition

MAPK cascades are signaling molecules that serve as important mediators of signal transduction from the cell surface to the nucleus.

Mitral Cell

Definition

Mitral cells are large glutamatergic neurons found in the olfactory bulb, which along with tufted cells, receive input from olfactory sensory neurons and project to central olfactory areas of the brain, including the anterior olfactory nucleus and piriform cortex. The primary dendrite of a mammalian mitral cell projects to a single olfactory glomerulus and thus receives information from olfactory sensory neurons expressing a single type of olfactory receptor. The extensive lateral dendrites of mitral cells mediate inhibitory interactions (via granule cell interneurons) with neighboring mitral cells that generates a bulb-wide spatio-temporal pattern of mitral cell activity in response to odor stimulation.

►Glomerular Map
►Olfactory Bulb
►Olfactory Pathways

Mixture Theory

Definition

The branch of continuum mechanics that deals with the equations governing the motion of mixtures, that is, of material bodies each of whose spatial positions is occupied simultaneously by particles of two or more different materials.

►Mechanics

MLF

Definition

►Medial Longitudinal Fasciculus

MMC

Definition

►Migrating Motor Complex

M-modes

►Postural Synergies

Mnestic Block Syndrome

Definition

A type of memory disorder characterized by a sudden onset of severe retrograde amnesia, usually without significant anterograde amnesia. It typically includes memory loss for personal identity and autobiographical memories, as well as a period of wandering. It is usually precipitated by severe psychological stress (e.g., marital discord, financial collapse). Episodes generally resolve over a short period of time, lasting from a few hours to a few days.

►Amnesia

Modafinil

Definition

Modafinil is a stimulant drug that is used clinically for the treatment of excessive sleepiness (narcolepsy). The mechanism of action of the drug is unknown.

►Narcolepsy
►Stimulants

Modal Logic

Definition

Modal logic studies reasoning that involve the use of the expressions "necessarily" and "possibly." However, the term "modal logic" "it is obligatory that" and "it is permitted that."

►Mental Models

Modality

Definition

Modalities refer to large classes of senses and the related sensory receptors, e.g. visual, auditory, olfactory, gustatory and tactile (the five classic senses) (Sensory Systems).

►Sensory Systems

Modality-specific

Definition

From a single sensory modality (i.e., unimodal). Used in two forms: (a) to categorize a neuron based on the stimuli to which it can respond (e.g., a neuron responsive only to light would be a modality-specific neuron), and (b) to categorize a particular neuronal response regardless of the type of neuron from which it is evoked (e.g., a response to light, even in a multisensory neuron, is a modality-specific response).

►Multimodal Integration

Model-based View

Definition

Characterization of a system in terms of a model. Data are referenced to the parameters and predictions of the model.

Model Estimator

Definition

A model estimator is a tool used to generate a mathematical model for a physical system. Typically, it consists of an assumed family of mathematical models and an algorithm. The algorithm uses available data (commonly, actions on the system – inputs, and measurements - outputs) to choose the "best" fit to the physical system.

►Adaptive Control

Model Presynaptic Release Sites

►Synaptic Transmission: Model Systems

Modeling of Human Postural Control

John Jeka[1], Tim Kiemel[2]
[1]Department of Kinesiology, Neuroscience and Cognitive Science Program, Bioengineering Graduate Program, University of Maryland, MD, USA
[2]Department of Kinesiology, University of Maryland, MD, USA

Synonyms

Modeling; control theory

Definition

Mathematical models represent the interaction of control processes with underlying physiological subsystems to develop testable predictions of behavior associated with stable, flexible upright stance control.

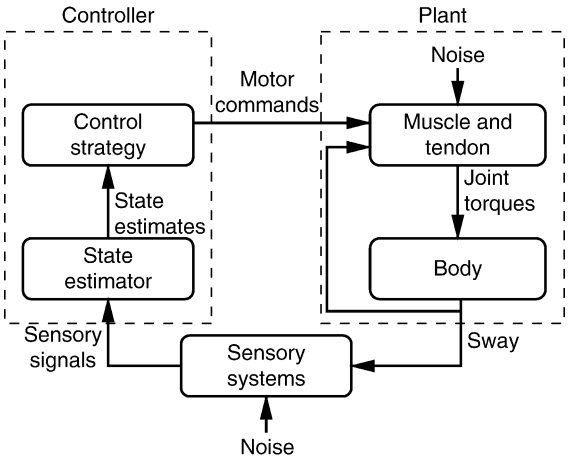
Description of the Theory

Human upright stance is inherently unstable. The small, continuous displacements referred to as "sway" reflect a complex control process that counteracts the torque due to gravity, which continually accelerates the body away from vertical equilibrium. The end result of this control process is corrective joint torques that maintain the body upright. There is considerable controversy about how the nervous system generates these corrective torques. Here we illustrate the issues by starting with the simplest possible model, a single-joint negative feedback model, and progress to the current state of more complex models.

The Control Theory Perspective

The predominant perspective for modeling postural control is based on principles of ▶control theory [1] In its most fundamental form, upright stance control has three elements a plant, sensory systems and a neural controller (see Fig. 1).

The plant is the mapping from motor commands to movement of the body and depends on musculotendon properties and the mechanics of the body. Sensory systems detect the body's position and movement and send related sensory signals to the neural controller. The neural controller then maps these incoming sensory signals into motor commands. Control theory addresses the question of how to design a controller based on the properties of the plant and sensory systems that is capable of producing the desired behavior of the plant, in this case maintenance of stable upright stance. The control theory perspective for postural control will be illustrated with simple plant and sensory models and a suitable neural controller.



Modeling of Human Postural Control. Figure 1 A schematic representation of the postural control system from a control theory perspective.

A Simple Plant Model

The body during "quiet stance" is often modeled as a single-joint inverted pendulum with the body bending only at the ankles and movement restricted to the sagittal plane [2,3]. "Quiet" means upright stance that is undisturbed externally by for example, a moving support surface. The motivation for the single-joint approximation is not only to simplify the control problem, but is also based on empirical results demonstrating that modulation of muscle activity during quiet stance is seen mostly for muscles of the lower legs, soleus and gastrocnemius. Since angular deviations of the body from vertical during quiet stance are small, the body model can be further simplified by linearizing its dynamics around vertical. In addition to simplifying body dynamics, musculotendon properties are often trivialized by assuming that the motor command is directly mapped into ankle torque. These simplifications result in the plant model

$$J\ddot{\theta}(t) = mgh\,\theta(t) + u(t) + \sigma\xi(t), \qquad (1)$$

where t is time, $\theta(t)$ is the angular deviation of the body from vertical, $\ddot{\theta}(t)$ is the body's angular acceleration, $u(t)$ (the motor command) is the net forward ankle-muscle torque specified by the neural controller and $\xi(t)$ is a white noise. The noise in the model is meant to account for the fact that the actual torque produced by ankle muscle will not be exactly equal to the torque specified by the motor command. The model parameters are: J, the body's moment of inertia around the ankle joint; m, the mass of the body; h, the height of the body's center of mass above the ankle joint (J, m and h do not include the mass of the feet); g, the acceleration due to gravity; and σ, the noise level.

M

Although the plant model (1) is highly simplified, it contains essential features of the control problem the nervous system must solve. Most importantly, the plant is unstable. If the control signal u is zero (or constant), the body will quickly deviate from vertical due to continual disturbances, both internal (e.g., physiological tremor) and external (e.g., uneven support surface, moving visual environment, etc.). Engineered devices, such as cars and robots, solve the stability problem by having a wide base of support and/or concentrating the bulk of their weight lower down. However, the human body has evolved with more than just upright stability as a constraint, with most of its mass concentrated higher up in the trunk, making it inherently unstable and prone to falls. Thus, the evolutionary development of bipedal stance, which freed the hands from locomotion and is considered the fundamental distinction between humans and our closest relatives, requires a sophisticated feedback control process to detect deviations from vertical and generate motor commands for a corrective torque to keep the body upright.

A Simple Sensory Measurement Model

There are two common approaches to modeling sensory feedback. In models that focus on sensory integration, sensory signals are often assumed to be noisy versions of plant variables such as the body's position and velocity, because biological sensors are inherently noisy. Models that focus on biomechanics often assume that the neural controller has access to the true values of all relevant plant variables. For simplicity, the second approach is illustrated. If the plant is assumed to be a single-joint inverted pendulum, as in (1) it is completely described by two variables, the angular position and velocity of the body. Therefore, we assume that the neural controller has access to these two sensory signals:

$$z_1(t) = \theta(t), \quad z_2(t) = \dot{\theta}(t). \tag{2}$$

Although the sensory model is not usually explicitly presented when it is this simple, here it paves the way for the discussion of more complicated sensory models below.

A Simple Neural Controller

It is well known from control theory that stabilization of an inverted pendulum requires that the control signal (corrective ankle torque) depends on both body position and velocity:

$$u(t) = -K_P\theta(t) - K_D\dot{\theta}(t). \tag{3}$$

This is an example of proportional-derivative (PD) control, where K_P and K_D are the proportional and derivative gains, which are assumed to be positive. Because of the negative signs, (2) describes *negative* feedback control. For example, if the body's position is forward and is moving forward, ankle torque will act to accelerate the body in the backward direction. If the body's position is forward but already moving backward toward vertical, the direction of the correcting ankle torque depends on the relative size of the proportional and derivative feedback gains.

A Simple Posture Model

Combining the plant model (1), the sensory measurement model (2) and the controller model (3) results in the postural control model

$$J\ddot{\theta}(t) = (mgh - K_\mathrm{P})\,\theta(t) - K_\mathrm{D}\,\dot{\theta}(t) + \sigma\xi(t). \tag{4}$$

There are two criteria for this model to stabilize the upright orientation of the body. First, the proportional gain K_P must be greater than mgh, so that ankle torque produced by muscles is greater than the torque produced by gravity. Such position feedback by itself turns the inverted pendulum of the uncontrolled body into a controlled system that is mathematically equivalent to a frictionless non-inverted pendulum. Thus, position feedback turns an unstable system, which actively moves away from equilibrium, into a neutrally stable system whose oscillations neither grow nor decay. For example, a large perturbation would lead to a large oscillation that never decays. Adding velocity feedback is like adding friction to the pendulum. Any movement is counteracted by a torque in the opposite direction leading to a damped oscillation. Because of noise in the model, the damped oscillation does not decay completely to zero. Instead the body's orientation fluctuates around vertical, providing a simple model of sway during quiet stance.

Current Models

Although model (4) provides insight into some of the essential features of postural control, such as the use of feedback control to stabilize upright stance, it is too simple to address other important features. Current research focuses on developing sophisticated models that explicitly represent features of the plant, feedback and control that allow for more complex behavior. For example, there is a long history of studying and modeling multi-joint postural control. When the support surface is translated backwards under standing subjects and they are instructed not to step, two patterns (or their combination) emerge. For small disturbances, the segments remain aligned in an ankle strategy, rotating predominantly around the ankle joint. Larger disturbances produce a hip strategy, a counter-rotation of the trunk relative to the legs [4]. A plant model with at least two joints, ankle and hip, are necessary to model the hip strategy.

Plant models may also include musculotendon dynamics so that muscle torques are no longer an instantaneous function of the motor commands (Fig. 1).

Musculotendon dynamics have been modeled using Hill type models, (e.g., [5]), or more simply as a time delay between the motor command and the generation of muscle torque. Time delays have also been added to sensory models. The inclusion of time delays in plant and sensory models are of interest because they tend to increase postural sway and can destabilize upright stance (e.g., [3]). Sensory integration models may also include dynamics specific to each sensory modality. For example, the vestibular dynamics is modeled as a low pass filter of the head's acceleration. At low frequencies, the vestibular signal that the neural controller receives is proportional to acceleration, whereas at higher frequencies it is proportional to velocity. Explicit modeling of sensory subsystems allows testing of model predictions that may help to identify important aspects of postural control in neurologically impaired populations such as individuals with loss of vestibular function [6,7]. Moreover, an open question is how to model ►adaptive control processes (e.g., sensory reweighting) that enable stability as environmental conditions change [6,7,8].

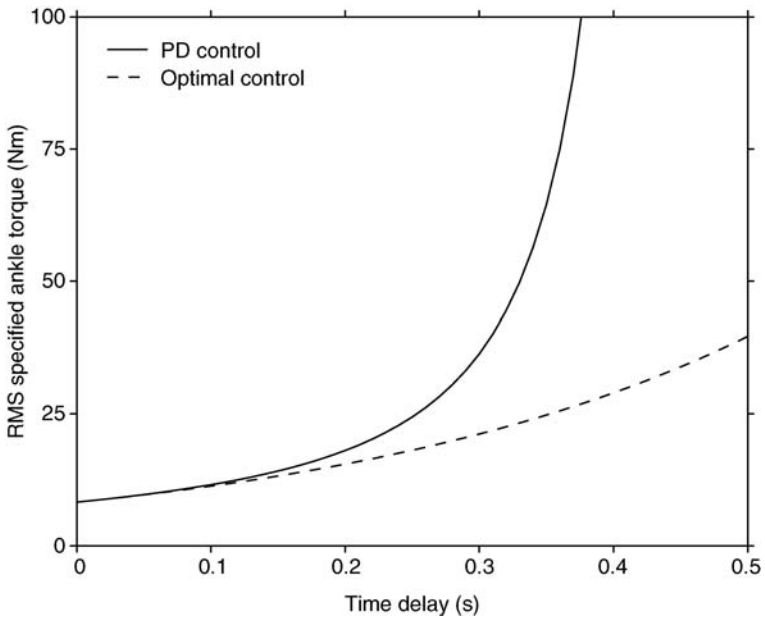
Optimal Control Models

When considering specific features of the plant and sensory systems, the great challenge is to determine whether the neural control strategy takes these features into account. One approach to this question is to study ►optimal control models. Such models contain neural controllers that are optimally designed for the specific features of the plant and sensory systems included in the model, such as multi-joint, musculotendon and sensory dynamics. For example, the human nervous system has well known time delays associated with processing sensory information and generation of muscle force. Do time delays influence the appropriate type of controller to stabilize posture? Adding a time delay to the plant and the sensory systems (same delay for all modalities) and using the same PD control strategy, the posture model (4) becomes

$$J\ddot{\theta}(t) = mgh\theta(t) - K_{\mathrm{P}}\,\theta(t-\tau) - K_{\mathrm{D}}\,\dot{\theta}(t-\tau) + \sigma\xi(t), \qquad (5)$$

where τ is the sum of the plant delay and the sensory delay. For larger values of τ more torque from ankle muscles is necessary to stabilize upright stance (solid line in Fig. 2).

The question is how much of this additional muscle activity is necessary. An optimal control model provides this answer (dashed line in Fig. 2). For time delays of about 100 ms or less, the PD control model is near optimal. However, for longer time delays, a control strategy other than PD control offers a substantial advantage. This result does not, by itself,



Modeling of Human Postural Control. Figure 2 The root mean square ankle torque specified by the neural controller as a function of time delay. For the PD control model (5), the proportional and derivative gains are adjusted to minimize ankle torque for each time delay. The optimal control model minimizes ankle torque across all possible controllers. The plant is characterized by the parameter $mgh/J = 9.83\ \mathrm{s}^{-2}$.

answer the question of which control strategy the nervous system uses, but it does provide insight into the challenge to postural control caused by time delays and how the nervous system *might* address this challenge.

As this example illustrates, optimal control theory provides a systematic method to generate a hypothesis about the control strategy the nervous system might use account for any (linear) feature of the plant or sensory systems. Determining the optimal control strategy requires three things, a model of the plant, a measurement model describing how sensory signals are related to plant variables, and a performance index. Models as in (1 and 2) above are examples of plant and measurement models respectively. Both plant and measurement models may contain noise terms. Also, there is no requirement that there be one measurement for every plant variable. An optimal control model uses an optimal state estimator, called a ►Kalman filter, to estimate the values of all plant variables, even those that are not directly measured (Fig. 1). The performance index is a quadratic function that describes the relative importance of minimizing the individual plant variables and control signals. Minimizing plant variables would include for example minimizing the deviations from vertical of body segments. Minimizing control signals involves minimizing the amount of motor neuron activity, which is related to the metabolic cost of muscle activity.

Optimal control models have addressed a variety of issues in postural control. For example, an optimal control model has been used to investigate how the performance index affects multi-joint coordination [9]. Appropriate choices of the performance index result in coordination patterns such as the ankle and hip strategies. Optimal control, or more specifically optimal state estimation, has also been used to investigate issues related to multi-sensory integration [2,10]. Incorporating a state estimator, such as a Kalman filter, into a model provides a potential solution to how non-comparable sensory signals such as position, velocity and acceleration signals can be fused to generate state estimates. For example, a Kalman filter in a posture model can estimate position and velocity based only on velocity signals.

Models with state estimation may also provide insight into underlying sources of sway variability. State estimation adds additional variables (there is one estimate for every plant variable) to a posture model and can therefore add dynamical components with additional time scales that increase sway variance. For example, it has been hypothesized that the slow dynamics observed in postural sway, which account for most of sway variance, are due to errors in state estimation [2]. This suggests that swaying is not due to errors of motor execution but because motor commands are based on inaccurate – estimates of self-motion.

Summary

Human postural control has historically been modeled within a control theory framework using simple approximations of the plant (single-joint inverted pendulum) and the controller (proportional-derivative). While these classical engineering models have been useful to investigate fundamental problems of upright stance control such as its inherent instability, current models use techniques such as optimal control to generate testable hypotheses about neural control schemes based upon specific features of the postural control system. The focus is now to investigate properties of multi-joint, musculotendon and sensory dynamics to promote a more biologically motivated understanding of human postural control.

References

1. Levine W (1999) Control system fundamentals. CRC, Boca Raton
2. Kiemel T, Oie K, Jeka J (2002) Multisensory fusion and the stochastic structure of postural sway. Biol Cybern 87:262–277
3. Peterka R (2000) Postural control model interpretation of stabilogram diffusion analysis. Biol Cybern 82(4): 335–343
4. Kiemel T, Oie K, Jeka J (2002) Multisensory fusion and the stochastic structure of postural sway. Biol Cybern 87:262–277
5. Menelgaldo LL, Fleury AT, Weber HI (2003) Biomechanical modeling and optimal control of human posture. J Biomech 36:1701–1712
6. Maurer C, Mergner T, Peterka RJ (2006) Multisensory control of human upright stance. Exp Brain Res 171(2):231–250
7. van der Kooij H, Jacobs R, Koopman B, van der Helm F (2001) An adaptive model of sensory integration in a dynamic environment applied to human stance control. Biol Cybern 84:103–115
8. Carver S, Kiemel T, van der Kooij H, Jeka JJ (2005) Comparing internal models of the dynamics of the visual environment. Biol Cybern 92:147–163
9. Kuo (1995) An optimal control model for analyzing human postural balance. IEEE Trans Biomed Eng 42:87–101
10. Kuo (2005) An optimal state estimation model of sensory integration in human postural balance. J Neural Eng 2: S235–S249

Models of Respiration

►Anatomy and Function in the Respiratory Network

Modulation of Memory Storage

Definition

A process of either strengthening or weakening of memory consolidation, typically induced by drug or hormone treatments, during a critical time-window shortly after the learning experience.

►Emotional Learning/Memory

Modulatory Inputs

►Modulatory Projection Neurons

Modulatory Projection Neurons

Michael P. Nusbaum
Department of Neuroscience, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Synonyms

Projection neurons; modulatory inputs; command neurons

Definition

Broadly defined, projection neurons are neurons whose axons extend from the neuronal cell body within the central nervous system (CNS) to one or more distant regions of the CNS. ►Modulatory projection neurons are the subclass of these neurons which have modulatory (generally synonymous with ►metabotropic) actions on their target neurons usually in addition to having classical (i.e., ►ionotropic) actions. Such neurons are likely to be essential to neuronal integration for all sensory, associative and motor systems, but to date they are most extensively studied and understood at the cellular-level in terms of their regulation of rhythmically active motor circuits. To more readily obtain a cellular-level understanding of their function, studies of modulatory projection neurons on these motor circuits are generally performed in the isolated CNS. The value of using the isolated CNS is enhanced by the fact that the projection neurons can be stimulated in a manner that mimics their in vivo activity. Moreover, their motor circuit targets continue to generate neuronal activity patterns that are similar to those that they generate in vivo [1–6].

Characteristics

Rhythmically active motor circuits, often called central pattern generators (CPGs), are small populations of CNS neurons that generate rhythmic neuronal output in response to non-rhythmic input, even in the isolated CNS. This type of circuit construct underlies all studied rhythmic motor behaviors, including various forms of locomotion, respiration, chewing and scratching [2–3,5]. CPGs are ►multifunctional circuits, each of which generates multiple neuronal activity patterns. These different activity patterns can be variations on a common pattern or else be quite distinct from one another [3–5,7].

The ability of CPGs to be multifunctional largely results from the presence of metabotropic (modulatory) receptors on the membranes of the individual circuit neurons [2–3,5,8]. Activation of this type of receptor elicits long-lasting biochemical cascades in the target neurons, which lead to changes in the intrinsic electrophysiological and synaptic properties of these neurons. Changes in these properties lead to changes in the related circuit activity.

In all systems studied, each different ►neuromodulator applied to the region of an isolated CNS that contains a CPG elicits a distinct activity pattern from that circuit [3,5]. Using applied neuromodulators to document the functional flexibility of CPG circuits led to the original paradigm shift in our understanding that neuronal circuits are in fact functionally flexible constructs. The ability of a tonically present neuromodulator to evoke a reproducible and stable change in the rhythmic output of a neuronal circuit results from the fact that these substances alter neuronal excitability by acting primarily on ►voltage-sensitive ion channels [8]. As their descriptor suggests, this class of ion channels is not open at all membrane potentials so that, despite changing the excitability of a neuron, the opening and closing of these channels can still be regulated by sufficiently strong synaptic inputs between the circuit neurons [3,5,8].

Modulatory projection neurons are a major source of metabotropic influence to CPG circuits [2–5,7]. These neurons typically reside in higher centers, from which they project to the region of the CNS where the relevant CPG is located. For example, the vertebrate locomotor CPG network in the spinal cord receives considerable input from projection neurons whose somata are located in the brainstem [2,5]. Similarly, CPGs in invertebrate ganglia are generally influenced by projection neurons that originate in higher-order ganglia [1,3–4,6–7].

In many small motor systems, individual projection neurons are physiologically and often neurochemically identified [4–5,7,9]. Consequently, these ►identified neurons are studied repeatedly in different preparations, allowing for the acquisition of considerable information about their function. The ability to work with identified neurons is facilitating the development of basic concepts regarding how these neurons are incorporated into larger network constructs [1,4,6–7].

Experimental activation of single projection neurons is sufficient for activating an entire CPG in small motor systems [4–7]. A comparable situation appears to occur for single populations of projection neurons in larger motor systems [2,9]. In the intact animal, however, sets of distinct projection neurons are more likely to be coactivated to drive a particular motor output [2,10]. Discerning the rules by which such populations are coactivated by natural stimuli, and determining their consequences for motor activity, is an active area of research.

Quantitative Description

The parameters most commonly used to assess the state of a modulatory projection neuron are its pattern and intensity of activity. Thus far, data from different projection neurons indicate that some are silent unless activated, while others are spontaneously active [1–2, 4–7,9]. The latter subset is readily separated both by whether their spontaneous activity is tonic or rhythmic, and whether that activity is sufficiently strong to influence the target circuit(s). Each of these conditions has been documented to occur for different identified projection neurons including, in some cases, different projection neurons in the same system. Additionally, some projection neurons impose their own rhythmic activity pattern onto the target circuit, while others exhibit the rhythmic pattern generated by the target circuit as a result of synaptic feedback from that circuit [1,6–7]. The intensity of projection neuron activity is commonly described either by its instantaneous firing frequency or its mean intraburst firing frequency.

The consequences of projection neuron activity are determined by characterizing the ►motor pattern generated by the target CPG circuit(s). The standard set of criteria used for this purpose include determining changes in: (i) speed (cycle frequency) of the resulting motor pattern; (ii) the activity level (burst duration, number of spikes and intraburst spike frequency) of each circuit neuron; (iii) the relative timing of activity (phase) of each circuit neuron; (iv) the duration of these changes; and (v) the interactions between separate CPGs [1,3,5–6,9].

Higher Level Structures

Modulatory projection neurons that influence the same neuronal network are often clustered into the same region of the CNS (e.g., brainstem, higher-order invertebrate ganglion). These projection neurons are not completely independent, parallel pathways whose actions only converge at the level of their shared targets. Instead, these neurons also interact to either facilitate or prevent their coactivation [2,4,7]. However, the extent to which there are well defined circuits among such populations of projection neurons remains to be determined. Further, although stimulation of an individual modulatory projection neuron is often sufficient to elicit or modulate an entire motor pattern, it appears likely that subsets of these neurons are normally coactivated by particular sensory or higher-order inputs [1–2,10].

Lower Level Components

The influence of modulatory projection neurons can reach every level of a motor system. These neurons commonly synapse directly with CPG neurons and thereby activate, terminate or alter circuit output [2–5, 8–9]. These synapses often include both ionotropic and metabotropic components, so there are generally both short-term and long-term actions. As indicated above, there are also synapses between different projection neurons. In parallel, projection neurons also directly influence the same motor neurons whose activity is driven by the CPG, thereby modifying the motor neuron response to CPG activity. Finally, some projection neurons also project to the periphery, where they regulate transmitter release from motor neuron terminals at their neuromuscular junctions as well as directly altering muscle fiber properties [3,5,8].

Structural Regulation

Focused sensory stimuli clearly activate modulatory projection neurons and thereby influence CPG activity [1–2,5,9]. Furthermore, any such focal sensory pathway stimulation appears to target subsets of the population of projection neurons relevant to any particular motor act [1,10]. However, the general organizing principles underlying this level of operation are yet to be determined. Thus far, the data set is small, but distinct sensory inputs are as likely to elicit distinct motor programs from the same CPG because they activate different or the same subset of modulatory projection neurons [1,10].

There is also feedback regulation from the target CPG(s) to the projection neurons. This often results in the projection neuron exhibiting a rhythmic activity pattern that is time-locked to that of the CPG [2,5–6]. The function of this feedback regulation remains obscure in most systems, although some recent work has documented a role for this feedback in enabling one CPG to regulate the activity of a distinct but related CPG circuit [6].

This general schema for sensorimotor organization implies a hierarchical organization for motor control. However, as we learn more about the cellular-level details at each level of organization, the lines between them have begun to blur. For example, some projection neurons also satisfy the criterion to be CPG members and some CPG members, when directly activated, can turn on the entire CPG [1,3–6].

Higher Level Processes

The basic organizational features represented by the population of modulatory projection neurons that influence different CPGs seem comparable, but there are few data sets available for comparison. It is clear that such populations include subsets that use different sets of co-transmitters [2–3]. Furthermore, selective activation of some individual projection neurons is sufficient to orchestrate complete activation or termination of a CPG in small motor systems in invertebrates and non-mammalian vertebrates [2,4–5,9]. However, it appears likely that behaviorally-relevant activation of projection neurons in all motor systems involves the coactivation of subpopulations of these neurons [1–2,10]. The current issues being addressed that relate to this organization include determining: (i) how any single population of distinct but functionally related projection neurons are influenced by distinct sensory and higher-order inputs, and (ii) the extent to which inter-projection neuron interactions sculpt the influence of these neurons on their CPG targets. It is also important to expand to additional systems an understanding of the function of rhythmic CPG feedback onto these projection neurons.

Lower Level Processes

Many of the concepts now known to be relevant to modulatory projection neurons were first established by studies in which neuromodulators were bath-applied to the isolated nervous system, as a model system for how modulatory neurons influence CPG activity [2–5,7–8]. Included among these now well-established concepts is that: (i) Neuromodulation alters CPG output, quantitatively and sometimes qualitatively, by changing the cellular and synaptic properties of the circuit neurons. (ii) Modulation works at multiple levels, often also altering the properties of pre-CPG interneurons and post-CPG targets, such as motor neurons and muscles. (iii) These modulatory consequences result from both convergence and divergence of modulator action. For example, different neuromodulators can evoke different motor patterns from the same CPG and yet have convergent actions on the same second messenger system(s) and/or ion channel(s). In such situations, the different motor patterns result at least partly from different CPG neurons having overlapping but distinct sets of receptors for the different modulators. There are also examples whereby a single modulator influences a CPG by altering the activity of a set of different ion channels, but the subset that it influences is distinct in each CPG neuron. (iv) Not all CPG neurons need be direct targets of any single modulator. (v) To completely understand modulation of a circuit, it is equally important to identify which CPG neurons are not targets and are targets of a modulator, because the synaptic actions of non-targets often alter the activity of the target neurons.

Studies using direct, intracellular recording and manipulation of individual projection neurons have revealed that, like bath-applying different modulators, stimulating different projection neurons elicits distinct outputs from the same CPG [3–5,7]. In addition to confirming the results of bath-applying neuromodulators, stimulating single projection neurons has revealed additional degrees of freedom available to these systems. For example, (i) many projection neurons contain co-transmitters, but each target neuron in a CPG does not necessarily contain receptors for all of the co-transmitters released by any single projection neuron; (ii) different projection neurons with the same co-transmitter complement can elicit different outputs from the same CPG; (iii) consistent with the belief that projection neurons provide no timing cues to the CPG, some projection neurons modulate CPG output by providing a non-rhythmic input to their target CPG; and (iv) the ability of a projection neuron to activate/modulate a CPG output cannot always be mimicked by bath application of its co-transmitters. This last point may be due to the difficulty in mimicking the temporal nature of the ionotropic actions of the projection neuron with either focal or bath application, or because of local regulation of transmitter release (see below).

Process Regulation

There is both biochemical and synaptic regulation of the actions of projection neurons. Regarding biochemical regulation, despite the general belief that neurally-released peptides freely diffuse, many of them are locally inactivated by extracellular peptidase activity [7]. Such focal regulation of released neuropeptide can enable different projection neurons to elicit distinct CPG outputs despite releasing the same peptide.

At the so-called lower levels, synaptic regulation of projection neuron activity originates from both sensory feedback and CPG feedback [1–7]. Various sensory systems either trigger, terminate or modify projection neuron actions onto CPGs. Triggering and terminating tends to occur at the level of the projection neuron dendrites/soma, thereby influencing the ability of the neuron to generate action potentials. In contrast, the modifying actions of a sensory input can occur either at that same location or via axo-axonic synapses,

thereby having focal actions on specific transmitter release sites of the affected neuron.

The activity of some projection neurons is time-locked to that of their target CPG [5–6]. This rhythmic projection neuron activity is generally a consequence of synaptic feedback from the CPG activated by that projection neuron. The feedback can either globally or focally affect projection neuron activity, depending on the site of the synapse [4–7]. In most such cases, the function of this rhythmic projection neuron feedback is not known. In one recently documented example, its function is to enable one CPG to regulate the activity of a behaviorally related CPG [6].

Function

Modulatory projection neurons integrate inputs from sensory and higher-order centers and, when activated, provide persistent drive to one or more rhythmically active motor circuits (CPGs). Different subsets of these projection neurons share the ability to activate a particular CPG, but their distinct actions enable them to generate different neuronal output patterns from that circuit. These distinct actions lead to the generation of particular coordinated rhythmic movements, such as walking, running or swimming from the spinal locomotor CPG. The collective influence of modulatory projection neurons appears to be necessary to enable CPGs to express their full potential. Their complete elimination may prevent the expression of any natural versions of the behaviors generated by that CPG.

Therapy

The loss of input from modulatory projection neurons, such as might occur for the vertebrate locomotor CPG after spinal cord injury, either eliminates or severely limits the ability to activate that CPG [2–3,6]. Thus, understanding the detailed cellular-level influences of these neurons on their CPG targets will be pivotal to understanding how to circumvent or replace their loss after injury or disease.

References

1. Beenhakker MP, Kirby MS, Nusbaum MP (2007) Mechanosensory gating of proprioceptor input to modulatory projection neurons. J Neurosci 27:14308–14316
2. Grillner S (2003) The motor infrastructure: from ion channels to neuronal networks. Nat Rev Neurosci 4:573–586
3. Marder E, Bucher D Schulz DJ, Taylor AL (2005) Invertebrate central pattern generation moves along. Curr Biol 15:R685–R699
4. Nusbaum MP, Blitz DM, Swensen AM, Wood D, Marder E (2001) The roles of co-transmission in neural network modulation. Trends Neurosci 24:146–154
5. Stein PSG, Grillner S, Selverston AI, Stuart DG (eds) (1997) Neurons, networks and motor behavior. MIT, Cambridge, MA
6. Wood DE, Manor Y, Nadim F, Nusbaum MP (2004) Intercircuit control via rhythmic regulation of projection neuron activity. J Neurosci 24:7455–7463
7. Nusbaum MP (2002) Regulating peptidergic modulation of rhythmically active neural circuits. Brain Behav Evol 60:378–387
8. Harris-Warrick RM (2002) Voltage-sensitive ion channels in rhythmic motor systems. Curr Opin Neurobiol 12:646–651
9. Perrins R, Walford A, Roberts A (2002) Sensory activation and role of inhibitory reticulospinal neurons that stop swimming in hatchling frog tadpoles. J Neurosci 22:4229–4240
10. Kristan WB, Shaw BK (1997) Population coding and behavioral choice. Curr Opin Neurobiol 7:826–831

Module

Definition

In neuroscience, "module" refers to a functional component of the brain, describable in terms of neurological structures, e.g. cells, columns, layers. In cognitive science, module refers to a specialized mental device that operates on specific types of information (domain-specificity), provides predetermined outputs for predetermined inputs (mandatory operation), has no access to information in mental systems except its own subsystems or dedicated input devices (informational encapsulation), delivers output restricted to relatively simple concepts (shallow output) and is subject to characteristic patterns of breakdown. The operations of a mental module are also fast and inaccessible to attention processes or consciousness.

►Theory Theory (Simulation Theory; Theory of Mind)

Module in Central Pattern Generator

Definition

A population of neurons within a central pattern generator (CPG) that acts in concert. Neurons in the module are active during a specific phase of a behavior and are quiet during other phases of the behavior. The unit-burst-generator and the half-center are examples of modules.

►Half-center
►Scratching

Molecular and Cellular Biomechanics

Walter Herzog
Professor, Faculty of Kinesiology, University of Calgary, Canada

Definition

Molecular and cellular biomechanics is the branch of biomechanics that deals with single molecules, molecular interactions, or cells as the system of interest. It deals with the effects that the mechanical environment has on gene expression, mRNA and protein production in cells, and transport and assembly of proteins in extracellular matrices, and further deals with the mechanical properties of isolated molecules or the interaction of proteins, specifically those that make up ►molecular motors that produce essential functions in living systems.

Characteristics

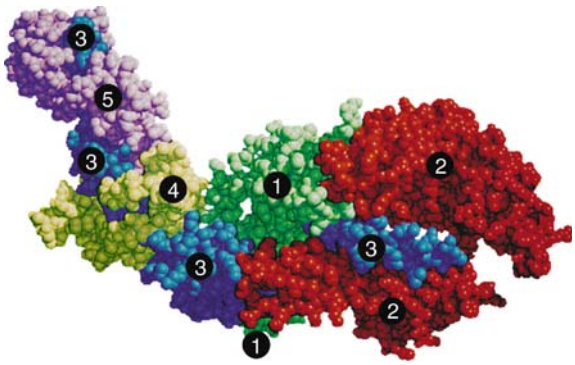
Molecular and cellular biomechanics is a relatively new branch of biomechanics. It was made possible by technological developments and by the interest of scientists to understand phenomena of tissue growth and adaptation, transport phenomena involving molecular motors, and material properties of isolated molecules, to name just a few of the emerging fields of research. Here, selected approaches are highlighted to provide insight into the field of molecular and cellular biomechanics, and to give specific examples of applications.

The first example will deal with the mechanisms of muscle contraction involving the molecular motor composed of ►myosin II and ►actin; the second example will deal with the giant molecular spring ►titin, which plays an important role in passive force production in skeletal and cardiac muscle.

Myosin-Actin Interactions and the Molecular Mechanisms of Contraction

In order to deal with molecular interactions, it is important to have a detailed structural description of the proteins that are considered. In the case of myosin II, Rayment et al. [1] described the portion of that molecule that is referred to as the subfragment 1, S1. This part of the molecule contains the actin and nucleotide binding sites, as well as the regulatory and essential light chains (Fig. 1).

The structure of the S1 was determined by x-ray diffraction in a two-step procedure: first, the positions of the metal binding sites were determined using x-ray data sets with a 4.5 Å resolution, and then these data were filled in with Synchroton radiation results to produce a 2.8 Å resolution. In a companion study, Rayment et al. [2] revealed the structure of the actin binding site, and they speculated on the interaction of S1 with the actin attachment site that produces muscle contraction.

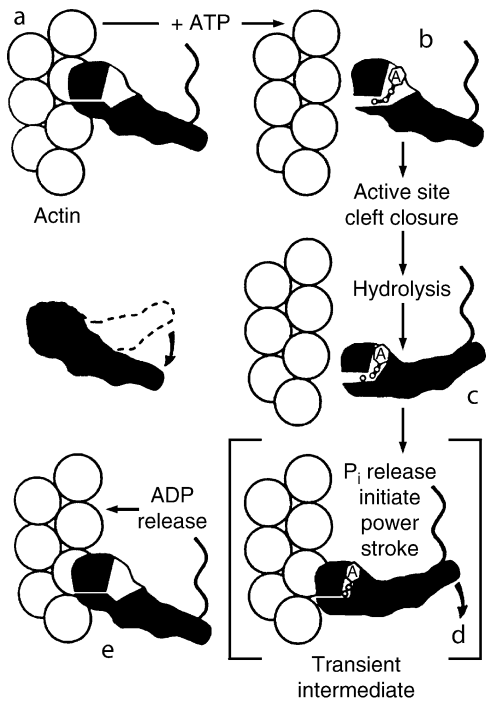


Molecular and Cellular Biomechanics. Figure 1 Space-filling representation of all atoms in the myosin subfragment 1 model. Segments labeled 1, 2, and 3 represent parts of the heavy chains, while those labeled 4 and 5 show the essential and regulatory light chains, respectively. The proposed actin binding site is located at the lower right-hand corner (2). The active nucleotide site is on the opposite side from the proposed actin binding surface; segment 1 (Reprinted with permission from Rayment et al. [1]. Copyright 1993 American Association for the Advancement of Science).

Starting from the rigor confirmation, Rayment et al. [2] suggested that the narrow cleft that splits the 50 kD segments of the myosin heavy chain into two domains is closed (Fig. 2a and e, horizontal gap, perpendicular to the actin filament axis).

The addition of ATP and initial ATP binding to myosin at the active site causes an opening of the narrow cleft between the upper and lower domains of the 50 kD segment. This in turn disrupts the strong binding between actin and myosin but still allows for a weak attachment (Fig. 2b). The final ATP binding to myosin causes a closure of the nucleotide binding pocket and a corresponding configurational change of the myosin molecule. ATP is now hydrolyzed (Fig. 2c). Rebinding of myosin to actin can occur, presumably in multiple steps. The gap between the upper and lower domain closes in this process to produce strong binding, and phosphate, P, is released. This event starts the so-called power stroke, the myosin molecule reverses its conformational change induced by ATP binding, and the active site pocket is reopened, establishing the ►rigor configuration (Fig. 2e). The cross-bridge cycle can then start all over again.

The studies by Rayment et al. [1,2] suggested the possible mechanism of contraction from a structural point of view. However, the actual movement produced by actin myosin interactions, the corresponding forces, and the relationship of the mechanical events with



Molecular and Cellular Biomechanics. Figure 2
Proposed molecular mechanism of contraction. (a) Rigor conformation. The narrow cleft that splits the 50-kD segments of the myosin heavy-chain sequence into two domains is closed (horizontal gap, perpendicular to the actin filament axis). (b) Addition of ATP, and initial binding of ATP to the active site, causes an opening of the narrow cleft and disrupts the strong binding between actin and myosin, but still allows for weak binding. The actin and myosin dissociate. (c) The final binding of ATP to myosin causes a closure of the nucleotide binding pocket and a corresponding configurational change of the myosin molecule. ATP is now hydrolyzed. (d) Myosin can now reattach to actin, presumably in multiple steps. The narrow cleft closes to produce strong binding. Phosphate, P, is released, and the power stroke starts. (e) During the power stroke, the myosin molecule reverses its conformation change induced by ATP binding, and the active site pocket is reopened, establishing the rigor conformation. The cross-bridge cycle can now start all over again (Reprinted with permission from Rayment et al. [2]. Copyright 1993 American Association for the Advancement of Science).

the corresponding biochemical steps cannot be determined using x-ray diffraction. In 1994, Finer et al. [3] showed the first results of forces produced by the interaction of a single cross-bridge with an actin filament using a double beam ►laser trap approach.

Single Myosin Mechanics

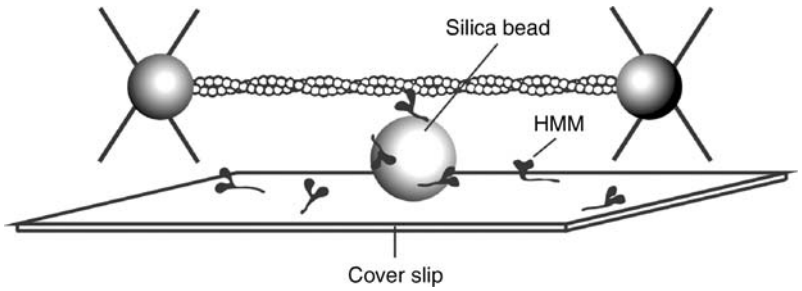
Finer et al. [3] attached silica beads to a microscope cover slip. The cover slip was coated with skeletal muscle heavy meromyosin (HMM) at a low density to allow for single attachments of cross-bridges to actin. Polystyrene beads coated with N-ethylmaleimide (NEM)-treated HMM were attached to actin filaments. An actin filament with two beads attached near its end was then caught and suspended in two optical traps (Fig. 3).

The image of one of the beads was projected to a photodiode detector for position detection. The actin filament was then pulled taut (with a force of about 2 pN) and was lowered to the silica bead with the HMM. Now, a single HMM molecule could interact and attach to the actin filament. When a cross-bridge head attached to the actin, a rapid transient movement of the silica bead along the axis of actin was observed. Consistent displacement traces were observed by keeping the stiffness of the optical traps high enough to decrease the noise caused by ►Brownian motion (i.e. about 0.02 pN/nm per trap), but small enough that a myosin molecule could produce a full displacement. The average size found for single myosin cross-bridge steps was about 11 ± 2.4 nm, independent of the ATP concentration (1μM–2mM ATP) and independent of the total trap stiffness (0.014–0.08 pN/nm).

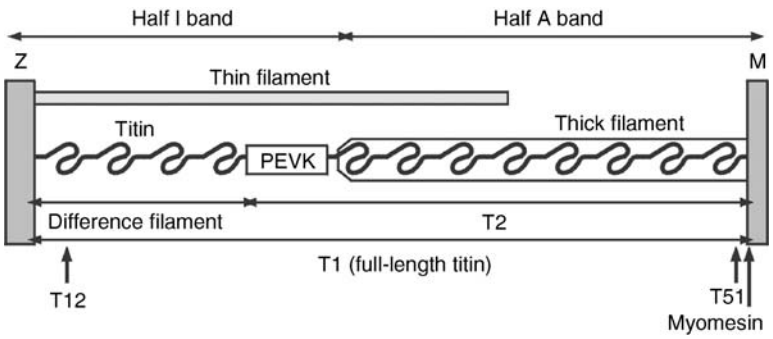
In order to measure the forces produced by single HMM molecules, the stiffness of the optical trap was increased to 6 pN/nm. Movements of the bead from the centre of the optical trap were proportional to the force applied on the actin filament. For the force measurements, movements of the bead were prevented by a feedback position system, which moved the optical trap (when force was applied to the bead) by the exact amount required to keep the bead stationary. Therefore, the displacement of the trap became a measure of the applied force. The magnitude of forces measured by single HMM interactions with actin were 1–7 pN, and they averaged 3.4 ± 1.2 pN. The force magnitudes were not affected by ATP concentration.

One of the limitations of the study by Finer et al. [3] was that it could not be determined with confidence whether a given mechanical event was produced by one or more HMM molecules or by one or both heads of the HMM molecule. Molloy et al. [4] addressed this issue using two optical traps in essentially the same way as Finer et al. [3], and measured the interactions of HMM molecules (two-headed cross-bridges) and myosin subfragment 1 (S1, single-headed cross-bridges) with actin. Molloy et al. [4] found that the average working strokes of S1 and HMM were comparable (about 4 nm) and were much smaller than those found by Finer et al. [3] for HMM (about 11 nm). Also, the average force values for both S1 and HMM interactions with actin were low (about 1.7 pN) compared to those measured by Finer et al. [3].

Muscle contraction with the myosin II-actin motor is just one example that could have been chosen to present



Molecular and Cellular Biomechanics. Figure 3 Schematic illustration of single heavy meromyosin, HMM, interaction with an actin filament. The silica bead on the cover slip is coated with skeletal muscle heavy meromyosin (HMM). Coated polystyrene beads are attached to the ends of actin. The actin filament with its two beads is caught and suspended in two optical traps. The suspended actin filament is then lowered to the silica bead, and single HMM interactions with the actin filament are now possible (Reprinted by permission from *Nature*, Finer et al. [3]. Copyright 1994 Macmillan Magazines Ltd).



Molecular and Cellular Biomechanics. Figure 4 Schematic illustration of titin and its association with other structures within a half-sarcomere. Titin spans from the Z-line to the M-band. It consists of about 300 immunoglobulin and fibronectin type III repeats and a proline (P), glutamate (E), valine (V), and lysine (K)-rich (PEVK) domain (Reproduced from Kellermayer et al. [8], with the permission of the American Association for the Advancement of Science).

some of the measuring techniques and approaches in molecular biomechanics. Excellent reviews describing the function of molecular motors are available (e.g. [5–7]).

Molecular Springs

Here, we would like to discuss the function and action of titin, a molecular spring that is particularly important in skeletal and cardiac muscle where it is thought to provide a big portion of the passive forces, and to play an important role in providing longitudinal stability of the myosin filament in sarcomeres. Titin, sometimes referred to as connectin, is a giant filamentous polypeptide, consisting primarily of about 300 immunoglobulin (Ig) and related fibronectin type III (FNIII) repeats, and a unique proline (P), glutamate (E), valine (V), and lysine (K)-rich (PEVK) domain. Titin spans each half-sarcomere and is anchored to the Z-line and the thick filament reaching all the way to the M-band (Fig. 4). Titin is thought to play a basic role in maintaining ►sarcomere structural integrity and producing passive force when muscle sarcomeres are stretched. Titin is also believed to provide a molecular scaffold for thick filament formation.

It has been argued that titin stabilizes the thick filament in the centre of the sarcomere when, upon contraction, small asymmetries in pulling forces are produced on the two halves of the thick filament. Furthermore, titin is assumed to produce passive force in muscles. Such passive forces might help stabilize what has been labelled the unstable [9], or softening, behavior of active muscle force on the descending limb of the force-length relationship. Finally, once a sarcomere is stretched beyond thick and thin filament overlap, cross-bridge attachments become impossible, and the forces required to re-establish myofilament overlap are thought to come primarily from the passive elastic forces of the highly stretched titin.

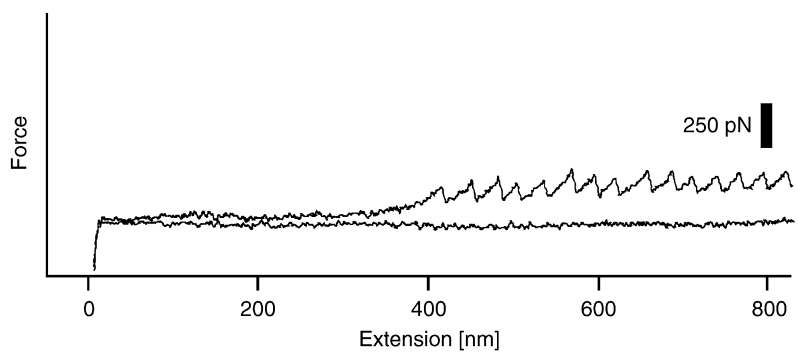
Despite the apparent importance of titin, the way it accomplishes its functional role has not been fully

resolved. If titin really provides most of the passive force in a stretched muscle, it should have several distinct characteristics: first, for centring the thick filament upon contraction, it should provide a low-level stiffness. The stiffness needs to be low because the asymmetries in active force acting on the thick filaments would presumably not be large, and the muscle (sarcomere) should still be stretchable without much resistance within its normal physiological range. Second, at some point titin should become stiff at a very fast rate in order to prevent large stretches of muscle against external forces that might cause injury. Finally, titin must accomplish its passive force at different lengths in different muscles, as the passive forces measured in different muscles occur at distinctly different sarcomere lengths. For example, in cardiac muscle, passive force is known to be high at about optimal sarcomere length, whereas in many skeletal muscles, passive force is negligible at optimal sarcomere length.

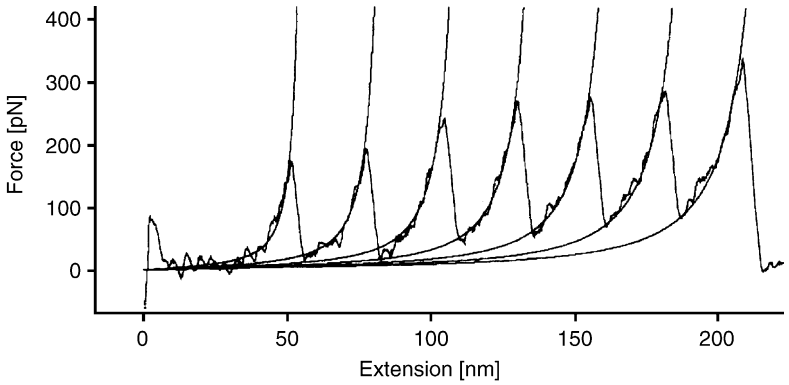
Rief et al. [10] used ►atomic force microscopy to study the mechanical properties of titin. Single titin molecules were stretched, and molecular elongation and the corresponding forces were recorded simultaneously. Rief et al. [10] found force-extension curves for titin that showed a sawtooth-type pattern (Fig. 5) that was typically preceded by a "smooth" increase in force of variable length. The periodicity of the force peaks was in the range of 25–28 nm, i.e. close to the expected full length of an Ig domain, and the force peaks varied from about 150–300 pN.

In order to test whether the peaks of the sawtooth pattern indeed reflect an unraveling of the Ig domains, two model recombinant titin fragments were constructed, consisting of either four (Ig4) or eight (Ig8) Ig segments in the I-band region (the flexible region) of titin. All traces obtained with these Ig segments showed a strict 25 nm periodicity. Furthermore, the force peaks were found to increase from the first to the last (Fig. 6), but stiffness was found to decrease from one force peak to the next (Fig. 6). Finally, when these Ig segments were released to one-half of their fully stretched length (but not to their resting length) and then pulled again, the sawtooth force-extension curve was not apparent. The sawtooth pattern was only fully recovered after complete relaxation of the titin to its resting length.

Based on their results, Rief et al. [10] concluded that each sawtooth pattern corresponded to an unfolding of one Ig domain: the force on the ascending part reflecting the molecular forces that must be overcome to produce the unfolding, the force decrease following the peak reflecting the fact that the molecular spring was now "abruptly" elongated by about 25 nm. The increasing peak forces with each subsequent sawtooth pattern were assumed to reflect increasingly stronger molecular bonds of the folded Ig domains; therefore, the "weakest" domain was unfolded first, followed by increasingly "stronger" Ig domains. The relative "smooth" increase in force preceding the sawtooth patterns was associated with a different molecular mechanism, possibly an elongation of the PEVK region, although this assumption was not rigorously tested. Finally, it took a full shortening of titin before a sawtooth pattern force-extension curve could be observed after the molecule had been stretched. Partial shortening did not produce partial sawtooth patterns, therefore it appears that a refolding of the Ig domains only occurs at or near titin's "resting" length or, in terms of force, at very low titin forces.



Molecular and Cellular Biomechanics. Figure 5 Force-extension curve of a single titin molecule obtained using atomic force microscopy. The force-extension curve shows a sawtooth-type pattern that is preceded by a smooth increase in force. The periodicity for the force peaks is about 25–28 nm, and the force peak magnitudes were in the range of 150–300 pN. The smooth increase in force preceding the sawtooth pattern was associated with an elongation of the PEVK region. The sawtooth pattern was associated with an unfolding of the Ig domains (Reproduced from Rief et al. [10], with the permission of the American Association for the Advancement of Science).



Molecular and Cellular Biomechanics. Figure 6 Force-extension curve of a recombinant titin fragment consisting of eight Ig segments. The curve shows a strict 25 nm periodicity. Force peaks increase from the first to the last sawtooth pattern, but the stiffness decreases. The force and stiffness on the ascending part of the sawtooth pattern likely reflect the molecular forces that must be overcome to produce unfolding of one Ig domain. The force decrease following the peak, reflects the sudden 25 nm elongation of the molecule once the molecular unfolding forces have been overcome (Reproduced from Rief et al. [10], with the permission of the American Association for the Advancement of Science).

Here we described the molecular motor myosin II-actin and the molecular spring titin as two examples of biomechanical investigation on the molecular level. Many other examples could have been advanced. However, these two covered some of the new technologies that are available today for performing mechanical experiments on the micro-scale level. We neglected a great number of studies relating to cell biomechanics. Many of these deal with the mechanical loading and the corresponding biological responses of cells, and tissue engineering. Regarding these issues, we would like to recommend the book by Mow et al. [11] for people with an interest in musculoskeletal tissues, and the book by Fung [12] for additional discussions on the cardiovascular system.

References

1. Rayment I, Rypniewski WR, Schmidt-Bäse K et al. (1993) Three-dimensional structure of myosin subfragment-1: a molecular motor. Science 261:50–58
2. Rayment I, Holden HM, Whittaker M et al. (1993) Structure of the actin-myosin complex and its implications for muscle contraction. Science 261:58–65
3. Finer JT, Simmons RM, Spudich JA (1994) Single myosin molecule mechanics: piconewton forces and nanometre steps. Nature 368:113–119
4. Molloy JE, Burns JE, Kendrick-Jones J et al. (1995) Movement and force produced by a single myosin head. Nature 378:209–212
5. Ait-Haddou R, Herzog W (2002) Brownian ratchet models of molecular motors. Cell Biochem Biophys; 38: 191–213
6. Astumian RD, Bier M (1996) Mechanochemical coupling of the motion of molecular motors to ATP hydrolysis. Biophys J 70:637–653
7. Julicher F (1999) Force and motion generation of molecular motors: a generic description. In: Muller SC, Parisi J, Zimmermann W (eds) Transport and structure in biophysical and clinical phenomena. Springer Berlin Heidelberg, New York, pp 1–27
8. Kellermayer MSZ, Smith SB, Granzier HLM, Bustamante C (1997) Folding-unfolding transitions in single titin molecules characterized with laser tweezers. Science 276:1112–1116
9. Hill AV (1953) The mechanics of active muscle. Proc R Soc Lond 141:104–117
10. Rief M, Gautel M, Oesterhelt F et al. (1997) Reversible unfolding of individual titin immunoglobulin domains by AFM. Science 276:1109–1112
11. Mow VC, Guilak F, Tran-Son-Tray R, Hochmuth RM (1994) Cell Mechanics and Cellular Engineering. Springer: Berlin Heidelberg New York
12. Fung YC (1993) Biomechanics: mechanical properties of living tissue, 2nd ed. Springer, Berlin Heidelberg New York

Molecular Cues

Signals in the extracellular environment that instruct the axon which way to grow during pathfinding.

Molecular Features in Odors

Definition

Based on the assessment of odor similarity in relation to the molecular structure, two different but overlapping

categories of odorant molecular characteristics have been identified. One category is a polar functional group that contains an oxygen, or a nitrogen, or a sulfur atom. The other category is the molecular profile that is formed mainly by the overall molecular shape. Polar functional groups and molecular profiles strongly influence the perceived odor quality.

►Odor Maps

Molecular Motors

Definition

Molecular motors are engines made up of individual molecules. There are a series of well-studied molecular motors that perform life essential functions in the human body. For example, the myosin II-actin motor is responsible for muscle contraction, kinesin and dynein transport organelles or vesicles from one location of a cell along polar and periodic tracks (actin and microtubules), and membrane bound motor proteins transport ions against chemical concentration gradients.

►Actin
►Dynein
►Kinesin
►Microtubule
►Molecular and Cellular Biomechanics
►Myosin
►Sarcomere Structural Proteins

Molecular Pharmacology

►New Developments in G Protein-Coupled Receptor Theory

Monaural

Definition

Sound presented to one ear.

►Hearing Aids

Monoaminergic Cell Groups

Definition

These are cell groups that use monoamines as neurotransmitters. The monoamines include the catecholamines (dopamine, norepinephrine, and epinephrine) and the indoleamine serotonin (5-hydroxytryptamine). The catecholamines are derivatives of the amino acid tyrosine. Serotonin is a derivative of the amino acid tryptophan. The major cell groups that use dopamine are the substantia nigra and the ventral tegmental area in the midbrain. A major cell group that uses norepinephrine is the locus ceruleus (Latin for blue spot) in the dorsal pons. There are few if any epinephrine neurons in the brain. Epinephrine is secreted into the blood by the adrenal gland near the kidney. The major cell groups that use serotonin are the raphe (Greek for ridge or seam – refers to nuclei near the midline) nuclei which scattered from the caudal pons to the medulla.

Monoamines

Definition

Brain monoamine synaptic transmitters consist of an aromatic ring and amino group attached by a two carbon chain (-CH2-CH2-). Monoamines are further classified as catecholamines or indolamines depending on the specfic essential aromatic amino acid, phenylalanine or tryptophan respectively, from which they are derived. Dopamine and norepinephrine (noradrenaline) are derived from L-tyrosine first by the action of the enzyme tyrosine hydoxylase to form L-Dopa which is subsequently decarboxylated by aromatic amino acid decarboxylase to form dopamine. Norepinephrine is synthesized following the β–oxidation of dopamine by dopamine beta hydroxylase, with the co-factor ascorbate serving as an electron doner. Epinephrine is synthesized from norepinephrine in a restricted group of neurons in the brain-stem by phenylethanolomine N-methyltransferace. Serotonin is synthetized from Ltryptophan in two enzymatic steps involving tryptophan hydroxylase and aromatic amino acid decarboxylase. The discovery by Falk and Hilarp of histochemical fluorescence enabled the visualization of catecholamines and serotonin within specific nuclei and efferent neural pathways, which could then be lesioned by specific neurotoxins. Preclinical experiments employing this lesion technique helped to identify the function of specific brain monoamines in

many aspects of behavior ranging from motor control to emotional and cognitive processes. Monoamine transmitters influence post-synaptic neurons via specific receptor sub-types and synaptic levels are determined mainly by the action of selective uptake mechanisms. These sites have served as targets for the development of highly effective drugs for the treatment of neuropsychiatric disorders, including the SSRI's (serotonin-selective reuptake inhibitors) and neuroleptic drugs for the treatment of schizophrenia.

►Antipsychotic Drugs
►Schizophrenia

Monochromatopsia

Definition
►Color Blindness

Monocular Deprivation

Definition
A condition in which normal visual experience is prevented for varying periods to one eye by a natural or artificial condition.

►Binocular Vision

Mononeuropathy

Definition
Damage or destruction of an isolated nerve or nerve group. It is a type of ►peripheral neuropathy (damage to nerves outside the brain and spinal cord). Mononeuropathy is most often caused by damage to a local area resulting from injury or trauma, although occasionally systemic disorders may cause isolated nerve damage (as with mononeuritis multiplex).

►Peripheral Neuropathies

Monophyletic

Definition
A set of taxa derived from a single common ancestor.

►Evolution, and the Concept of Homology

Monophyletic Group

Definition
Taxon that includes all descendants of a last common Ancestor.

Monoplegia

Definition
Paralysis of one limb. If occurring without muscle wasting, the most frequent cause is a local lesion to the ►cerebral cortex (e.g., a vascular lesion such as thrombosis or embolism; local injury, tumor of abscess); if occurring with muscle atrophy, the lesion affects the ►motor unit (e.g., ►brachial plexus trauma or neuritis, ►poliomyelitis, ►syringomyelia, ►amyotrophic lateral sclerosis).

►Amyotrophic Lateral Sclerosis (ALS)
►Brachial Neuralgia
►Poliomyelitis
►Syringomyelia

Monopolar Recording

Synonym
Unipolar Recording

Definition
Recording of an electrical potential difference between an active region (by means of a small electrode: different electrode) and an inactive region (by means of a large-surface electrode: indifferent electrode) of an excitable tissue (e.g., nerve or muscle).

►Extracellular Recording

Monotreme

Definition

Platypus and echidna are monotremes (trema means hole and refers to the cloaca). These animals are the only mammals that lay eggs and do not give birth to live young. They are also the first and only mammals which were shown to have electroreception.

►Electric Senses in Monotremes: Electroreception and Electrolocation in the Platypus and the Echidna

Morbus Bleuler

►Schizophrenia

Mormyromasts

Definition

Tuberous organ subtype found in mormyrid fishes, used primarily for electrolocation.

►Evolution of Mechanosensory and Electrosensory Lateral Line Systems
►Electroreceptor Organs

Morning/Evening Oscillators

Michael N. Nitabach
Department of Cellular and Molecular Physiology, Yale School of Medicine, New Haven, CT, USA

Definition

Morning ("M") and evening ("E") oscillators are distinct circadian oscillators that control the peaks of activity of twilight-active animals that occur during the morning and evening twilight.

Characteristics

Theoretical and Descriptive Analysis of M and E Oscillators

In animals, the circadian clocks that control the timing of rest and activity are embodied in groups of ►circadian pacemaker neurons in the central nervous system. Many animals are crepuscular – i.e. twilight-active – and thus concentrate their activity around dawn and dusk. It was theorized in the 1970s that crepuscular rodent activity rhythms are controlled by independent, but coupled, ►Morning and Evening (M and E) oscillators [1]. Later measurements of circadian rhythms of pacemaker neuron firing in the rodent ►suprachiasmatic nucleus (SCN) revealed two distinct subpopulations of neurons whose firing rhythms were out of phase, suggesting that these could be the M and E oscillators [2]. However, it has not been possible to experimentally test the hypothesis that a particular subset of rodent pacemaker neurons does indeed function as an M or E ►oscillator. This would require functionally inactivating the subset of pacemaker neurons constituting a putative M or E, followed by measurement of the effect of this inactivation on the morning and evening peaks of activity.

Experimental Demonstration of M and E Oscillators

Like many rodents, *Drosophila melanogaster* fruit flies are crepuscular, exhibiting peaks of activity centered on the transitions from night to day and from day to night. And unlike in rodents, readily available techniques exist for functionally inactivating defined subsets of pacemaker neurons. In one study, flies were generated that lacked either the lateral–ventral anatomical subset of pacemaker neurons or several dorsal anatomical subsets of pacemaker neurons [3]. Flies lacking the lateral–ventral subset lost the morning peak of activity, but retained the evening peak. Flies lacking the dorsal subgroups lost the evening peak of activity, but retained the morning peak. In a different study, flies were generated that had functional ►cellular clocks either only in the lateral–ventral subgroup, or in both the lateral-ventral and dorsal subgroups [4]. Flies with functional cellular clocks solely in the lateral-ventral subgroup exhibit only the morning peak of activity, while flies with functional cellular clocks in both subgroups exhibit both the morning and evening peaks of activity. These findings demonstrate that the fly M and E oscillators reside in the lateral-ventral and dorsal pacemaker neurons, respectively.

Communication of Phase Information Between M and E Oscillators

Those experiments were performed in 12 h:12 h light: dark (LD) conditions, where both M and E oscillators

can be independently synchronized to the environment and thereby maintain a constant phase relationship. When flies are synchronized to LD and then released into constant darkness (►constant conditions, DD), the morning and evening peaks still occur – although they ►free-run and gradually drift out of phase with the rotation of the Earth. But even in free-running conditions, the morning and evening peaks maintain a constant phase relationship with each other. So there must be some mechanism for keeping that relationship constant in free-running DD conditions even in the absence of any environmental cues.

One possible mechanism for maintaining constant phase between M and E oscillators is a ►master–slave relationship, so-called because one of the oscillators controls the other. To test this hypothesis, flies were genetically modified so that the M and E oscillators run with intrinsic periods that differ by 3–4 h [5]. Under ►free-running DD conditions, the period of the behavioral rhythm of locomotor activity is always determined by the intrinsic period of the M oscillator, suggesting both that there is a master–slave relationship and that M is the master. Furthermore, the period of oscillation of the cellular clock in the E cells is determined by that of M, and not by the intrinsic period of the E cells themselves. These results demonstrate that M cells send a signal to the E cells that controls the oscillation of their cellular clocks. A good potential candidate for this signal is a neuropeptide produced and secreted by the lateral-ventral M pacemaker neurons and known to be important for circadian function [6].

References

1. Pittendrigh CS, Daan S (1976) A functional analysis of circadian pacemakers in nocturnal rodents V. Pacemaker structure: a clock for all seasons. J Comp Physiol 106:333–355
2. Jagota A, De la Iglesia HO, Schwartz WJ (2000) Morning and evening circadian oscillations in the suprachiasmatic nucleus in vitro. Nat Neurosci 3(4):372–376
3. Stoleru D, Peng Y, Agosto J, Rosbash M (2004) Coupled oscillators control morning and evening locomotor behaviour of Drosophila. Nature 431(7010):86286–86288
4. Grima B, Chelot E, Xia R, Rouyer F (2004) Morning and evening peaks of activity rely on different clock neurons of the Drosophila brain. Nature 431(7010):869–873
5. Stoleru D, Peng Y, Nawathean P Rosbash M (2005) A resetting signal between Drosophila pacemakers synchronizes morning and evening activity. Nature 438 (7065):238–242
6. Renn SC, Park JH, Rosbash M, Hall JC, Taghert PH (1999) A pdf neuropeptide gene mutation and ablation of PDF neurons each cause severe abnormalities of behavioral circadian rhythms in Drosophila. Cell 99(7):791–802

Morphogen

Definition

A substance whose concentration varies across a tissue and to which cells respond differently at different concentrations.

►Morphogens and Neural Development

Morphogenetic Compartment

Definition

Subdivision of an organ or body part (for example, a specific area or sector of the neuroepithelium) specified by a particular combination of developmental regulatory genes, that gives rise to a particular body division or subdivision. It constitutes a major unit of development and evolution, and the natural comparison character for homology considerations.

►Evolution and Embryological Development of the Forebrain

M

Morphogens and Neural Development

Esther T. Stoeckli
Institute of Zoology/Developmental Neuroscience, University of Zurich, Zurich, Switzerland

Definition

In the development of organisms the organization of cells into tissues is a major achievement. Precursor cells or undifferentiated cells have to be organized in a spatial pattern that allows their differentiation to distinct cell types. To this end, positional information has to be transferred to cells. The term morphogen describes such positional signals that are secreted by a source, and therefore form a gradient emanating from this source by mechanisms that are still unclear (see below). Cells responsive to a particular morphogen will then sense their position in response to the concentration of the morphogen. Thus, ►morphogens are capable of specifying body axes or give polarity to tissues, in other words are responsible for the patterning of the

embryo. In vertebrates, morphogens include members of the Hedgehog, the ►Wnt, the FGF (Fibroblast Growth Factor), and the TGF-β (Transforming Growth Factor-β) families. In human there are three Hedgehogs (Sonic, Indian, and Desert Hedgehog), 19 Wnts (Wnt1 – Wnt16), and 22 FGFs. The TGF-β family is subdivided into several subfamilies, the TGF-βs, activin, and the bone morphogenetic proteins (BMPs). For the developing nervous system, the BMP subfamily is most relevant. In Drosophila, where development starts in a ►syncytium, transcription factors, e.g. bicoid, have also been identified as morphogens. In this essay I will concentrate on vertebrate morphogens, however.

Characteristics

Neural development starts with neural induction and neurulation giving rise to the neural tube, which will form the central nervous system, and to the ►neural crest, from where cells will delaminate to form the peripheral nervous system. A hallmark of neural development is the considerable distances that cells migrate to reach their final destination from where they send out their long processes, ►axons and ►dendrites, to connect to their target cells. This is particularly true for the brain. The migratory routes are much shorter and less complicated in the caudal neural tube, the ►spinal cord. Therefore, early events of neural development, ►neurogenesis, ►cell differentiation, and patterning have been studied extensively in the spinal cord. Cell migration has been studied predominantly in the brain. Morphogens are involved in all steps of neural development from neural induction to axon guidance and ►synaptogenesis, the final step in neural circuit formation.

Methods to Study Morphogen Function

Common to all morphogens is their involvement in the regulation of ►cell proliferation, differentiation, and patterning. Because all morphogens are involved not only in spatially distinct but also in temporally distinct processes, their functional analysis has to take time into account. This is quite difficult to achieve with classical genetic tools, as they allow only for the analysis of gene function in the first window of activity. Analysis of later events is often prevented by aberrant development due to the absence of gene activity during early time windows or even early embryonic lethality. Inducible knockout strategies or ►RNAi approaches have opened new possibilities in temporal control of gene expression and are therefore better suited for functional analyses of morphogens [1].

Morphogens in Early Neural Development

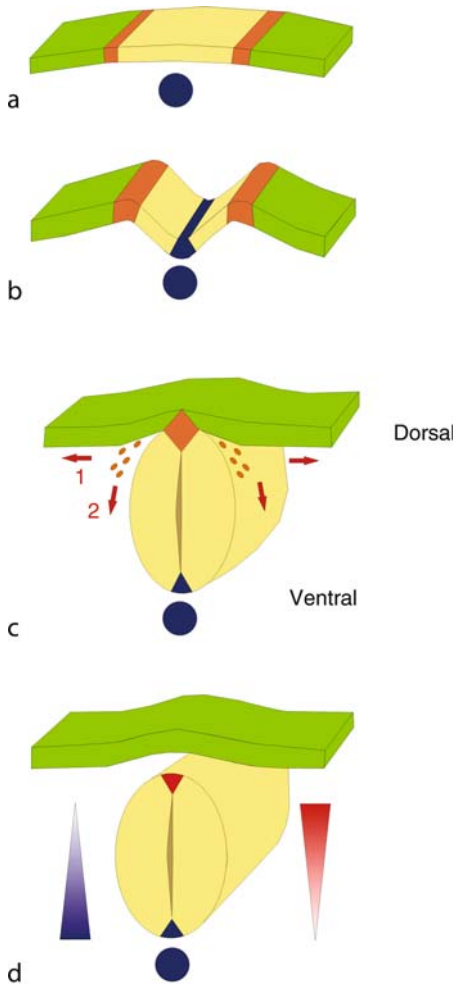
Neural induction starts with or even before gastrulation: Cells of the ►ectoderm are set aside to become neural ectoderm [2]. This process requires blocking the activity of ►bone morphogenetic proteins (BMPs), a subfamily of the TGF-β family of morphogens. BMPs drive differentiation to epidermis, thus, neural ectoderm will be formed only where this activity can be blocked by Chordin, Noggin, and Follistatin, three BMP inhibitors originally identified in Xenopus. In addition to BMPs, members of the FGF, and the Wnt family of morphogens have also been implicated in neural induction [2]. Once the neural epithelium has been defined it starts to undergo changes in shape, i.e. it folds up in a process called neurulation (Fig. 1).

Morphogens and Neural Crest Formation

►Neural crest cells give rise to cells of the peripheral nervous system, pigment cells (melanocytes), and skeletal elements of the head. Neural crest cells arise from the border between the neural and the non-neural ectoderm and depend on the presence of BMPs (Fig. 1). The requirement for BMP signaling in neural crest cell formation was demonstrated for instance in zebrafish mutants (for references see [3]). In addition to BMPs, other morphogens, such as Wnts and FGFs were also implicated in neural crest induction and proliferation. Because neural crest specification cannot be separated from cell migration along distinct pathways, roles of morphogens in neural crest migration have also been demonstrated (reviewed by [3]).

Morphogens in Differentiation and Patterning

The newly formed neural tube is specified from the beginning with respect to the antero-posterior and the dorso-ventral orientation. At the anterior end of the neural tube, the brain will form, the caudal neural tube will develop into the spinal cord. The ►notochord, a mesodermal structure underlying the neural plate, specifies the ventral midline of the neural tube, called the ►floor plate (Fig. 1). The roof plate originates during the closure of the neural tube and marks the dorsal midline of the spinal cord. Both the floor plate and the roof plate are important signaling centers, as they are the source of morphogens [4]. BMPs are produced in the roof plate, ►Sonic hedgehog (►Shh) is produced by the floor plate. Wnts are also expressed in the roof plate and in the adjacent dorsal neural tube. Under the influence of these morphogens ►neuroepithelial cells differentiate to distinct types of cells. In the dorsal neural tube, cells are predominantly under the dorsalizing effect of the BMPs, whereas cells in the ventral neural tube turn into ventral interneurons or motoneurons depending on the concentration of Shh [4]. High concentrations of Shh will induce V3 interneurons and motoneurons, successively lower concentrations will give rise to V2, V1, and V0 interneurons, respectively. These broad domains are distinguished by their characteristic expression of transcription factors used as markers. These transcription factors regulate



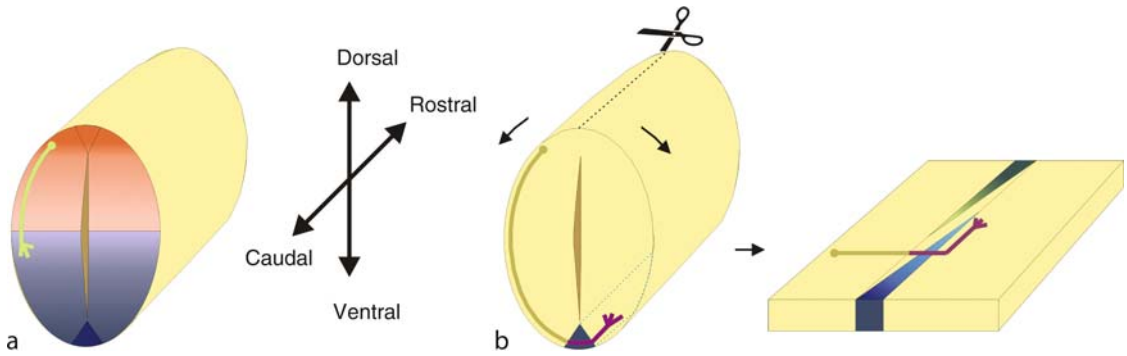
Morphogens and Neural Development.
Figure 1 During neural induction ectodermal cells that are under the influence of BMP inhibitors develop into neural ectoderm (yellow in (a)). The remaining ectoderm (green) develops into epidermis. The notochord, a mesodermal structure underlying the neural ectoderm (blue), acts as an organizer for the neural tube. It expresses high levels of Shh and is responsible for the differentiation of the ventral midline cells of the developing neural tube into floor-plate cells (blue in (b)). The border between the neural and the non-neural ectoderm expresses BMPs and Wnts (orange) that are responsible for the delamination of neural crest cells during the closure of the neural tube (c). Neural crest cells migrate along a dorsal route (1) to turn into melanocytes and along a ventral route (2) to turn into cells of the peripheral nervous system. The fusion of the neural tube results in the formation of the roof plate (red triangle in (d)). Thus, the newly formed neural tube contains two organizing centers, the floor plate (blue triangle in (c) and (d)), the source of Shh with ventralizing activity, and the roof plate, the source of BMPs with dorsalizing activity. Cells along the dorsoventral axis adopt different cell fates depending on the concentration of BMPs and Shh that they experience (d).

specific gene expression patterns. The segregation of cells driven by selective cell-cell adhesion concludes the formation of the final classes of neurons along the dorso-ventral axis of the spinal cord. Similar processes are thought to occur in the brain but due to the increased complexity of the anterior neural tube the specific interactions and molecular processes are less well understood. In contrast, patterning of the anteroposterior axis of the neural tube has been studied in more detail in the brain [5]. The anterior end of the neural tube is subdivided into forebrain, midbrain, and hindbrain. The hindbrain and the borders between the individual segments of the hindbrain, the ►rhombomeres, are thought to be local signaling centers for the anteroposterior axis. The mid-hindbrain boundary, or isthmus, is the source of FGFs, in particular FGF8 that was shown to be most important for the organization of the midbrain and the ►cerebellum [6]. In addition to their role in differentiation and patterning morphogens regulate cell proliferation in the neural tube and thus define not only cell type but also cell number [7].

Morphogens in Axon Guidance

More recently, a function of morphogens in axon guidance has been found [8–10]. First evidence for a role in ►axonal pathfinding was obtained in the visual system for FGFs in frog [6] and Shh in chicken embryos [9]. BMPs expressed by the roof plate were shown to act as axon guidance cues by repelling dorsolateral ►commissural axons (Fig. 2).

At the same time, these axons are attracted by ►Netrin-1, the first ►chemoattractant that was identified. Interestingly, the attractive effect of Netrin is supported by Shh that is expressed by the floor plate, as is Netrin. The activity of Shh is much weaker than the activity of the classical axon guidance cue, Netrin-1. Therefore, the attractive effect of Shh on commissural axons could only be detected in the absence of Netrin-1. More recently, Shh was identified as a ►repellent for the same commissural axons once they have crossed the ventral midline [9]. Interestingly, the repellent effect of Shh on postcommissural axons did not depend on the same receptor and the same signaling mechanism that was responsible for the patterning and axon guidance activities of Shh during earlier stages of development. Shh was shown to act as repellent for postcommissural axons that expressed Hedgehog-interacting protein (Hip). While the axon guidance function of Shh on postcommissural axons was detected in chicken embryos in vivo, a similar function was found for Wnt4 in mouse using in vitro assays. However, Wnt4 was shown to act as an attractant in accordance with its graded expression in the floor plate, with high levels rostrally and low levels caudally. Interestingly, Wnts were also found to act as repellents in longitudinal axon guidance in the corticospinal tract, where Ryk



Morphogens and Neural Development. Figure 2 Commissural neurons located in the dorsolateral spinal cord (green in (a)) send out their axon under the repellent influence of BMPs emanating from the roof plate (red) and the attractive effect of Netrin-1 and Shh (blue). Patched and Smoothened expressed by commissural neurons mediate the attractive effect of Shh. When commissural axons reach the floor plate (blue triangle in (b)) they express Hedgehog-interacting protein (Hip; purple). Cells that express Hip no longer perceive Shh as attractive, and instead respond with repulsion. Thus, postcommissural axons are directed rostrally along the contralateral border of the floor plate in response to the decreasing Shh gradient, with high levels caudally and low levels rostrally. At the same time, a Wnt gradient with high levels rostrally and low levels caudally attracts postcommissural axons (see text and references [8–10] for details).

is involved as a co-receptor with the Wnt receptor Frizzled.

Morphogens in Topographic Mapping

Axons reaching their target area have to select individual cells to form a ►synapse. In the visual system ►topographic mapping, i.e. the connection between the retinal ganglion cell (RGC) axons with the appropriate target cell in the tectum, has been studied for decades. Two coordinate systems, with perpendicular orientation to each other, specify the target for each incoming RGC axon. ►Eph-Ephrin interactions are responsible for both the antero-posterior and the medial-lateral orientation [10]. Recent studies have now added a Wnt gradient for medial-lateral retinal axon mapping, another example where a morphogen acts in parallel to a classical axon guidance cue (see above), in this case EphrinB1.

Morphogens in Synaptogenesis

Finally, morphogens have also been implicated in the last step of neural circuit formation, synaptogenesis [7]. In the spinal cord, Wnt3 expressed by motoneurons was shown to play a role in the formation of terminal branches of proprioceptive neurons that contact dendrites of motoneurons in the ventral spinal cord. Similarly, in the cerebellum, ►mossy fibers that form a special type of nerve ending called rosettes with dendrites of ►granule cells undergo morphological changes that depend on the presence of Wnt7a in granule cells. In the absence of Wnt7a, axonal remodeling is perturbed and appropriate presynaptic structures fail to form [7].

Morphogen Transport

The mechanism of morphogen gradient formation is not well understood, as morphogens are not freely diffusible due to ►posttranslational modifications, such as palmitoylation in the case of Wnt and Shh, or the covalent attachment of a cholesterol molecule in the case of Shh. Models for morphogen transport and gradient formation include transcytosis, i.e. the repeated endocytosis and release of morphogen molecules, or their transport in form of lipoprotein particles or argosomes. Furthermore, facilitated diffusion by binding to cell surface heparan sulfate ►proteoglycans has also been suggested for Wnt, Shh, and FGFs.

Morphogen Signaling

In general, signaling by morphogens results in the activation of gene expression in the nucleus. Signaling by BMPs and FGFs has obtained a lot less attention than Wnt and Shh signaling. FGFs bind to one of four FGF receptors that are single-pass transmembrane receptor tyrosine kinases [6]. Heparan sulfate proteoglycans are co-factors for the activation of FGF receptors by FGFs. BMPs bind to a receptor complex consisting of type I and type II serine/threonine kinases. Receptor activation results in ►phosphorylation of SMAD family members [3]. Common to signaling of the Wnt and Shh families are structural features of the surface receptors. Both use seven-pass transmembrane receptors, Frizzleds in the case of Wnts and Smoothened in the case of Hedgehogs. It is important to note, however, that Hedgehogs do not bind to Smoothened directly but rather to the twelve-pass transmembrane receptor Patched. Upon binding of Hedgehogs, Patched

de-represses Smoothened activity. The mechanism of Patched/Smoothened interaction is not yet known.

Intracellular components of both the Hedgehog and the Wnt signaling cascade are multiprotein complexes containing a ►scaffold protein and kinases. These complexes phosphorylate and stabilize β-catenin downstream of Wnts, and control levels of Gli repressor and Gli activators downstream of Shh.

Wnt signaling includes three different pathways, the canonical and the non-canonical pathway with the latter being subdivided into planar cell polarity (PCP) and Ca^{2+} pathways. The canonical pathway involves the stabilization of β-catenin. In the absence of Wnt, β-catenin is recruited to a multi-component complex consisting of the scaffold protein Axin, the tumor suppressor APC and two kinase families, CK1 and GSK. Subsequent ►ubiquitination results in degradation of β-catenin. If Wnt binds to the surface receptor Frizzled and co-receptors, such as Lrp5/6, phosphorylation of β-catenin is suppressed. Thus, β-catenin accumulates and can be transported to the nucleus, where it activates transcription by binding to LEF/TCF transcription factors.

In general signaling downstream of morphogens has only been studied in detail during early stages of development, including neural induction, differentiation and patterning. Signaling involved in later stages of development, such as axon guidance or synaptogenesis is not well understood. In axon guidance along the longitudinal axis of the spinal cord, the receptor for Shh is Hedgehog-interacting protein and no longer Patched [9,10]. Wnts appear to use Frizzled receptors for both axon guidance and earlier functions, but the intracellular signaling pathways have not been identified and do not seem to be identical to any of the well-known pathways (see above). In contrast to the classical roles of morphogens in tissue patterning, their role in axon guidance does most likely not involve changes in gene transcription but is restricted to more rapid changes in signaling affecting directly the cytoskeleton of growth cones.

References

1. Baeriswyl T, Stoeckli ET (2006) In ovo RNAi opens new possibilities for temporal and spatial control of gene silencing during development of the vertebrate nervous system. J. RNAi Gene Silencing 2:126–135
2. Stern CD (2005) Neural induction: old problem, new findings, yet more questions. Development 132:2007–2021
3. Liu A, Niswander LA (2005) Bone morphogenetic protein signalling and vertebrate nervous system development. Nat Rev Neurosci 6:945–954
4. Jessell TM (2000) Neuronal specification in the spinal cord: inductive signals and transcriptional codes. Nat Rev Genet 1:20–29
5. Kiecker C, Lumsden A (2005) Compartments and their boundaries in vertebrate brain development. Nat Rev Neurosci 6:553–564
6. Mason I (2007) Initiation to end point: the multiple roles of fibroblast growth factors in neural development. Nat Rev Neurosci 8:583–596
7. Ciani L, Salinas PC (2005) WNTs in the vertebrate nervous system: from patterning to neuronal connectivity. Nat Rev Neurosci 6:351–362
8. Charron F, Tessier-Lavigne M (2005) Novel brain wiring functions for classical morphogens: a role as graded positional cues in axon guidance. Development 132:2251–2262
9. Stoeckli ET (2006) Longitudinal axon guidance. Curr Opin Neurobiol 16:35–39
10. Zou Y, Lyuksyutova AI (2007) Morphogens as conserved axon guidance cues. Curr Opin Neurobiol 17:22–28

Mosaic Analysis with a Repressible Cell Marker

Veronica G. Rodriguez Moncalvo, Ana R. Campos
Department of Biology, McMaster University, Hamilton, ON, Canada

M

Synonyms

MARCM

Definition

Mosaic Analysis with a Repressible Cell Marker or MARCM is a set of genetic tools developed in the fruitfly *Drosophila melanogaster* for the positive labeling of individual cells or groups of cells derived from the same lineage. In addition, labeled cells may be generated that are homozygous mutant for genes of interest or that express constructs that modulate gene expression and/or function. This system was created by Liqun Luo and Tzumin Lee [1] and has been used extensively in this model organism for the analysis of neuronal differentiation, cell lineage and other biological processes outside of the nervous system.

Characteristics

Overview

The nervous system is arguably one of the most complex tissues in the animal kingdom. Even in the simplest of the model organisms, its assembly requires not only the generation of a large number of diverse cell types but also the complex wiring of these cells. Therefore, the study of nervous system development and function is aided by the identification and genetic manipulation of a small number of neurons. Genetic tools unique to the *Drosophila* model system have

greatly facilitated the analysis of the molecular mechanisms underlying neuronal pattern formation by providing investigators with exquisite spatial and temporal control of gene expression and function. In this context, mobile DNA elements (►P-elements), carrying heterologous transcription factors (e.g. *GAL4*) under the regulation of *Drosophila*-specific promoters have been used extensively for the targeted expression of reporter molecules, genetically modified alleles or more recently constructs capable of mediating gene silencing via RNA interference (►RNAi).

The ability to induce, isolate and characterize the phenotypic consequence of single gene mutations has been fundamental to our current understanding of nervous system development and function in *Drosophila* and other model organisms. Relevant genes are for the most part expressed in a temporal and spatial complex pattern, which is reflected in the pleiotropic phenotype displayed by mutant organisms. Moreover, homozygous mutant animals may not survive to adulthood making it difficult to study the consequence of lack of gene function beyond a certain stage. In order to overcome these limitations, developmental biologists have relied on genetic ►mosaic organisms in which homozygous mutant clones are generated in an otherwise wild type and heterozygous background. This approach has been used extensively in *Drosophila melanogaster* as well as in mice and *C. elegans*, to investigate the stage-specific cell autonomous requirement of gene function. Recent improvements to this system include the ability to generate small homozygous clones at specific times during development and to unambiguously identify individual homozygous mutant clones such that the cellular phenotype can be studied appropriately.

Mechanism

Traditionally, genetic mosaics in *Drosophila* have been generated through chromosomal loss (e.g. ring X chromosome) or X-ray induced mitotic recombination. More recently, sequence-specific recombination systems (FLP/FRT or Cre/LoxP) have been introduced allowing efficient gene-specific mitotic recombination. While the generation of genetically distinct somatic clones is technically straightforward, a reliable way to unambiguously label specific cell types within mutant clones has been missing. In the past, external markers have been used to infer the genotype of internal tissue. An improvement on this approach was the introduction of reporter constructs whose loss would mark the presence of homozygous clones in an otherwise heterozygous-labeled organism. The shortcoming of this method was that mutant clones still remained unlabelled and thus not available to detailed morphological analysis.

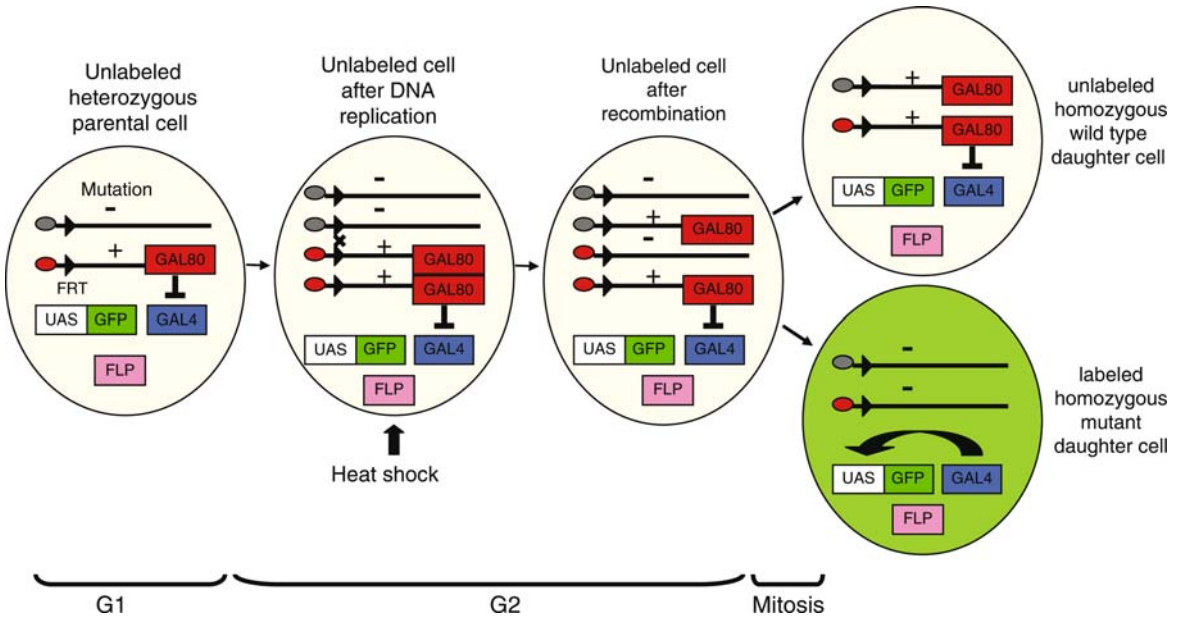
MARCM is a major advance because it combines the ability to positively label small numbers of cells with the FLP-FRT recombination system previously used to generate genetic mosaics (Fig. 1). This was made possible by the introduction of a repressible cell marker. In MARCM, the expression of reporter genes such as ►GFP, driven by a tissue-specific *GAL4* construct, is repressed due to the ubiquitous expression of a *GAL4* inhibitor, *GAL80*. The *GAL80* gene is inserted in the same chromosomal arm as the wild type allele of a gene of interest *X*. The homologous chromosome carries a mutant allele of the gene *X* and no copy of *GAL80*. Mitotic recombination generates two daughter cells that differ from the parental cell regarding the genotype of the *FRT*-bearing chromosome in that they are homozygous for one or the other homologous chromosome. Therefore, the mitotic recombination event not only yields homozygous mutant cells but also relieves in these cells the repression of the *GAL4* construct through the loss of *GAL80* ►transgene. The outcome is the generation of flies carrying single or multiple cells derived from a single progenitor that are homozygous mutant for a gene of interest. Specific cell types within the mutant clone will be positively labeled by the expression of a reporter construct that facilitates their morphological analysis. The size of the labeled clone depends upon the timing of FLP expression (refer to [2] for a detailed protocol). Moreover, as illustrated below, MARCM can be used to label clones of specific neurons without manipulating gene function. In this context, MARCM has been employed to investigate the developmental architecture – pattern of projection and clonal relationship – of specific neurons (see Fig. 2 for examples of MARCM generated clones).

The caveat is that, while labeling is found only in cells homozygous for the mutant chromosome (not carrying the *GAL80* repressor), not all mutant cells are labeled. Labeling of mutant cells is restricted to the cell types in which *GAL4* driver is expressed. Modifications to this method introduced recently address this issue but have not yet been used as extensively as MARCM [3].

Components

All constructs described below are found within P-element vectors and were inserted into the *Drosophila* genome via ►P-element mediated transformation.

1. *GAL4* is a yeast transcription factor that binds to specific DNA elements known as upstream activating sequence (*UAS*) and activates RNA transcription of reporter genes. It is often referred to as a "driver element." In *Drosophila*, expression of GAL4 under the control of tissue-specific regulatory sequences has been employed to activate the expression of reporter genes such as *GFP* or *β-Galactosidase* in specific cell types. Alternatively, one can increase the expression of a target gene (up-regulation), by introducing a full-length cDNA downstream from the *UAS* or silence a gene



Mosaic Analysis with a Repressible Cell Marker. Figure 1 Schematic representation of the MARCM system. MARCM requires two *FRT* sites (™) situated at the same location and one copy of the *GAL80* gene downstream to one of the *FRT* sites. The genes encoding Flipase (FLP) recombinase, the tissue-specific *GAL4* driver, and the *UAS-GFP* may be located anywhere in the genome. Additionally, the *FRT*-bearing, non-*GAL80* chromosome may carry a mutation (−) distal to the *FRT* site. A brief heat shock induces *FLP* expression. At the *FRT* sites, FLP recombines the wild type (+) *GAL80*-containing chromosome with its homologous mutant (−) chromosome. The resulting wild type (+/+) daughter cell will carry two copies of *GAL80*, which suppresses GAL4-dependent expression of the *UAS-GFP* (unlabeled cell). In the other daughter cell, which may be homozygous mutant for a gene of interest (−/−), the absence of GAL80 allows for GAL4-mediated expression of the GFP (labeled cell). (Adapted from [2]).

(knock-down), by introducing a construct capable of mediating RNA interference (RNAi).

2. *UAS-mCD8-GFP* This construct encodes a *GAL4* responsive reporter gene. In this case, the reporter is the green fluorescent protein (GFP), which has been fused to the transmembrane mouse lymphocyte marker CD8. This allows for targeting of GFP to the cell surface.
3. Flipase (FLP) recombinase. FLP recombinase is a yeast enzyme that catalyzes mitotic recombination at FRT sites. *Drosophila* strains have been created carrying the FLP gene under the regulation of a ubiquitous promoter, such as the *tubulin* gene promoter (*tubP*), or a conditional promoter such as that of the *Heat Shock Protein 70* gene (*HSP70*).
4. *FRT* sites. *FRT* sites are DNA sequences recognized by FLP recombinase. High frequency mitotic recombination is catalyzed by FLP at these sites. In flies heterozygous for a recessive allele of a gene of interest (+/−) in which FRT sequences are also present in the same chromosome, mitotic recombination at these sites yields homozygous mutant clones (−/−) as well as homozygous wild type twin clones (+/+). The latter are indistinguishable from the wild type heterozygous background (+/−).
5. *tubP-GAL80*- GAL80 is a yeast protein that represses GAL4 function as a transcription factor. In MARCM, the *GAL80* gene is under the control of the *tubulin* promoter (*tubP*) thereby providing ubiquitous repression of GAL4 function. Mitotic recombination at *FRT* sites catalyzed by the *FLP* gene product eliminates the *GAL80* gene from one of the daughter cells thereby relieving GAL4 from GAL80 repression while at the same time inducing a loss of heterozygosity event in the same chromosome.

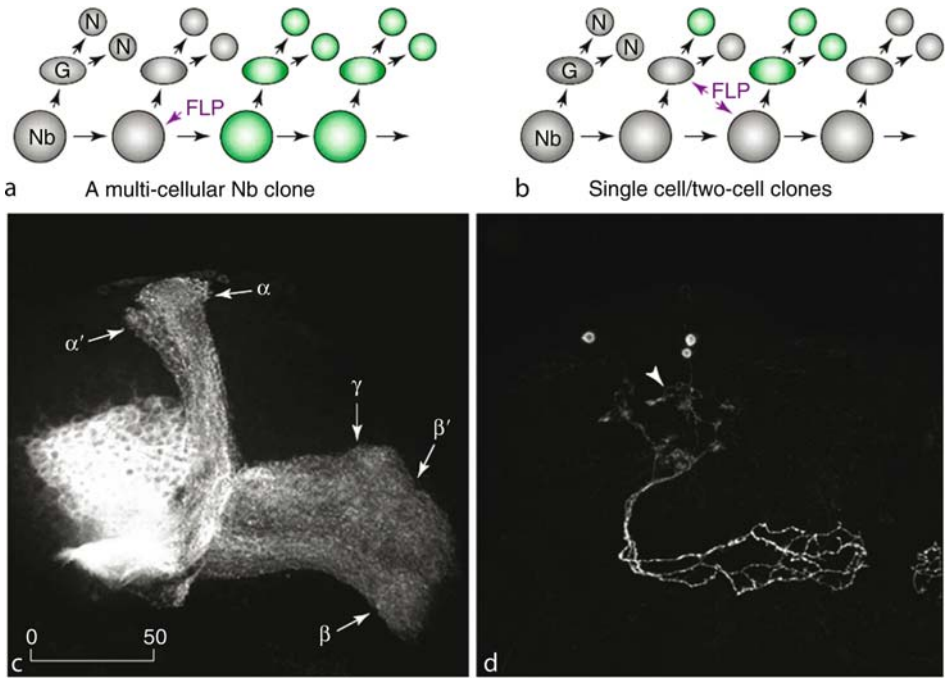
Uses of MARCM

Since it was first published, MARCM has been used extensively. It has become an essential component of the ever-expanding *Drosophila* genetics toolbox. Below we describe briefly a few examples in which the use of MARCM system played an essential role in the genetic analysis of nervous system development.

Neuronal Morphogenesis

MARCM has been effective in the investigation of axonal and dendritic branching patterns as well as neuronal wiring and circuitry formation. For instance, Grueber and colleagues employed MARCM to study dendrite

M



Mosaic Analysis with a Repressible Cell Marker. Figure 2 MARCM clones in *Drosophila* mushroom bodies (MB). A neuroblast (Nb) generates a series of ganglion mother cells (GMC, G in Fig.). Each GMC generates two post-mitotic neurons (N). (a) A GAL80-negative Nb (GAL80–) gives rise to a multi-cellular clone. (b) If a GMC loses GAL80, a two-neuron labeled clone is generated. If mitotic recombination occurs in a dividing GMC, only one of the two post-mitotic neurons will be labeled. (c) and (d) Confocal images of MARCM clones of MB neurons. (c) A MB Nb clone produced by an early mitotic recombination event consists of hundreds of neurons at the adult stage visualized by mCD8-GFP expression. There are five axon bundles in the adult MB: γ, β′ and β projecting towards the midline and α′ and α projecting dorsally. (d) Single cell labeling shows that each cell body extends a single process from which dendrites (*arrowhead*) branch out. (Modified with permission from Lee T, Luo L (2001) Trends Neurosci 24(5):251–254).

branching morphology and the establishment of dendritic territories of specific neurons of the *Drosophila* third instar larva peripheral nervous system [4]. They focused their studies on the dendritic arborization neurons (da), which spread their dendrites in a two-dimensional coverage of the larval epidermis. By examining single cell clones generated using MARCM and labeled by the expression of a pan-neuronal driver (*elav-GAL4*), da neurons were grouped into four morphological classes (I-IV) according to differences in dendrite branching complexity. Most importantly, these authors reported that neurons of the same class show dendritic exclusion or heteroneuronal tiling whereas those in different classes show extensive overlap of their dendritic fields. These pioneer studies set the stage for further investigations addressing the molecular genetic mechanisms underlying dendritic branching and tiling briefly discussed below.

Gene Function Requirement

The MARCM system has been successfully employed to assess the role of candidate genes in different biological processes. Of particular note are recent findings that further elucidate the role of *Down's syndrome cell adhesion molecule* (*Dscam*) in dendrite self-avoidance or isoneuronal tiling. The *Drosophila Dscam* gene shows a remarkable degree of alternative splicing with the potential to generate more than 38,000 different isoforms and has been implicated in axonal and dendritic patterning. Using MARCM, three different groups addressed the cell autonomous requirement for *DsCam* gene in the patterning of the larval epidermis da sensory neurons [5,6,7]. These workers showed that *Dscam* mediates isoform-specific homophilic interactions required for self-avoidance within a single sensory neuron arbor. Interestingly, heteroneuronal tiling such as that of class II and IV sensory neurons is not affected by *Dscam* mutations suggesting the existence of an additional pathway. Thus, the current view of the molecular underpinnings of dendrite morphogenesis in *Drosophila* has been made possible by the high level of resolution afforded by single cell labeling and genetic manipulation unique to the MARCM system.

Mosaic Genetic Screens

Mutant screens constitute a powerful tool in the identification of genes essential for diverse biological processes. A forward genetic approach can be combined with the MARCM system, thereby bypassing pleiotropic

effect of mutations (i.e. early lethality) and increasing the sensitivity of the phenotype analysis. This strategy is well illustrated in the report of Reuter et al. [8]. These investigators carried out a genetic screen aimed at identifying genes that play a role in the morphogenesis of the larval MB neurons. To that end, homozygous mutant clones generated by MARCM were examined by virtue of expression of MB-specific *GAL4* drivers, which in turn activated the transcription of target reporter constructs (*UAS- mCD8-GFP*). In order to increase the frequency of MB clones, FLP expression was heat- induced in newly hatched larvae. At that time, the only dividing neuroblasts are those giving rise to the MB neurons. Nearly 20% of the genome was sampled by this approach. Larvae bearing mutant clones showing abnormal distribution of GFP, large cells, defective axonal transport and abnormal axon and dendrite morphogenesis were isolated. Further characterization of these mutations led to identification of new genes that play a role in neuronal morphogenesis as well as discovery of new functions of previously identified genes.

Cell Lineage Analysis

The ability to induce mitotic recombination at different times during development makes MARCM particularly well suited for cell lineage analysis. Several investigators have taken advantage of these properties to investigate clonal relationships in the olfactory glomeruli and the mushroom body (MB), the area of the insect brain involved in olfaction-mediated learning and memory. As one of the earliest contributions of MARCM system, Lee et al. [9] showed that, in the *Drosophila* CNS, a single identified neuroblast sequentially gives rise to at least three distinct types of neurons. More interestingly, their projection into different MB lobes depends upon their birth order [9]. Similar strategy when applied to clonal relationship of projecting neurons of the *Drosophila* olfactory system demonstrated that their dendritic arborizations in the antennal lobe and thus odour representation, depends upon their birth order (reviewed in [10]).

Acknowledgements

This work was supported by Canadian Institute of Health Research and Natural Sciences and Engineering Research Council grants to A.R. Campos. V.G. Rodriguez Moncalvo is supported by a Canadian Institute of Health Research grant to A.R. Campos (MOP-12700).

References

1. Lee T, Luo L (1999) Mosaic analysis with a repressible cell marker for studies of gene function in neuronal morphogenesis. Neuron 22:451–461
2. Wu JS, Luo L (2007) A protocol for mosaic analysis with a repressible cell marker (MARCM) in *Drosophila*. Nat Protoc 1(6):2583–2589
3. Lai S-L, Lee T (2006) Genetic mosaic with dual binary transcriptional systems in *Drosophila*. Nat Neurosci 9(5):703–709
4. Grueber WB, Jan LY, Jan YN (2002) Tiling of the *Drosophila* epidermis by multidendritic sensory neurons. Development 129:2867–2878
5. Hughes ME, Bortnick R, Tsubouchi A, Baumer P, Kondo M, Uemura T, Schmucker D (2007) Homophilic *Dscam* interactions control complex dendrite morphogenesis. Neuron 54(3):417–427
6. Matthews BJ, Kim ME, Flanagan JJ, Hattori D, Clemens JC, Zipursky SL, Grueber WB (2007) Dendrite self-avoidance is controlled by *Dscam*. Cell 129(3):593–604
7. Soba P, Zhu S, Emoto K, Younger S, Yang SJ, Yu HH, Lee T, Jan LY, Jan YN (2007) *Drosophila* sensory neurons require *Dscam* for dendritic self-avoidance and proper dendritic field organization. Neuron 54(3):403–416
8. Reuter JE, Nardine TM, Penton A, Billuart P, Scott EK, Usui T, Uemura T, Luo L (1999) A mosaic genetic screen for genes necessary for *Drosophila* mushroom body neuronal morphogenesis. Development 130:1203–1213
9. Lee T, Lee A, Luo L (1999) Development of the *Drosophila* mushroom bodies: sequential generation of three distinct types of neurons from a neuroblast. Development 126:4065–4076
10. Komiyama T, Luo L (2006) Development of wiring specificity in the olfactory system. Curr opin Neurobiol 16:67–73

M

MOSAIC Model

Definition

Modular selection and identification control (MOSAIC) model, proposed for solving a large-scale sensorimotor problem using multiple pairs of a forward (estimation) model and an inverse (control) model. An important ingredient in the model is how well a forward model predicts movement outcome or reward, defined as a responsibility signal. Those responsibility signals in turn determine which controllers will be used for a particular movement and which internal models will be updated accordingly. The MOSAIC model attempts to decompose a large-scale sensorimotor problem automatically by making each module specialized for a particular situation or task.

►Theories on Motor Learning

Mossy Fibers

Definition

Most afferents from the brainstem or spinal cord to the cerebellum terminate in the granule cell layer of the

cerebellar cortex as "mossy fibers". They are so named because of the appearance of their terminals under the microscope. Mossy fibers carry almost all the information to the cerebellar cortex that affects the short-term firing rates of granule cells and other cells in the cerebellum. Mossy fibers terminate bilaterally in discrete areas of the vermis and of the hemispheres, evidencing a partial somatotopic arrangement. They are differentiated from "climbing fibers" that originate only in the inferior olive, terminate on Purkinje cells, and affect the firing rate of cerebellar neurons over the long-term.

►Cerebellum
►Cerebellar Functions

Motion Aftereffect

Definition

A visual motion illusion that occurs as a negative aftereffect of adaptation to motion. Often called the waterfall illusion after Robert Addams' description of his experience when viewing the Falls of Foyers in Inverness, Scotland. The effect is produced by adapting to a stimulus that moves in a particular direction for a prolonged period. On subsequent viewing of a stationary object, e.g., the rocks beside the waterfall, results in their appearing to move in the opposite direction. Addams (1834) commented: "I saw the rocky surface as if in motion upwards, and with an apparent velocity equal to that of the descending water, which the moment before had prepared my eyes to behold this singular deception."

►Perceptual Filling-in
►Visual Illusions

Motion Analysis

Stephen J. Piazza
Department of Kinesiology, The Pennsylvania State University, University Park, PA, USA

Definition

For the purposes of this essay, "motion analysis" is defined as the recording of the three-dimensional movements of human body segments, and the subsequent computation of meaningful parameters that describe the movement from raw kinematic data. The collection of motion data may be accompanied by measurements of external forces acting on the body. In such cases, ►inverse dynamic analysis may be performed to estimate joint forces and moments internal to the body.

Purpose

It is often necessary to track the motions of the human body in three dimensions in order to answer questions about the biomechanics and neural control of movement. Examples of such investigations include studies of posture, gait, movement perturbation, and reaching. Motion analysis is applied on a routine basis in ►clinical gait analysis, for the purpose of gathering data that is used to inform surgical decision-making for patients with gait abnormalities secondary to neurological conditions such as cerebral palsy and stroke.

Principles

Motion Analysis Systems: Image-Based

Three-dimensional image-based motion analysis involves the use of two or more cameras to track markers applied to the skin of a subject. Markers are usually spherical and covered with reflective tape in order to maximize the reflection of either visible or infrared light. Image-based motion analysis came of age in the 1970s, when sufficient computing power became available to rapidly transform two-dimensional camera views into three-dimensional marker coordinates. Making this transformation requires information about the position and orientation of each camera, as well as camera-specific corrections to account for optical distortion. The process of determining these parameters is known as ►camera calibration. One widely-used calibration procedure is called the ►direct linear transformation [1], and involves linear least-squares determination of camera parameters given a set of control points whose locations within the laboratory are known. Today, most commercially available systems use a two-step calibration process consisting of a static calibration followed by a dynamic calibration, with the correction for lens distortion handled separately. The static calibration establishes a laboratory-fixed coordinate system and involves the placement of stationary markers that define this coordinate system in view of all cameras. In the dynamic calibration, a rigid rod fitted with two markers is waved in front of the cameras, and parameters defining the position and orientation of the cameras are determined by iteratively minimizing deviations in the intermarker distance throughout the motion. In a process called ►reconstruction, camera parameters determined during the calibration procedure are used to compute three-dimensional marker locations following actual motion trials.

To establish the position and orientation of a body segment within the laboratory coordinate system, it

is necessary to locate a minimum of three markers attached to that segment during each timeframe. If these three markers are placed on bony landmarks, they may be used to define both an ►anatomical coordinate system and a 4 × 4 matrix specifying a ►homogeneous transformation [2] between the laboratory coordinate system and the anatomical coordinate system. Alternatively, a cluster of three or more markers not located on landmarks may be tracked. If the segment-fixed locations of the cluster markers within the anatomical coordinate system are known, it is possible to determine the homogeneous transformation between the laboratory and segment anatomical coordinate systems using a least-squares approach [3].

Motion Analysis Systems: Magnetic

Motions may also be tracked in three dimensions using magnetic tracking devices. Such devices consist of a transmitter unit, which broadcasts three superimposed electromagnetic fields in the volume of interest, and one or more sensors that are applied to body segments. Each sensor contains three mutually-orthogonal passive antenna coils. Measurement of the currents induced in the sensor coils permits computation of the homogeneous transformations between the transmitter and each sensor.

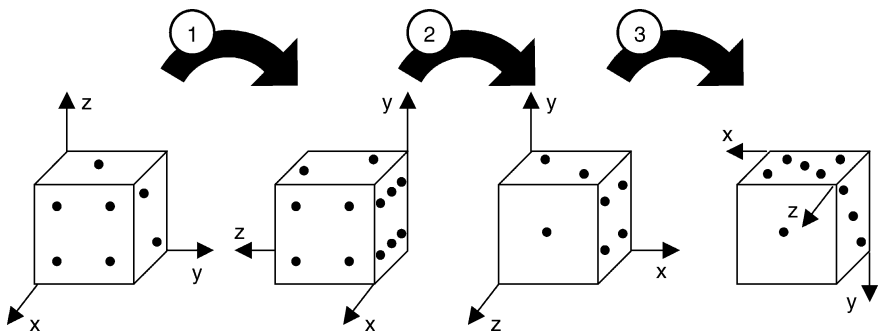
Measurement of Ground Reaction Force

Measurements of human movement are often accompanied by determination of the ground reaction force carried out using a force plate. A force plate is a flat steel plate supported at each of its four corners by a pillar instrumented for measurements of triaxial force (gauges affixed to these pillars actually measure strain) [4]. Forces measured at the four corners are summed to obtain the three-dimensional ground reaction force vector. A force plate gives no information about the distribution of ground reaction force underfoot, but forces measured at the individual pillars can be used to locate the ►center of pressure, the point at which the resultant ground reaction force could be assumed to act if it acted at a single point. The motion of the center of pressure during standing is a commonly-used indicator of postural stability.

Computation and Reporting of Joint Angles

Once laboratory-to-anatomical homogeneous transformations have been determined, it is possible to compute from them the transformations between the anatomical coordinate systems of adjacent segments. These transformations may then be decomposed in a variety of ways to arrive at the joint angles that are often of experimental or clinical interest. For example, we might use a motion analysis system to establish the locations of the thigh and shank anatomical coordinate systems, and then decompose the transformation between those two coordinate systems to the flexion-extension, abduction-adduction, and internal-external rotation angles of the knee joint. The most commonly used technique for obtaining joint angles is ►Euler/Cardan angle decomposition (Fig. 1).

A set of Euler/Cardan angles describes the three-dimensional rotation of one coordinate system into another, by starting with the coordinate systems initially aligned and applying a series of three rotations about the axes of one of the coordinate systems [2]. These rotations may occur about the axes of the coordinate system considered to be moving (resulting in "body-fixed" rotations) or about the axes of the fixed coordinate system ("ground-fixed" rotations). Rotation sequences must be specified (e.g. X-Y-Z) when reporting joint angles, as their selection will influence the angles computed [5], and a sequence may include two rotations about the same axis (e.g., Z-X-Z). Care must be taken when choosing a rotation sequence to avoid selecting one that will result in singularities that will prevent decomposition of the transformation matrix. A widely-used convention for reporting human knee joint angles [6] has been adapted for use at other joints and involves rotation of the tibia first about the



Motion Analysis. Figure 1 Example of an Euler/Cardan rotation sequence of the type often used to describe three-dimensional joint rotations. In this example, the first rotation is 90° about the *x*-axis and is followed by a second rotation of 90° about the new *y*-axis. The third rotation is 180° about the twice-rotated *z*-axis. This is an example of an X-Y-Z body-fixed rotation sequence.

M

flexion axis (shared by femur and tibia), then about a tibia-fixed abduction-adduction axis, and finally about a tibia-fixed internal-external rotation axis. An alternative method for quantifying the relative rotations between body segments is ►helical axis decomposition [5]. It is always possible to describe the transformation from one coordinate system into another using a single rotation about an axis fixed in both coordinate systems coupled with a translation along that axis. Scaling the unit vector along the rotation axis by the magnitude of the rotation gives three components of the rotation that are analogous to joint angles. A second alternative to Euler/Cardan angles for reporting three-dimensional rotations involves the use of Euler parameters (or quaternions), a singularity-free method that is more robust computationally though less intuitively appealing.

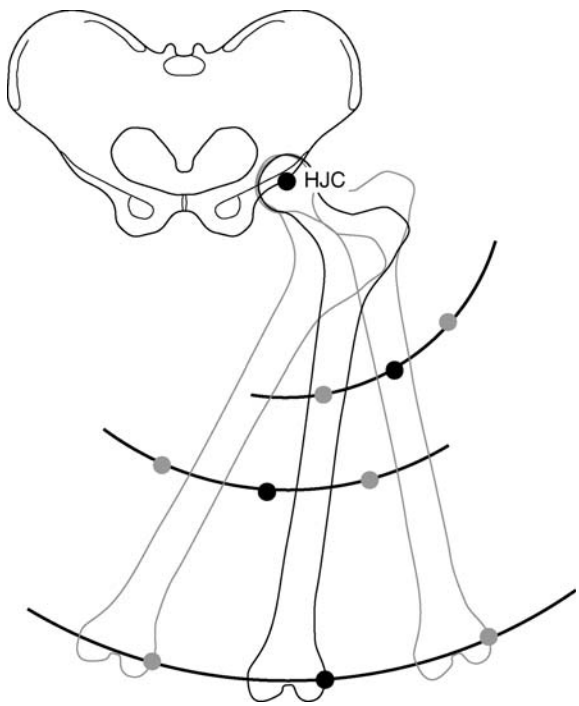
Inverse Dynamic Analysis

The direct measurement of muscle forces is too invasive to perform on a routine basis, but muscle actions are often estimated from motion and force data in inverse dynamic analysis. This procedure involves computing the internal joint reaction forces and moments acting at the proximal end of a body segment for which the external force acting at the distal end is known. The external force may be measured (using a force plate in the case of a foot on the ground) or assumed to be zero (when the distal segment does not contact the ground). The Newton-Euler equations are used to compute proximal forces and moments from external forces and the position, velocity, and acceleration of the segment. Masses and moments of inertia that appear in the Newton-Euler equations must be determined using anthropometric estimation techniques. The forces and moments computed for the most distal segment are then used to compute the forces and moments at the next most proximal joint, and so on. The joint moments computed in this manner do not give information about the actions of individual muscles, but muscle forces are often obtained from these moments by applying optimization theory. Joint moments may be combined with measurements of the rate of joint rotation to compute the joint power, the rate at which energy is generated or absorbed by the muscles crossing a given joint.

Advantages and Disadvantages

Modern motion analysis systems are capable of highly accurate measurements of the locations of individual markers. Marker location errors are typically less than 1 mm for image-based systems that use digital cameras. These systems permit image processing to occur at the individual cameras rather than at a central processor, and thus permit increased resolution and capture rates. Despite this high degree of marker location accuracy, significant methodological barriers remain to the accurate measurement of joint kinematics. As markers cannot be mounted on bones, movements of skin and other soft tissues contribute to errors in measured motion. Attempts to reduce these errors have included the identification of locations on body segments that are less susceptible to skin movement [7], and mathematical weighting techniques that correct for soft tissue deformation [8].

The reliable establishment of anatomical coordinate systems is sometimes difficult in practice. When coordinate systems are not created properly, one potential consequence is "kinematic crosstalk," which is the misinterpretation of motion about one joint axis as motion about another axis [9]. For example, if the knee flexion axis is misidentified, then pure knee flexion may be taken to be a combination of flexion and abduction. The accurate location of joint centers is important for the creation of anatomical coordinate systems, and for effectively carrying out inverse dynamic analyses, but some joint centers, such as that of the hip are deep, and thus difficult to locate from bony landmarks. This issue



Motion Analysis. Figure 2 Illustration of the basis for functional location of the hip joint center. Markers affixed to the thigh trace out paths on spheres whose shared center is the hip joint center. Measurement of the motions of these markers and subsequent sphere-fitting permits location of the hip joint center, which does not rely upon location of bony landmarks near the joint center. Similar techniques have been employed to establish the joint centers or joint axes of all the joints of the upper and lower extremities.

has been addressed by the development of "functional" methods for fitting joint centers and joint axes to measured motions [10] rather than predicting their locations from the locations of bony prominences (Fig. 2).

Conventional motion analysis methods serve well when used to track the motions of large body segments, but fall short when they are employed to measure motions of less well-defined segments. Motion analysis of the foot, for example, is problematic because it contains joints, such as the subtalar and tarsometatarsal joints, which join body segments not easily tracked with external markers.

References

1. Abdel-Aziz YI, Karara HM (1971) Direct linear transformation from comparator coordinates into object space coordinates in close range photogrammetry. In: Proceedings of Symposium on Close Range Photogrammetry, Falls Church, VA, pp 1–18
2. Craig JJ (1986) Introduction to robotics: mechanics and control, 2nd edn. Addison-Wesley, Reading, MA
3. Veldpaus FE, Woltring HJ, Dortmans LJ (1988) A least-squares algorithm for the equiform transformation from spatial marker co-ordinates. J Biomech 21:45–54
4. Winter DA (2004) Biomechanics and motor control of human movement. Wiley, New York
5. Woltring HJ (1994) 3-D attitude representation of human joints: a standardization proposal. J Biomech 27:1399–1414
6. Grood ES, Suntay WJ (1983) A joint coordinate system for the clinical description of three- dimensional motions: application to the knee. J Biomech Eng 105:136–144
7. Cappello A, Cappozzo A, della Croce U, Leardini A (1997) Bone position and orientation reconstruction using external markers. In: Allard P, Cappozzo A, Lundberg A et al. (eds) Three-dimensional analysis of human locomotion. Wiley, New York, 1997, pp 147–171
8. Andriacchi TP, Alexander EJ, Toney MK, Dyrby C, Sum J (1998) A point cluster method for in vivo motion analysis: applied to a study of knee kinematics. J Biomech Eng 120:743–749
9. Piazza SJ, Cavanagh PR (2000) Measurement of the screw-home motion of the knee is sensitive to errors in axis alignment. J Biomech 33:1029–1034
10. Cappozzo A (1984) Gait analysis methodology. Hum Mov Sci 3:27–50

Motion and Direction Sensitivity in Cutaneous Mechanosensation

Definition

Motion and direction sensitivity is studied using air jets, brushes and probes applied to different body regions. Its functional significance relates to both manual dexterity and postural control. The capacity for human subjects to identify the direction of stimulus motion on the skin is dependent on stimulus velocity, contact force and length of movement. It also varies in proportion to the innervation density of the fast and slowly adapting type I mechanoreceptive afferents.

►Cutaneous Mechanoreceptors, Anatomical Characteristics
►Cutaneous Mechanoreceptors, Functional Behavior
►Processing of Tactile Stimuli

Motion Correspondence in Vision

Definition

When viewing a series of discrete frames, such as a video sequence, objects and their features in motion relative to the camera change position from one frame to the next. The motion correspondence problem is to track motion by identifying the correspondence between features across time.

►Visual Motion Processing

Motion Opponency in Vision

Definition

A mechanism is said to be motion opponent if it is excited by motion in one direction and inhibited by motion in the opposite direction.

►Visual Motion Processing

Motion Parallax in Vision

Definition

Motion parallax is a cue resulting from our own motion to the relative distance of objects. As we move, objects that are closer to us move farther across our field of view than do objects that are in the distance.

►Visual Motion Processing

Motion Perception

Definition

The ability to perceive movement.

Motion Sickness

Bill J. Yates
Department of Otolaryngology, University of Pittsburgh, School of Medicine, Eye & Ear Institute Building, Pittsburgh, PA, USA

Definition

Motion sickness is a malady triggered by movement or perceived movement in the environment. In humans it is characterized by the presence of nausea and vomiting, pallor, cold sweating and a large increase in the circulating levels of the hormone arginine vasopressin.

Characteristics

Conditions that Produce Motion Sickness

Typically, motion sickness is elicited during conditions where multiple sensory inputs are present that provide contradictory information regarding body position in space [1]. Often, the sensory mismatch involves the vestibular and visual systems, as well as the somatosensory system. For example, when an individual is traveling within a boat or aircraft, there may be no tangible visual cues indicating the presence of movement, whereas vestibular receptors and proprioceptors signal that movement is taking place. Moving visual scenes, such as those generated by virtual reality devices, can also induce motion sickness, as the visual system indicates that the individual is moving whereas the vestibular system indicates that the head is stationary. However, other mismatched sensory inputs can also induce motion sickness. For example, many astronauts experience "space motion sickness" after entry into zero gravity, which is presumably triggered during head movements because the semicircular canals provide inputs indicating that the head is rotating, but the vestibular otolith organs (which are no longer subjected to gravitational forces, and thus do not signal the presence of head tilts) fail to indicate that head position has been altered [2].

The most critical signals required for the generation of motion sickness come from the vestibular system, as evidenced by that fact that this malady cannot be induced in individuals with bilateral vestibular dysfunction by stimuli that are typically highly provocative [3]. Furthermore, diseases that affect the vestibular system, such as inner ear infections, often produce signs and symptoms that are similar to those that occur during motion sickness. Fortunately, the vestibular system is very plastic and rapid adaptation occurs during conditions involving the disruption of the normal pattern of inputs from the inner ear to the brainstem. Such plasticity in the vestibular system probably explains why space motion sickness resolves after a few days of spaceflight. Visual inputs are not essential for producing motion sickness, since blind individuals have normal sensitivity for this condition (see [4] for a review).

Minimizing sensory conflict can often reduce the susceptibility for motion sickness. For example, motion sickness is less prevalent in drivers of automobiles, who are attending to visual cues reflecting the presence of movement, than in passengers who may be minimizing visually related movement cues by focusing their eyes on objects within the vehicle. Furthermore, repeated exposure to a provocative environment reduces the incidence and severity of motion sickness when that environment is experienced again. For instance, space motion sickness is less prevalent in veteran astronauts than individuals experiencing their first space flight [2]. Nonetheless, there are considerable individual differences in susceptibility to motion sickness that probably have a complex etiology and are not well understood.

Physiological Manifestations of Motion Sickness

Motion sickness in humans is typically associated with several prominent symptoms and signs, including nausea and vomiting, pallor and cold sweating. Another physiological manifestation of the malady is a large increase in the levels of the posterior pituitary hormone arginine vasopressin circulating in the blood [1]. However, these indicators are not present in all species. For example, many animals, including rodents and lagomorphs (i.e. rabbits and hares), lack the ability to vomit and thus do not exhibit this hallmark sign of motion sickness. Non-emetic species often will ingest non-nutritive substances such as clay after exposure to stimuli that would produce vomiting in humans Animals that lack the capacity to vomit exhibit increases in the posterior pituitary hormone oxytocin rather than vasopressin, after exposure to nauseogenic stimuli (see [4] for discussion).

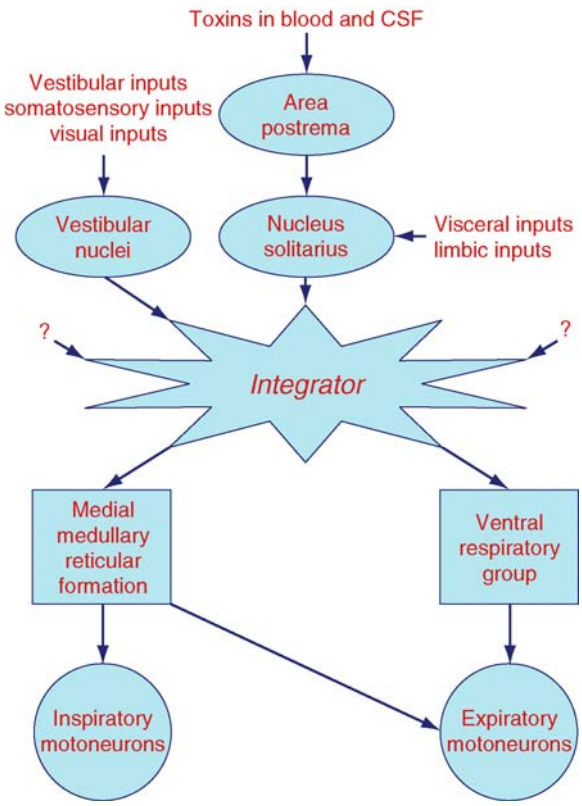
Neural Mechanisms that Produce the Physiological Manifestations of Motion Sickness

Retching and vomiting are mainly the result of the coordinated contractions of the major respiratory

muscles and upper airway muscles [5]. The pattern of contraction of these muscles differs during breathing and emesis. During breathing, inspiratory muscles such as the diaphragm and expiratory muscles such as the abdominal muscles contract out of phase, to generate the forces that move air into and out of the lungs. In contrast, the diaphragm and abdominal muscles contract together during retching and vomiting to place considerable pressure on the stomach, thereby pushing the gastric contents towards the mouth. The autonomic nervous system contributes to generating vomiting by producing marked reductions in gastric tone and motility, changes in gastric myoelectric activity and a retrograde giant contraction that moves contents from the upper part of the small intestine back into the stomach before expulsion. Furthermore, a longitudinal contraction of the esophagus occurs that pulls open the relaxed gastroesophageal junction and thus forms a funnel that facilitates free flow of gastric contents to the esophagus.

It is generally believed that a common neural circuitry mediates vomiting, elicited by a variety of triggering signals, including motion-related inputs relayed to the vestibular nuclei, circulating toxins detected by the area postrema, visceral signals conveyed to the nucleus solitarius and even psychological perceptions (e.g. thought of a disgusting situation) processed through the limbic system. Figure 1 provides a synopsis of current information regarding the neural circuitry that produces the contractions of inspiratory and expiratory respiratory muscles that generate retching and vomiting.

The rhythmic contractions of the diaphragm and expiratory muscles during breathing are controlled by neurons located in the dorsal and ventral respiratory groups in the brainstem. However, the firing of many of these respiratory group neurons, particularly neurons with inspiratory-related activity, is inhibited during vomiting. This suggests that separate pattern generators coordinate the contractions of respiratory muscles during breathing and emesis. Recent anatomical [6] and physiological [7] evidence suggests that some of the neurons that are part of the vomiting pattern generator are located within the medial reticular formation of the medulla. Presumably, a neural integrator processes trigger signals for vomiting and when appropriate activates the pattern generator that produces this response. The identity of this neural integrator is unknown, although there is evidence that the neurons that form the integrator are located in the medulla. Vomiting can be produced in a reduced animal preparation in which all parts of the nervous system except the medulla and spinal cord are removed, indicating that the essential neural circuitry for producing emesis is confined to these regions [8].



Motion Sickness. Figure 1 Neural pathways that produce vomiting. A common circuit produces vomiting in response to a number of triggering signals, including conflicting motion information, toxins in the blood or visceral inputs. This circuit includes an integrator that processes the triggering signals and a pattern generator that mediates the contractions of respiratory muscles that produce vomiting. The pattern generator is comprised in part of neurons located in the medial medullary reticular formation and the ventral respiratory group.

The neural pathways that produce nausea have remained elusive, but almost certainly are distinct from the pathways that generate vomiting (i.e. although nausea and vomiting are frequently triggered together, distinct circuits coordinate each response). The level of nausea is typically correlated with the concentration of the hormone vasopressin circulating in the blood, although this hormone does not appear to be critical for the production of nausea and is released as part of a parallel physiological response [4].

As noted above, conflicting sensory information regarding the position of the body in space is believed to be the primary trigger for motion sickness-related nausea and vomiting. Stimulation of the vestibular nerve can produce vomiting in animal preparations lacking the cerebellum, suggesting that the cerebellum is not a necessary component of the circuitry

that produces motion sickness. Nonetheless, there is evidence to suggest that regions of the cerebellum particularly the nodulus and uvula are typically engaged in generating the signs and symptoms of motion sickness.

Pharmacological Agents that Suppress Motion Sickness

Drugs employed to treat motion sickness fall into two categories: (i) those that are only effective in alleviating motion-related nausea and vomiting and not the symptoms produced by other emetic triggers and (ii) those that serve as broad-spectrum anti-emetic drugs and suppress nausea and vomiting despite the trigger. Drugs in the former category presumably affect receptors in the vestibular nuclei and central vestibular system, whereas those in the latter category probably act on receptors of cells that form the central integrator responsible for producing nausea and vomiting [4].

Anticholinergic drugs that act on muscarinic receptors are the most effective agents in clinical use for treating motion sickness, but have limited efficacy in ameliorating nausea and vomiting elicited by other trigger signals. Scopolamine, which blocks all five subtypes of muscarinic receptors, is the most commonly employed anticholinergic drug for treating motion sickness. Scopolamine has a number of significant side effects, including sedation and dry mouth and is only available by prescription in most countries.

Antihistamines form another class of drugs that have some efficacy in reducing the symptoms of motion sickness, but not nausea and vomiting elicited by triggers such as toxins and visceral signals. Most "over the counter" anti-motion sickness drugs, such as dimenhydrinate (marketed under the brand names Dramamine and Gravol) and meclizine (Antivert, Bonine), belong to this drug class. Antihistamines are less effective than anticholinergics in combating motion sickness, but have a longer duration of action and are considerably safer and thus are used more frequently. Nonetheless, antihistamines do produce some drowsiness and dizziness.

A third type of drug employed to treat motion sickness has mixed antimuscarinic and antihistamine actions. An example of such a drug is promethazine (Phenergan), which is employed by NASA to treat space motion sickness in astronauts. The side effects of promethazine are similar to those of anticholinergics and antihistamines and include drowsiness.

Drugs that increase the release of norepinephrine in the central nervous system (sympathomimetics) also have efficacy in treating motion sickness. Drugs in this class include amphetamine and ephedrine. Sympathomimetics do not produce drowsiness, a side effect shared by anticholinergics and antihistamines, and thus have been used by individuals who must perform work while in an environment that may induce motion sickness. However, amphetamine is addictive and some states and countries have forbidden the use of this drug to treat motion sickness. Similarly, benzodiazepines such as diazepam (Valium) have some effectiveness in treating motion sickness, but are not commonly used for this purpose due to the risk of addiction and the occurrence of side effects when minimal required doses are delivered.

Several drugs are broad-spectrum anti-emetics and have promise in reducing the nausea and vomiting elicited by any trigger. Amongst these drugs are agonists for the serotonin 5-HT_{1A} or 5-HT_2 receptors, antagonists of n-methyl-d-aspartate (NMDA) or neurokinin type 1 (NK-1) receptors and some calcium channel blockers.

Evolutionary Significance of Motion Sickness

Since all individuals with an intact vestibular system have some predisposition for developing motion sickness, it is tempting to speculate that this condition has evolutionary significance. Treisman [9] hypothesized that motion sickness is a poison response in that toxins could affect the processing of visual and vestibular inputs and induce the sensory conflict that elicits nausea and emesis. In other words, modern circumstances such as space and air travel that result in conflicting sensory information regarding body position in space can trigger mechanisms that evolved to prevent poisoning. However, there is little experimental evidence to support Treisman's theory. It is now well established that the vestibular system provides influences on the brainstem circuitry that regulates blood pressure and respiration and elicits the changes in blood distribution in the body and alterations in respiratory muscle activity that are needed during movement and changes in posture [10]. It is thus feasible that the signs and symptoms of motion sickness are due to an aberrant activation of neural circuits that typically function to maintain homeostasis. Such a notion is impossible to test experimentally, but it raises the possibility that motion sickness has no evolutionary significance and is in fact a "mistake" that was never corrected because the circumstances that generate the condition (e.g. travel in airplanes and boats) have only become commonplace in the modern world.

References

1. Money KE, Lackner JR, Cheung RSK (1996) The autonomic nervous system and motion sickness. In: Yates BJ, Miller AD (eds) Vestibular autonomic regulation. CRC, Boca Raton, pp 147–173
2. Oman CM (1998) Sensory conflict theory and space sickness: our changing perspective. J Vestibular Res 8:51–56

3. Cheung BS, Money KE, Jacobs I (1990) Motion sickness susceptibility and aerobic fitness: a longitudinal study. Aviat Space & Environ Med 61:201–204
4. Yates BJ, Miller AD, Lucot JB (1998) Physiological basis and pharmacology of motion sickness: an update. Brain Res Bull 47:95–406
5. McCarthy LE, Borison HL (1974) Respiratory mechanics of vomiting in decerebrate cats. Am J Physiol 226:738–743
6. Billig I, Foris JM, Enquist LW, Card JP, Yates BJ (2000) Definition of neuronal circuitry controlling the activity of phrenic and abdominal motoneurons in the ferret using recombinant strains of pseudorabies virus. J Neurosci 20:7446–7454
7. Miller AD, Nonaka S, Jakus J, Yates BJ (1996) Modulation of vomiting by the medullary midline. Brain Res 737:51–58
8. Miller AD, Nonaka S, Jakus J (1994) Brain areas essential or non-essential for emesis. Brain Res 647:255–264
9. Treisman M (1977) Motion sickness: an evolutionary hypothesis. Science 197:493–495
10. Yates BJ (1996) Vestibular influences on the autonomic nervous system. Ann NY Acad Sci 781:458–473

Motion Vision

►Visual Motion Processing

Motivation

Definition

Motivation is a theoretical construct employed by experimental psychologists and philosophers when they seek to explain specific patterns of behavior. This term also refers to processes by which behavior is activated and directed. Physiological psychologists postulated that homeostatic imbalance within specific regulatory systems such as those responsible for energy, fluid or thermoregulation, gave rise to specify "drive" states. Reduction of a specific "drive" state by consumption of food or water reduced motivation to seek these stimuli and also provided reinforcement to repeat action patterns that brought the organism into contact with these natural reward stimuli.

►Learning and Motivation

Motoneuron

Definition

Motoneurons are neurons whose cell bodies lie in motor nuclei of cranial nerves in the brainstem or in the anterior horn of the spinal cord and whose efferent axons leave the central nervous system (CNS) to innervate muscle fibers. There are three classes of motoneurons. Large motoneurons with extensive dendritic trees and fairly thick myelinated axons and high action potential conduction velocity innervate skeletal muscle fibers and may thus be called skeleto-motoneurons. Among these, one class innervates skeletal muscle fibers only and is called α-motoneuron. A second class innervates skeletal muscle fibers and intrafusal muscle fibers of muscle spindles and is called β-motoneuron. The third class of smaller motoneurons with thinner myelinated axons innervates intrafusal muscle fibers of muscle spindles only and is called γ-motoneuron (or fusimotor neuron).

►Motor Units
►Muscle Spindle

Motoneuron Pool

Definition

The set of spinal or brainstem skeletal motoneurons that innervate a given skeletal muscle.

►Motor Cortex – Hand Movements and Plasticity

Motor Actions

Definition

Any changes in state variables; may be elicited by external forces while control variables remain constant (involuntary actions, e.g., motion of the arm to a new position elicited by unloading) or by changes in control variables (e.g., intentional actions), or both.

►Equilibrium Point Control

Motor Axon

Definition

The axonal projection of a motoneuron that leaves the spinal cord via a ventral root (or the brain stem via a cranial nerve), travels through a peripheral nerve, and terminates within its target muscle in multiple fine twigs, each of which projects to a single muscle fiber.

►Motor Units

Motor Centers

Definition

Broad term used to describe all structures in the brain concerned with motor behavior.

►Evolution of the Optic Tectum: In Amniotes

Motor Command

Definition

Signals carried by neurons of brain descending systems, for example, corticospinal neurons, to motoneurons in the spinal cord or brainstem. These signals are the final product of the central motor process that translates the plan for a movement into descending signals specifying the muscle synergies and activation profiles needed to achieve the desired movement.

►Corticospinal Neurons
►Motor Cortex: Output Properties and Organization
►Muscle Synergies

Motor Control

Uwe Windhorst
Göttingen, Germany

Introduction

In order to live, grow, survive and reproduce, organisms must be capable of at least two things. Firstly, they must be able to move because movement is the very prerequisite of life, even at the molecular level. Secondly, they must be able to ►control this movement in relation to relevant aspects of their natural environment, which in turn implies that they must be able to detect, categorize, recognize, and act on, aspects of their environment. The term "motor control" encompasses all these aspects. This overview article concentrates on some general aspects and principles of motor control.

As an introductory concrete example, consider the cat's, dog's or turtle's scratch "reflex" (►Scratching). In cats or dogs, the scratch reflex is "switched on" by a stimulus to a defined skin area on the upper forelimbs, neck, pinnas and adjacent skin areas (for review see [1]). The reflex consists of several components. Since an ipsilateral hindlimb needs to be flexed for scratching and, hence, taken off the ground, the posture (►Postural control) of the body must be changed and equilibrium re-stabilized by the other three limbs. The flexed hindlimb is then brought into a "postural" position for aiming at the stimulus. Subsequently, the scratching limb falls into a sequence of oscillations with long flexor and short extensor phases.

This example suggests that the system organizing the scratch reflex is composed of several subsystems executing particular tasks:

- ►*Sensory systems*, that are adequately tuned to detect, locate and identify the stimulus as well as the positions of the body parts throughout the sequence of events, involving cutaneous mechanoreceptive and proprioceptive senses, in particular.
- *Motor system* with
  - Central control system that organizes the goal-directed movement.
  - Executive system (skeleton, ►muscles etc.).
- *Interfaces* connecting the sensory and motor systems.

At a closer look, this simplified scheme can be elaborated by including

- ►*Information systems*, that select, represent, transfer, process, store and retrieve pertinent information (see ►Sensory systems).
- ►*Central pattern generators* (CPGs), which generate the rhythmical components of movement, and other generators of goal-oriented movements.
- *Coordinate transformations*, here from a sensory frame of reference into a motor frame of reference (►Sensory Systems). Such transformations are required because the sensory and motor frames are different. For example, cutaneous receptors are distributed across a 2D surface intricately folded in 3D space, while scratching movements are executed in multi-dimensional joint space, with certain restrictions such as exclusion of the own body.

- *Body schema*, i.e., a neural representation of the body's anatomical (spatial) configuration, which allows the localization of sensory stimuli and motor events with respect to the body, and integrates and aligns various reference frames (see ►Sensory systems).
- *Adaptability* of neuronal connections to particular circumstances, conditions and contexts.

Classes of Movement

A cat's or dog's scratch reflex is composed of several components. We may suspect that these components are organized by different neural sub-systems. In order to explore this idea further, we will start by provisionally classifying movements into the following categories, with subsequent qualifications:

- ►*Rhythmic movements* (e.g., over-ground ►locomotion, ►swimming, ►flying, scratching, ►mastication, ►Respiration – neural control).
- ►*Reflexes*: Reflexes provide an appropriate response closely coupled to a sensory input of some sort.
- *Motor activity to maintain equilibrium and posture* (►Postural control).
- *Free, goal-oriented movements*, such as reaching, grasping and object manipulation (►Voluntary movement; ►Reaching movements).

Actually, most movements involve aspects of more than one of these classes, as evidenced by the above scratch reflex. All movements in some way require posture as a basis to work on. In terrestrial vertebrates, whose bodies are maintained above the ground by legs, posture depends on some basic excitatory "tone" of anti-gravity muscle groups as well as on reflexes. Also, rhythmic and free goal-oriented movements may be modulated by, or make use of, reflexes. Conversely, reflexes may incorporate rhythmic components, or can be modulated by free goal-oriented or other activities of the organism. However, these classes may still be useful guidelines to unveil neuronal networks and their operations underlying movements.

Rhythmic Movements

Generally, movements should be as easy to generate, efficient and economic as possible. This "design principle" is readily apparent in rhythmic movements. Even unicellular organisms such as *Paramecium* easily move by rhythmic beats of flagellae. The ease in generating rhythmic movements is likely due to the repetitive succession of similar movement components and patterns. While, in multi-cellular organisms, the actual movement pattern is of course profoundly co-determined by the mechanics of the body components (to include invertebrates) and the environment, the driving and organizing control signals must be delivered by the nervous system. Conceptually, this task can be divided into two components:

- *Clock* (*oscillator*): There should be a mechanism providing the basic rhythm.
- *Pattern generator*: Additionally, the specific ►coordination of muscle activations required for a particular movement must be orchestrated in detail.

Central Pattern Generators

In order to produce these features, the central nervous system (CNS) contains complex networks of neurons, which are generally called ►central pattern generators (CPGs) (e.g., [2–5]). In such CPGs or their constituent nerve cells, the two tasks defined above (clock (oscillator) and pattern generation) may or may not be identifiable as separate components (for respiration see [6]). In the first case, there are potential ►pacemaker neurons, which oscillate spontaneously due to intrinsic properties of their membranes and then impose their intrinsic rhythmic activity onto the network [7]. In the second case, the entire network may oscillate without any single inherent neuron being able to oscillate on its own, the rhythm thus being an emergent network property. In many invertebrates, CPGs have been identified and analyzed, and much progress has been made in this respect in lower vertebrates (i.e., lamprey), but not so in higher vertebrates such as mammals [2,4,5]. This applies to locomotion (swimming, walking, running, flying), mastication, feeding and breathing, respiration being a special case in that in many animals it goes on uninterrupted throughout life, as does the heart beat.

Neuronal networks generating rhythmic motor activities almost constantly reorganize and reconfigure themselves according to the task at hand and the context in which they operate. In fact, the operation of CPGs must be adaptable to various extrinsic circumstances and conditions:

- *Peripheral conditions* monitored by sensory signals.
- *Higher-level influences such as* ►*motivation, visual guidance etc.*
- *Internal conditions of the CNS.*

Role of Sensory Inputs

Since rhythmic movements occur in complex and changing environments, it is obvious that they must adapt. For example, an uneven ground must be taken into account while walking on it, which in turn necessitates sensory inputs. In other words, CPGs must be amenable to, and change their properties and activities in response to, sensory inputs, to the extent that some of these inputs are able to reset the rhythm. In particular, the switch between different locomotor phases, e.g., the transition from stance to swing of a limb, depends on certain states of sensory inputs

or combinations thereof. Thus, rather than regulating motor output variables in an analog way, sensory inputs are often used to make discrete choices between motor alternatives, akin to technical finite-state systems [8]. These systems work using "if-then" rules as follows. The general rule is: IF sensory state 1 AND sensory state 2, THEN perform this particular action. For example, for slow forward gait of a cat: IF in a hindleg the extensor force is low AND the hip is extended AND the contralateral leg is loaded, THEN flex the ipsilateral leg. Or, for backward gait: IF the extensor force is low AND the hip is flexed AND the contralateral leg is loaded, THEN flex the ankle and knee and extend the hip. This description in terms of rules is likely to be heuristic and does not say anything about how the nervous system really performs this action [8].

Conversely, sensory inputs and their processing must be weighted according to the prevalent tasks in different phases of a rhythmic movement. For example, in human walking, the leg currently supporting the body weight must extend and should not easily yield to a flexor reflex initiated by a noxious stimulus to the foot (see below), while the situation is not that pressing in the other leg flexing anyway. This calls for a *CPG-dependent modulation of reflex effects*.

This discussion underscores the notion that classes of movement, in this case reflexes and rhythmic movements, are not absolutely separated, but depend on each other. Although rhythmic activities in the scratch reflex may be triggered by sensory stimuli, the CPGs do not depend on somatosensory ►feedback to maintain their activity. The CPG generating the scratch reflex is probably different from that generating locomotion [9].

Descending Control

In vertebrates, the spinal CPGs provide the basic rhythm and pattern-generating networks for locomotion, scratching and paw shakes. However, left on its own, e.g., in spinalized cats, the spinal cord has problems providing sufficient locomotor vigor and speed, ensuring lateral stability, and dealing with foreseeable obstacles. To do so, the spinal cord needs sensory feedback for timing, support and adaptive functions. In addition, it needs signals from supraspinal neural sources, such as [10–12]:

- *General activating systems* arousing the animal to new and unexpected stimuli and initiating appropriate actions. For example, sudden attack by a predator must alert the animal to make an immediate decision about *fight, flight* or *play dead*, in all cases implicating changes in posture and locomotion.
- *Motivational drive*. Locomotion mostly serves a purpose in being directed towards a goal. The pursuit of goals is in part determined by motivational brain systems, in particular the ►limbic system.
- *Supraspinal locomotor drive* provides energizing sources for posture and for "stirring up" the CPGs.
- *Adaptive fine-tuning of locomotor functions*, in particular anticipatory reactions to upcoming events, whose detection and processing need higher-level senses.

Many different supraspinal structures are involved in various sub-functions, including the brainstem, basal ganglia, cerebellum, and cerebral cortex. These structures exert their influences directly or indirectly via various descending tracts to several brainstem and spinal targets.

Neuromodulation of Central Pattern Generators

An important influence on locomotion and supporting posture is exerted by a variety of ►neurotransmitters and ►neuromodulators. These can (i) tonically facilitate or depress motor patterns; (ii) initiate motor activity and/or prime neuronal networks to more strongly respond to other inputs; (iii) modify cellular and synaptic properties [4]. Among the known neuromodulators are amino acids, ►neuropeptides, ►histamine, ►serotonin, ►catecholamines, and purinergic substances [13].

Neuromodulators generate temporal variability in many of the cellular, synaptic and network properties of CPGs. Neuromodulators may also change the properties of short-term ►synaptic plasticity, which in turn co-determine how networks operate in a task-and context-dependent way [14]. The effects of neuromodulators on network properties make each particular network a versatile instrument that is able to perform or contribute to a number of different motor tasks. On the other hand, similar tasks can actually be carried out by different types of network configurations [4].

Reflexes

The term "reflex" traces back to René Descartes ("Traité de l'homme" 1680) who lived in a time when research on optics surged. Ever since, a reflex has often been defined as a stereotypic motor response tightly coupled to a sensory stimulus. However, the term is now used in a wider sense. Consider a few examples.

Withdrawal Reflex

Reflex responses must occasionally be fast, for example, in emergency situations when potentially noxious stimuli must be avoided or evaded. The basic concept seems best exemplified by the withdrawal reflex, which was discussed by Descartes himself. The withdrawal reflex [15] is the motor response to a noxious stimulus to a body part, e.g., the withdrawal of the hand from a hot plate inadvertently touched. At first glimpse, this reflex seems to be the "simplest possible" response in that it appears generated by an causal chain

of events leading from a stimulus to a motor reaction, and represented, in technical terms, by a ►feedforward system. However, while there are true feedforward reflexes (e.g., the ►vestibulo-ocular reflex), in which the motor response (output) does not have a feedback effect on the stimulus (input), things usually are a bit more complicated. Many reflexes have a feedback effect, such that the motor (or other) response influences the stimulus. For instance, the withdrawal and scratch reflexes eliminate the original stimulus, thereby reverting the organism to the initial non-stimulated situation. Thus, for proper evaluation of many reflexes, the environment and its relation to the body must be taken into account. This latter factor may also force the withdrawal reflex to include more complicated actions. For instance, if during bipedal quiet upright stance, a human being is hit by a noxious stimulus to one foot, he or she will withdraw the injured leg by flexing the leg joints (►flexion reflex); but in order to secure upright stance and equilibrium, the extensor muscles of the contralateral leg must be activated (crossed extension reflex) so that the body mass can be shifted to the contralateral side. Finally, and most importantly, even the "simple" withdrawal reflex depends on the context. For example, during walking, a human may withdraw (flex) his swinging leg a bit further when the foot is hit by a noxious stimulus, but withdrawal of the stance leg would be counterproductive. This implies that *reflexes must be, and are, context-dependent in that their magnitude and at times their sign (excitatory or inhibitory) can be modulated, for example as a function of the phase of the locomotor cycle*.

Stretch Reflex

Feedback action is also exerted by the so-called ►stretch reflex. When a physician uses his reflex hammer to hit, say, the Achilles tendon, the calf muscles contract after some short delay (in this narrow paradigm, the reflex is also called "tendon reflex"). What happens here is that the hammer indents the tendon and thereby slightly and transiently stretches the attached (calf) muscle fibers (►Muscle; ►Skeletal muscle architecture). Dispersed among these muscle fibers are ►muscle spindles, sensory receptors, which are excited by the stretch. The excitation is conveyed to the spinal cord by afferent nerve fibers that innervate the sensory receptors of the muscle spindles, where it activates skeleto-►motoneurons that in turn activate muscle fibers to contract. Note that the stretch stimulus is, at least partially, counteracted by the reflex contraction. It thus looks as if the reflex would serve to control muscle length by keeping it fairly constant.

The notion of "►control" resonates with that of ►feedback systems conceived to regulate the actual value of a control variable so as to keep it close to some *set value* or *reference value*. Regulation is often achieved by negative feedback systems (►Negative feedback control), which are capable of suppressing effects of disturbances. An inanimate example is the thermostatic control of room temperature by a heating or air conditioning system, and a biological example is the regulation of core temperature in warm-blooded animals. Other output variables can be made to change with time and, if these changes are also effected by negative feedback systems for the sake of disturbance suppression, the control process is called a ►servomechanism (see ►Computational motor control). An inanimate example is power steering in cars. A biological example is, again, the stretch reflex. As a matter of fact, skeleto-motoneurons receive inputs other than those from muscle spindles. After all, muscles should not just be kept at approximately constant length, but shorten and lengthen in movements of different sorts. There must therefore be time-variable reference signals that are handled by the muscle stretch reflex to yield the output. However, the situation is a bit more complicated in the case of the stretch reflex (►Feedback control of movement).

Multiple-Loop Feedback Systems

Most often, several loops are meshed to control single or several variables, which in turn may act on single or several controllers. Indeed, even a closer look at the muscle stretch reflex reveals a complicated picture.

Firstly, the sensory fibers emanating from muscle spindles in a particular muscle exert actions on motoneurons other than those innervating the muscle of origin. Conversely, motoneurons innervating a particular muscle receive convergent inputs from spindle fibers originating in different muscles (e.g., [16]). This is the structure of a multiple input-multiple output system, which couples muscle activities via sensory feedback.

Secondly, muscle contraction is regulated by more than one type of feedback system. For simplicity, just one more system is mentioned here. In addition to muscle spindles, there are other receptors in the muscle, among which so-called ►Golgi tendon organs play an important role. These receptors lie at the transition from muscle to tendon fibers and are stretched and excited whenever the muscle fibers produce force. Their afferent nerve fibers exert widely divergent reflex effects, via ►interneurons, on many different motoneuron pools, such that the sign and distribution of these effects depend on the instantaneous motor task. Under rest conditions, the nerve fibers emanating from Golgi tendon organs have inhibitory effects (via inhibitory interneurons) on the motoneurons of their muscles of origin (particularly extensors), so that increases in muscle force reduce motoneuron activation. This would constitute another negative feedback circuit, but with muscle force being the controlled variable. It is still not

clear why two systems based on muscle spindles and Golgi tendon organs are needed to control muscle contraction [17]. This picture is still very simplified and needs qualification. An important one is task-dependency based on modulation of reflex magnitude and sign. For instance, during the stance phase of normal walking (e.g., in cats), sensory afferents from Golgi tendon organs in hindlimb extensor muscles exert not inhibitory but excitatory effects on extensor motoneurons, thus inverting the sign from rest and creating a positive feedback system [18,19], with its own problems of stability [20].

Complexity of Reflexes

Today, the term "reflex" has lost its original connotation of simplicity and stereotypy, except for a few examples, such as the artificial tendon reflex. There are several major reasons that make reflexes complex.

- *Composition*. Today, the notion of "reflex" subsumes complicated sequences of events, such as the scratch reflex of the cat or dog, or the frog's wiping reflex [1,21–23]. The wiping, scratch and similar reflexes are intricate behaviors involving sequences of postural, goal-oriented and rhythmic components triggered by sensory input.
- *Modulation*. Reflexes are not stereotyped and hard-wired, as is often maintained even today, but flexible and modifiable. Firstly, reflexes are task- and context-dependent. Examples have been given above. Secondly, the magnitude and sign of reflexes often vary throughout a movement, e.g., during locomotion (e.g., [24]).
- *Sensory-motor transformations*. The complex effects of sensory inputs on muscle activities via skeleto-motoneurons involve transformations, of two basic kinds:
  - *Spatial transformations*. Vectors of spatially distributed sensory signals are converted into vectors of spatially distributed muscle actions. For example, in the scratch or wiping reflex, the 2D array of cutaneous receptors must be transformed into 3D space of limb movement [23].
  - ►*Kinematic*-to-►*kinetic transformations*. Sensory inputs are, at least to some extent, cast in kinematic terms related to movement, while muscle activities also express kinetic (dynamic) variables related to forces. This requires kinematic-to-kinetic transformations ([23]; see below).
- *Plasticity*. Reflexes are not fixed in time, but subject to "adaptation" and "learning" (see ►Learning and memory; ►Motor learning, and Computational motor control), such as gain adaptation (spinal reflexes: [25]; vestibulo-ocular reflex: [26], ►habituation, ►sensitization and others [27]). Hence, reflexes are very versatile instruments indeed.

Posture and Equilibrium

When an animal performs a movement, it changes the coordinates of body parts in relation to each other and to the surrounding world. It is reasonable to assume that this change should not end up in chaos, but in some other ordered state. To define this order requires references and constraints, in regard to the outside world and the own body.

- *Outside-world references* are needed and used for orientation and ordered movement in the outer world. One important reference is up and down, where ►gravity supplies a convenient potential signal (►Graviception). In fact, gravity is not only a load acting on the body and its appendages, but is also used by the CNS as a dynamic orienting reference for the organization of movement [28]. Some animals may use other fields as reference, such as electromagnetic fields (sunlight, earth magnetism (►Vision; ►Magnetic and electric senses)). For many sea and terrestrial animals, the proper alignment of one of their body axes with the up-down axis is essential for organizing movement. This is particularly evident for terrestrial animals standing and moving on legs with the trunk suspended above the ground. These animals, including humans, need to maintain equilibrium and must therefore have sensory-motor mechanisms to do so.
- *Own-body references* are needed to define a framework, within which one body part (e.g., a limb) moves with respect to the rest of the body. Such a framework is usually called a body schema (see ►Sensory systems). The geometric relation of body parts to each other are subsumed under the rubric of posture. Posture is subject to constraints imposed by anatomical means such as ►joints and ►ligaments.
- *Statics and dynamics*. Whereas the above distinctions are valid for both static and dynamic conditions, dynamic movements pose another important problem resulting from acceleration. For instance, when a limb is accelerated, the generating force is counteracted by a reaction force that affects the rest of the body. There must be neuromuscular mechanisms accounting for these effects in order to prevent disturbances of equilibrium.

Thus, an essential basis and frame for the execution of dynamic movements, whether rhythmic, reflexive or freely goal-oriented, are equilibrium and posture. The two closely related aspects of equilibrium and posture (often simply referred to as posture) may be considered as reference values, which must be maintained against internal or external disturbances [29].

Reference Values

The reference value of equilibrium is, in humans under static conditions, the projection of the body's center of

gravity (►Center of mass (CoM)) onto the supporting surface defined as the area of contact of the feet or other body parts with the ground. Reference values of posture are the positions of certain body segments, e.g., the arm, leg, trunk or head. Dynamic movements of some body parts interfere with these reference values, and appropriate compensations must therefore be pre-programmed in parallel with them. This ►anticipatory compensation, though highly significant, is often not easily recognizable. Massion [29] wrote that "in fact, the motor act might be compared to an iceberg, the apparent being the movement and the hidden part, which is often the most important, being the maintenance of reference values" (p. 36). Such anticipatory compensatory adjustments are generated in an open-loop (feedforward) fashion in parallel with the movement command.

Learning Anticipatory Adjustments

Such anticipatory adjustments are mostly learned from experience, many of them in early childhood. Apparently, the postural disturbance is first corrected for in a feedback mode which is then transformed into a feedforward mode by modification of some as yet unknown adaptive network building up an internal representation of the disturbance to be minimized or the control signal used to cancel it [29].

Free Goal-Oriented Movements

There is a class of movements that appear freer and less restricted than reflexes and locomotion and typically include reaching, grasping and object manipulation. Still, they may make use of reflexes and CPGs as subsidiary devices. And, as a matter of fact, they require postural adjustments. These skilled forearm movements may have their evolutionary precursors in food-handling behavior, dating back to early tetrapods [30], and are expressed in mammals (e.g., cats) in precision walking on complex ground, where accurate foot placement is of essence, and in arboreal locomotion of monkeys, which requires precise reaching for, and grasping of, tree branches [31]. They usually require excellent visuomotor coordination at cerebro-cortical level (►Viscomotor integration).

Many of the processes involved in organizing free goal-oriented reaching/grasping movements can be inferred from one's insight, experience and common sense. Others, however, must be hypothesized from a careful analysis of human and animal movements, often using conceptual frameworks borrowed from robotics and computational motor control [32,33].

For the purpose of discussion, suppose a monkey is hungry and in search for food. He moves close to an orange, tennisball-sized object. What neural processes need to take place to make the monkey reach out and successfully grasp the object? The following is a conceptual account that does not imply that the processes are run in a series of distinct steps.

- *Target perception*: Obviously, the object (possible target) must first be noticed and then visually perceived and recognized, in terms of its physical properties (size, shape, color), and location and orientation (►Vision).
- *Evaluation:* Once perceived, the object's physical properties must be evaluated in relation to the monkey's ►attention, drive and motivation, and to ►procedural memories (internal representations) of previous experiences with the present or similar objects.
- *Decision*: Once the object has been recognized as edible, desirable and attainable, a decision must be taken whether or not a movement should be made towards that object.
- *Planning*: If the decision is positive, the reaching/grasping movement must be planned, which involves several sub-processes, some of which take place in the posterior parietal cortex and premotor cortex [34,35].
- *Sensory-motor transformations*.
- *Selection processes*: A number of selections must be made, initially as reasonable guesses in a predictive feedforward mode, based on previous experience:
  - *Particular among equivalent motor acts*. Since there are many ways of moving the hand to a target, one among the possible ways must be selected.
  - *Adequate postural adjustments*. By intersegmental mechanical interactions, movement of the arm alters the equilibrium conditions of the whole body, which requires the selection of adequate compensatory postural adjustments executed in anticipation of, and in parallel with, the arm movement.
  - ►*Kinematic* and ►*kinetic parameters*. Reaching/grasping requires anticipatory, initially tentative, parameter settings based on internal representations of the object and on ►internal models of the own motor apparatus.
  - *Grip force*. Before contact, grip forces must be selected tentatively, small enough so as not to squeeze the object and large enough so as not to drop it.
  - *Expected feedback signals* must be estimated, using internal models, in order to be able to compare them with the actual feedback generated during the motor act.
- *Execution*: The desired hand path thus planned must be transformed into appropriate muscle activation patterns by some poorly understood implementation process composed of many sub-processes involving essentially the entire neuraxis.

- *Sensory update*: During the ongoing movement, the central selections listed above are updated by sensory feedback from various sensory systems, including visual and cutaneous receptors and proprioceptors. The sensory feedback serves for:
  - *Fast error correction*.
  - *Triggering of successive steps* in the movement sequence.
  - *Revision and updating of the internal model* of body and limb [32,36].
- *Memory*: The role of memory systems in the above processes cannot be overestimated. In fact, they dynamically interface sensory systems with motor commands. In addition to providing the basis for ►motor learning (see below), memory systems serve to retrieve pertinent object properties based on visual, haptic or olfactory information, identification of task features and the initial state of the skeleto-motor system and of sensory events during task progress [37].

Degrees of Freedom and Constraints

The diversity, speed, accuracy and elegance of animal movements provide the overwhelming impression of freedom. However, these qualities can be fully appreciated only when due consideration is given to the delicate interplays between freedom and its constraints, which give rise to problems as well as to solutions.

Although musculo-skeletal assemblies may vary widely, their basic structures appear to be more consistent than body shape itself. Still, these elements have adapted by specializing to the particular demands of particular organisms. While these specifications open certain options to an organism, they also constrain it. Internal constraints have a mechanical component in that the peripheral instruments or tools that an organism uses to move not only enable movement, but also limit its extent, speed etc., by their specific properties. These also have to be taken into account by the nervous system when controlling and thereby using these tools [38].

Problems and Constraints

Moving organisms meet many problems and constraints, which, on the one hand, arise in the organism's environment and, on the other, in its internal structure.

External Problems and Constraints

External problems and constraints arise from properties of the world, in which the organism lives and moves. The main properties are:

- *Mechanics*. Movement in the external world is subject to its mechanical properties, the most important ones being (►Classical mechanics; ►Mechanics):
  - *Newtonian mechanics*, defining the movements of bodies in space and including *inertia* and *gravity*. Gravity is, however, of different importance in different habitats.
  - *Material nature of habitat(s)*. Movements meet with different resistances and dynamics in gaseous (air), liquid (water), or solid (soil) media and have to be adequately adjusted and controlled.

Internal Problems and Constraints

Internal problems and constraints arise from the very means that have been developed by organisms to move under conditions on earth. The materials used, and their combinations, could not, and cannot, be chosen entirely freely. Skeletons (►Bone), ►joints, ►articular cartilages, capsules, ►ligaments, ►tendons and ►muscles have properties that, on the one hand, provide opportunities for movement, but on the other hand impose constraints (e.g., [39,40]. Opening new opportunities by solving one problem may in parallel open new problems calling for new solutions. In the end, the solutions must and will be provided by the nervous system that controls the actions of muscles and, in so doing, must take into account the properties of its peripheral instruments in addition to those of the external world [38]. It comes as no surprise that ►proprioception (see ►Sensory systems), in particular, appears well suited to contribute to the solution of problems resulting from the mechanics of the musculo-skeletal system. It has been proposed [17,38] that proprioception contributes to: (i) ►linearization of (correction for) nonlinear muscle properties; (ii) compensation for a muscle's lever-arm variations at joints; (iii) correction of interjoint interaction effects (see below).

Degrees of Freedom

The vertebrate skeleton immediately unveils the fundamental principles of construction and the potentials afforded. It is a multi-segmented structure made up of hundreds of bones linked at joints. This construction principle should provide for a multitude of options for moving the segments relative to each other and through space. The options are commonly referred to as "degrees of freedom" (DOFs).

Degrees of freedom (DOFs) are the number of variables (coordinates) needed to describe a body's motion in space [41,42]. The DOF of a system of rigid segments is obtained by the general relationship:

$$\mathrm{DOC} = (\text{number of generalized coordinates}) - (\text{number of constraints})$$

The DOFs can change during a motor act, as easily seen when a human being lands from a jump. In the sagittal plane, the number of DOFs decreases by 2 when the toes make contact with the ground and by 1 more when the sole is flat on the ground. In vertical jumping, this sequence is reversed, with the number of DOFs increasing [42].

Bernstein's Problem

Upon closer examination, the multi-segmented skeleton poses serious problems (see ►Coordination).

Dependent upon the type of joint, the distal segment (bone) can be moved in up to three DOFs with respect to the proximal segment. For example, in a ball-and-socket joint, such as the human shoulder joint, there are two dimensions for, say, extension-flexion and abduction-adduction, and one for rotation. This allows the humerus to be aimed at any point in almost half a sphere. Assembling bones into limbs with several joints increases the number of DOFs. This leads to the effect that, for instance, some desired position of the index finger in external 3D space could principally be realized by an infinite number of different combinations of joint angles. This problem arises whenever the combined number of directions, into which joints of multi-joint limbs can move, exceeds the three-dimensionality of external space. For example, the position of the hand (wrist) can be specified by three coordinates in external space, but it is defined by four joint angles (elevation and yaw of both the shoulder and the elbow; [43]). This ►redundancy of degrees of freedom (see ►Coordination) holds for many postures and movements. Hence, theoretically, there should be an infinite number of possible movement trajectories to reach the same target. Nonetheless, most arm and hand movements do not take advantage of the theoretical redundancy afforded, but are performed in fairly stereotyped manners, suggesting that there must be solutions for reducing the redundancy. The problem of providing such solutions has been clearly highlighted by Bernstein [44].

The query for solutions to ►Bernstein's problem has to be conducted at various levels. A rough distinction can be made between mechanical constraints deriving from specifics of the musculo-skeletal system itself and the nervous system dealing with the peripheral system.

Constraining Freedom

Consider the cat hindlimb with its three large joints: hip, knee and ankle joint. If, in a first approximation, each of these joints is assumed to be a hinge joint of one DOF, the limb would be a 3-DOF assembly of segments, allowing for 2D movement of the limb endpoint in the parasagittal plane. Hence, despite the possibility of movements about three joints, the end-point movements are confined to two dimensions, implying a reduction in DOFs. How is this implemented? One possibility is to restrict the independence of movements in the different joints, i.e., to tightly couple changes in the three joint angles. This is indeed what happens during both passive and active hindlimb movements. That is, the relationship among the three joint angles shows a planar or 2D co-variation over a large range of limb positions [23,45].

►*Biomechanics*. In the passive limb, the mechanism underlying the joint-angle coupling is presumably of biomechanical nature, as indicated by post-mortem assessment. For example, biarticular muscles spanning two joints as well as passive structures such as joint shapes, joint capsules and ligaments may play a role in coupling different joints. During movements, inertial intersegmental interaction forces (see below) may contribute to couple the movements of limb segments [45].

Neural Control Mechanisms. In addition to passive biomechanical factors, neural control mechanisms may come into play. Awake cats trained to maintain quiet upright stance on a tilting support platform also show a linear co-variation of hindlimb joint angles. This pattern of joint-angle covariance is, however, different from that in the passive limb. Firstly, the coupling is tighter, suggesting that neural control may actually further reduce any independent motion in the individual limb segments. Secondly, the co-variance plane has a different orientation in 3D joint space, due mostly to a sign inversion of the relationship between the hip and ankle angles [23,45]. The difference between the passive state and the active state shows that the CNS should determine the particular form of joint angle co-variation (the orientation of the plane in joint space). Similarly, in human reaching movements, segment excursions are coupled, and so are joint torques [46].

Exploiting Freedom

While there are mechanical and neural mechanisms that constrain the freedom of movement, the redundancy in DOFs also has advantages. Indeed, it allows for flexibility, stability and accuracy. Again taking the example of fingertip localization, arm orientation at the shoulder joint is usually less precise than fingertip location, such that more distal joints can compensate for errors committed by more proximal joints [47]. Therefore, redundancy can also be considered a virtue to be exploited rather than a problem that should be solved. One method to exploit the redundancy is to represent all the possible solutions by means of a multiple controller [48]. Another approach is to exploit redundancy in order to minimize the variance by means of optimal control [49]. Yet another recent approach has hypothesized a "principle of abundance," stating that no DOF is ever eliminated or frozen, but instead all DOFs always participate in all the tasks, thereby assuring both flexibility and stability of performance ([50,51]; see also ►Coordination).

Representations of Space

Since movements take place in space and time, a basic requirement for any meaningful action based on perception and orientation is the construction by

the CNS of spatial frames of reference and their transformations (►Sensory Systems). This involves:

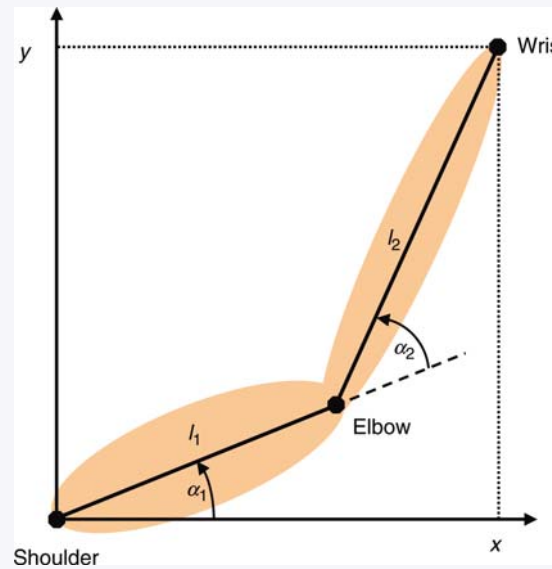
- *Spatial orientation,* depending on the perception of the position, orientation and motion of external objects and that of an animal's own body parts within reference frames. There is more than one frame that the nervous system makes use of. The particular subjective reference frame that an observer takes as stationary is called "rest frame." It is selected according to availability of sensory cues, convenience and circumstances. For example, on earth, astronauts choose a rest frame based primarily on gravity and visual scene polarity, while in microgravity (in a spaceship), the rest frame is based on visual scene polarity cues from the spaceship interiors and other crew members as well as on the internal head and body *z*-axes (ideotropic vector). It appears as if astronauts switch between rest frames depending on variables such as the task being performed [52].
- *Multiple representations of sensory spaces and muscle spaces*. The representations of the position, orientation and motion of external objects and those of an animal's own body parts are based on different sensory signals, which are coded in different frames of reference. For instance, reaching and grasping require the localization of the object in peripersonal space as well as the localization of the initial position of arm and hand. Object location is coded predominantly by ►vision (and/or hearing audition), arm/hand position by vision and/or proprioception, which each possesses its own reference frame (see ►Sensory systems). Finally, spatial aspects of muscle actions are coded in their own frame. All this calls for:
- *Sensory-motor transformations* characterized by several aspects [34,53,54]:
  - *Multi-sensory integration (►Mutimodal integration)*: Signals from different senses must be integrated and thus converge onto common neurons. This also applies to other senses such as hearing (for sound-emitting objects) and touch (for tactile shape perception after contact with the object).
  - *Construction of a unified sensory frame of reference*. The different sensory reference frames must be put in register and thus unified; for arm (►Voluntary movement) and eye movements (►Neural control of eye movement) this appears to be an eye-centered (oculocentric) frame established in the posterior parietal cortex.
  - *Sensory-motor coordinate transformation*: The sensory coordinate frame must be transformed into the motor frame.

Kinematics

The spatio-temporal representations that the nervous system needs have several aspects and dimensions. The first important distinction to be made is between kinematic and kinetic (dynamic) descriptions, which nonetheless are closely related. The kinematic description simply deals with the spatio-temporal paths or trajectories of objects (head, eyes, limbs etc.). For this purpose, the kinematic description requires reference frames or coordinate systems to relate a moving object to for quantification. The dynamic aspect deals with the forces involved in, and required to drive, movements. Since forces are spatially directed and hence vectors, their description, too, involves spatial coordinate systems. Another connection between kinematic and dynamic descriptions is Newtonian dynamics.

Extrinsic and Intrinsic Coordinate Systems

As exemplified in Fig. 1, the position (and movement) of the hand (wrist) can be described with respect to two coordinate systems. For simplicity, the right arm is here supposed to be held in a horizontal plane, and the arm is viewed from above (direction of the *z*-axis). The hand position can be given in terms of an extrinsic, rectangular Cartesian coordinate system, where the *x*-axis is in a parafrontal and the *y*-axis in a parasagittal plane through the right shoulder. (Alternatively, it could be described in *polar coordinates* as the direction and distance of the hand from the shoulder.) A second



Motor Control. Figure 1 Representation of hand (wrist) position in two frames of reference. For simplicity, the right arm is supposed to be held in a horizontal plane, and the arm is viewed from above (direction of the *z*-axis). The hand position can then be given in terms of a rectangular Cartesian coordinate system, where the *x*-axis is in a parafrontal plane through the shoulders, and the *y*-axis in a parasagittal plane through the right shoulder, or in terms of segment lengths, l_1 and l_2, and joint angles, a_1 and a_2.

way of determining hand position with respect to the shoulder is by segment lengths, l_1 and l_2, and joint angles, a_1 and a_2, establishing an intrinsic system based on body geometry (see ►Arm trajectory formation).

Coordinate Transformations

The existence of different coordinate systems requires the nervous system to continuously transform the positions of limbs and their trajectories during movements from one system into the other. For example, consider the transformation from joint angles to Cartesian coordinates (Fig. 1), which is given by the trigonometric relations:

$$x = l_1 cos(a_1) + l_2 cos(a_1 + a_2) \qquad (1a)$$

$$y = l_1 sin(a_1) + l_2 sin(a_1 + a_2). \qquad (1b)$$

This transformation is referred to as forward or direct kinematics [55]. It is called forward because it describes the natural causal flow of events from muscle activations, which determine muscle lengths, which determine joint angles, which finally determine hand position in relation to the body.

There is also the *inverse transformation* from extrinsic to intrinsic coordinates, which is obtained by solving (1a and b) for the joint angles a_1 and a_2, each of which will be a function of both x and y [55]. This transformation is called *inverse kinematics*. At first glimpse, it does not appear to have a natural counterpart as does the forward kinematics. However, it has been suggested that, at the highest stages of movement planning, the final hand position or the movement towards it is planned in extrinsic coordinates, x and y [23], from which the related set of joint angles would have to be obtained by an inverse transformation (however, there are other suggestions; see below). It merits emphasis that, in this case, there is a unique solution only because we consider the relation between two extrinsic and two intrinsic coordinates in a plane. In 3D space, three external coordinates and four joint angles are needed to specify hand position, leading to the well-known redundancy problem without a unique solution, as discussed above.

Another important implication can also be drawn from (1a,b). Any neuronal network to implement one or the other of the above transformations would have to incorporate neural elements, which would receive convergent input signals from the independent variables. This requirement may be one of the reasons for the widespread existence of *convergence* of many inputs onto many central neurons. Conversely, the inputs may affect more than one output, which in neural terms accounts for *divergence* of neural signals to affect more than one output. In general, of course, transformations between coordinate systems involve many more than just sets of two variables as in Fig. 1; they therefore become exquisitely complex.

Algorithms for Inverse Transformations

In principle, there are several possibilities of performing inverse transformations, as illustrated here for inverse kinematics [55].

- *Computer program*: In robotics, inverse kinematics can be solved by a computer program. Obviously, the CNS cannot do it exactly this way, although the term "program" is being used in the field of biological motor control in a loose analogous way. Its use may be misleading, though, and has been criticized [56].
- *Lookup table*: Another possibility is that the CNS could use is a lookup table, which contains entries associating particular pairs (x,y) and (a_1,a_2). In general, these tables can come as "computational maps" [57,58], which map values of a particular sensory and/or motor variable along at least one spatial dimension of nervous tissue. Such maps indeed exist in several places in the CNS. For example, the ►superior colliculus (tectum opticum in lower vertebrates) contains maps of spatial sensory information as well as motor maps of the amplitude and direction of orienting movements of the eye (gaze), head, pinna and vibrissae [59–61]. These maps are dynamically maintained or altered according to experience during development, but also in adults. Sensory and motor maps have to be aligned, with early visual experience being highly important in doing so [59].
- *Internal model*: The equations describing the inverse kinematics could also be solved by special analog circuits representing an internal model. For limb and trunk motor control, such models would certainly be much more complicated than that which has been considered to be at work in certain ► eye movements, because as compared to the latter systems, the former ones have to deal with varying loads including those resulting from gravity. Yet, internal models probably exist, at least for certain purposes [33,36,62–64].

Kinetics (Dynamics)

The kinetic (dynamic) aspect of movement organization results from the fact that the body or its parts have visco-elastic and inertial properties and are suspended in a gravitational field (albeit to very different extents in different species living in different habitats). Hence, their movement requires forces in order to counteract visco-elastic forces or achieve acceleration against inertial and gravitational forces. The description in terms of forces or torques at joints is by kinetic (or dynamic) variables [55].

Muscles and Intersegmental Interactions

However, dynamics play a role not only in the interactions of the body and its segments with the environment, but also in the interactions between the different body

segments themselves. Since body segments are movably coupled at the joints, motion of one segment acts on those of other segments. This implies that any individual muscle not only accelerates the segments that it originates from and inserts on, but also remote segments via intersegmental dynamic interactions, which in addition depend in complicated ways on the joint angles and angular velocities [38]. These interactions in turn yield new insights into the functions of individual muscles and into how many muscles must be coordinated in order to serve movement goals (e.g., [65]). Consider a few examples.

Swinging a Leg during Walking and Running

During human walking, stance and swing phases follow each other in each leg. From a naive standpoint, we might assume that, in order to lift and clear the swing leg from the ground and move it forward, all joints should be flexed, with the flexions to be initiated by concomitant activation of hip, knee and ankle flexor muscles. However, simple mechanics suggests another possibility. If the hip flexors alone were activated, then the thigh would be accelerated forward relative to the trunk and, due to inertia, the shank would lag behind, resulting in (passive) knee flexion. This indeed plays a major role in the hindlimb of cats during gallop, where knee flexion is sustained by inertial torques related to linear hip and angular leg acceleration, rendering activation of the knee-flexor semitendinosus muscle unnecessary. By contrast, at lower gait speeds, this muscle shows two bursts of activity during the movement cycle [66]. Conversely, the extension of the knee at the end of the swing phase is assisted by a whip-like forward movement of the lower leg while the upper limb is already decelerating. In human walking, there is only one problem concerning the ankle. If joint motions during the initial swing phase were sustained by hip flexor activation only, the foot would also remain behind due to its inertia, thus extending the ankle. This would be too little to clear the foot from and above the ground during swing. Hence, ankle dorsi-flexor activity (mainly in the tibialis anterior muscle) is also required. This is evident in patients suffering from paralysis of the nerve innervating the tibialis anterior, which leads to dragging of the foot in the swinging leg. In any case, intersegmental mechanics clearly contribute to dynamic motor acts, which must be taken into account by the nervous system in organizing the coordinated muscle activations.

Paw Shake

During the cat's oscillatory paw shake elicited by an irritant stimulus to the paw, the hip, knee and ankle joints undergo rhythmic angle changes at ca. 11–12 Hz, with a proximo-to-distal increase in amplitude. At the ankle joint, interactive and gravitational torques do not contribute significantly to net joint torques, whereas at the knee joint they do. Here, torques related to the angular acceleration of the paw dominate over interactive contributions to the knee torque. At the ankle, the torques produced by ankle muscle activation account for much of the net joint torque and thus directly determine the paw segment dynamics. In contrast, knee muscles produce torques, which rather compensate for interactive torques, thus controlling intersegmental dynamics between paw and shank [67].

Pedaling

A deeper insight into muscle functions during complex motor acts is provided by dynamical simulations of seated pedaling of humans. Seated pedaling is mechanically simpler than walking because it has fewer mechanical DOFs, the hips being essentially stationary and the foot path being constrained by the pedal trajectory [65]. The important points can be summarized as follows.

(i) The intersegmental interactions depend in a complicated way on joint angles and velocities, and the dynamics are different at different joints. If these interactions were to be described by sets of dynamic equations, different sets of equations would have to be set up for different situations. (ii) To understand the role of muscles in the above processes, deriving their function from their anatomical position, knowing just their origins and insertions alone, is insufficient. (iii) In fact, a muscle's function depends on the configuration of the body and its parts and on their interaction with external objects such as the ground or obstacles; it can thus vary with motor task and within a motor task [42]. (iv) Since muscle activations depend on peripheral circumstances, in order to organize their activations properly, the CNS needs information on these circumstances, that is, sensory feedback [38].

Forward Dynamics

Consider the causal sequence of events in the musculoskeletal periphery, say an arm, referred to as *forward or direct dynamics* [76]. In this system, motoneuron activity provides the inputs, and body motions are the outputs. Thus, if there are m muscles, their inputs are reflected in the electromyographic signals, $EMG^1 \ldots EMG^m$ (►Electromyography (EMG)). These activation signals are transformed into the set of muscle forces, $F^1 \ldots F^m$. These in turn are converted, depending on musculo-tendon dynamics and moment arms $R(F's)$, into a set of muscle torques at n joints, $T_1^{mus} \ldots T_n^{mus}$. These torques finally are transformed into sets of joint angles $\Theta_1 \ldots \Theta_n$, their velocities and accelerations, which ultimately result in the motion of the limb endpoint. Note that there are some ►feedback loops because, for example, joint angles determine muscle lengths and these in turn co-determine muscle forces. On the whole, however, this is a feedforward scheme,

which indicates that the input signals should be precisely tuned to achieve the correct output.

Inverse Dynamics

It has been suggested that the CNS plans reaching/grasping movements in terms of extrinsic coordinates, say of hand position and/or trajectory in extrapersonal space (e.g., [23]). Although other suggestions have been put forward (e.g., planning in terms of kinetic variables such as joint torques; [46]), it is instructive to consider the consequences of the kinematic model. The CNS must perform a number of transformations in order to provide the appropriate muscle activation patterns. The sequence of transformations is as follows:

Desired trajectory (*assumed to be coded in kinematic extrinsic coordinates*) → *joint angles* → *joint torques* → *muscle forces* → *muscle activation patterns*.

If the CNS used this approach, it would have to take into account the forward dynamics discussed in the preceding section by "inverting" them. That is, in order to achieve the desired movement trajectory, the planned trajectory must be implemented by a process compensating for the forward dynamics described above. Thus, from the desired end-point movement in extrinsic coordinates, intrinsic joint angles (muscle lengths) and their first two time derivatives must be derived via an "*inverse kinematics*" algorithm. Through an "*inverse dynamics*" algorithm, joint angles and their first two time derivatives would determine the net muscle torques needed to achieve them, and subsequently the muscle forces needed to generate the torques, and then the excitations needed to generate the forces. The desired excitations thus computed from the desired trajectory could serve as the template of motoneuronal activations.

However, this approach would raise formidable problems. The computation of such inverse dynamics is complex and often requires non-unique transformations. For example, individual muscle forces are not uniquely determined by net muscle torques, i.e., the torques can be achieved with many combinations of muscle forces. Also, the neuromuscular periphery has complex nonlinear properties. Furthermore, the different segments in multi-joint limbs exert mutual interaction forces on each other (intersegmental interactions). These complexities results in myriads of equations of motion, all of which would be task-dependent. In order to solve the problems, then, the CNS would have to "know" these equations as well as precise estimates of the initial and boundary conditions and parameters involved, such as the masses, locations of the centers of mass, principal axes of inertia, moments of inertia (see [68–70]). Moreover, the computation itself would have to be extremely accurate because even small errors, or small mis-estimates of initial and boundary conditions, would lead to large movement errors. Because of the complex computational capacity required, the inverse-dynamics computations have usually been thought to be performed, if at all, by the cerebral cortex or cerebellum, although the vertebrate spinal cord might also contribute its share [23]. Still, completely precise inverse-dynamics computations do not appear feasible.

The above considerations are based on the presumption that the inverse-dynamics calculations are performed in a feedforward (open-loop) fashion, i.e., without the CNS receiving feedback on the results of its actions, which could be used to correct for errors. Incorporating such feedback would alleviate some of the problems. However, this would raise new problems. First, in the neuro-muscular system, sensory feedback occurs with considerable delays (for visual or proprioceptive processing). Therefore, fast (ballistic) movements, precisely those movements posing the most severe dynamic problems, would have to do without it, at least initially. (However, CNS-internal feedback based on an ►efference copy of the motor command and sensory information as well as an internal model of peripheral dynamics could make early corrections to the unfolding motor plan; [62]). Second, the gains in feedback systems are usually low because high gains with long delays run the risk of instability (e.g., [71,72]). Perhaps this is one reason for ballistic movements being more imprecise than slow movements, unless well learned.

Motor Control Schemes

Equilibrium-Point Hypothesis

A concept purported to dispose of all the dynamic issues and thus provide a simpler solution than the inverse-dynamics approach is the so-called ►equilibrium-point hypothesis (EPH) [21,68,69,73,74]. The basic ideas are:

- Passive and active muscles have (nonlinear) spring-like properties (like rubber bands).
- At each moment of time, the relative levels of activity in the sets of agonist and antagonist muscles and the resulting muscle forces (or joint torques) specify a virtual position of each joint, at which all the torques, including those deriving from external loads, are in equilibrium, i.e., the net torque is zero.
- Following its dynamics, the limb moves to this equilibrium position unless some obstacle interferes with it.

The important point is the concept of the virtual equilibrium position because this is the "attractor" pulling on the limb. Movement comes about by a smooth and continuous change in virtual equilibrium position, which has to be specified by the CNS in terms of appropriate muscle activation patterns. Once the brain has acquired the ability to represent and control equilibrium positions, it can master movements as temporal

sequences of such positions [68]. The adherents of this hypothesis claim that the inverse-dynamics problem is simplified (or even obviated) because explicit representations of inertial, viscous, gravitational and other opposing forces are unnecessary.

One of the merits of this hypothesis is that it has stimulated attempts at taking into account real neuronal networks. This has been tried by both groups of its major proponents [73,75]. Feldman et al. [73] original approach is more explicit in dealing with particular networks including the stretch reflex, ►reciprocal inhibition and ►recurrent inhibition. However, it suffers from the weaknesses outlined above as to sensory feedback [71].

Adaptable Internal Models

Another solution is to revert to the inverse model concept, but conceive of these models as *adaptable.* Such a model would then represent some properties of the musculo-skeletal periphery, and well so, by adapting to them through learning (see ►Computational Motor Control; ►Adaptive control). In this scheme, sensory feedback (e.g., vision and proprioception) attains a novel significance by being used to update internal models before the event rather than correcting for movement errors in real time.

Depending on the requirements, inverse models can also be combined with forward models that represent the forward dynamics of the "plant" (i.e., the physical system to be controlled; see ►Control). If plant and forward model are fed with the same motor command, the difference in outputs will tell how well the model represents the plant. This output can be used in various ways, one way being as an error signal teaching the model to adapt optimally. The keywords then are adaptation and learning.

Neural Networks

The distinction between kinematic and dynamic aspects of movement control can be avoided in neural network models. In such networks, kinematics could be encoded by sensory receptors at the input level and dynamics by effectors at the output level, so that kinematics or dynamics, or both, or neither, are encoded anywhere in the brain [76].

Plasticity and Sensory-Motor Learning

The CNS must adapt its actions to changing conditions of its environment, including the body, and learn from their effects, at very different levels of organization and time scales. This requires its neuronal networks to be not rigid, but plastic. The terms plasticity, learning and memory are not precisely defined, but are commonly applied to a diversity of processes. In a narrow ►behavioral sense, motor learning implies the acquisition of new behaviors or skills by practice [77]. But the term is often used with wider connotations including processes and mechanisms at much lower levels of complexity (►Learning and memory; ►Motor learning). The structures subject to plasticity are manifold and distributed throughout the neuraxis, even extending to the neuromuscular junction [78].

There are a number of different processes and mechanisms that contribute to learning (in the wide sense), such as axonal sprouting or pruning and modifiability of synaptic efficacy. The establishment of the proper neuronal connections and topographical maps at some critical stage of ontogenetic development in part relies on such processes, as does the adaptive change in such maps in adult life. Many of the basic events underlying learning, information storage (memory) and retrieval are thought to take place at a molecular level, in particular at ►synapses. Synaptic transmission is vastly flexible or plastic, at time scales ranging from the order of milliseconds to probably life-long.

Acknowledgment

Dedicated to the outstanding scientist, academic teacher and friend Rainer F. Greger (3.1.1946–16.12.2007). I am grateful for encouragement and suggestions for improvement to Marc D. Binder, Amir Karniel, and Douglas G. Stuart."

References

1. Gelfand IM, Orlovsky GN, Shik ML (1988) Locomotion and scratching in tetrapods. In: Cohen AH, Rossignol S, Grillner S (eds) Neural control of rhythmic movements in vertebrates. Wiley, New York, pp 167–199
2. Arshavsky YI (2003) Cellular and network properties in the functioning of the nervous system: from central pattern generators to cognition. Brain Res Rev 41:229–267
3. Grillner S, Markram H, De Schutter E, Silberberg G, LeBeau FEN (2005) Microcircuits in action – from CPGs to neocortex. Trends Neurosci 28:525–533
4. Pearson KG (1993) Common principles of motor control in vertebrates and invertebrates. Annu Rev Neurosci 16:265–297
5. Stein PSG, Grillner S, Selverston AI, Stuart DG (eds) (1997) Neurons, networks, and motor behavior. MIT, Cambridge (Mass)
6. Smith JC (1997) Integration of cellular and network mechanisms in mammalian oscillatory circuits: insights from the respiratory oscillator. In: Stein PSG, Grillner S, Selverston AI, Stuart DG (eds) Neurons, networks, and motor behavior. MIT, Cambridge (Mass), pp 97–104
7. Ramirez J-M, Tryba AK, Peña F (2004) Pacemaker neurons and neuronal networks: an integrative view. Curr Opin Neurobiol 14:665–674
8. Prochazka A (1996) The fuzzy logic of visuomotor control. Can J Physiol Pharmacol 74:456–462
9. Burke RE (1999) The use of state-dependent modulation of spinal reflexes as a tool to investigate the organization of spinal interneurons. Exp Brain Res 128:263–277

10. Armstrong DM (1988) The supraspinal control of mammalian locomotion. J Physiol (Lond) 405:1–37
11. Garcia-Rill E, Homma Y, Skinner RD (2003) Arousal mechanisms related to posture and locomotion: 1. Descending modulation. Prog Brain Res 143:279–286
12. Grillner S, Georgopoulos AP, Jordan LM (1997) Selection and initiation of motor behavior. In: Stein PGS, Grillner S, Selverston AI, Stuart DG (eds) Neurons, networks, and motor behavior. MIT, Cambridge (Mass), London, pp 3–19
13. Katz PS, Harris-Warris RM (1990) Actions of identified neuromodulatory neurons in a simple motor system. Trends Neurosci 13:367–373
14. Nadim F, Manor Y (2000) The role of short-term synaptic dynamics in motor control. Curr Opin Neurobiol 10:683–690
15. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC (2005) The lower limb flexion reflex in humans. Prog Neurobiol 77:353–395
16. Windhorst U (1996) On the role of recurrent inhibitory feedback in motor control. Prog Neurobiol 49:517–587
17. Stuart DG (1999) The segmental motor system – advances, issues, and possibilities. Prog Brain Res 123:3–28
18. Donelan JM, Pearson KG (2004) Contribution of sensory feedback to ongoing ankle extensor activity during the stance phase of walking. Can J Physiol Pharmacol 82:589–598
19. Duysens J, Clarac F, Cruse H (2000) Load-regulating mechanisms in gait and posture: comparative aspects. Physiol Rev 80:83–133
20. Prochazka A, Gillard D, Bennett DJ (1997) Implications of positive feedback in the control of movement. J Neurophysiol 77:3237–3251
21. Berkinblit MB, Feldman AG, Fukson OI (1986) Adaptability of innate motor patterns and motor control mechanisms. Behav Brain Sci 9:585–638
22. Fukson OI, Berkinblit MB, Feldman AG (1980) The spinal frog takes into account the scheme of its body during the wiping reflex. Science 209:1261–1263
23. Poppele RE, Bosco G (2003) Sophisticated spinal contributions to motor control. Trends Neurosci 26:269–276
24. Zehr EP, Stein RB (1999) What functions do reflexes serve during human locomotion? Prog Neurobiol 58:185–205
25. Wolpaw JR, Tennissen AM (2001) Activity-dependent spinal cord plasticity in health and disease. Annu Rev Neurosci 24:807–843
26. Du Lac S, Raymond JL, Sejnowski TJ, Lisberger SG (1995) Learning and memory in the vestibulo-ocular reflex. Annu Rev Neurosci 18:409–441
27. Hawkins RD, Clark GA, Kandel ER (1987) Cell biological studies of learning in simple vertebrate and invertebrate systems. In: Plum F (ed) Handbook of physiology, Sect. 1: The nervous system, vol V: Higher functions of the brain, Part 1. Am Physiol Soc, Bethesda, pp 25–83
28. Pozzo T, Papaxanthis C, Stapley P, Berthoz A (1998) The sensorimotor and cognitive integration of gravity. Brain Res Brain Res Rev 28:92–101
29. Massion J (1992) Movement, posture and equilibrium: interaction and coordination. Prog Neurobiol 38:35–56
30. Iwaniuk AN, Whishaw IQ (2000) On the origin of skilled forelimb movments. Trends Neurosci 23:372–376
31. Grillner S, Wallín P (2004) Innate versus learned movement – a false dichotomy? Prog Brain Res 143:3–12
32. Ghez C, Hening W, Gordon J (1991) Organization of voluntary movement. Curr Opin Neurobiol 1:664–671
33. Schaal S, Schweighofer N (2005) Computational motor control in humans and robots. Curr Opin Neurobiol 15:1–8
34. Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220
35. Graziano MS, Gross CG (1998) Spatial maps for the control of movement. Curr Opin Neurobiol 8:195–201
36. Baev KV, Shimansky YP (1992) Principles of organization of neural systems controlling automatic movements in animals. Prog Neurobiol 39:45–112
37. Johansson RS, Cole KJ (1992) Sensory-motor coordination during grasping and manipulative actions. Curr Opinion Neurobiol 2:815–823
38. Hasan Z, Stuart DG (1988) Animal solutions to problems of movement control: the role of proprioceptors. Annu Rev Neurosci 11:199–223
39. Alexander RMcN (1981) Mechanics of skeleton and tendons. In: Brooks VB (ed) Handbook of physiology, vol II, Part 1: The nervous system. Amer Physiol Soc, Bethesda, pp 17–42
40. Nigg BM, Herzog W (eds) (1994) Biomechanics of the Musculo-Skeletal System. Wiley, Chichester
41. Shrive NG, Frank CB (1994) Joints. In: Nigg BM, Herzog W (eds) Biomechanics of the musculo-skeletal system. Wiley, Chichester, pp 154–190
42. Zajac FE, Gordon ME (1989) Determining muscle's force and action in multi-articular movement. Exerc Sport Sci Rev 17:187–230
43. Lacquaniti F (1989) Central representations of human limb movement as revealed by studies of drawing and handwriting. Trends Neurosci 12:287–292
44. Bernstein NA (1967) The co-ordination and regulation of movements. Pergamon, London
45. Bosco G, Poppele RE (2001) Proprioception from a spinocerebellar perspective. Physiol Rev 81:539–568
46. Thomas JS, Corcos DM, Hasan Z (2005) Kinematic and kinetic constraints on arm, trunk, and leg segments in target-reaching movements. J Neurophysiol 93:352–364
47. Darling WG, Miller GF (1993) Transformations between visual and kinesthetic coordinate systems in reaches to remembered object locations and orientations. Exp Brain Res 93:534–547
48. Karniel A, Meir R, Inbar GF (2001) Polyhedral mixture of linear experts for many-to-one mapping inversion and multiple controllers. Neurocomputing 37:31–49
49. Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor coordination. Nature Neurosci 5:1226–1235
50. Latash ML, Scholz JP, Schöner G (2002) Motor control strategies revealed in the structure of motor variability. Exerc Sport Sci Rev 30:26–31
51. Scholz JP, Schöner G (1999) The uncontrolled manifold concept: identifying control variables for a functional task. Exp Brain Res 126:289–306
52. Reschke MF, Bloomberg JJ, Harm DL, Paloski WH, Layne C, McDonald V (1998) Posture, locomotion, spatial orientation, and motion sickness as a function of space flight. Brain Res Rev 28:102–117

53. Crawford JD, Medendorp WP, Marotta JJ (2004) Spatial transformations for eye-hand coordination. J Neurophysiol 92:10–19
54. Engel KC, Flanders M, Soechting JF (2002) Oculocentric frames of reference for limb movement. Arch Ital Biol 140:211–219
55. Atkeson CG (1989) Learning arm kinematics and dynamics. Annu Rev Neurosci 12:157–183
56. Alexander GE, DeLong MR, Crutcher MD (1992) Do cortical and basal ganglionic motor areas use "motor programs" to control movement? Behav Brain Sci 15:656–665
57. Knudsen EI, du Lac S, Esterly SD (1987) Computational maps in the brain. Annu Rev Neurosci 10:41–65
58. Nelson ME, Bower JM (1990) Brain maps and parallel computers. Trends Neurosci 13:403–408
59. Knudsen EI (1991) Dynamic space codes in the superior colliculus. Curr Opin Neurobiol 1:628–632
60. Sparks DL (1991) The neural control of orienting eye and head movements. In: Humphrey DR, Freund HJ (eds) Motor control: concepts and issues. Wiley, Chichester New York Brisbane Toronto Singapore, pp 263–275
61. Sparks DL, Mays LE (1990) Signal transformations required for the generation of saccadic eye movements. Annu Rev Neurosci 13:309–336
62. Desmurget M, Grafton S (2000) Forward modeling allows feedback control for fast reaching movements. Trends Cogn Sci 4:423–431
63. Kawato M (1999) Internal models for motor control and trajectory planning. Curr Opin Neurobiol 9:718–727
64. Wolpert DM, Gharhamani Z (2000) Computational principles of movement neuroscience. Nat Neurosci 3:1212–1217
65. Zajac FE, Neptune RR, Kautz SA (2002) Biomechanics and muscle coordination of human walking. Part I: Introduction to concepts, power transfer, dynamics and simulation. Gait Posture 16:215–232
66. Smith JL, Chung SH, Zernicke RF (1993) Gait-related motor patterns and hindlimb kinetics for the cat trot and gallop. Exp Brain Res 94:308–322
67. Smith JL, Zernicke RF (1987) Predictions for neural control based on limb dynamics. Trends Neurosci 10:123–128
68. Hasan Z (1991) Biomechanics and the study of multijoint movements. In: Humphrey DR, Freund HJ (eds) Motor control: concepts and issues. Wiley, Chichester New York Brisbane Toronto Singapore, pp 75–84
69. Bizzi E (1993) Intermediate representations in the formation of arm movements. Curr Opin Neurobiol 3:925–931
70. Bizzi E, Hogan N, Mussa-Ivaldi FA, Giszter S (1992) Does the nervous system use equilibrium-point control to guide single and multiple joint movements? Beh Brain Sci 15:603–613
71. Kawato M, Gomi H (1992) The cerebellum and VOR/OKR learning models. Trends Neurosci 15:445–453
72. Rack PMH (1981) Limitations of somatosensory feedback in control of posture and movement. In: Brooks VB (ed) Handbook of physiology, Sect. 1: The nervous system, Vol 2, Part 1: Motor control. Am Physiol Soc, Bethesda, MD, pp 229–256
73. Feldman AG, Adamovitch SV, Ostry DJ, Flanagan JR (1990) The origin of electromyogram – explanations based on the equilibrium point hypothesis. In: Winters JM, Woo SL-Y (eds) Multiple muscle systems. Springer, Berlin Heidelberg New York, pp 195–213
74. Feldman AG, Latash ML (2005) Testing hypotheses and the advancement of science: recent attempts to falsify the equilibrium point hypothesis. Exp Brain Res 161:91–103
75. Bizzi E, Giszter SF, Loeb E, Mussa-Ivaldi FA, Saltiel P (1995) Modular organization of motor behavior in the frog's spinal cord. Trends Neurosci 18:442–446
76. Soechting JF, Flanders M (1998) Movement planning: Kinematics, dynamics, both or neither? In: Harris L, Jenkin M (eds) Vision and action. Cambridge University Press, New York, pp 352–371
77. Doyen J, Benali H (2005) Reorganization and plasticity in the adult brain during learning of motor skills. Curr Opin Neurobiol 15:161–167
78. Schouenborg J (2004) Learning in sensorimotor circuits. Curr Opin Neurobiol 14:693–697

Motor Control Hierarchy

Definition

The motor systems are organized in both a hierarchical and parallel fashion. For example, cortical motor areas stand above motor neurons in the spinal cord in a hierarchical fashion, and can command lower motor neurons to activate. However, there are multiple routes from cortical and brainstem motor areas to lower motor neurons, also allowing a parallel control. Aspects of motor planning are also hierarchically organized. At the top of the hierarchy seem to be invariant properties of movements that are independent of the particular patterns of muscle activations used to achieve a motor goal.

Motor Control Models

Stan C. A. M. Gielen
Department of Biophysics, Radboud University Nijmegen, Nijmegen, The Netherlands

Definition

The aim of models in motor control is to reproduce experimental data and to make predictions for new experiments, where different models make different predictions so as to discriminate between various models for human movement control. Typically, models have been developed for different levels of motor control: for specific parts of the neuromuscular system as well as for neural feedback and feedforward control mechanisms. For each model, the modeller has to specify (i) the

family of admissible control signals, (ii) the characteristics of the neuromusculo-skeletal model, and (iii) a quantitative definition of task performance.

Characteristics

Introduction

A pointing or reaching movement to a target in three-dimensional space defines a redundant task at the geometric, kinematic and dynamic level of control. An infinite number of possible hand trajectories can be selected for moving the hand to the target, leading to an infinite set of possible arm postures for every hand location in 3D space. In this perspective, it is remarkable that human movements are quite reproducible and that the variability of movements starting from the same beginning position towards the same end position is relatively small. This observation has been considered to reflect some underlying principles, which reduce the number of degrees of freedom.

Several models have been proposed to explain the characteristics of human movements. The aim of these models is not only to see whether they can reproduce the experimental observations, but also to make predictions about movement characteristics for movements in new, complex situations, which have not been studied so far. The use of models to predict the behavior for complex movements is important to test and validate models and to suggest new experiments to discriminate between models.

Kinematics

One of the influential theories in movement control, was the equilibrium-point (EP) hypothesis [1]. This theory assumes that the neuromuscular system has (nonlinear) elastic properties. For a linear spring force F depends on the stiffness K and the excursion from the equilibrium point x_0: $F = K(x-x_0)$. The EP-model postulates that the position of a limb corresponds to the position, where the external force (e.g. gravity, weight of objects) is equal (but opposite) to the force exerted by the muscles. Therefore, kinematics should follow directly from the elastic properties of the neuro-muscular system and the properties of external loads.

In general, the position of an end effector, like the finger tip, can be obtained by multiple postures of the arm. Yet, the variability of postures for the same position of the end effector is small. This reproducibility of postures has often been described as Donders' law, which states that limb postures for a given finger, eye, or head position are invariably the same for the same pointing or gaze direction, respectively. This law is certainly not trivial since it is well known that rotations in 3 dimensions do not commute. This implies that the orientation of an object after two rotations along different rotation axes, depends on the order of rotations. Eye movements perfectly obey Donders' law. The specific relation between direction of gaze and eye orientation is known as Listing's law [2]. However, Donders' law is not valid for limb postures. Experimental results by Soechting et al. [3] revealed consistent variations of postures for the same position of the index finger depending on the history of previous finger positions. These authors suggested that the history-dependence of limb postures could be explained by the minimal-work model, which assumes that movements are made under the constraint of minimal work (see below). This is consistent with the observation that final posture after a movement does not depend on ►movement velocity [4].

Dynamics

In general ►point-to-point movements, which start and end at rest, follow a more or less straight path and have a bell-shaped velocity profile (►Bell-shaped speed profile), in agreement with predictions by the minimum jerk-model (see Fig. 1).

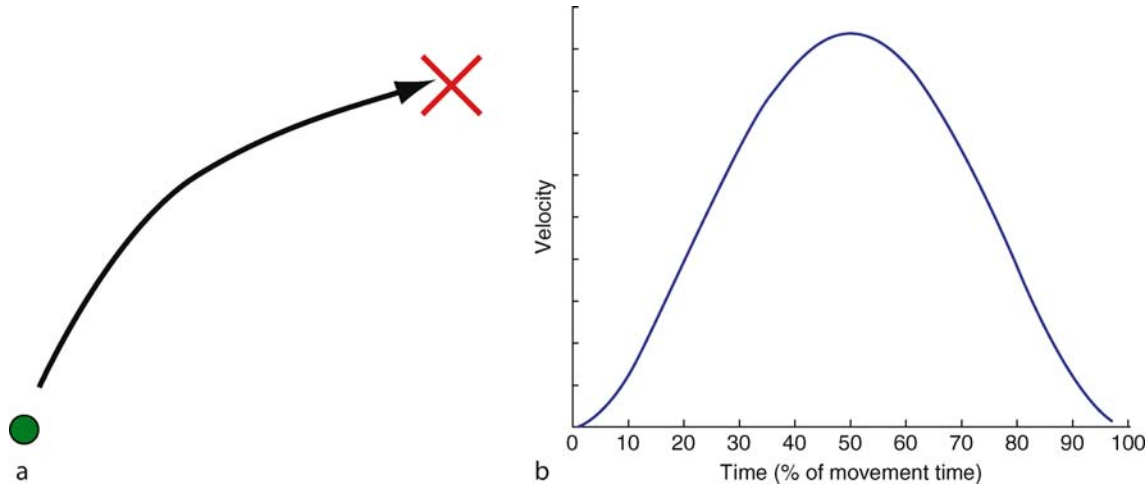
However, movement paths may differ depending on the instruction to the subject or depending on movement task. When subjects are instructed to make point-to-point movements in the dark, the movement trajectory is curved. This curved path has been interpreted as the result of movement planning in joint space, where joint rotations may give rise to curved movement paths of the end effector. However, when subjects are instructed to move an object (for example a cursor or mouse) between the same to positions with vision, the movement path is straight, suggesting that movement planning is in external work space. This illustrates that the movement trajectory is task-dependent, presumably because movement planning takes place in different frames of reference (e.g. joint space versus work space).

Models to Explain Human Movements

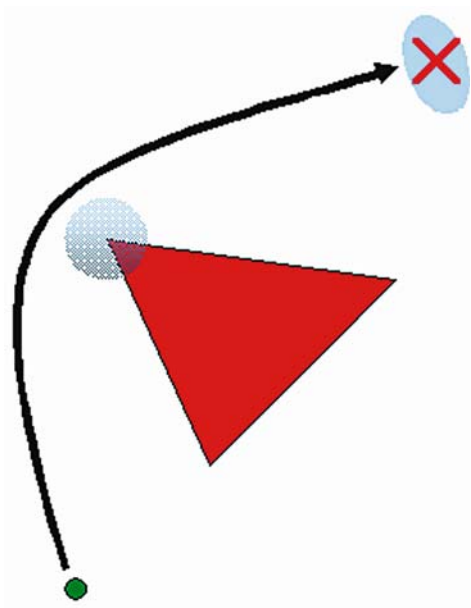
In general, models to explain human movement control belong to the general class of ►optimal control models [5]. Optimal control assumes that movements are made based on some ►optimization principle. Optimal control seeks to find the control (i.e. the muscle activation pattern), which optimizes the time-integral of some cost. This cost might be related to extrinsic features, such as e.g. end-point variability, smoothness of movement, and collision avoidance (see Fig. 2).

However, the cost should also include the properties (e.g. noise) in afferent sensory signals and in neuronal feedforward and feedback signals. The cost may be different for different types of movements. For example, movements, which have to be as fast as possible, require that movement time is minimal, whereas accurate movements require that the variability at the end of the movement is as small as possible.

Most models in the literature to explain properties of human movements focus on a single optimization principle. The most well-known models are



Motor Control Models. Figure 1 For a typical movement (start position at the green circle) to target (red cross, Fig. 1a) the corresponding velocity profile (Fig. 1b) has a bell-shaped profile.

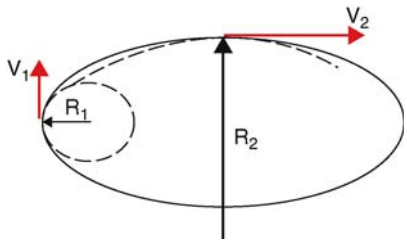


Motor Control Models. Figure 2 For a movement from the green circle to the red cross the movement path should keep a sufficiently large distance from the triangle to avoid collision. Given the intrinsic noise of action potential firing and force generation in muscle, this requires that the movement path should remain outside a circle centered at the corner of the triangle. It should also reach the target with a particular accuracy (indicated by elliptic shape). For optimal control, there are several cost criteria, depending e.g. on the internal noise of the motor system, on target accuracy of the movement, on movement time. The total cost C, which should be minimized, is a weighed summation of the various cost criteria C_i involved ($C = \sum w_i C_i$), where the weighting coefficients w_i depend on the relative importance of the cost criterion C_i.

- Minimum jerk model. Jerk is the third derivative of position. Minimization of jerk assumes that movements are smooth and predicts that movement velocity profiles are bell-shaped [6].
- ►Minimum torque-change model [7]. This assumes that changes in joint torque are minimized. A variation on the minimum-torque-change model is the minimum force-change model, which assumes that movements are made under the constraint that changes in muscle force are minimized. Since torque is the product of force and lever arm, the predictions by the minimum-torque change and minimum force-change models are very similar.
- Minimum-work model [3] assumes that work is minimized. This is equivalent to assuming that kinetic energy at peak velocity is minimized.
- Minimum variance model [8] uses the fact that muscle noise increases proportionally with muscle force and assumes that those forces are selected that minimize variance at the end of the movement.

Advanced mathematical analyses make it possible to calculate the best control given an optimality criterion in the absence of noise. However, the human motor system has to deal with internal noise [8] and movements are made in an environment, which may change in an unpredictable way. The theoretical framework for these cases (called "stochastic optimal control") is far from complete and is an important topic for further research.

Quite surprisingly, many models make the same predictions for planar movements but differ greatly in their predictions for movements in three dimensions [9]. Because of the complexity of simulating models for 3D movements and of analyzing and interpreting movements in three dimensions, a thorough comparison



Motor Control Models. Figure 3 For periodic movements along an elliptic path, the relation between radius R of the movement path and tangential velocity v is given by $V = CR^{1/3}$. The dashed and dashed-dotted lines are local fits of a circle segment to the ellipse. For a high curvature (small radius R_1) the corresponding tangential velocity V_1 is smaller than the tangential velocity V_2 for the less curved part of the ellipsoid. The ratio V_1/V_2 is equal to $\sqrt[3]{R_1/R_2}$.

between predictions of various models and experimental data for movements in 3 dimensions has not been made yet.

Two-Third Power Law

It is a well-known phenomenological observation that velocity of curved movements is tightly related to the curvature of the movement. This relation has been referred to as the ►two-third power law, since angular velocity ω appears to be related to curvature κ of the movement path by the exponential relation $\omega = Ck^{2/3}$. Since for circular movements tangential velocity v is related to angular velocity ω by the radius R of the movement ($v = R\omega$) with R equal to the inverse of curvature κ, the two-third power law can also be written as $v = CR^{\beta}$, where the exponent β equals 1/3 (see Fig. 3).

This relation can be derived mathematically when it is assumed that planar movements, such as elliptic movements, are made by a superposition of two orthogonal components with a sinusoidal and cosine modulation in time. As an alternative to the explanation that movements are built up by sine- and cosine modulated orthogonal components, Richardson and Flash [10] demonstrated that the two-third power law also follows from the smoothness constraint that underlies the ►minimum-jerk model.

References

1. Feldman AG (1986) Once more on the equilibrium point hypothesis (lambda model) for motor control. J Motor Behav 18 (1):17–54
2. Tweed D, Vilis T (1987) Implications of rotational kinematics for the oculomotor system in three dimensions. J Neurophysiol 58:832–849
3. Soechting JF, Buneo CA, Herrmann U, Flanders M (1995) Moving effortlessly in three dimensions: Does Donders' law apply to arm movement? J Neurosci 15:6271–6280
4. Nishikawa KC, Murray ST, Flanders M (1999) Do arm postures vary with the speed of reaching? J Neurophysiol 81:2582–2586
5. Todorov E (2004) Optimality principles in sensorimotor control. Nat Neurosci 7:907–915
6. Flash T, Hogan N (1985) The coordination of arm movements – an experimentally confirmed mathematical model. J Neurosci 5:1688–1703
7. Uno Y, Kawato M, Suzuki R (1989) Formation and control of optimal trajectory in human multijoint arm movement – minimum torque-change model. Biol Cybern 61:89–101
8. Harris CM, Wolpert DM (1998) Signal-dependent noise determines motor planning. Nature 394:780–784
9. Hermens F, Gielen S (2004) Posture-based or trajectory-based movement planning: a comparison of direct and indirect pointing movements. Exp Brain Res 159:340–348
10. Richardson MJE, Flash T (2002) Comparing smooth arm movements with the two-thirds power law and the related segmented-control hypothesis. J Neurosci 22:8201–8211

Motor Cortex

M

Definition

A general term that historically has been used to refer to primary motor cortex. This term is now also used in a more general way to refer collectively to primary and secondary motor areas of the frontal lobe.

►Motor Cortex – Hand Movements and Plasticity
►Motor Cortex - Output Properties and Organization
►Primary Motor Cortex (M1)

Motor Cortex – Hand Movements and Plasticity

Marc H. Schieber
Departments of Neurology and of Neurobiology and Anatomy, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Definition

The primary motor cortex, in primates located just anterior to the central sulcus, plays a crucial role in control of fine hand and finger movements. The organization of movement representations in the motor cortex undergoes

plastic changes in response to altered internal and external requirements for finger movements.

Characteristics

Voluntary Use of the Hand and Fingers

►Grasping an object is the most frequent voluntary use of the hand. Depending on the object and goal, humans use a wide variety of grasps – from precision (►Grip – precision grip) pinch between the tip of the thumb and index finger as used in picking a raspberry, to power grip (►Grip – power grip) as used in holding a hammer [1]. As the hand is transported toward an object by the reaching movement of the arm, the fingers open and form into a shape that approximates the shape of the object to be grasped. Such visually guided pre-shaping of the hand is mediated by a flow of information from the anterior intraparietal area (AIP) to the ventral premotor cortex (PMv) to the primary motor cortex (M1) [2]. As the fingers close on the object, forces at the contact surfaces on the fingers and palm must be balanced to provide a stable grip that does not rotate or crush the object unintentionally.

Less frequently the hand is used to perform delicate manipulation or even such specialized acts as typing on a keyboard, or playing a musical instrument. Although one often has the impression that during such movements each finger is moved independently, recordings show considerable correlated motion of adjacent fingers [3]. Even when normal humans are asked to exert flexion force with one finger only, force is produced in adjacent digits, a phenomenon referred to as ►enslavement of the adjacent digits. Similarly, when asked to move only one finger, motion appears in other fingers as well. In part, this incomplete ►individuation results from biomechanical coupling of the digits, and in part it reflects control from the nervous system as well.

For both grasping and fine manipulation, use of the right versus left hand is not necessarily random. Hand preference has three levels: (i) individual subjects tend to use the same hand repeatedly for a given task; (ii) individual subjects prefer to use the same hand for many different tasks; and (iii) most individuals in a population tend to prefer the same hand. Whereas non-human primates systematically show only the first level of hand preference, humans show all three levels. Approximately 80% of any human population is right-handed. In general, right-handed people prefer to use the right hand for delicate tasks that require precise control of dynamically changing forces, while the left hand may perform better in tasks requiring accurate control of static position [4].

Control of the Fingers From the Motor Cortex

Control of such relatively independent finger movements relies heavily on the hand representation in the primary motor cortex, and its corticospinal projection (►Motor cortex – output properties and organization 06078). When lesions affect this pathway, individuated finger movements are the first and most severely affected, and the last to recover. In macaque monkeys, a central core of Brodmann's area 4 representing hand movements and muscles is surrounded by a horseshoe-shaped band representing the more proximal upper extremity. This entire upper extremity representation lies between the representations of the face laterally and the lower extremity medially.

Throughout the M1 hand representation, neurons in cortical layer V send corticospinal axons to the lower cervical enlargement to control the motoneurons of hand muscles. Corticomotoneuronal (CM) cells that make monosynaptic connections to hand motoneurons are restricted to the posterior part of the hand representation, which in macaque monkeys lies in the anterior bank of the central sulcus [5]. CM cells are thought to be particularly important in the fine control of relatively independent finger movements. The firing rate of single neurons in the M1 hand representation – including corticospinal neurons and CM cells – varies depending on which type of grasp is used, or depending on which finger is moved. Although single neurons only rarely discharge selectively for a particular type of grasp, or for movement of a particular finger, the discharge of a large population of M1 neurons transmits information that specifies the hand or finger movement being made.

The M1 hand area classically was thought to contain an orderly somatotopic representation of the digits, with the thumb most lateral and the little finger most medial, but the representation of each digit now is known to be more widely distributed. This results from a number of structural features [6]. First, the cortical territory from which corticospinal axons converge on the motoneurons of a given hand muscle occupies several square millimeters. Given the number of hand muscles, these territories are so large that they overlap extensively with one another. Second, single cortical neurons often provide monosynaptic output connections to the spinal motoneuron pools of multiple muscles. Single cortical neurons thus may provide output to muscles acting on multiple digits, and even on the wrist, elbow and shoulder as well. Third, the entire M1 upper extremity representation is interconnected by horizontal axon collaterals that interlink not only the central digit core, but also the surrounding representation of more proximal muscles. As a consequence of this convergence, divergence and horizontal interconnectivity, neuronal activity appears throughout the hand representation during voluntary movement of even a single finger. In addition to this widely distributed base of activation, in humans a somatotopic gradient is superimposed, with more activation laterally during thumb movements, and more activation medially during movements of the little finger.

Plastic Changes in Cortical Finger Movement Representations

The widely distributed organization provided by convergence, divergence and horizontal connectivity in the pathway from the primary motor cortex to spinal ►motor neuron pools also provides a flexible substrate that can undergo plastic reorganization. Some plastic changes are mediated very rapidly by altered patterns of intracortical inhibition. The hetero-synaptic processes of long-term potentiation and depression also contribute to plastic reorganization. As time passes, some existing synapses are pruned away and new synaptic connections form. All these underlying processing contribute to reorganization of ►motor maps.

Plastic reorganization occurs during motor learning (►Motor learning) in normal subjects [7]. Repeated practice of particular hand and finger movements expands the representation of the practiced movements and of the muscles involved in producing them. Reorganization also occurs after injury [8]. After amputation of the hand, stimulation of the M1 hand representation evokes larger than normal contractions of the remaining proximal muscles. Voluntary attempts to move the phantom hand result in contractions of proximal muscles that would not normally contract during hand movements [9]. Reorganization of the motor map occurs as well after damage to the primary motor cortex [10]. If damage to the hand representation is partial and the subject is made to use the affected hand, some cortical territory that previously had represented proximal movements changes to represent distal movements. If damage to the primary motor cortex hand representation is complete, representation of finger movements in other cortical motor areas expands. Plastic reorganization of finger movement representations thus underlies both normal motor learning and recovery from nervous system injury.

Acknowledgments

This work was supported by R01/R37-NS27686 from the National Institute of Neurologic Disorders and Stroke.

References

1. Napier JR (1956) The prehensile movements of the human hand. J Bone Joint Surg 38:902–913
2. Rizzolatti G, Fogassi L, Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci 2(9):661–670
3. Schieber MH, Santello M (2004) Hand function: peripheral and central constraints on performance. J Appl Physiol 96(6):2293–2300
4. Sainburg RL (2005) Handedness: differential specializations for control of trajectory and position. Exerc Sport Sci Rev 33(4):206–213
5. Rathelot JA, Strick PL (2006) Muscle representation in the macaque motor cortex: an anatomical perspective. Proc Natl Acad Sci USA 103(21):8257–8262
6. Schieber MH (2001) Constraints on somatotopic organization in the primary motor cortex. J Neurophysiol 86(5):2125–2143
7. Sanes JN, Donoghue JP (2000) Plasticity and primary motor cortex. Annu Rev Neurosci 23:393–415
8. Chen R, Cohen LG, Hallett M (2002) Nervous system reorganization following injury. Neuroscience 111(4): 761–773
9. Reilly KT, Mercier C, Schieber MH, Sirigu A (2006) Persistent hand motor commands in the amputees' brain. Brain 129(Pt 8):2211–2223
10. Nudo RJ (2003) Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. J Rehabil Med (41 Suppl):7–10

Motor Cortex, Primary

Synonyms

►Gyrus precentralis; ►Precentral gyrus
►Precentral Gyrus (Area 4)
►Telencephalon

Motor Cortex, Supplementary

Definition

Together with the premotor cortex, forms the secondary motor field. Involved in planning movement.

►Telencephalon

Motor Cortex: Output Properties and Organization

Paul Cheney
Dept. Molecular and Integrative Physiology,
University of Kansas Medical Center,
Kansas City, Kansas, USA

Synonyms

Corticospinal system organization; Pyramidal system organization; Upper motor neuron organization

Definition

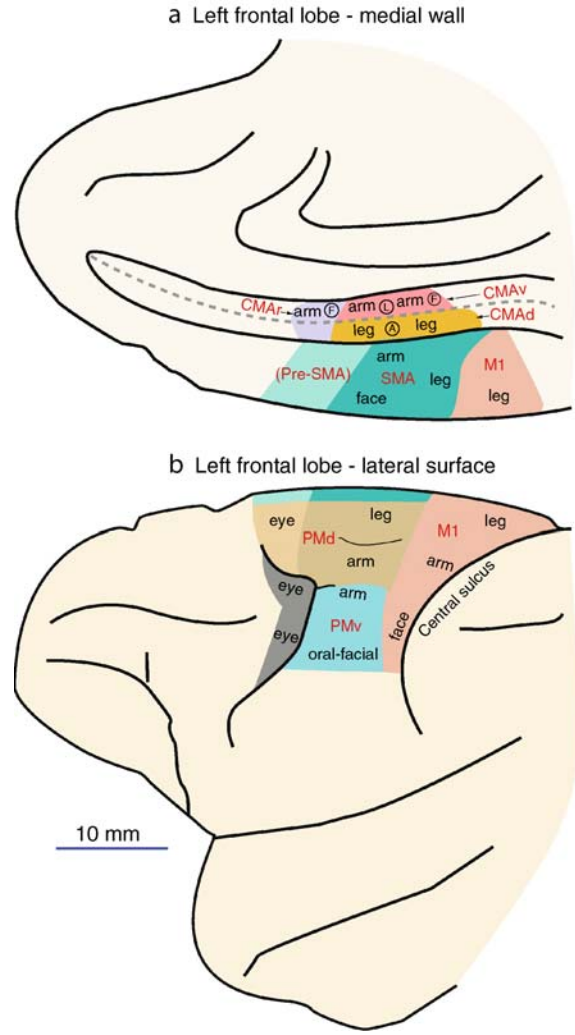
Movement planning and execution are the products of distributed neural processing involving many areas of the brain. This essay focuses on the role of motor areas of cerebral cortex, particularly primary motor cortex, in movement execution. Cortical motor areas are identified and their output capability is summarized in terms of the movements evoked by electrical stimulation. The synaptic organization of ►corticospinal neurons with motoneurons in the spinal cord is explained in terms of the selection of muscle synergies needed for producing coordinated limb movements.

Characteristics

Identification and Somatotopic Organization of Cortical Motor Areas

The cerebral cortex of mammals can be categorized into a number of specialized sensory, motor and association areas. In primates, these areas are particularly well developed and large. The motor areas of cerebral cortex are contained within the frontal lobe and include primary motor cortex or M1 located in the precentral gyrus just anterior to the central sulcus as well as several ►secondary motor areas. Six secondary motor areas have been identified in primates including the ►SMA (supplementary motor area) medial and anterior to primary motor cortex, dorsal and ventral ►premotor areas (PMd and PMv) on the lateral surface of the frontal lobe anterior to M1 and three ►cingulate motor areas located ventral to SMA in the cingulate gyrus [1,2]. The location of the primary and secondary motor areas is shown in Fig. 1 for a rhesus monkey cerebral hemisphere. Analogous areas have been identified in the human brain.

Primary motor cortex was first identified in the 19th century by applying electrical currents to the cerebral cortex of anesthetized animals. It was discovered that this electrical current evoked movements of specific body parts and that the representation followed an orderly pattern paralleling the anatomy of major body parts. The neuronal representation of motor and sensory functions associated with specific body parts is termed ►somatotopic organization and is a distinctive feature of cortical motor areas. The discovery of a somatotopic organization of electrically evoked movements in the cerebral cortex was strong evidence for localization of function in the brain. Cortical areas from which movement could be evoked were referred to as "electrically excitable". Electrical excitability or the ability to evoke movements with electrical stimulation is used as a means of identifying motor areas of the cerebral cortex. Movements can be evoked from both primary and secondary cortical motor areas, although significantly higher currents are required for secondary motor areas.



Motor Cortex: Output Properties and Organization.
Figure 1 Location and general somatotopic organization of cortical motor areas of the macaque monkey brain based on ICMS evoked movements. (a) Motor areas on the medial wall of the left frontal lobe. (b) Motor areas on the lateral surface of the left frontal lobe. Motor areas are labeled in *red* and include primary motor cortex (*M1*), supplementary motor area (*SMA*), cingulate motor areas (*CMA*) and lateral premotor areas (*PMd* and *PMv*). The cingulate gyrus has been "unfolded" and represented as a two dimensional map. The *dotted line* represents the fundus (bottom) of the sulcus. The *small-circled letters* in the cingulate motor areas are included to show that in addition to the principal representation indicated, small patches of representation of the face (*F*), arm (*A*) and leg (*L*) also exist. (Modified from [3]).

Primary and secondary cortical motor areas can also be identified on the basis of their distinctive histological appearance including the thickness of various layers and the size of various cell types. This approach is

referred to as cytoarchitectonics. Based on this type of analysis, the cerebral cortex has been divided into numerous separable regions. An important principle of cortical organization is that areas of cerebral cortex identified on the basis of these anatomical criteria are often found to align closely with regions identified by functional criteria. For example, primary motor cortex corresponds with Broadman's cytoarchitectonic area 4.

Another identifying feature of cortical motor areas is the presence of corticospinal neurons. These are neurons that have a cell body contained within the cortex and an axon that projects to the spinal cord for the control of limb and trunk musculature. Similar neurons for control of facial and tongue muscles are called corticobulbar neurons because their axons terminate in the brainstem where motoneurons of these muscles are located. In primates, some corticospinal neurons, referred to as corticomotoneuronal cells, make monosynaptic connections directly with motoneurons and these connections are thought to be an important neural substrate underlying skilled use of the distal extremities, particularly the ability to make independent finger movements. Corticospinal neurons are found throughout primary motor cortex and secondary cortical motor areas, although the number of neurons is smaller for secondary cortical areas because the size of these areas is much smaller than primary motor cortex [1,2].

Electrical stimulation of cerebral cortex has been a highly informative approach to understanding cortical motor output organization. The classical early studies in humans by Penfield [4] and in non-human primates by Woolsey established the major features of body somatotopic organization that can be found today in nearly every textbook of neuroscience. Penfield and Woolsey summarized the general pattern of evoked movements from cortical stimulation by drawing a body surface representation, superimposed on the cortical surface and distorted in size to reflect the amount of cortex devoted to movements of each body part. These body surface representations, referred to as homunculi and simunculi for humans and monkeys respectively, indicate the location along the precentral gyrus where movements of different body parts can be evoked by electrical stimulation. The major features of the somatotopic organization of motor output from ►primary motor cortex (M1) are (i) largely separate areas devoted to the representation of the lower extremity, trunk, upper extremity, face and tongue with the lower extremity located medially and the tongue most laterally along the precentral gyrus, (ii) the representation is contralateral except for tongue, jaw and upper facial muscles and (iii) there is preferential representation of distal muscles, particularly muscles of the hand, face and tongue. These are the muscles most heavily involved in skilled movements and require the highest degree of fractionation in the patterns of activity across different muscles.

While the basic body plan of somatotopic organization revealed by the early stimulation studies is universally accepted, the degree to which a consistent and orderly somatotopic organization exists for muscles/movements within a major body segment has only been addressed in more recent studies [5]. Some of these studies have used cortical microstimulation in monkeys to identify activated muscles of the forelimb. Microstimulation consists of applying weak current pulses through a recording microelectrode. Using this approach, a consistent representation of forelimb muscles has been identified, consisting of a core representation of distal muscles (wrist and digit), a peripheral zone of proximal muscle (shoulder and elbow) representation and a large zone representing combinations of distal and proximal muscles separating the pure distal and pure proximal representations [6]. This pattern of forelimb representation is also supported by anatomical studies in which distal and proximal forelimb corticospinal neurons have been labeled with tracers and identified histologically [1,2]. Does the existence of a consistent somatotopic organization extend to movements of the hand including the wrist and individual digits? The homunculi and simunculi drawings based on early work would suggest this but the answer to this question is clearly no. Neurons involved in motor responses of the wrist and individual digits are completely overlapping within primary motor cortex [5]. In part this is due to the fact that the simplest movement of an individual digit actually involves the activation of a large number of distal muscles, not just the muscles of the digit to be moved but also muscles involved in stabilizing the other digits. Another factor is that individual corticospinal neurons rarely make synaptic connections with motoneurons of just one muscle. Rather these neurons activate combinations of muscles as functional synergies [7].

Cortical mapping using repetitive microstimulation of the cortex has typically involved applying brief (30 ms) trains of high frequency stimuli (330 Hz) to evoke twitch like movements. This has been and continues to be a very useful approach to cortical output mapping. However, if the stimulus train duration is lengthened from 30 ms to 500 ms, more complete movements can be evoked. These movements more closely resemble the time course, trajectory and velocity profile of normal voluntary movements. Graziano and colleagues [8] have exploited this approach to map the movements evoked from primary motor cortex and premotor areas on the lateral surface of the hemisphere (PMd and PMv). An important feature of these movements is that long duration repetitive stimulation brings the hand to the same end point in space regardless of the starting position. The cortical map

obtained using this approach contains four subregions from which different, seemingly purposeful movement responses can be elicited. Long duration stimulation of one subregion tends to bring the contralateral hand to locations in space in front of the chest. Stimulation within this part of the map also evokes a variety of hand postures similar to ones observed during object manipulation behavior including (i) grip with the thumb against the forefinger, (ii) fist formation, (iii) opening of the hand with all digits splayed, (iv) various rotations of the wrist and (v) pronation and supination of the forearm. The cortex from which these movements can be evoked corresponds to the forelimb representation of primary motor cortex, an area that has long been known to emphasize the control of manual dexterity. A second subregion corresponds to hand locations at the mouth and stimulation within this region produces a grip posture with movement of the hand to the mouth and often opening of the mouth. This area corresponds to a part of area PMv known to be involved in the cortical representation of grasp postures and interactions between the hand and mouth. A third subregion termed PZ or polysensory zone contains neurons that respond to tactile stimuli on the face and arms and visual stimuli near the face and arms. Stimulation of sites in the polysensory zone evokes apparent defensive movements. This is a multimodal subregion that is also largely within area PMv. The fourth subregion is contained with PMd. Stimulation within this subregion produces reaching movements in which the wrist straightens, the fingers open as if to prepare for grasp and the arm extends outward from the body.

Organization of Corticospinal Output

Historically, a major controversy has existed over the issue of what is represented by the corticospinal neurons that constitute primary motor cortex output. Is it muscles that are represented or movements? To some extent, this controversy has lingered on because terms have not been adequately defined, but also because there is a genuine and important issue to be resolved. Obviously muscles are represented in the sense that corticospinal neurons make synaptic connections with motoneurons and activate muscles. However, the real issue might be redefined in terms of the way in which muscles are represented and its possible significance. For example, what would be implication of an output representation in which small pieces of motor cortex, like pieces of a mosaic or keys of a piano, were devoted to the representation of single muscles? This would constitute a muscle representation in the most extreme sense. In this case, the central motor program, containing information about the movement to be produced would select the appropriate keys (muscles) of the motor cortex keyboard to produce the desired movement. The role of motor cortex output would then simply be to devote a piece of tissue and corresponding corticospinal neurons to each individual muscle and give appropriate parts of the brain access to these muscle specific representations. It is now known that this is not the way motor cortex output is organized. In large part, individual corticospinal neurons do not have synaptic contacts confined to motoneurons of individual muscles. Rather, individual corticospinal neurons make synaptic contacts with motoneurons of multiple muscles representing functional muscle synergies [7,9–11]. The set of muscles influenced by a corticospinal neuron are referred to as its ►muscle field. Corticospinal neurons have a clustered organization in layer V of primary motor cortex and there is evidence that the individual neurons within a cluster have similar muscle fields. The set of corticospinal cells selected for activation by the central motor program is obviously dependent on the desired movement. Simple isolated movements of the wrist involve coactivation of forearm, wrist and digit synergist muscles and the corticospinal neurons activated for this task tend to have only distal muscle fields. Most importantly, single neurons engaged in isolated wrist movements do not act upon single muscles; rather, these neurons activate combinations of wrist and digit synergist muscles. Many of the same corticospinal neurons that facilitate motoneurons of multiple agonist muscles also simultaneously inhibit motoneurons of multiple antagonist muscles. To aid with the movement, the activity of the antagonist muscles must be suppressed as the agonist muscles contract and shorten. This combination of multiple facilitated agonist muscles and suppressed antagonist muscles constitutes a simple functional synergy for movement about a single joint. The representation of such functional muscle synergies goes beyond a simple muscle representation – it is the representation of a set of muscles for a particular movement. Hence, it can be argued that movements are, in fact, represented in the synaptic output organization of primary motor cortex. The corticospinal representation of functional muscle synergies also extends to more complex multi-joint movements. Reaching to grasp an object requires coactivation of muscles at multiple proximal and distal joints. Many corticospinal neurons involved in such reaching tasks make synaptic connections with motoneurons of both distal and proximal muscles [7]. These muscle combinations represent multi-joint functional synergies involved in reaching. To conclude, the output organization of primary motor cortex can be viewed in terms of the functional muscle synergies represented in the synaptic connections of corticospinal neurons with motoneurons. These muscle synergies and their combinations are the cortical building blocks the central motor program must work with to produce the diversity of skilled movements characteristic of primates.

References

1. He SQ, Dum RP, Strick PL (1993) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J Neurosci 13:952–980
2. He SQ, Dum RP, Strick PL (1995) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. J Neurosci 15:3284–3306
3. Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. EEG and Clin Neurophysiol 106:283–296
4. Penfield W, Rassmussen AT (1950) Cerebral cortex of man. A clinical study of the localization of function. Macmillian, New York
5. Schieber MH, Hibbard LS (1993) How somatotopic is the motor cortex hand area? Science 261:489–492
6. Park MC, Belhaj-Saif A, Cheney PD (2001) Consistent features in the forelimb representation of primary motor cortex of rhesus macaques. J Neurosci 21:2784–2792
7. McKiernan BJ, Marcario JK, Hill-Karrer J, Cheney PD (1998) Corticomotoneuronal (CM) postspike effects on shoulder elbow wrist digit and intrinsic hand muscles during a reach and prehension task in the monkey. J Neurophysiol 80:1961–1980
8. Graziano MS (2006) The organization of behavioral repertoire in motor cortex. Ann Rev Neurosci 29:105–134
9. Buys EJ, Lemon RN, Mantel GWH, Muir RB (1986) Selective facilitation of different hand muscles by single corticospinal neurons in the conscious monkey. J Physiol 381:529–549
10. Fetz EE, Cheney PD (1980) Post-spike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. J Neurophysiol 44:751–772
11. Woolsey CN (1964) Cortical localization as defined by evoked potential and electrical stimulation studies. In: cerebral localization and organization (Eds. G. Schattenbrand and CN Woolsey). The University of Wisconsin press, Madison.

Motor Disorders

Definition

Motor disorders may be neurologically classified as (i) paralysis due to dysfunctions of ►skeletal muscle, ►neuromuscular junction, ►brainstem or spinal skeleto-►motoneurons; (ii) paralysis due to damage to the ►corticospinal tract, ►corticobulbar tracts, or fibers descending from the brainstem (see ►spasticity); (iii) non-paralytic and ►apraxic dysfunctions of purposive movements resulting from lesions of the ►cerebral hemispheres; (iv) disorders of the ►basal ganglia (see ►Parkinson disease, Huntington's disease; Tourette's syndrome); (v) dysfunctions of coordination (►ataxia) resulting from lesions of the ►cerebellum and its inputs and outputs.

►Basal Ganglia
►Cerebellar Functions
►Corticospinal Tract
►Huntington's Disease
►Neuromuscular Junction
►Parkinson Disease
►Spasticity
►Tourette's Syndrome

Motor Efference

Definition

The motor commands from the brain leading to movement.

►Large-Fiber Sensory Neuropathy
►Effect on Proprioception

Motor Equivalence

Definition

Motor equivalence implies that the same movement or motor program can be executed by different muscle and/or joint assemblies.

►Motor Control Models

Motor Error

Definition

The difference between the present location of an effector (e.g., the hand or the eye) and its desired location. Neural correlates of motor error have been described in a variety of brain centers.

►Movement Sequences
►Eye-Hand Coordination

Motor Evoked Potential (MEP)

Definition

Electrical potential recorded over a muscle, evoked by electrical or magnetic stimulation of the nervous system.

►Transcranial Magnetic Stimulation

Motor Fluctuations in Parkinson Disease

Definition

Fluctuations in the severity of motor symptoms of Parkinson disease several times per day, related to the long term use of levodopa and disease progression

►Parkinson Disease
►Structures/Processes/Conditions: Parkinson Disease

Motor Imagery

Definition

The ability to mentally simulate a particular movement without actual execution. Neuroimaging studies have shown the involvement of several motor brain areas during motor imagery.

►Action Representation

Motor Invariant

Definition

An invariant is a quantity that remains unchanged under a set of transformations. For example, the curvature of a curved hand movement trajectory is invariant under the transformations of rotation and translation.

►Arm Trajectory Formation

Motor Learning

Vlastislav Bracha, James R. Bloedel
Department of Biomedical Sciences, Iowa State University, Ames, IA, USA

Definition

►Motor learning is the process of acquiring new motor skills. Common examples of motor learning are learning to ride a bicycle or to play tennis. Motor learning is essential for success under novel or changing environmental contexts and is thus ubiquitous. It participates in speech acquisition, in learning to use tools and machines, in the acquisition of artistic and athletic skills, in tuning motor performance during development and aging, and in compensating for movement deficits associated with a bodily injury.

Characteristics

In the current literature, the term motor learning has been applied to a heterogeneous group of adaptive phenomena and as such it defies a simple definition. In general, motor learning pertains to processes of adaptively modifying the spatio-temporal structure of movements, of forming new or adjusting existing sensori-motor transformations and of forming new movement sequences.

Motor learning is distinct from other forms of learning, such as learning the spatial structure of the environment, remembering events and temporal associations between events, learning symbols and concepts, or autobiographical memory. The outcome of motor learning is an acquired modification of sensori-motor processing resulting in meaningful changes in motor performance that achieves a desired behavioral goal in specific environmental and motivational circumstances. A typical property of motor learning is that it progresses through a series of trial and error performances. Motor learning usually requires a large number of repetitions to achieve an asymptotic performance. The ►motor error, which is derived from the difference between the expected and actual results of movement, is a pivotal notion in conceptual and computational models of motor learning.

Similar to other forms of learning and memory, motor learning is thought to have explicit and implicit components or phases. When learning a new motor skill, successful movement generation frequently requires involvement of attention and awareness. At this stage, the movements are under an explicit, i.e., conscious and verbally describable control. As the learning progresses, movements become smoother, faster and automated. Eventually, well-trained movements become implicit, i.e. fully automatic, requiring

little or no conscious effort. However, some types of motor learning, such as the adaptation of hand movements to altered visual feedback or the classical conditioning of eyeblink responses, can occur exclusively in the implicit domain, with the subject either being unaware of the learning or being unable to report on the relevant details of learning.

Motor learning in natural conditions involves the complex coordination of a number of motor subsystems. For example, an efficient tennis stroke requires hitting the incoming ball at a precise time and place relative to the tennis player's body with a tennis racquet having precise speed, orientation and trajectory of movement. To achieve this, the player has to learn to observe the ball and extrapolate its trajectory, to run to the anticipated place of stroke execution, assume the appropriate posture and execute a complex and precisely timed kinetic chain of leg, torso and arm movements. These movements are synchronized with eye and head movements and with respiration, and they have to be adapted to the physical properties of the court, ball and the tennis racquet. To reduce this complexity to a level amenable to scientific analysis, motor learning is studied in simplified motor learning models.

Models of Motor Learning

The neural substrates of motor learning are investigated in experimental models that focus on its specific aspects in specific motor sub-systems. The motor learning paradigms are usually designed to control the learning environment, to provide reliable measurements of executed movements and access to measurements or manipulations of the nervous system. The most common learning paradigms fit in one of the following categories.

Adaptive Modifications of the Vestibulo-ocular Reflex

The purpose of the vestibulo-ocular reflex (VOR) is to stabilize images on the retina during head movements. Head movements stimulate the vestibular apparatus and the resulting sensory information is processed in VOR neural circuits to produce compensatory eye movements that stabilize the visual field. The VOR is under strong visual control. Inadequate VOR operation produces slip of the visual image on the retina, and this visual error signal drives adaptive VOR modifications. To induce VOR adaptation, experimenters usually introduce an artificial visual error by moving the subject's surroundings or by placing reversing or magnifying optical devices in the visual path. By using these tools, the VOR could be canceled, its direction reversed or its amplitude changed. VOR adaptation is one of the oldest models of motor learning, and it has yielded an advanced understanding of cerebellar and brainstem circuits controlling this adaptive process. This knowledge makes the VOR model well suited for studies at the neural network and cellular levels [1].

Classical Conditioning of Withdrawal Reflexes

Withdrawal reflexes protect body parts from injury by withdrawing them from aversive stimuli. Withdrawal reflexes, such as an eyeblink response or a limb withdrawal, can be classically conditioned. In classical conditioning, subjects are presented with an initially irrelevant stimulus (conditioned stimulus) that is followed by the withdrawal-eliciting aversive stimulus (unconditioned stimulus). During repeated pairings of these stimuli, the subject learns to respond to the conditioned stimulus before the unconditioned stimulus reaches the body surface. The learned anticipatory response is called the conditioned response. Although eyeblink conditioning was originally studied in the context of associative learning, more recently it has also been categorized as a form of motor learning, most likely because of its dependence on the cerebellum and because it results in the formation of new, well timed motor response. Similar to the VOR, researchers employing the eyeblink conditioning model have been extremely successful in delineating involved neural circuits and in developing experimental strategies that address the nature and location of underlying plastic changes [2,3]. It has been shown that a simple form of eyeblink conditioning, known as ►delay eyeblink conditioning, is controlled predominantly by cerebellar, mesencephalic, pontine and medullar neural circuits. The more complex forms of conditioning, such as ►trace eyeblink conditioning, recruit additional CNS components, such as the hippocampus.

Learning New and Optimizing Existing Visuo-motor Skills

This broad category of motor learning paradigms incorporates movements executed under visual feedback. An example of visuo-motor skill adaptation is learning to trace two-dimensional objects by hand or learning to reach for visually detected objects. In a typical tracing task the subject traces repeatedly a two-dimensional object with a pen. It has been shown that with training, tracing movements become faster, smoother and more accurate. The tracing task can be experimentally manipulated by altering the visual feedback. This can be achieved by asking the subject to trace the image reflected in a mirror, which reverses the normal relationship between directions of the eye and hand movements. Another common variant of this task involves tracing objects on a computer screen with an input device such as a computer mouse or tablet. The relationship between the direction and amplitude of the hand and cursor (and therefore the eye) movements can be manipulated with appropriate software. Since tracing tasks require close coupling between eye and hand movements, disrupting their normal relationship

leads to motor errors that drive a powerful and surprisingly fast motor learning.

Visuo-motor learning attracted large attention following the discovery that amnesiac subjects with injuries of the medial temporal lobe and hippocampus can learn the mirror tracing task despite being severely deficient in explicit memory tasks. This observation led to the modern concept of relatively independent explicit and implicit memory systems. It should be noted, however, that although motor learning is frequently considered to be a form of implicit memory, many motor learning tasks have explicit components or could be affected by explicit factors.

Adaptation to Movement Perturbations

Models in this category utilize external forces to interfere with ongoing movements. Some paradigms perturb movements with continuously applied mechanical loads that are attached to moving body parts or with robotic devices that can apply arbitrary force fields to the moving limb. Other paradigms in this category use temporary interference of the movement, such as a sudden presentation of an obstacle in the movement trajectory, a sudden change of the speed of a treadmill on which the subject walks, or a sudden movement of a platform on which the subject stands. The motor learning in these tasks results in formation of various task-dependent anticipatory feedforward strategies and feedback adjustments that counter the effects of the interference and improve task performance.

Learning of Movement Sequences

This popular category of motor learning paradigms requires subjects to learn sequences of movements [4]. Common variants are the serial reaction time task (SRT) and the 2xN task. In the SRT task subjects are presented with a series of targets that appear, one by one, on the computer screen in one of several possible positions. Subjects are required to press as fast as possible a key that corresponds to the presented target position. The repeated presentation of a specific sequence of targets leads to motor learning as evidenced by a significant decrease in key press reaction time. The 2xN task was originally developed to make sequence learning amenable for studies in primates. In this task, subjects are presented with a sequence of N (5 or 10) pairs of lighted keys on a 5×5 or 10×10 keypad. The subject is required to press the keys in each pair in the correct order (initially unbeknown to the subject). Once the subject determines by trial and error the correct order in the first pair, the next pair of keys in the sequence is presented. Any error resets the sequence, and the sequence presentation starts with the first pair of keys again. The presentation of the sequence continues until the correct order in each pair is mastered and the movement sequence is learned.

Sequence learning tasks are popular among neuropsychologists, who use them to address questions such as the participation of awareness in motor learning or the role of explicit and implicit memory systems.

Rodent Motor Learning Paradigms

Advancements in motor learning research will depend on a thorough knowledge of how the underlying neural circuits become modified during learning and what are the cellular and molecular mechanisms of this process. For studies at the cellular and molecular levels, developing motor learning models in rodents will be necessary. Much progress has already been made in exploring neuronal function using genetically modified rodent models (e.g. knockout mice). Traditional models of motor learning in rodents are learning of the skilled forelimb reaching movement, modifications and conditioning of licking movements and learning acrobatic tasks, such as maintaining balance on a rotating horizontal cylinder. More recently, the eyeblink conditioning paradigm and the adaptation of the VOR were successfully implemented in rodents.

Neural Substrates of Motor Learning

Motor learning depends on motor circuits that generate the movement to be learned and on associated components of sensory systems. Since the sensory and motor systems are organized in a modality-specific and somatotopic manner, circuits for specific forms of motor learning should be at least partially segregated based on involved parts of the motor system and on the type of sensory information utilized.

Research on motor learning involves several stages of analysis. At the first stage, an adequate model of motor learning is developed and its behavioral properties are characterized. Next, circuits that are involved in and essential for the studied form of motor learning are identified. This second stage involves a variety of methods, such as the recording of brain activity, lesions or pharmacological manipulations of individual circuit components, and neuroanatomical tracing techniques. At the third stage, the operating mechanism of the circuit that produces and modifies the behavior is addressed to reveal components that likely undergo plastic changes resulting in motor adaptation. At this stage, a combination of brain activity recording, brain stimulation and neuropharmacological techniques is most relevant. By the fourth stage, the techniques of cellular and molecular biology are deployed to reveal the cellular mechanisms of plasticity in brain regions identified during the previous stage of investigation.

The more complex forms of motor learning, such as learning of motor sequences, now are mostly at stages one and two where their properties and the underlying circuits are being identified. Because a large portion of these studies are being done in human subjects, most of

them focus on testing patients with brain pathologies and on using non-invasive brain imaging methods, such as functional MRI. A common conclusion from several paradigms is that at higher levels, the complex forms of motor learning are executed by circuits that include motor, sensory and associative areas of the cerebral cortex, basal ganglia and cerebellum [5,6]. This lively area of research produced important insights into the roles of awareness and explicit and implicit processes in movement sequence learning [4]. In another interesting development, circuits participating in movement sequence learning and in perturbation adaptation were shown to change over the course of learning, with some structures being more active at initial stages of learning and less involved during the recall of consolidated memory traces [7,8].

Research on simple forms of motor learning, such as VOR adaptation and eyeblink conditioning, has reached the more advanced stages. Their underlying circuits have been described in large detail, and although not all important issues pertinent to circuit operation have been resolved, some investigators are pursuing possible molecular mechanisms of neural plasticity. This research is driven mostly by the cerebellar learning hypothesis, which proposed the cerebellar cortex as a likely place of motor learning plasticity [1,9]. One intriguing feature of these models is that the underlying learning most likely occurs within circuits that generate the learned or modified response. Consequently, most attempts to interfere with learning at the circuit level also affect response execution. This produces uncertainty in whether the failure to learn was related to the animal's incapacity to execute the behavior properly (a performance deficit) or to the disruption of learning mechanisms. This dilemma, the conflicting of learning and performance hypotheses, has been partially overcome in the eyeblink conditioning model using techniques of temporary inactivation during response acquisition or consolidation. This is uniquely possible in eyeblink conditioning because the animal does not need to generate responses in order to learn them.

One major challenge in neuronal circuit level studies of eyeblink conditioning is that the underlying neuronal networks are comprised of mutually interconnected structures with an abundance of feedback connections. In networks of this kind, contributions of individual nodes to properties of the behavior or learning are difficult to discriminate, because neuronal activity patterns at a particular node of the network are usually influenced by a set of both up-stream and down-stream structures, and because effects of manipulations of individual parts of the circuit can propagate to much larger areas of the network via non-specific tonic interactions [10]. Such network properties of motor learning circuits will have to be accounted for during cellular and molecular studies. Ultimately, a full understanding of motor learning will include the synthesis of multi-paradigm hierarchical knowledge acquired at the behavioral, neural network and cellular levels.

References

1. Boyden ES, Katoh A, Raymond JL (2004) Cerebellum-dependent learning: the role of multiple plasticity mechanisms. Annu Rev Neurosci 27:581–609
2. Bracha V, Bloedel JR (1996) The multiple pathway model of circuits subserving the classical conditioning of withdrawal reflexes. In: Bloedel JR, Ebner TJ, Wise SP (eds) Acquisition of motor behavior in vertebrates. MIT Press, Cambridge, pp 175–204
3. Christian KM, Thompson RF (2003) Neural substrates of eyeblink conditioning: acquisition and retention. Learn Mem 10:427–455
4. Rhodes BJ, Bullock D, Verwey WB, Averbeck BB, Page MP (2004) Learning and production of movement sequences: behavioral, neurophysiological, and modeling perspectives. Hum Mov Sci 23:699–746
5. Halsband U, Lange RK (2006) Motor learning in man: a review of functional and clinical studies. J Physiol (Paris) 99:414–424
6. Sanes JN (2003) Neocortical mechanisms in motor learning. Curr Opin Neurobiol 13:225–231
7. Ungerleider LG, Doyon J, Karni A (2002) Imaging brain plasticity during motor skill learning. Neurobiol Learn Mem 78:553–564
8. Krakauer JW, Shadmehr R (2006) Consolidation of motor memory. Trends Neurosci 29:58–64
9. De Zeeuw CI, Yeo CH (2005) Time and tide in cerebellar memory formation. Curr Opin Neurobiol 15:667–674
10. Zbarska S, Holland EA, Bloedel JR, Bracha V (2007) Inferior olivary inactivation abolishes conditioned eyeblinks: extinction or cerebellar malfunction? Behav Brain Res 178:128–138

Motor Map

Definition

A map of the movements or muscle contractions evoked by stimulation of a brain region at multiple different locations, typically using electrical or magnetic stimuli.

►Motor Cortex – Hand Movements and Plasticity

Motor Neuron Pool

Definition

►Motoneuron Pool

Motor Nucleus

Definition
►Motor Neuron Pool

Motor Pattern

Definition
The rhythmic, repeating sequence of motor neuron activity produced during an actual or fictive motor act.

Motor Pattern Generator

Definition
Motor pattern generator in neuroscience is sometimes called "central pattern generator," which can be defined as neural networks that can endogenously, without rhythmic sensory or central input, produce rhythmic patterned outputs or as neural circuits that generate periodic motor commands for rhythmic movements such as locomotion. Central pattern generator produces rhythmic outputs even in isolation from motor and sensory feedback from limbs and other muscle targets.

►Central Pattern Generator (CPG)
►Rhythmic Movements

Motor Primitive

Definition
A building component of body movements, usually consisting of coordinated kinematic variables (i.e., joint angles) or dynamic variables (i.e., muscle activations). In animal locomotion, for example, motor primitives are coordinated hip, knee, and ankle angles that operate cooperatively either inphase or antiphase. Motor primitives are believed to be a neural mechanism that realizes coordinated body movements, without handling all individual degrees of freedom in body movements independently.

►Degrees of Freedom
►Rhythmic Movements

Motor Responsiveness

►Sleep – Motor Changes

Motor Schema

Definition
Set of non-conscious programmes and habits underpinning skilled automatic movements. These involve both sensory input to coordinate and motor output to effect.

►Large-Fiber Sensory Neuropathy
►Effect on Proprioception

Motor Set

Definition
The process by which the central nervous system optimizes the capacity to perform a movement prior to movement onset. This is achieved by invoking predictive or feed forward control mechanisms usually derived based on previous, related experience under the same behavioral conditions.

Motor Stereotypies

Definition
Motor stereotypy refers to repetitive motor behaviors that do not produce tissue damage, such as the same movement occurring multiple times in a short time period like arm-waving, body-rocking, leg-kicking, and head-nodding. Stereotypic motor behavior is a widespread phenomenon of many neurologic and psychiatric disorders. Studies on the mechanisms controlling motor stereotypies have suggested roles of nigrostriatal dopamine and an enhanced activation of neurons located in the striosomal compartment in the striatum.

►Dopamine
►Sensorimotor Learning and the Basal Ganglia
►Striatum

Motor Strategy

Definition
A specific way of performing a behavior. Examples of choices between different motor strategies are forward walk vs. backward walk, trot vs. gallop, and rostral scratch vs. caudal scratch.

►Scratching

Motor Synergy

Definition
Effective reduction of degrees of freedom in body movements by coordination and regulation of kinematic (i.e., joint angles) or dynamic (i.e., muscle tensions) variables.

►Degrees of Freedom
►Theories on Motor Learning

Motor Threshold

Definition
The minimal intensity of magnetic or electrical stimuli, which evokes muscle activation. Note that when stimulation is applied over the scalp, the motor threshold corresponds to the cortical threshold and can be taken as an estimate of the global excitability of the motor pathway.

►Transcranial Magnetic Stimulation

Motor Unit

Definition
The motor unit is a single motoneuron plus the number of muscle fibers it innervates. In fine movements made by, for example, the small muscles of the hand or the eye muscles, there are only a few muscle fibers per motor unit, whereas in large muscles like the gastrocnemius, a muscle used in walking, there are 2,000 muscle fibers per unit.

Motor Unit Action Potential

Definition
Extracellular potential detected when all of the muscle fibers in a single motor unit are stimulated.

►Electromyography

Motor Unit Enlargement

Definition
When some of the nerve supply to a skeletal muscle is disconnected to partially denervate the skeletal muscle, the nerve fibers or axons that have intact connections with muscle fibers can sprout axons to reinnervate denervated muscle fibers. Thereby each motor unit will include more muscle fibers than normal – motor unit enlargement.

►Axonal Sprouting in Health and Disease

Motor Units

Robert E. Burke
Laboratory of Neural Control, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Definition
First defined by Sherrington in 1925, the ►motor unit is the combination of an ►alpha motoneuron or a ►beta motoneuron (or motor neuron) and the set of extrafusal striated muscle fibers (called the ►muscle unit portion) that are innervated by it. ►Gamma motoneurons that exclusively innervate specialized muscle fibers in muscle spindle stretch receptor organs do not form conventional motor units. In normal limb and trunk

muscles, each muscle fiber in a muscle unit receives a synaptic contact, or ►neuromuscular junction, from the same motoneuron and no other. The motoneurons that innervate muscle units in a given muscle are arranged within the spinal cord or brain stem in localized groupings called "motor nuclei," which occur in predictable locations in the ventral horn of the spinal cord. From a functional standpoint, muscles are simply populations, or "pools," of muscle units arranged more or less in parallel to generate force.

Characteristics

Quantitative Description

Muscles vary widely in size and function, from tiny muscles that move the eyeball and eardrum, to relatively huge masses that control limbs and trunk movements. Motor unit populations exhibit an equivalent range of characteristics that represent important functional specializations. In limbs and trunk, the number of muscle units in a given muscle (or motoneurons in its ►motor nucleus) is usually larger in more massive muscles than in small ones, varying from dozens in small intrinsic finger muscles to hundreds in knee extensors in man. In normal muscles, the fibers in an individual muscle unit are intermingled with those of dozens of other units, such that few fibers of a given unit are contiguous. The average number of muscle fibers in a given muscle unit ("►innervation ratio") also varies in a similar pattern, i.e., generally larger in large muscles than in small ones. These generalizations do not apply to small, specialized muscles innervated by cranial nerves (e.g., extraocular muscles), which can contain many hundreds of individual muscle units, many of which receive innervation from more than one motoneuron.

Higher Level Structures

Motor units are the final elements in the control of body movements by the central nervous system. Motoneurons integrate synaptic information delivered by peripheral sensory afferents, local neural circuits within the spinal cord itself, and control signals descending from the brainstem and higher centers in the brain, to produce trains of action potentials that activate muscle units that generate output force. These control systems are organized to produce coordinated patterns of action by multiple motor nuclei.

Lower Level Structures

The motor units in virtually all mammalian muscles can be divided into two broad groups, called slow twitch or fast twitch, based on the mechanical, morphological, and biochemical properties of their muscle unit fibers (►muscle fiber types). In general, all fibers in a muscle unit display the same muscle fiber type. Slow twitch muscle units (called type S) contract relatively slowly because of the molecular forms of contractile and regulatory proteins that they contain. Type S generally produces relative small forces, but they exhibit great resistance to mechanical fatigue during prolonged activation because they contain a high proportion of enzymes and mitochondria that provide energy by efficient oxidative, or aerobic, metabolism. Fast twitch units obviously contract more rapidly because they have a different complement of contractile and regulatory proteins, and they exhibit a wide range of resistance to mechanical fatigue. In many muscles, the fast motor units fall into two subgroups, one (called type FR) that is much more resistant to fatigue than the other (called type FF). Although the FR and FF muscle units have slightly different molecular species of contractile proteins, the major difference between them is that FR units have higher concentrations of oxidative enzymes and mitochondria than the FF units. However, both FR and FF units have a relatively high abundance of enzymes that can metabolize substrates like glycogen anaerobically, while type S units have much less anaerobic capacity. Both FR and FF fibers contain large stores of glycogen, a polymerized sugar that represents a stored source of energy that enables them to function during short bursts of forceful activity. In contrast, type S fibers have relatively little glycogen and anaerobic enzymes. These differences have important functional consequences. In general, type S motor units produce the smallest force output, type FF units are the largest forces, and type FR units are intermediate. These differences are related to the numbers of muscle fibers in the respective muscle units (FF > FR > S), by differences in the cross-sectional areas of the individual fibers (FF ≥ FR > S), and, to a lesser degree, by the specific force that can be generated by each fiber (FF = FR > S).

Structural Regulation

Motoneurons differentiate early during embryonic spinal cord formation and migrate to the ventral part of the gray matter. The motoneuron axons that will innervate a specific muscle leave the spinal cord via the ventral roots and find their way to the primordial muscle, where they branch repeatedly to make neuromuscular synaptic junctions on the newly formed muscle fibers. During fetal and early postnatal life, immature muscle fibers receive innervation from multiple motoneurons. However, this polyneuronal innervation subsequently disappears during a competitive process that leaves only one motoneuron per muscle fiber in the mature muscle. At the same time, muscle fibers differentiate into the three major types described above. There is evidence for a strong element of genetic pre-specification of both motoneurons and muscle fibers, which results in the relative proportions of the different ►motor unit types found in various muscles.

Higher Level Processes

Increasing and decreasing the number of motor units active in a given muscle (►recruitment and de-recruitment, respectively) is the major mechanism by which the central nervous system adjusts muscle force. The identities (i.e., types) of the active motor units are also critical to this process. Under many conditions, units in a given muscle (a motor unit pool) are recruited in a predictable sequence starting with type S, progressing to include type FR, and ending with type FF units as more and more force is required. De-recruitment ordinarily follows the reverse sequence. This sequence is often referred to as the "size principle," because the first units (type S) recorded generally produce small forces, while the largest force (type FF) units are normally activated only when maximum force is demanded. Simultaneous activation of an entire motor unit pool can occur in sudden, ballistic movements. In unusual situations, such as rapid alternating movements, there may be selective recruitment of the larger, fast twitch units. A second mechanism for force control, often called "rate coding," involves highly non-linear relations between the frequency and pattern of motoneuron firing and the force output from its muscle unit. Orderly recruitment sequences and rate coding both depend on interactions between intrinsic properties of the motoneurons themselves and the organization of synaptic input to them.

Lower Level Processes

The motoneurons of type S motor units exhibit greater intrinsic excitability than those of the fast twitch units because of a complex interaction between their smaller size, the higher density of certain synaptic input systems, and the influence of active membrane conductance channels that promote repetitive firing. Certain voltage-sensitive conductances (including calcium and persistent sodium channels), located mainly in motoneuron dendrites, can produce self-sustained depolarization ("plateau potentials") and firing under certain conditions, particularly in the presence of neuromodulator substances such as serotonin. Specialized membrane conductances activated by action potentials produce after hyperpolarizations that limit the maximum frequencies at which motoneurons can fire, which are lower in slow than in fast twitch cells. These features of motoneurons fit the properties of their muscle units. Type S units attain their maximum force output at lower frequencies than fast twitch units. The pattern of motoneuron firing also affects force output, because insertion of short intervals in a train can generate sustained, non-linear enhancement of output force.

Process Regulation

The properties of muscle units are malleable to some extent by usage. For example, endurance exercise training (e.g., distance running) can greatly enhance the oxidative capacity of muscle fibers, as well as their blood supply. Muscle fibers shrink somewhat, facilitating oxygen and substrate entry, which increases their resistance to fatigue at the price of some loss of overall force capacity. On the other hand, resistance training (e.g., weight lifting or sprint running) favors growth of muscle fiber diameter (hypertrophy), particularly among the fast twitch fibers, greatly enhancing force production but with little change in oxidative capacity or fatigue resistance. Neither form of exercise training produces significant change in the molecular nature of the contractile or regulatory proteins in muscle fibers (i.e., fiber types remain basically unaltered).

Function

Motor units are the quantum elements in all movements. Type S motor units are ideally suited to maintain posture, which requires sustained activity without fatigue but generally small forces. Precise postural adjustments can be made by recruitment and de-recruitment of the small force type S units. Movements that are more vigorous like walking and running require more rapid contraction with moderate forces, with considerable resistance to fatigue. Such actions can be generated by recruitment of the type FR units. Greater force demands, such as during jumping and lifting heavy weights, are intermittent actions that need power but little fatigue resistance. Recruitment of the large force but fatigue-sensitive type FF motor units occurs mainly during this type of activity. The proportions of S, FR, and FF motor units in different limb and trunk muscles accurately reflect differences in the way muscles are used in different mammals. Muscle units with greater oxidative capacities exert a relatively high cost on metabolic maintenance, so their proportions are adjusted quite precisely to fit lifestyle demand.

Pathology

The most common cause of motor unit dysfunction is trauma to peripheral nerves. Motoneurons usually survive damage to their axons unless the site is very close to the spinal cord. ►Motor axons have considerable ability to re-grow to reinnervate muscles, although the specificity found in the original process during embryonic life is largely lost in adult animals. Muscle fibers that are reinnervated after nerve damage are re-specified to the type dictated by the motoneuron, but there is eventually some return to the coordinated properties described above. Motoneurons are especially susceptible to viral infection in poliomyelitis, which can cause cell death and permanent disability. There are several neurodegenerative diseases that cause motoneuron death, the most well known being amyotrophic lateral sclerosis (ALS). In most victims, these dreadful diseases progress inexorably to complete motor disability.

Therapy

Prompt surgical repair to injured peripheral nerves can result in good recovery of motor functions, although the process is slow. Happily, thanks to vaccination programs, poliomyelitis has almost disappeared in industrialized countries. Unhappily, the cause of motoneuron degeneration in ALS and allied disorders remains unknown, and there are no effective therapies for them.

References

1. Binder M, Heckman C, Powers R (1996) The physiological control of motoneuron activity. In: Rowell L, Shepherd J (eds) Handbook of physiology. Oxford University Press/ American Physiological Society, New York, pp 3–53
2. Burke RE (2001) The structure and function of motor units. In: Karpati G, Hilton-Jones D, Griggs R (eds) Disorders of voluntary muscle. Cambridge University Press, Cambridge, UK, pp 3–25
3. Burke RE (1981) Motor units: anatomy, physiology and functional organization. In: Brooks VB (ed) Handbook of physiology, vol. II. American Physiological Society, Washington, DC, pp 345–422
4. Edgerton VR, Bodine-Fowler S, Roy RR, Ishihara A, Hodgson JA (1996) Neuromuscular adaptation. In: Rowell LB, Shepherd JT (eds) Handbook of physiology. Oxford University Press, New York, pp 54–88
5. Kernell D (1992) Organized variability in the neuromuscular system – a survey of task-related adaptations. Arch Ital Biol 130:19–66
6. McComas AJ (1996) Skeletal muscle: form and function. Human Kinetics, Champaign, IL
7. Powers R, Binder M (2001) Input–output functions of mammalian motoneurons. Rev Physiol Biochem Pharmacol 143:137–263
8. Winderbank A, Mulder D (1994) Motor neuron disease in adults. In: Engel A, Franzini-Armstrong C (eds) Myology, 2nd edn. McGraw-Hill, New York, pp 1854–1869
9. Zajac FE (1990) Coupling of recruitment order to the force produced by motor units: the "size principle hypothesis" revisited. In: Binder M, Mendell L (eds) The segmental motor system. Oxford University Press, New York, pp 96–111

Movement Direction

Definition

The line or course pursued by a moving body part (e.g. the hand). If the position in space of the body part, at a given instant, is represented by a vector (i.e. a triple of coordinates in a specific reference frame), its motion is described by a vector-valued function of time (movement trajectory). The time derivative of this function, the movement velocity, is a vector-valued function. At each instant, this vector is tangent to the trajectory and describes the instantaneous direction of movement as well as the instantaneous rate of change of the distance traveled along the trajectory (speed or tangential velocity).

►Reaching Movements

Movement Discrimination

►Proprioception and Orthopedics

Movement Field (of a Neuron)

Definition

The region of space that will elicit a discharge in a motor-related neuron when movements are directed to the region. In particular, for eye movements, movement fields are regions of visual space for which saccade-related neurons will discharge when the saccade terminates in the region.

►Saccade, Saccadic Eye Movement
►SC – Motor Map terminates in the region

Movement Field (of Saccade-related Neurons)

Definition

The oculomotor space occupied by saccades accompanied by the discharges of the neuron in question (often defined in retinotopic coordinates but other coordinate systems are sometimes used).

►Saccade, Saccadic Eye Movement
►SC – Tectal Long-Lead Burst Neurons

Movement (or Motor) Planning

Definition

Processes whereby the global goal of the action is strategically defined, and the sequence of elementary

movements between intermediate goals is organized. These processes are based on the use of a large set of sensory and memorized information about the subject's environment, as well as on the subject's motivational drive resulting from the behavioral value of the anticipated outcome of the upcoming action.

►Eye-Hand Coordination

Movement (or Motor) Programming

Definition

The motor program comprises all information necessary to send to the motor apparatus the motor commands to execute a movement. Whereas movement planning processes specify how the global action will be implemented, motor programming processes are invoked for the detailed preparation of each individual movement (localization of the target, choice of a desired final posture and/or trajectory, and of response duration or speed, …). The result of this pre-movement programming phase is a set of motor commands which, when launched will activate the motor apparatus in a proper way to bring the effector close to its desired position (even accurately programmed movements require additional online control to reach optimal accuracy).

►Eye-Hand Coordination

Movement Sense

Janet L. Taylor
Prince of Wales Medical Research Institute and University of New South Wales, Sydney, NSW, Australia

Synonyms

Kinesthesia; Proprioception

Definition

Movement sense is the process by which movements of parts of the body relative to one another are perceived. The sense includes detection of movements as well as sensations that convey the timing, distance and velocity of such movements. Examples of such movements include movements about a single joint e.g. bending the elbow, simple movements about multiple joints e.g. turning the head and complex movements about multiple joints e.g. closing the hand. Both passive movements, which are imposed on body parts by an external force while the muscles remain relaxed and active movements, which are made by the contraction of muscles, can be perceived. It is difficult to separate movement sense from position sense. A movement is a change of position and a position can only be reached by a movement. However, if a change of position is imposed extremely slowly, then no sensation of movement arises. This implies that joint position and movement can be sensed separately.

Characteristics

Quantitative Description

Movement sense can be tested by determining the smallest imposed movement that subjects can detect with the muscles relaxed [1]. Such testing has been performed for movements about most joints in the limbs and for movements of the neck and trunk. For all joints, faster movements can be detected more easily than slower movements. At velocities >1°/s, movements of 0.1–0.5° are commonly reported as detectable at limb joints and for rotation of the neck and trunk. At slower velocities (down to 0.1°/s) larger amplitudes (∼1–3°) are needed for movements to be detected. At even slower velocities (<∼0.1°/s), the threshold amplitude for detection no longer depends on velocity and subjects have no sensation of movement. Here, subjects detect change of position. The movement velocity is below that required to engage the movement sense. At the interphalangeal joints of the fingers and toes, much larger movements are needed for detection. The big toe has the largest reported detection thresholds (∼2° for velocities >10°/s and ∼20° at 1°/s) [2]. Movements can also be imposed during muscle contraction. It is not clear whether detection of movement is improved or impaired by active contractions as both results have been reported.

Movement sense includes the perception of velocity of movement. Discrimination between velocities of imposed movement has been tested at the finger, elbow and shoulder joints. Subjects are able to detect smaller differences in velocity when the reference velocity is slower. For movements of ∼50°/s, differences of ∼10°/s can be discriminated. For movements of 15°/s, differences of ∼4°/s can be discriminated at the elbow. At the shoulder, differences as small as 2°/s can be detected. When subjects match the velocity of an imposed movement with a movement of the other limb they are accurate to within ±5°/s over a range of velocities from 15°/s to 78°/s [3].

Higher Level Structures

Movement sense is one of the components of the sense of proprioception, which allows perception of events intrinsic to the body. The other senses of vision, hearing, touch, taste and smell allow perception of events outside the body. Of all the senses, proprioception is most closely connected with the control of voluntary movement. Explicit knowledge about the body can be used to plan and direct movements. In addition, neural signals that contribute to the sense of proprioception can act directly at different levels of the motor system to influence muscle contractions.

Lower Level Components

Perception of movements of parts of the body involves sensory receptors in the muscles, in the skin and in the joints. Muscle spindle primary endings are activated dynamically by stretching of the muscle. They respond to the velocity and acceleration of muscle stretch. Slowly adapting type II endings respond to the skin stretch that accompanies joint movements. Receptors located in joint capsules and ligaments respond to stretch of these structures. All of these sensory receptors are at the termination of fast conducting afferent neurons, which have cell bodies in the dorsal root ganglia. Signals from the receptors are mostly conveyed via these neurons directly to the medulla, although signals from the muscle receptors in the legs pass through a synapse in the spinal cord. From the medulla, signals are conveyed via the thalamus to the contralateral primary somatosensory cortex. The signals also go to other areas of the brain including the secondary somatosensory cortex, motor cortical areas and the cerebellum.

Higher Level Processes

Central Nervous System

Signals from muscle, joint and skin receptors are all conveyed to the contralateral primary somatosensory cortex. Imaging studies show that a number of other cortical areas are also activated when movements are imposed on a limb or when illusions of movement are generated by tendon vibration. These include the secondary somatosensory cortex, primary motor cortex, supplementary motor area, supplementary somatosensory area and the primary and associative auditory cortex [4]. The specific functions of the different cortical areas in perceiving movements are not known. However, the activation of the primary motor cortex appears to be strongly related to the perception of illusions of movement [5]. The cerebellum and basal ganglia are also activated by passive movements. Additional areas of the brain are activated during voluntary movements. One of these areas, the superior parietal lobe, may aid in matching internal knowledge about the production of the movement with the afferent signals that the movement generates [6].

Lower Level Processes

Sensory Receptors

Sensory receptors in the muscles, joints and skin respond both when movements are imposed on parts of the body and during movements made through active contraction of muscles.

Muscle Spindles

Muscles on one side of a joint lengthen with a movement while those on the other side shorten. Muscle spindles lie in parallel with muscle fibers and respond to lengthening of muscles. They contain two types of sensory endings, primary and secondary muscle spindle endings. While both types of endings increase their firing with stretch of a muscle, the primary endings have a larger dynamic response. They respond to the velocity of a stretch and to its acceleration, as well as to the change in length. Primary muscle spindle endings are major contributors to the sense of movement. Activation of these endings by vibration over the tendon of a muscle can generate an illusion of movement [7]. For example, when vibration is applied over the tendon of the biceps brachii, subjects feel that the arm is moving into extension. Higher frequencies of tendon vibration generate faster illusory movements. This implies that the velocity of movement is encoded by the frequency of firing of the muscle spindle endings.

Muscle spindles are under the control of the nervous system. In actively contracting muscles, muscle spindles fire in response to output from the nervous system as well as to any stretch of the muscle. Despite this complication, signals from the contracting muscle are still interpreted as movements.

Joint Receptors

Joint receptors are located in joint capsules and ligaments and respond to stretch of these tissues. Although most joint receptors fire near the ends of joint range, occasional receptors signal joint angle across the range of movement and could contribute to a sense of joint movement. When the axons of individual joint afferents are stimulated in humans, sensations of joint movement including twisting are reported. Muscle contraction can increase the stress on joints and ligaments and can increase signals from joint receptors.

Skin Receptors

Some areas of skin are stretched during movement of parts of the body. For example, in the leg, when the knee is bent, the skin over the kneecap is stretched while that behind the knee is compressed. Slowly adapting type II

(SAII) receptors in the skin fire in response to the direction, speed and extent of stretch and are therefore likely to contribute to the sense of movement. Illusions of movement of the fingers can be generated by pulling on the skin over the joints to mimic the stretch and compression of the skin that usually accompanies joint movement.

Function

Sensory

Movement sense allows detection of movements imposed on parts of the body and perception of the velocity and timing of such movements. It also allows perception of the velocity and timing of movements made by active muscle contractions and of movements to which external forces and muscle contractions both contribute. Perception of movements imposed by external forces including gravity allows reaction to such perturbations to prevent injury. Ongoing knowledge of where and how the parts of the body are moving is crucial for motor control.

Movement signals can be processed in conjunction with various other proprioceptive signals.

1. Perception of the current position of the parts of the body has contributions from movement sense, position sense and sensations of muscle force and effort. Limb positions are most accurately detected immediately after movement to a new position.
2. Judgment of weight combines sensations of muscle force and effort with movement sense. If an object does not move when force is applied, its weight cannot be judged.
3. Judgment of stiffness also relies on sensations of muscle force and effort combined with movement sense.
4. Perception of the orientation and movement of the trunk relative to the outside world combines vestibular sensations, which signal position and movement of the head relative to the world, with sensations of movement and position from the neck.

Together with other senses, like vision and touch, proprioceptive sensations including movement sense generate a body image and awareness of self. If illusions of arm movement are generated by activating muscle spindles with tendon vibration while a person touches a finger to their own nose, remarkable changes in body image can occur, e.g. the nose may seem to grow or may feel like it is pushed into the face.

Motor Control

Apart from providing perceptions, the signals that convey sensations of movement as well as other proprioceptive signals are integrated into the motor system. Movement sense provides feedback for the control of movement. Even common movements like lifting a cup to the lips, do not always require the same muscle activity. When the cup is full it is heavier and the movement requires more muscle activity than when the cup is empty. Feedback of the results of motor output is crucial to guide the muscle activity. Even if an action is too fast to allow ongoing correction, the sensations of movement can be used to adjust motor output in subsequent attempts, i.e. movement sense is used when learning motor tasks through repetition.

Coordination of muscle actions about different joints also relies on movement signals. For example, if a ball is thrown to hit a target, the hand must be opened when the velocity and direction imparted by shoulder, wrist and elbow movements are appropriate [8].

Pathology

Impairment of movement sense can occur with non-pathological occurrences like muscle fatigue as well as in a range of pathological conditions. These include:

1. Musculoskeletal disease or injury including sprains, ligament damage, osteoarthritis, back pain, whiplash
   Impairment can result from change in the mechanical properties of the tissues around the sensory receptors. Pain without tissue changes can also impair movement detection. This may occur through a reduction in muscle spindle sensitivity or through interactions in the central nervous system.
2. Peripheral nerve injury or peripheral neuropathy
   Whether it occurs through disease or injury, damage to the neurons that carry the movement signals from the periphery to the spinal cord, will impair movement sense in the affected region.
3. Lesions or pathology in the central nervous system
   Lesions anywhere in the sensory pathway to the cortex, e.g. in the spinal cord, brainstem or thalamus
   i. *Basal ganglia lesions.* Patients with Parkinson's disease have a reduced ability to detect passive movements.
   ii. *Cerebellar lesions.* Patients with cerebellar pathology have a normal ability to detect passive movements but have impaired discrimination of velocity and duration.
   iii. *Cortical lesions.* Lesions of the primary somatosensory cortex can lead to loss of movement sense. Lesions of somatosensory association areas can impair kinesthesia [9]. Lesions of other areas (e.g. secondary somatosensory cortex, superior parietal lobule) may disrupt the perception of active movements.

►Proprioception Role of Joint Receptors

References

1. Goldscheider A (1889) Untersuchungen über den Muskelsinn. Arch Anatomie und Physiologie, Leipzig 3:369–502
2. Refshauge KM, Taylor JL, McCloskey DI, Gianoutsos M, Mathews P, Fitzpatrick RC (1998) Movement detection at the human big toe. J Physiol 513:307–314
3. Kerr GK, Worringham CJ (2002) Velocity perception and proprioception. Adv Exp Med Biol 508:79–86
4. Radovanovic S, Korotkov A, Ljubisavljevic M, Lyskov E, Thunberg J, Kataeva G, Danko S, Roudas M, Pakhomov S, Medvedev S, Johansson H (2002) Comparison of brain activity during different types of proprioceptive inputs: a positron emission tomography study. Exp Brain Res 143:276–285
5. Naito E, Roland PE, Ehrsson HH (2002) I feel my hand moving: a new role of the primary motor cortex in somatic perception of limb movement. Neuron 36:979–988
6. MacDonald PA, Paus T (2003) The role of parietal cortex in awareness of self-generated movements: a transcranial magnetic stimulation study. Cereb Cortex 13:962–967
7. Goodwin GM, McCloskey DI, Matthews PB (1972) The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. Brain 95:705–748
8. Cordo PJ (1990) Kinesthetic control of a multijoint movement sequence. J Neurophysiol 63:161–172
9. Roland PE (1987) Somatosensory detection of microgeometry, macrogeometry and kinesthesia after localized lesions of the cerebral hemispheres in man. Brain Res 434:43–94

Movement Sequences

John F. Soechting
Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA

Definition

It has long been hypothesized that complex movements are generated by concatenating simpler, elementary movements in a serial order. This hypothesis seems intuitively obvious for motor behaviors such as speech, handwriting and typing, the elementary movements in these instances being the vocalization of phonemes, the generation of individual letters or strokes and the production of targeted keypresses. However, the hypothesis has been extended more generally to skilled motor tasks. With respect to this hypothesis several questions (that have been addressed experimentally to varying degrees) arise: (i) How is the proper serial order of elements in a sequence established? (ii) To what extent is there overlap between the expression of elements in the sequence and to what extent does the expression of one element depend on the preceding and succeeding movement in a sequence? and (iii) What are the properties of elemental movements?

Characteristics

The strongest evidence that complex movements are generated by serially ordering simpler movements arises from motor deficits following damage to the frontal lobe in human subjects [1]. For example, Luria [2], in patients with damage to the premotor region, described the phenomenon of ►perseveration of movement, which he defined as the "continuation of a voluntary movement once it has started." On simple tasks such as drawing a circle, this deficit was expressed as the repeated production of the same circle. However, on more complex tasks, such as drawing a human figure, only some individual elements such as the fingers or the legs were drawn repeatedly. Additional evidence in favor of this hypothesis is provided by spontaneous errors in normal subjects, especially in speech and typing. In such behaviors, errors in serial ordering are not uncommon; most typically, they involve the transposition of adjacent phonemes or keystrokes.

Serial Ordering

The question of how a proper serial ordering of elements in a sequence would be established was taken up in an influential work by Lashley [3] in 1951. He considered two alternative processes according to which serial order of a movement sequence could be established. In one, the associative chaining theory, each element in a sequence would trigger the generation of the succeeding element. For example, a sensory event signaling the completion of one element could trigger the initiation of the next one. Based primarily on spontaneous errors in speech and typing, Lashley argued against this hypothesis in favor of an alternative, in which all elements of a sequence are prepared in parallel. He left open the problem of how one particular element would be selected at the proper time. One possibility would be that the element that was most strongly represented in neural activity at any point in time would be translated into action, and that representations for individual elements could mutually inhibit each other.

The question is still largely unresolved. However, recently Averbeck et al. [4] have provided electrophysiological evidence in support of Lashley's proposition. They recorded activity of prefrontal cortical neurons while monkeys performed a task that required them to copy geometric figures such as squares and triangles by moving a joystick to control the motion of a cursor on a screen. They used standard criteria (minima in speed, see below) to determine the extent of each

segment. Distinct patterns of activity of neural ensembles (obtained from averages over each of the segments) were used to determine classifiers for each of the segments, using discriminant analysis. They then used these classifiers to determine the extent to which each of the segments was represented at different intervals during a trial. Their main result is presented in Fig. 1, which shows the average over all ensembles when the monkey drew a square, consisting of five segments. The fact that the strength of the representation for a particular segment is maximal when that segment is drawn is not remarkable, since that was the basis for constructing the classification scheme.

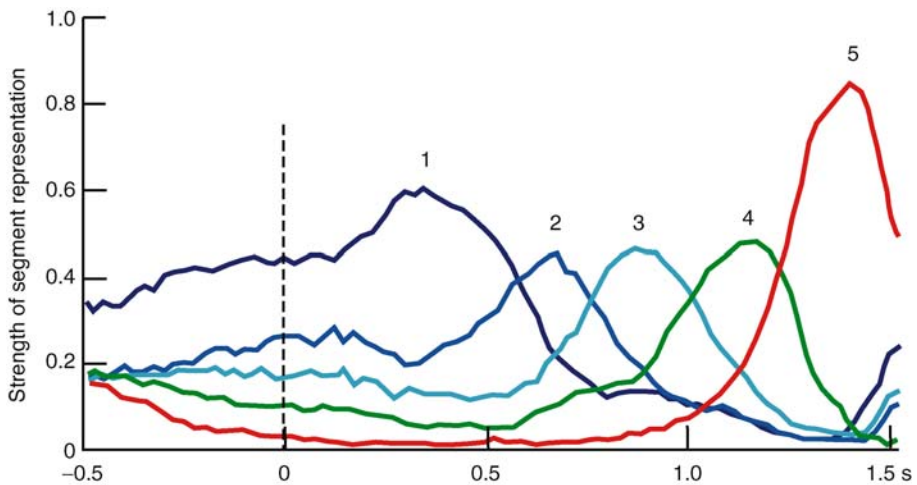
However, it is remarkable that the strength of representation throughout the trial, and in particular prior to the onset of the drawing at time 0, reflects the temporal order in which the segments were drawn.

Serial Execution

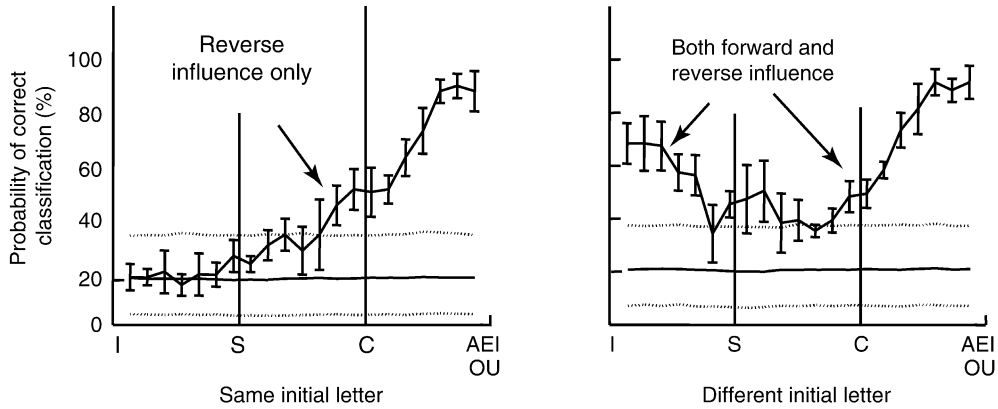
Assuming all of the segments of a movement sequence are planned in parallel, this still leaves open the question of how they are executed. Specifically, parallel planning would still be consistent with the possibility that each of the segments is executed in strict sequential order, without overlap. Such a possibility would imply that the kinematics of each segment would be identical to the kinematics if that segment were executed in isolation. This question has been addressed most extensively in speech, where it is known that the acoustic quality of a given phoneme can depend on the phonemes that precede and follow it, a phenomenon known as coarticulation [5]. The motions of the articulators responsible for sound production are difficult to measure, thus little is known about exactly how they are modified in generating words from individual phonemes.

The evidence from studies in limb motions suggests that, in that case, there is a preference to produce segments in a strictly serial fashion. Thus in typing [6], it was found that the finger and hand movements to generate a particular keypress did not depend on the preceding or subsequent keypress. Anticipatory modification of hand movements was observed in some instances in piano playing, for example in executing the thumb-under maneuver as a pianist played an ascending scale [7]. The clearest evidence for the equivalent of coarticulation was provided by a study of fingerspelling by signers fluent in American Sign Language [8]. In that study, signers spelled a set of words, all containing the same set of three letters (e.g., "*isc*") but with different vowels following the trigram. In one set of trials, the letter preceding the trigram was always the same, whereas in another set, each terminal vowel was associated with a different initial letter (Fig. 2).

Hand and finger movements were recorded as the signers spelled the words, and discriminant analysis was used to determine the time at which the final vowel could be predicted from the handshape. As is shown in Fig. 2, there was an anticipatory modification of the handshape about 1.5 letters prior to the generation of the vowel (reverse influence, beginning between the "*s*" and the "*c*"). A particular letter also influenced subsequent handshapes (forward influence in right panel of Fig. 2).



Movement Sequences. Figure 1 Strength of representation of movement segments in the activity of prefrontal cortical neurons as a function of time. The drawn shape (a square) consisted of five segments and the traces depict the proportion of neuronal ensembles whose pattern of activity encoded a specific segment at a given time. Note that the relative strength of representation encodes the serial order in which the segments were drawn. Adapted from [4].



Movement Sequences. Figure 2 Probability of correctly predicting the vowel following the trigram "*isc*" from the shape of the hand during fingerspelling in American Sign Language. The letters at the bottom of each panel denote the time at which handshape was static; intervening points denote the transition from one handshape to another. The solid horizontal line at 20% indicates chance performance, and the dotted lines indicate 95% confidence limits. In the left panel, the letter preceding the "*i*" was always the same; in the right panel it was different for each of the vowels following the "*c*." Adapted from [8].

The modifications of the finger movements during signing could take two different forms: a "dissimilation" in which differences between the handshapes for subsequent signs were emphasized, and an "assimilation" in which the motion at a joint was minimized during the transition from one handshape to the next one. Assimilation and dissimilation were found to occur, at different joints, in the same movement sequence, suggesting a sophisticated level of control of the execution as well as the planning of serial movements.

Defining Segments in a Movement Sequence

This topic has received relatively little attention and the question is largely unresolved. Investigators have typically assumed that each segment of a sequence would have the same kinematic characteristics as a simple movement executed in isolation. Since such simple movements typically demonstrate a "bell-shaped" speed profile, kinematic landmarks such as local minima in speed have been used to demarcate individual segments. In other instances, abrupt changes in the plane of limb motion have been observed [9], and they have been assumed to denote transitions from one segment to another. Neurons in the supplementary and presupplementary motor area (SMA) have been shown to encode the transition from one segment to another while other neurons encoded the rank order of a particular movement [10]. Thus it appears possible to answer this question more definitively on the basis of neural activity.

References

1. Ashe J, Lungu OV, Basford AT, Lu X (2006) Cortical control of motor sequences. Curr Opin Neurobiol 16:213–221
2. Luria AR (1966) Higher cortical functions in man. Basic Books, New York
3. Lashley KS (1951) The problem of serial order in behavior. In: Jeffress LA (ed) Cerebral mechanisms in behavior. Wiley, New York, pp 112–136
4. Averbeck BB, Chafee MV, Crowe DA, Georgopoulos AP (2002) Parallel processing of serial movements in prefrontal cortex. Proc Natl Acad Sci USA 99:13172–13177
5. Kent RD, Minifie FD (1977) Coarticulation in recent speech production models. J Phonetics 5:115–133
6. Soechting JF, Flanders M (1992) Organization of sequential typing movements. J Neurophysiol 67:1275–1290
7. Engel KC, Flanders M, Soechting JF (1997) Anticipatory and sequential motor control in piano playing. Exp Brain Res 113:189–199
8. Jerde TE, Soechting JF, Flanders M (2003) Coarticulation in fluent fingerspelling. J Neurosci 23:2383–2393
9. Soechting JF, Terzuolo CA (1987) Organization of arm movements: motion is segmented. Neuroscience 23:39–51
10. Shima K, Tanji J (2000) Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. J Neurophysiol 84:2148–2160

Movement Time

Definition

The time from the onset of a movement to its end, usually derived by setting a threshold on speed.

►Movement Sequences
►Eye-Hand Coordination

Movement Velocity

Definition

Movement velocity is the first derivative of 3D position.

►Motor Control Models

Moving-Average Model

Definition

A model of a system as a differential equation where the output at a given time instant is a linear combination of the inputs at previous time instances and at the current time.

►Signals and Systems

MRI

Definition

►Magnetic Resonance Imaging

mRNA

Definition

Messenger RNA is the intermediate between information encoded on the DNA and the ribosomes that translate this information into proteins. DNA is transcribed into mRNA after which ribosomes read the information encoded on triplets of the RNA bases, and translate it into a polypeptide chain.

mRNA Targeting: Growth Cone Guidance

Barbara Lom
Biology Department and Program in Neuroscience, Davidson College, Davidson, NC, USA

Synonyms

Local protein synthesis; Axonal RNA translation; Translational regulation; Local translation; Extrasomatic translation; Compartmentalized protein synthesis; Cytoplasmic mRNA localization; RNA localization

Definition

Growing axons are tipped by highly dynamic and motile growth cones that navigate through the brain by detecting and responding to guidance molecules. When a growth cone reaches its target location it transforms into a presynaptic terminal. Thus, accurate growth cone guidance is critical in establishing functional brain circuitry. Messenger RNA (mRNA) targeting to growth cones refers to the selective transport of specific mRNAs along an axon out to the growth cone so translation of these mRNAs can occur locally within the growth cone, away from the soma. Growth cones contain protein synthetic machinery including ribosomes, translation factors, and specific mRNAs. Previously it had been thought that proteins were synthesized in the cell body then transported to specific regions of the neuron, but evidence now indicates that some mRNAs can be translated into proteins locally within the growth cone and this local translation is required for growth cones to respond to a variety of guidance cues. mRNA targeting allows new protein supplies to be rapidly and regionally mobilized that change growth cone motility via ►cytoskeletal alterations and change growth cone sensitivity to guidance cues by up- or down-regulating receptor expression.

Characteristics

Growth Cones

Neurons are extremely polarized cells with axons that extend long distances from the cell body. Most proteins are thought to be synthesized and modified in the cell body then transported along the axon via fast and slow axonal transport mechanisms. The growth cone region has autonomous local navigation and steering mechanisms because growth cones can navigate accurately *in vitro* and *in vivo* even after being separated from their somas. A variety of guidance molecules (including extracellular matrix components, secreted factors, and molecules associated with the membranes of other cells) steer growth cones by signaling through specific

receptors expressed on the growth cone. When a growth cone detects an attractive or repulsive guidance cue (or combination of cues) the growth cone's shape, trajectory, and/or motility are altered to steer it toward its appropriate target and/or away from inappropriate regions. Specific guidance molecules are located at precise locations along a growth cone's route and the growth cone's responsiveness to these guidance cues can change dramatically as the expression of specific receptors are up- or down-regulated *en route*. Rapid changes in ►cytoskeletal structure underlie a growth cone's remarkable motility. A growth cone's ►cytoskeleton contains both microfilaments and microtubules, with actin-based microfilaments occupying the growth cone's particularly dynamic finger-like filopodia that sample the molecular terrain and steer the axon's growth. Guidance cues trigger changes in growth cone trajectories by inducing asymmetric filopodial extension and/or collapsing particular regions of a growth cone. Translation of mRNAs targeted to the growth cone can cause rapid and localized changes in protein composition that are necessary for accurate growth cone navigation.

Protein Synthetic Machinery Localized to Growth Cones

Growth cones are equipped to synthesize proteins locally. Essential components of protein synthetic machinery including polyadenylated mRNAs, polyribosomes, ribosomal RNA, and factors that regulate translation such as elongation factors, ►ZBP, and ►RNA interference (RNAi) have been observed within vertebrate growth cones [1,2]. Functional evidence for local translation comes from experiments that separated growth cones from their cell bodies and measured the synthesis of new proteins in isolated growth cones [3]. The ability of isolated growth cones to navigate properly without contributions from somatic protein synthesis suggests that the cellular machinery to detect and respond to guidance cues is contained within the growth cone. Guidance molecules can functionally alter translation factors within growth cones. For example, the guidance cues netrin-1 and semaphorin 3A (Sema3A) cause a rapid rise phosphorylation of eIF-4PB1, which liberates the translation initiation factor eIF-4E [3]. The identities of mRNAs targeted to growth cones have not yet been thoroughly cataloged, but many of the mRNAs identified thus far code for proteins that comprise, influence, and/or associate with the cytoskeleton [4]. As an example, β-actin mRNA has been observed in association with microtubules in growth cones and has been implicated as a key player in protein synthesis dependent growth cone guidance [2,5].

Growth Cone Responses to Guidance Cues Require Local Protein Synthesis

In just the past few years it has become apparent that local protein synthesis is involved in several distinct and important aspects of growth cone responsiveness to molecular guidance cues: directed movement, ►cytoskeletal organization, receptor expression, and sensitization. For example, neurotrophin-3 (NT-3) can stimulate axon elongation and act as a guidance cue for growth cones that express the appropriate neurotrophin receptor(s). Within minutes, NT-3 application causes β-actin mRNA to localize to growth cones *in vitro* in a cAMP-dependent manner [6]. NT-3-regulated β-actin mRNA localization to the growth cone requires interaction of the ►zipcode sequence in β-actin mRNA's ►3′ untranslated region (UTR) with ►zipcode binding protein 1 (ZBP1) to form ribonucleoprotein particles (RNPs). RNPs are heterogeneous complexes of translational components that can include ribosomes, mRNA binding proteins, elongation factors, and mRNAs. RNPs are thought to be transported by motor proteins to targeted subcellular locations where they become tethered to the ►cytoskeleton and translation regulators then allow precisely localized translation of targeted mRNAs. The identities of specific mRNA ►zipcode sequences and the ways they interact with other molecules to form RNPs are currently being elucidated. Experimentally disrupting interactions between β-actin mRNA's ►zipcode region and ►ZBP1 revealed that zipcode-ZBP1 binding is essential to the mRNA localization, protein levels, and growth cone mobility [6].

Several well-characterized guidance cues stimulate local translation within growth cones. Normally growth cones change their trajectory dramatically toward a netrin-1 gradient and turn away or collapse when they encounter Sema3A. When the ability to synthesize new proteins is pharmacologically inhibited, isolated growth cones cannot respond to either the attractive netrin-1 or the repulsive Sema3A guidance cues [3]. Other guidance cues including Slit2 and BDNF (brain-derived neurotrophic factor) also require protein synthesis to guide growth cones [2,4]. Thus, local protein translation is critical to a growth cone's ability to respond to a variety of guidance molecules in its pathway.

Translation of mRNAs within the growth cone also plays a critical role in regulating a growth cone's ►cytoskeleton. Evidence comes from observations of asymmetrical β-actin translation in growth cones orienting in response to netrin-1 gradients [5] and BDNF gradients [2]. When netrin-1 is presented on one side of a growth cone, a homolog of ZBP1 rapidly translocates into filopodia and both the translation initiation regulator 4EBP and β-actin translation become rapidly enhanced on the side nearest the netrin-1 source. These translational asymmetries within the growth cone are observed even before growth cones physically turn toward an attractive netrin source, indicating a netrin-induced mechanism can bias actin polymerization to steer growth cones. In another example of local translation affecting growth cone ►cytoskeleton and motility, the

repulsive guidance molecule Sema3A induced localized translation of RhoA, a member of the Rho family of small GTPases that are widely implicated in regulating actin alterations underlying filopodial dynamics [7]. RhoA transcripts localize to growth cones via targeting sequences with their ►3′ UTR and localized RhoA translation is necessary for Sema3A-induced growth cone collapse. In addition, the repulsive cue Slit2 initiates both a protein synthesis dependent decrease in growth cone F-actin and an increase in the actin depolymerizing protein cofilin within growth cones [4]. Taken together, these studies indicate that local translation of proteins that compose or influence the ►cytoskeleton can play critical roles in steering growth cones toward attractive cues and in collapsing in response to repulsive cues.

Local translation also alters a growth cone's responsiveness to guidance cues. Evidence for this role emerged from experiments that examined local translation in the distal regions of developing spinal axons as they crossed the midline of the spinal cord. These axons are initially attracted to the midline but after they have reached and crossed the midline their responsiveness to guidance cues expressed at the midline changes, presumably to prevent the axon from getting trapped at this intermediate target and/or to allow the axon to respond to subsequent cues that will guide it to its ultimate target. The EphA2 receptor is normally expressed in the distal regions of some spinal commissural axons after they have crossed the midline. When RNA containing a sequence in the ►3′ UTR of the EphA2 receptor fused with a green fluorescent protein (GFP) reporter construct was introduced into these neurons, GFP was expressed within growth cones only after crossing the midline, spatially and temporally similar to EphA2 expression [8]. Moreover, growth cones separated from their cell bodies demonstrated similar upregulation of gene expression, indicating that growth cones are capable of local protein synthesis. While this study did not demonstrate the existence of endogenous EphA2 mRNAs in growth cones, it suggests a plausible mechanism by which local translation could rapidly alter the expression receptors on a growth cone. In addition to changes in growth cone receptor expression, growth cones can adapt to persistent guidance cues, demonstrating desensitization and resensitization behaviors *in vitro*. Local protein synthesis is required for the resensitization phase of adaptation in netrin-1, BDNF, or Sema3A gradients [9]. Thus, changing a growth cone's responsiveness to guidance cues uses a protein synthesis-dependent mechanism.

Signal Transduction Mechanisms and Translational Regulation

How do extracellular guidance cues stimulate protein synthesis within the growth cone cytoplasm? The intracellular signaling cascades that transduce guidance cue signals into local translation are only beginning to be elucidated, but it is clear that different guidance cues enlist different signaling molecules to regulate translation within growth cones. Caspase-3, TOR (target of rapamycin), p38 MAPK (mitogen activated protein kinase), and p42/44 MAPK have been differentially implicated in protein synthesis stimulated by the distinct guidance molecules Sema3A and netrin-1 [10]. By mobilizing distinct intracellular signaling cascades, different guidance cues could elicit the translation of target mRNAs into the proteins necessary for a growth cone's response. Translational regulators are likely the targets of signal transduction cascades stimulated by receptor activation. Mechanisms that regulate targeted translation of mRNAs within growth cones are just beginning to be identified. ►RNAi, which can repress translation or trigger degeneration of specific mRNAs, has recently been implicated in Sema3A-induced growth cone collapse [1].

Proteolysis in the Growth Cone

In order to regulate the protein composition of a subcellular structure such as a growth cone, cells must coordinate protein synthesis and protein degradation. Both processes occur within growth cones, though proteolytic contributions to growth cone guidance mechanisms are not as well characterized. Proteolysis machinery such as proteosomes, signalosomes, ubiquitin, and the ubiquitin-activating enzyme E2 have been detected within growth cones [3]. Functionally, netrin-1 can induce rapid, local increases in ubiquitin-protein conjugates within growth cones and inhibiting proteolysis can abolish an isolated growth cone's ability to respond to the cue netrin-1 [3]. Sema3A, however, does not rely on proteolysis in the same way as netrin-1 in guiding growth cones, further suggesting that individual guidance cues regulate protein synthesis and degradation within the growth cone by distinct signaling mechanisms.

Localized Protein Synthesis Elsewhere in the Nervous System

While the roles of localized protein synthesis are just becoming established in embryonic growth cones, it is becoming evident that regenerating axons also require localized protein synthesis when reestablishing neuronal connections. Moreover, the ability to translate specific mRNAs locally is not unique to growth cones. Spatially regulated translation within dendrites plays an important role in facilitating synaptic plasticity and insights into mechanisms of targeted dendritic translation have great potential to inform future studies of growth cone translation. Thus, it is becoming clear that neurons use localized protein synthesis as a rapid mechanism to reconfigure regional protein

composition in response to stimuli for navigation, repair, and memory.

References

1. Hengst U, Cox LJ, Macosko EZ, Jaffrey SR (2006) Functional and selective RNA interference in developing axons and growth cones. J. Neurosci 26:5727–5732
2. Yao J, Sasaki Y, Wen Z, Bassell GJ, Zheng JQ (2006) An essential role for β-actin mRNA localization and translation in Ca^{2+}-dependent growth cone guidance. Nat Neurosci 9:1265–1273
3. Campbell DS, Holt CE (2001) Chemotropic responses of retinal growth cones mediated by rapid local protein synthesis and degradation. Neuron 32:1013–1026
4. Piper M, Anderson R, Dwivedy A, Weinl C, van Horck F, Leung KM, Cogill E, Holt C (2006) Signaling mechanisms underlying Slit2-induced collapse of *Xenopus* growth cones. Neuron 49:215–228
5. Leung K-M, van Horck FPG, Lin AC, Allison R, Standart N, Holt CE (2006) Asymmetrical b-actin mRNA translation in growth cones mediates attractive turning to netrin-1. Nat Neurosci 9:1247–1256
6. Zhang HL, Eom T, Oleynikov Y, Shenoy SM, Liebelt DA, Dictenberg JB, Singer RH, Bassell GJ (2001) Neurotrophin-induced transport of a beta-actin mRNP complex increases beta-actin levels and stimulates growth cone motility. Neuron 31:261–275
7. Wu KY, Hengst U, Cox LJ, Macosko EZ, Jeromin A, Urquhart ER, Jaffrey SR (2005) Local translation of RhoA regulates growth cone collapse. Nature 436:1020–1024
8. Brittis PA, Lu Q, Flanagan JG (2002) Axonal protein synthesis provides a mechanism for localized regulation at an intermediate target. Cell 110:223–325
9. Piper M, Salih S, Weinl C, Holt CE, Harris WA (2005) Endocytsis-dependent desensitization and protein synthesis-dependent resensitization in retinal growth cone adaptation. Nat Neurosci 8:179–186
10. Campbell DS, Holt CE (2003) Apoptotic pathway and MAPKs differentially regulate chemotropic responses of retinal growth cones. Neuron 37:939–952

MS

►Multiple Sclerosis

MT1, Mel1a, MTNR1A

►Melatonin Receptors

MT2, Mel1b, MTNR1B

►Melatonin Receptors

MT Complex

Definition

The middle temporal (MT) complex is a region of extrastriate visual cortex containing a high concentration of direction-selective neurons receiving input largely from the magnocellular pathway.

►Extrastriate Visual Cortex
►Visual Motion Processing

MTPT

Definition

►1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Mucus on Olfactory Epithelium

Definition

The mucus is physiological liquid, which is a one of the body's defense systems. It contains numerous proteins to protect epithelium. In the case of olfaction, the mucus traps small particles and bacteria, which may enter the nose as a person breathes. It contains also high concentrations of proteins called odorant-binding proteins, which are good candidates for carrying airborne odorants towards olfactory receptors.

►Odorant-Binding Proteins
►Olfactory Epithelium

Multiform Layer

Definition

The multiform layer of the cerebral cortex is layer VI. It has this name because it contains neurons of a wide variety of sizes and shapes. Projection neurons in layer VI send their axons to terminate in other parts of the cerebral cortex and to the thalamus.

Multilayer Networks

Definition

Neural networks composed of multiple layers, namely the input layer and the output layer with or without hidden layers between them.

►Neural Networks

Multimerization (of Ion Channels)

Definition

Multimerization is the process in which individual subunits (monomers) aggregate to form a functional ion channel. For example, voltage-gated potassium channels and glutamate receptors form tetramers of four subunits, the Cys-loop channel family (acetylcholine (Ach), GABA, glycine) consist of five subunit pentamers. These multimers may be derived from a single gene subunit (homomultimer) or from many different genes (heteromultimers).

►Acetylcholine
►GABA
►Glutamate Receptors
►Glycine
►Ion Channels from Development to Disease
►Neuronal Potassium Channels

Multimodal Enhancement

Definition

Enhanced modulation of the activity of a sensory neuron when the target activates more than one sensory modality.

Multimodal Integration

Nicholas P. Holmes[1], Gemma A. Calvert[2], Charles Spence[3]
[1]Espace et Action, Bron, France
[2]Department of Experimental Psychology, Oxford University, Oxford, UK
[3]Department of Psychology, University of Bath, Bath, UK

Synonyms

Crossmodal integration; Multisensory integration; Intermodal; Heteromodal; Polymodal; Supramodal

Definition

Multimodal (or ►multisensory) integration refers to the neural integration or combination of information from different sensory modalities (the classic five senses of vision, hearing, touch, taste, and smell, and, perhaps less obviously, proprioception, kinesthesis, pain, and the vestibular senses), which gives rise to changes in behavior associated with the perception of and reaction to those stimuli [1,2]. Information is typically integrated across sensory modalities when the sensory inputs share certain common features. For example, although vision is concerned with a certain frequency band of the electromagnetic energy spectrum, and hearing is concerned with changes in pressure at the ears, stimulus features such as spatial location, movement, intensity, timing, and duration, as well as other higher-order features such as meaning and identity can apply equally to information from several (or all) sensory modalities. ►Crossmodal integration is often used synonymously with multimodal integration, however the latter term has various other associations in different disciplines, including in describing the use of more than one measuring system. The former term, crossmodal, may therefore be preferable.

Multimodal integration is more often used to refer to integrative processes operating at the systems level, and studied most commonly using brain imaging techniques alongside behavioral and perceptual measurements. ►Multisensory integration on the other hand, tends to refer to the combinatorial effects of stimulation of two or more senses on the activity of single neurons, measured electrophysiologically in experimental animals. Since multisensory integration is more commonly used in the context of single-cell recordings, often made under anesthetised recording conditions, causal relationships to the behavioral outcomes of multisensory integration are less certain, although this is currently an area attracting considerable research interest.

Characteristics

Upstream Events/Conditions

An extensive body of experimental research has shown that many cognitive systems operate in a multimodal manner. Such systems include those responsible for selective attention and orientation to external stimuli, along with both more elementary perceptual effects, and higher-level cognitive systems such as memory. For example, the familiar experience of both hearing another person speak in natural conversation, and seeing the speaker's lip movements while they speak, is an everyday example of multimodal integration involving both low-level perceptual features, such as detecting sounds and lip movements, as well as higher-level linguistic and semantic factors [3].

In a typical experiment designed to study multimodal attentional orienting, participants may be asked to pay attention and respond only to tactile stimuli presented to a certain hand (e.g., their left hand), and to ignore both tactile stimuli presented to the other hand (i.e., the right hand) or visual stimuli presented to either hand. Typically, visual stimuli presented close to the attended hand result in larger activation (as measured, for example, using electroencephalographic (EEG) or functional magnetic resonance (fMRI) techniques) than for visual stimuli presented to the unattended side. This is true even though the visual stimuli were not relevant to the participants' task. These, and many other similar results, suggest that the mechanisms of spatial attention may operate in a multimodal or supramodal fashion, facilitating the detection and discrimination of stimuli from a given location regardless of the stimulus modality. The behavioral and neurophysiological effects of attending to a primary modality on the response to the secondary modality, however, are usually smaller than the effects in the primary modality itself. This latter result suggests that both unimodal and multimodal perceptual and attentional mechanisms operate in concert.

Downstream Events/Conditions

In order for multisensory or multimodal integration to occur, information must have been processed initially within the component unimodal sensory systems. The level and extent of this prior unimodal processing, however, depends on the system under study. In the superior colliculus (SC), for example, visual and auditory inputs are integrated very early on, after transmission along only several synapses following sensory transduction at the periphery. The retina sends visual projections directly onto the SC, while auditory inputs reach the SC only several neural synapses after initial sensory transduction at the cochlea. Conversely, those stimuli that are involved in multisensory integration in the cerebral cortex may undergo substantial unimodal processing prior to integration, lasting many tens or even hundreds of milliseconds. Recent research, on the other hand, is beginning to detail the extent to which different sensory processing streams interact at very early stages of processing – as early as 45 ms in the example of visual and auditory processing. This physiological evidence is supported by the existence of distinct anatomical connections between the primary sensory areas of several different sensory systems. More and more it appears that multimodal integration and interaction is the rule, not the exception, at all levels of processing.

Involved Structures

Following many years of detailed study on the integration of multisensory inputs in neurons of the superior colliculus, several guiding principles of multisensory integration have emerged [4]. These principles have later been applied in order to determine whether a particular brain region is involved specifically in multisensory integration, both at the level of single-cells, in neurophysiology, and the whole-brain, in neuroimaging.

First, inputs to any given neuron or any given brain area must typically arrive at that area at the same time in order to be integrated and to have significant behavioral consequences. Depending on the specific brain area, "at the same time" typically refers to a "temporal window for multisensory integration." The width of the temporal window, that is, the maximum temporal delay between the arrivals of inputs from different sensory modalities, may be on the order of 100–300 ms.

Second, in many brain areas, particularly those concerned with spatial representations of visual, tactile, and auditory stimuli, multisensory integration is enhanced for those stimuli that arise from the same external spatial location as compared to different locations. The "same" location in the case of audio-visual speech integration, for example, would be the speaker's mouth, from which both visual and auditory signals arise. In the case of visual and tactile stimuli, the same location might refer, for instance, to the lower left portion of the visual field, and to the animals' front left leg, or the lower-left side of the organism's face.

Third, one important aspect of multisensory integration at the neural level relates to the relative strength of inputs from different sensory modalities and the relative amplification that occurs in the process of multisensory integration. This "principle of ▶inverse effectiveness" thus states that the relative enhancement due to multisensory integration is larger for those stimuli that produce weak sensory effects on their own, and is smaller for stimuli that cause strong activations at the neural level.

The *Superior Colliculus* in the midbrain integrates visual, somatosensory, and auditory inputs in the

generation and control of spatial orienting behaviors, particularly those concerning eye and head movements. The SC has been studied intensively as a potential model system for multisensory integration in animals. More recent research has examined the extent to which the ►spatial rule of multisensory integration and ►temporal rule of multisensory integration as measured in the SC also apply to higher-order behaviors and cognition.

The *posterior parietal cortex* contains multiple cortical regions, which respond in a variety of ways to visual, somatosensory, auditory, proprioceptive, and vestibular inputs, such as Brodmann's areas 5 and 7 (or the superior and inferior parietal lobules, respectively), and the multiple, heterogeneous areas within the intraparietal sulcus (e.g., ventral, anterior, and medial intraparietal areas). Somatosensory information is processed initially in Brodmann's areas 3 and 1, the primary somatosensory cortices. Somatosensory processing then proceeds posteriorly through areas 2 and 5, into the anterior or medial bank of the intraparietal sulcus. Visual stimuli are processed initially in the primary and secondary visual cortices, proceeding along the dorsal and ventral visual streams. In the intraparietal sulcus (IPS), the dorsal visual stream meets the somatosensory processing stream. Neurons in area 5 have been shown to integrate proprioceptive stimuli with visual information in the representation and updating of postural information.

At the *fundus of the intraparietal sulcus*, the *ventral intraparietal area* (VIP) contains a variety of neurons with responses ranging from purely somatosensory to purely visual. The *lateral intraparietal area* (LIP), on the posterior or lateral bank of the intraparietal sulcus is thought to be involved in the planning, generation, and control of eye movements. This area, dubbed the "parietal eye field" because of its close functional association with the frontal eye fields, integrates multisensory information in generating eye movements to expected, current, and remembered target locations originally specified in a variety of different possible sensory modalities. Other areas in the intraparietal sulcus display a variety of multisensory responses. The *anterior intraparietal area* (AIP) integrates visual and somatosensory information in planning and generating object-related movements such as grasping, while the *medial intraparietal area* (MIP), as part of the *parietal reach region* (PRR) is involved in the generation and control of reaching movements.

Neurons in the *superior temporal sulcus* in macaques and humans, and the *anterior ectosylvian gyrus* in cats respond to stimulation in a number of sensory modalities, but have been studied particularly in connection with audiovisual speech and vocalizations, in both monkeys and man. This area is often activated in studies that pair both audible and visual (lip movements) speech.

The *premotor cortex* in the frontal lobe is thought to integrate multisensory information involved in the planning and execution of movements. A small portion of the *ventral premotor cortex*, known as the *polysensory zone*, responds to somatosensory, visual, and auditory inputs, and seems to be involved in representing multisensory "peripersonal space" – the space immediately surrounding certain parts of our bodies, particularly the hands and face. This area is connected to functionally similar areas in the posterior parietal cortex such as the ventral intraparietal area. Neurons in the polysensory zone of the premotor cortex respond both to objects approaching a certain portion of the animal's skin (i.e., a visual receptive field surrounding the neuron's corresponding somatosensory receptive field), and to the generation of defensive or avoidance movements in response to these objects.

Certain areas of the orbitofrontal cortex also respond to multisensory stimuli, particularly those concerned with appetitive rewards, such as food, flavors, tastes, and aromas, along with emotionally salient multisensory signals.

Multiple feedforward and feedback connections between the frontal and parietal cortices subserving the processing of multisensory information, and the planning, and execution of movements following multisensory stimulation probably constitute a network of multimodal perception-action or attentional systems. Neural studies of multimodal integration, at least in recent years, have been based largely on the findings of multisensory integration in the SC concerning the generation of orientation movements. Since these early studies, however, research has unveiled numerous brain areas that process and integrate information from a number of sensory systems. Each of these areas seems to be specialized for particular domains of environmental stimuli, or for particular forms of action. Underlying the various approaches to the study of multisensory integration is the hope that general rules of multisensory integration can be discovered that apply to a wide range of behavioral situations, and across a variety of distinct brain regions.

Methods to Measure this Event/Condition

Multisensory integration is typically measured via single-unit recordings in cats, ferrets, barn owls, or macaque monkeys. Both anesthetized and awake behaving preparations have been used, often in conjunction with behavioral studies in the same species and under similar stimulus conditions, or with human studies under similar experimental conditions.

A variety of neuroanatomical and neurophysiological techniques have been used in the model system of the SC,

including single-unit recording and stimulation, lesion studies, tract-tracing, cooling and other forms of inactivation and deactivation of the colliculi themselves, or of brain regions projecting to or receiving from the SC [4]. These studies have shown, for example, that selective lesions or deactivation of the SC abolishes the integration of auditory and visual information arising in those regions of space that the affected portion of the SC represented. Multisensory integration in those parts of the SC left intact was unaffected. Early work on the SC focused on the developmental time-course of multisensory integration, the temporal and spatial characteristics of the stimuli required for effective multisensory integration, the spatial arrangement of the different multisensory representations in the SC, and the ways in which this particular organization came about. (i.e., in part genetically determined, but influenced very strongly by visual and multisensory experience throughout development).

A number of behavioral methods are available to measure multimodal integration in human participants, including reaction-time measures, threshold determination, two (or more)-alternative-forced-choice measures (speeded or unspeeded) and signal detection analyses, which have been used on studies of sensory modalities in isolation for many years. The variety of experimental techniques now available for studying multimodal integration in healthy human participants as well as in brain-damaged neuropsychological patients is now considerable, and an adequate summary is beyond the scope of this article. However, certain important recent trends can be highlighted.

Modern neuroimaging techniques, such as fMRI, positron emission tomography (PET), and magnetoencephalography (MEG), are increasingly being used to address questions concerning multisensory integration. Such experiments often require the development of new stimulation equipment that can be brought into the scanner environment itself. Studying the effects of tactile, olfactory, and gustatory stimulation in the scanner has involved overcoming some difficult technical problems, due to the very strong electromagnetic fields involved in fMRI, and to the very sensitive equipment required to detect small changes in electrical (EEG) or magnetic (MEG) fields over the scalps of human participants. But it is now possible to present stimuli in a number of sensory modalities simultaneously to participants lying in the scanner while they perform simple behavioral tasks. This line of research will provide much-needed theoretical and empirical links between the neurophysiological literature derived from experimental animals, typically macaque monkeys, cats, or ferrets on the one hand, and the human behavioral, psychophysical, and neuropsychological literature on the other hand. It will be crucial to know, for example, to what extent the principles and properties of multisensory integration at the single-neuron level measured in experimental animals can be related to the principles and properties derived from human behavioral studies. In short, do those behaviors that reflect multimodal integration depend directly on cells displaying multisensory integration?

There has been much interest in the effects of a variety of brain lesions in adult humans on multimodal integration and associated behaviors. Several neuropsychological syndromes that have traditionally been studied as if they were unimodal deficits, such as tactile ►extinction and unilateral visuospatial neglect, have, upon closer inspection, been found to be multisensory in nature (►crossmodal extinction). For example, many patients with unilateral visuospatial neglect often have deficits in the detection of auditory and tactile stimuli that occur on their affected side, in addition to visual impairments. Similarly, patients suffering from tactile extinction (a condition where contralesional tactile stimuli are easily detected in isolation, but when two stimuli are presented together on opposite sides of the body, the detection of the contralesional stimulus is impaired), may also have impairments in detecting tactile stimuli on the contralesional hand, for example, when a simultaneous *visual* stimulus is presented near to the ipsilesional hand. The discovery of deficits that cut across the senses in disorders that have typically been thought of as being confined to a single sensory modality, suggests that disorders such as neglect and extinction may also be characterized as disorders of supramodal functions and processes such as spatial perception, and attention, rather than as impairments of a more sensory-specific (►modality-specific) perceptual nature.

Another important line of research involving human participants involves examining the multimodal consequences of sensory-specific impairments, for example in blind and deaf adults and children [5]. Such work has shown that impairments in a single modality have rather intriguing consequences for other sensory systems. In neuroimaging experiments, for example, it has been shown that, when blind participants read Braille, their visual cortex is activated suggesting a functional role for "visual" cortex in complex tactile spatial discrimination. Such visual activations are not observed when participants with unimpaired vision read Braille, nor in people who lose their sight late in life (i.e., after puberty). This neural activation was shown to be functionally relevant to the Braille reading task by the significant disruptive effects of transcranial magnetic stimulation (TMS) over the *occipital* cortex of the same volunteers that exhibited visual activations during Braille reading. Additionally, and perhaps more strikingly, it has recently been shown that normal participants, when completely blindfolded for 5 days while learning to recognize Braille characters, also show activation in the visual cortex, along with an

improved ability to learn the Braille task. These changes were not seen in normal participants who were blindfolded only during the learning and testing phases of the experiment, suggesting that this form of neural plasticity may take several days to take effect. Several different forms of ►crossmodal plasticity seem to be operating – one that occurs only in those patients who lose their sight before puberty, and another that results from the short-term recruitment of visual cortex following temporary blindfolding. Further research is needed to understand what neural mechanisms underpin these physiological changes.

The consequences of such findings for our views of the functional organization of the brain could hardly be more important: the assignment of visual cortex as strictly visually responsive may be rather premature. Rather, the visual cortex may be specialized for processing detailed spatial information in order to make complex spatial discriminations (e.g., in reading Braille). In normal circumstances, visual inputs are functionally the most useful for such spatial discrimination tasks, but in the absence of input from the eyes, inputs from the tactile and auditory receptors may help to perform such tasks. A similar line of research on the multimodal consequences of hearing impairments has reached analogous conclusions.

Finally, and quite recently, multimodal integration is now being approached from a mathematical modeling perspective, particularly with regard to modeling the precision and reliability of information arising from different sensory modalities [6]. Bayesian and maximum-likelihood methodologies have been used to model a variety of phenomena in multimodal integration. Such work suggests that the central nervous system integrates information from the different sensory modalities in an optimal fashion, based on the variability of responses under increasingly noisy stimulus conditions. This relates well to the foregoing conclusions of the work in blind and deaf people – the brain is a highly interconnected network dealing with vast quantities of information, and different neural subsystems are able to share that information effectively to the best advantage of the organism. The visual cortex will receive and process auditory and tactile inputs given a certain amount of visual deprivation, in order to process the relevant information and complete the designated task. Under less extreme conditions of visual deprivation, where the quality of the visual signal is degraded (e.g., on a misty day, or when we remove correcting lenses), information from other modalities may be weighted more strongly in the performance of certain cognitive tasks.

In conclusion, multimodal integration is an exciting and rapidly developing field of enquiry that spans numerous academic disciplines, from basic neuroscience, to medicine, physiology, psychology, cognitive science, and mathematical modeling. From each of these disciplines, multiple well-developed methodological approaches are now available to facilitate the study of the multimodal brain. By progressively questioning the assumption that we are born with only five senses, and that, throughout life, these five senses are both anatomically and phenomenologically distinct, the study of multimodal integration is beginning to provide intriguing answers to historically difficult questions.

References

1. Calvert GA, Spence C, Stein BE (2004) The handbook of multisensory processes. MIT Press, London
2. Spence C, Driver J (2004) Crossmodal space and crossmodal attention. Oxford University Press, Oxford
3. de Gelder B, Bertelson P (2003) Multisensory integration, perception and ecological validity. Trends Cogn Sci 7:460–467
4. Stein BE, Meredith MA (1993) The merging of the senses. MIT Press, Cambridge, MA
5. Pascual-Leone A, Hamilton R (2001) The metamodal organization of the brain. Prog Brain Res 134:427–445
6. Ernst MO, Bülthoff HH (2004) Merging the senses into a robust percept. Trends Cogn Sci 8:162–169

M

Multi-Oscillator System

Eric L. Bittman[1], Tanya L. Leise[2]
[1]Department of Biology, University of Massachusetts, Amherst, MA, USA
[2]Department of Mathematics, Amherst College, Amherst, MA, USA

Definition

A multi-oscillator system is composed of potentially dissociable but normally coordinated rhythmic mechanisms which exist within the same organism, and may fall into mutual or hierarchical coupling arrangements.

Characteristics

Organization of Multi-Oscillator Circadian Systems

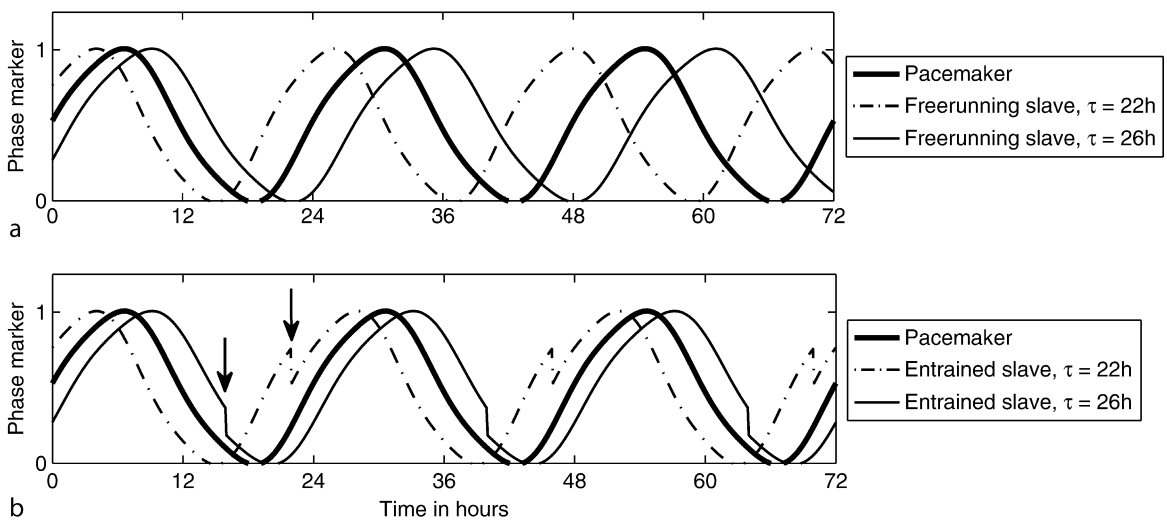
Many physiological functions are intrinsically rhythmic, and oscillations underlie the operation not only of organs, but also of individual cells. Sensory neurons fire action potentials in bursts, the frequency of which carries biological information such as the coding of stimulus intensity. Circadian oscillations provide another excellent example of physiological encoding of information, in this case, time of day. Multiple circadian ►oscillators occur in many different organisms, forming a complex network of internal clocks that increase the ability to coordinate internal functions and

execute them at appropriate times with respect to the environment.

The organization of circadian multi-oscillatory systems can take different forms and involve multiple levels of clock interactions. However, there is a common thread underlying all such systems: the constituent oscillators entrain, i.e, they match periods and maintain a steady relative phase (Fig. 1). This communication between oscillators does not require that they be synchronous. In other words, they often do not have the same phase; some components may even be antiphase to others so that incompatible processes occur at diametrically different times of day. In order for a set of heterogeneous oscillators (differing in period and other properties) to become mutually entrained, components with shorter periods must experience a ►phase delay each cycle (to lengthen the effective period), while components with longer periods must experience a ►phase advance (to shorten the effective period). The coupled components respond to coupling signals with appropriate delays and advances at specific phases (i.e., manifest a phase response curve) in order to achieve hierarchical or mutual ►entrainment. This coupling along with the intrinsic period of each component determines the phase differences between the components.

In multi-oscillator systems that are organized in a hierarchical manner, the ►pacemaker entrains "slave" oscillators. Some slaves may not be capable of sustaining oscillations in the absence of the pacemaker, i.e., they are damped oscillators. The pacemaker is often entrainable by an external signal, e.g., the 24 h light-dark cycle, and the pacemaker in turn entrains the rest of the circadian system. The nature of the signal from pacemaker to slave determines the entrained phase of the slave, just as the photic ►phase response curve of a pacemaker determines its entrained phase relative to dawn and/or dusk. The phase of an entrained slave oscillator can be either earlier than (leading) or later than (lagging) the phase of the pacemaker. For example, the ►suprachiasmatic nucleus (SCN) of mammals acts as a pacemaker that is believed to entrain circadian oscillators in peripheral tissues. The system is probably not strictly hierarchical, as the peripheral tissue clocks may in turn generate signals that influence the phase, amplitude, or ►period of the pacemaker. Other circadian systems are composed of autonomous oscillators which couple as a network through mutual interactions, with no dominant pacemaker involved.

Oscillatory tissues contain cells that generate circadian rhythms via a molecular clock mechanism that is composed of multiple loops in which rhythmic transcription of genes is achieved through feedback effects of the proteins they encode. In some circadian systems however, post–transcriptional events may play a predominant role in the clock mechanism. The roles of



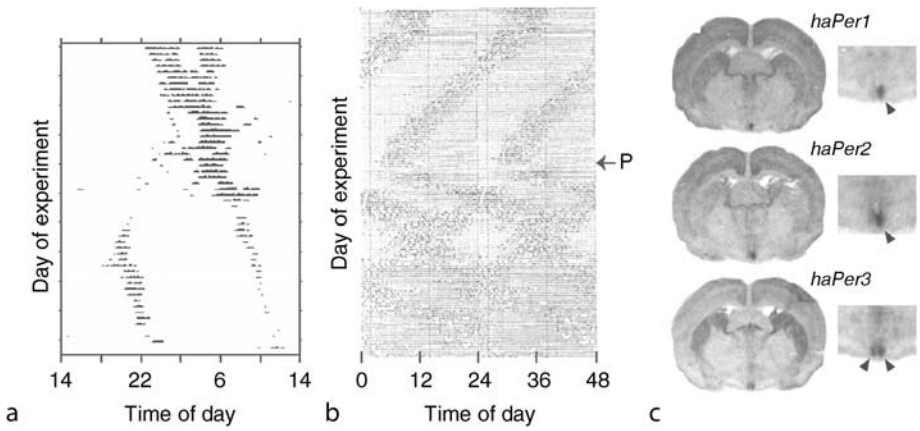
Multi-Oscillator System. Figure 1 (a) Three oscillations that are not coupled are depicted. Note that the phase difference between the ►pacemaker and each "slave" increases over time. The "phase marker" may be an mRNA or protein level resulting from rhythmic expression of a clock gene, for example. Sinusoidal waveforms are indicated for simplicity, but need not be reflected in a biological system. (b) Appropriate signals from the pacemaker can entrain the slave oscillators, resulting in steady phase angles. Note that the two slaves take different phase angles to the pacemaker. A pacemaker signal reset the phase of the short period slave with a pulse at time 22 (and every 24 h thereafter) to correct for the difference in oscillator periods. This achieves a delay of 2 h, so that the slave repeats a 2 h portion of its cycle. The pacemaker entrains the long period slave with a pulse that falls at time 16 (and every 24 h thereafter) to advance its phase by 2 h, so that the slave skips 2 h of its cycle.

specific genes may differ between tissues, leading to qualitatively different clocks in the pacemaker and the peripheral tissues. Multi-oscillatory systems can be quite complex, spanning cell, tissue, and organismal levels. Furthermore, groups of organisms can act as multi-oscillatory circadian systems where mutual coupling is achieved through social cues.

Evidence for Multi-Oscillatory Circadian Systems

The idea that independent oscillators couple to achieve a common period with a specific phase relationship may be traced to the Dutch astronomer Christian Huygens, who observed such phenomena in mechanical clocks. In the biological realm, Erwin Bunning proposed that individual organs including segments of gut were capable of sustained circadian oscillations when isolated from the whole animal. It was Colin Pittendrigh, however, who first established that circadian systems are comprised of multiple oscillators. Pittendrigh applied entrainment theory to model inter-oscillator coupling. He showed that although pupal eclosion of Drosophila is driven by a temperature-compensated circadian ("A") pacemaker, the phase of emergence depends upon temperature. Pittendrigh offered as an explanation the existence of slave ("B") oscillators that have circadian properties but are not temperature-compensated. The slave oscillators are thought to most directly control hormone release, motor patterns, etc., that lead to emergence of the adult fly. As environmental temperature changes, the intrinsic period of the slave changes, but not that of the pacemaker. Thus whether the slave must advance or delay its phase in order to adopt the period of the master pacemaker depends upon temperature. This implies that the entrained phase of the slave relative to the pacemaker must change as the temperature changes. Determination of this phase difference by temperature through the differential sensitivity of master and slave oscillators may serve an adaptive purpose, because the optimal time of emergence relative to sunrise depends upon season and relative humidity.

Pittendrigh extended the idea of multiple circadian oscillators to the phenomenon of splitting, which takes place upon exposure of hamsters to constant light. A high percentage of animals maintained in such conditions show bimodal activity rhythms, with two components free running with different circadian periods until they couple in an antiphase relationship (Fig. 2a). Pittendrigh argued that the capacity of an organism to sustain multiple



Multi-Oscillator System. Figure 2 Activity rhythms can dissociate to reflect multioscillatory circadian organization, and pacemaker anatomy reflects dissociation among cell populations. (a) Splitting of activity rhythms (►split rhythm) in a golden hamster. Actogram represents locomotor activity of an animal maintained in constant light. Each horizontal line represents 24 h of wheel running behavior; successive days are represented one below the other. After about 30 days, two circadian components dissociate and free run with different periods before coupling in an antiphase relationship. (b) Pinealectomy of a Texas spiny lizard (*Sceloporus olivaceus*) induces dissociation of circadian components of locomotor activity. The animal was held in constant light for the duration of the record. After about 2 months, during which the animal showed a free running period of less than 24 h, the pineal was surgically removed (P). It was necessary to also remove the parietal eye in order to gain access to the pineal, but other experiments indicate that parietalectomy by itself has no consistent effect on circadian rhythms. Note that rhythmic components free ran with different periods and did not couple in the months following the surgery. From [1], reprinted with permission from AAAS (c) Splitting in constant light is accompanied by lateralization of clock gene expression in hamster SCN. Film autoradiograms illustrate expression of the clock genes *Per1, Per2*, and *Per3*, as assessed by *in situ* hybridization, in coronal sections of the brains of hamsters sacrificed 3 h before the anticipated onset of activity. Insets show that expression of *Per1* and *Per2* in the SCN (arrows), which normally peaks during subjective day, is laterally asymmetrical in split animals. Expression of *Per3* is not altered. From [2], reprinted with permission from AAAS.

periods, at least transiently, indicates the existence of dissociable, and hence multiple, oscillators. He subsequently developed the idea of a "temporal program" whereby the multi-oscillatory organization of the circadian system would lead to complex, seasonally changing scheduling of physiological events and might explain phenomena such as ►jet lag and ►photoperiodism [3].

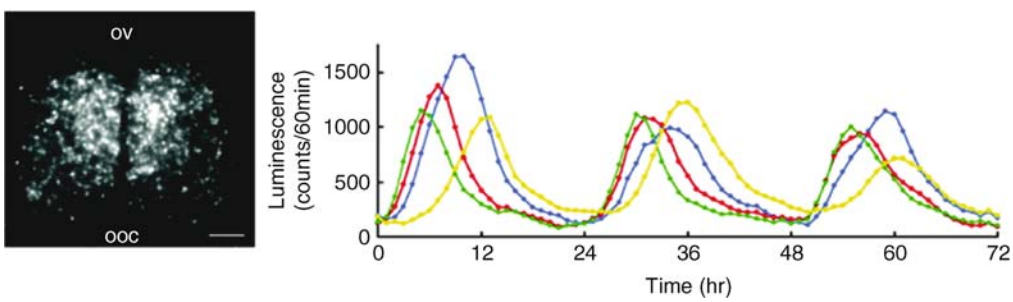
Multi-oscillatory models of circadian organization are supported by studies in a variety of species. For instance, Page [4] discovered that removal of the optic lobes of cockroaches eliminates circadian rhythms of locomotor behavior. The powerful technique of transplantation of optic lobes between animals with different circadian periods established that the period of the rhythm reinstated by the transplant was that of the donor. This proved that the optic lobe contains a pacemaker, rather than acting merely to permit expression of rhythmicity by a clock located elsewhere in the organism. Since the insect has bilateral optic lobes, it follows that there must be at least two circadian oscillators in the organism. Page further showed that the period of the intact animal is shorter than that of either optic lobe alone, arguing for coupling between the bilaterally paired pacemakers.

Other experiments in which circadian oscillators were localized to particular structures facilitated further insight into the multi-oscillatory structure of the circadian system. Electrophysiological recordings in the gastropod mollusks *Aplysia californicus* and *Bulla gouldiana* demonstrated that retinal neurons show circadian oscillations in action potential frequency. Dissociation of basal retinal neurons demonstrated their capacity to oscillate independently, proving the existence of multiple cellular oscillators. Among vertebrates, the ►avian pineal gland provided further evidence of multiple circadian oscillators. Not only do individual pinealocytes oscillate in their synthesis and secretion of ►melatonin, but in some species removal of the ►pineal gland causes a gradual decay of circadian rhythms of locomotor behavior. This argues for the existence of damping circadian oscillators whose coherence is normally maintained by the pacemaker. Using lizards, Underwood [1] showed that pinealectomy can lead to dissociation of circadian rhythms that free run with different periods (Fig. 2b). This not only indicates the multi-oscillatory structure of the circadian system, but also suggests a role for the pineal in maintaining coupling relationships between oscillators.

The suprachiasmatic nucleus (SCN) of mammals contains a set of neurons that can each generate a ~24 h rhythm via an intracellular molecular clock mechanism. While this group of oscillatory SCN neurons collectively forms the mammalian pacemaker, subpopulations can dissociate from each other. Antiphase patterns of gene expression have been observed in the left and right SCN of hamsters induced to split their circadian activity patterns by constant light ([2]; Fig. 2c). Ventral and dorsal regions of the rat SCN appear to dissociate when driven to the limits of entrainment. When SCN neurons interact synaptically, a consensus period emerges and neurons fall into phase-grouped populations (Fig. 3; [5]). Deficiency of vasoactive intestinal polypeptide (VIP) or the VPAC2 receptor compromises synchrony of both cellular oscillations and behavioral circadian rhythms. This suggests a role for these molecules in coupling between SCN neurons.

Cellular Oscillators: Molecular Mechanisms

Demonstrations that individual basal retinal neurons of snails, suprachiasmatic neurons of rodents, and pinealocytes of chicks can sustain circadian oscillations not only force the conclusion that multiple oscillators exist within tissues, but also raise the question of whether individual cells may contain more than one oscillator.

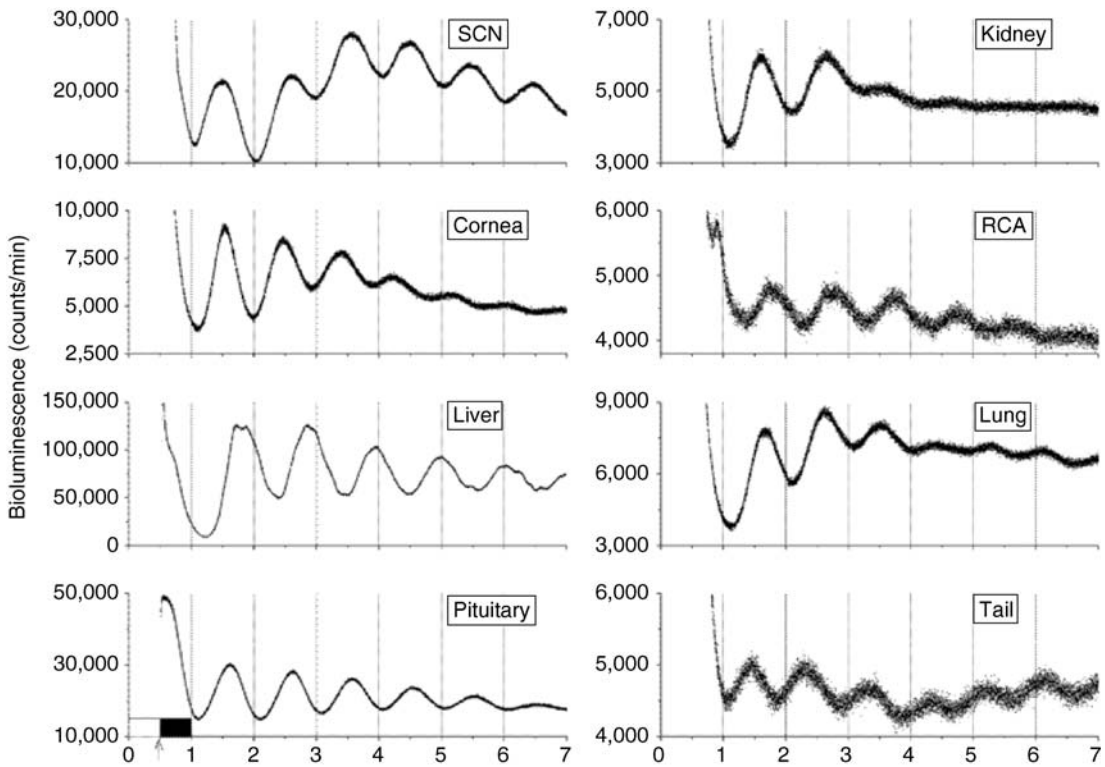


Multi-Oscillator System. Figure 3 Expression of core circadian clock genes can be visualized in organotypic slices of the SCN, and in individual SCN neurons in culture. (a) Photomicrograph of an SCN slice prepared from a transgenic mouse carrying a Per1::Luciferase reporter construct. Ooc, optic chiasm; ov, third ventricle. Scale bar, 10 μm. (b) Luminescence due to reporter expression, reflecting PER concentrations, in four individual neurons visualized in the slice over a 3-day interval in culture. Note that individual neurons exhibit circadian periodicity of bioluminescence, but that the neurons depicted in blue and yellow peak at a phase later than the main cluster shown in green and red. From [5], reprinted with permission from AAAS.

Hastings and Sweeney found that the alga *Gonyaulax polyedra* expresses at least three distinct circadian oscillations: the intensity of bioluminescent glow, the frequency of flashing rate, and vertical migration in the water column. When these events occur with the same period, even in constant conditions and different phases, it remains possible that all are driven by a common oscillator mechanism. Under some lighting conditions, however, these three rhythms dissociate so that they free run with different periods. This argues for the existence of multiple oscillators within a single cell.

The modern era of study of multioscillator circadian systems began with characterization of molecular mechanisms that generate rhythmicity. In Drosophila the protein products of the ►Period, Timeless and ►*Cryptochrome* loci are engaged in a reciprocal interacting feedback loop with those of ►Cycle and ►Clock. Elegant studies utilizing a fluorescent reporter demonstrated not only that *Per* expression oscillates in individual isolated organs of the fly, but that these separate peripheral oscillators may be entrained by light in culture. With the discovery that several orthologs of Period are expressed in vertebrates, it became possible to investigate the multioscillatory organization of mammalian tissues and to study circadian rhythms in cell lines. Balsalobre et al. [6] demonstrated that a serum shock initiates an oscillation in cultures of immortalized cells and in primary hepatocytes. They proposed that the damping of cyclic *Per* expression that occurs after a few cycles reflects differences in period of individual cell oscillations leading to loss of phase coherence. This speculation has been validated through microscopic visualization of Period or ►*Bmal1*-driven luminescent reporters [7,8]. A mammalian organization similar to that of Drosophila, in which circadian oscillations persist in isolated organs, has now been demonstrated in mice ([9]; Fig. 4).

Not only do such studies establish that individual cells are oscillators, but they recall Pittendrigh's models of how a central neural pacemaker may coordinate and control the phasing of circadian rhythms throughout the body. According to the current model, entraining signals that originate in the pacemaker are relayed through appropriate pathways in order to set the phase and determine the period of peripheral oscillators. This communication may occur through innervation: the SCN in mammals communicates with paraventricular neurons that drive sympathetic output and thus may



Multi-Oscillator System. Figure 4 Circadian rhythms of expression of *mPer2*, a core clock gene whose protein levels are reflected by bioluminescence in a mouse reporter strain, persist after isolation of brain regions (SCN, RCA: retrochiasmatic area) and peripheral organs (cornea, kidney, liver, lung, pituitary, tail) *in vitro*. The light:dark cycle experienced by the mouse prior to sacrifice and organ removal is depicted at the lower left. From [9]; copyright (2004) National Academy of Sciences, USA.

regulate the autonomic control of peripheral organs. Indeed, trans-synaptic retrograde tracing indicates the existence of multisynaptic pathways that connect the SCN with multiple visceral organs [10]. Furthermore, removal of vagal input interferes with rhythmicity of clock gene expression in the lung. On the other hand, humoral signals may carry SCN signals to the periphery. Secretion of a variety of pituitary hormones is clearly under circadian control, and glucocorticoids can set the phase of clock gene expression in liver and kidney. Importantly, cultured fibroblasts show a high amplitude phase resetting response to dexamethasone, a glucocorticoid analog [8]. Furthermore, circadian rhythms of fibroblasts fall under central control soon after their implantation to subcutaneous sites that lack innervation. Also among time cues that may serve to regulate peripheral circadian oscillators are those that arise from meal patterns. These could include carbohydrates, fats, and amino acids absorbed from the gut, or other food-associated signals. Fluctuations in temperature that may result from feeding or activity, whose rhythmicity may be pacemaker-regulated, can also regulate clock gene expression and thus potentially set the phase of peripheral oscillations. Cues arising from social signals may also play an important role in vertebrates. Regulation of clock gene expression by any of these signals – or perhaps more likely, by several in combination – may fit the definition of entrainment. It remains to be determined whether any such cues set the phase of ►peripheral oscillators in a physiological situation. It is also possible that physiological cues (such as hormones) that influence the period or amplitude of slave oscillators in the periphery alter temporal programs by determining the phase they take to signals from the pacemaker.

References

1. Underwood H (1977) Circadian organization in lizards: the role of the pineal organ. Science 195:587–589
2. de la Iglesia HO, Meyer J, Carpino A Jr, Schwartz WJ (2000) Antiphase oscillation of the left and right suprachiasmatic nuclei. Science 290:799–801
3. Pittendrigh CS (1981) Circadian organization and the photoperiodic phenomena. In: Follett BK, Follett DE (eds) Biological clocks in seasonal reproductive cycles, Colston Papers No. 32. Scientechnica, Bristol, pp 1–35
4. Page TL (1982) Transplantation of the cockroach circadian pacemaker. Science 216:73–75
5. Yamaguchi S, Isejima H, Matsuo T, Okura R, Yagita K, Kobayashi M, Okamura H (2003) Synchronization of cellular clocks in the suprachiasmatic nucleus. Science 302:1408–1412
6. Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schütz G, Schibler U (2000) Glucocorticoid hormones can reset time in peripheral tissues. Science 289:2344–2347
7. Welsh DK, Yoo S-H, Liu AC, Takahashi JS, Kay SA (2004) Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. Curr Biol 14:2289–2295
8. Nagoshi E, Saini C, Bauer C, Laroche T, Naef F, Schibler U (2004) Circadian gene expression in individual fibroblasts: Cell-autonomous and self-sustained oscillators pass time to daughter cells. Cell 119:693–705
9. Yoo S-H, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Siepka SM, Hong H-K, Oh WJ, Yoo OJ, Menaker M, Takahashi JS (2004) PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. Proc Natl Acad Sci USA 101:5339–5346
10. Kreier F, Kap YS, Mettenleiter TC. van Heijningen C, van der Vliet J, Kalsbeek A, Sauerwein HP, Fliers E, Romijn JA, Buijs RM (2006) Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology 147:1140–1147

Multiple Innervation

Definition

The excess number of axonal innervations converging on a single target cell in the immature brain. The redundant inputs are eliminated through the process of synapse elimination and axon retraction during development.

►Synaptic Elimination

Multiple Realization

Definition

The thesis in the philosophy of mind that a given mental property, state or event is realized by different physical properties, states or events, which share no significant description at the physical level. Functionally defined kinds can be realized in a variety of physical states and processes, e.g. the kind "clock" can be multiply realized by a sun dial, a water clock, a mechanical mechanism or a silicon chip. If mental states like belief or pain are characterized functionally, i.e. in terms of their causalinferential relations to sensory input, to other mental states and to behavioral output, then they can in principle be realized by a variety of physical states and properties, e.g. by neural states in human beings and by silicon in Martians. The prospect of multiple realization

has served as an argument against the mind-body identity theory, which claims that types of mental states are identical to types of physical states, and against the reduction of the mental to the physical more generally.

►Theory Theory (Simulation Theory, Theory of Mind)

Multiple Sclerosis

Sylvia Lucas
Department of Neurology, University of Washington Medical Center, Seattle, WA, USA

Synonyms

MS; Variants of MS include acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO or Devic's disease) and Balo's concentric sclerosis

Definition

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system characterized by a clinical course of neurologic dysfunction (relapses), periods of improvement (remissions) and for most patients a loss of functional capability which may be physical as well as cognitive. Focal demyelinated lesions or plaques are found in the white matter of the brain and spinal cord. Recent evidence [1] has shown that MS may include demyelination in the cortex and deep gray matter nuclei and diffuse axonal injury in normal-appearing white matter.

Characteristics

Epidemiology

MS affects approximately 350,000–400,000 Americans and 1.1 million patients world wide. It is second only to trauma as the most disabling neurologic condition in young adults. There is a female to male ratio which may be increasing and has been reported as high as 4:1. Though the clinical onset of the disease is uncommon under age 15 and over 45, it is most often diagnosed in young women of reproductive age in the 20's or 30's. A latitudinal prevalence exists which is lowest at the equator and increases above 40° north latitude and below 40° south latitude [2].

Besides environmental risk, there appears to be a genetic susceptibility as well, with a family history of MS in 15–20% of patients. The risk of a second sibling developing MS if one sibling has it is 3–5% with concordance in monozygotic twins of 31% compared to dizygotic twins.

Polygenic inheritance is likely and the major histocompatibility complex (MHC) on chromosome 6p21 encoding antigen-presenting proteins to T cells is an important susceptibility region. HLA-DR2 is associated with a three to four-fold increased risk of sporadic and familial cases of MS [3].

Clinical Features

The onset of MS can be insidious without clinical symptoms (as evident on MRI obtained for other reasons) or abrupt and rapidly progressive. MS presenting symptoms are extremely varied and depend on lesion location in the brain or spinal cord (Table 1). An initial clinical event is known as clinically isolated syndrome (CIS) with a recurrent or second event (in time and space) defining clinically definite MS (CDMS). Any MS event may be monosymptomatic, involving a single clinical symptom with focal nervous system involvement, or polysymptomatic indicative of involvement of multiple areas of the nervous system.

Signs or symptoms of MS are non-specific and include all symptoms resulting from injury to any part of the brain or spinal cord. Approximately 85% of patients will have a relapsing-remitting course (RRMS) at disease onset. Acute attacks (the relapse) evolve over

Multiple Sclerosis. Table 1 Initial symptoms of MS

Symptom	Percent of cases	Symptom	Percent of cases
Sensory Loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesia	24	Visual Loss	2
Diplopia	15	Facial Palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal Attacks	4	Seizures	1
Bladder	4	Falling	1

Source: After WB Matthews et al. (1991) McAlpine's multiple sclerosis, New York, Churchill Livingstone

several days to weeks followed by stabilization and spontaneous recovery of symptoms (the remission). Between attacks patients are neurologically stable. As the disease progresses, however, attacks may become less frequent but MS patients may experience a steady deterioration in neurological function and accumulate disability (secondary progressive MS; SPMS). Prior to the advent of disease-modifying therapies, approximately 50% of MS patients with RRMS would develop SPMS after 15 years [4]. SPMS represents a late evolution of MS and is likely associated with axonal loss and loss of compensatory mechanisms (Fig. 1).

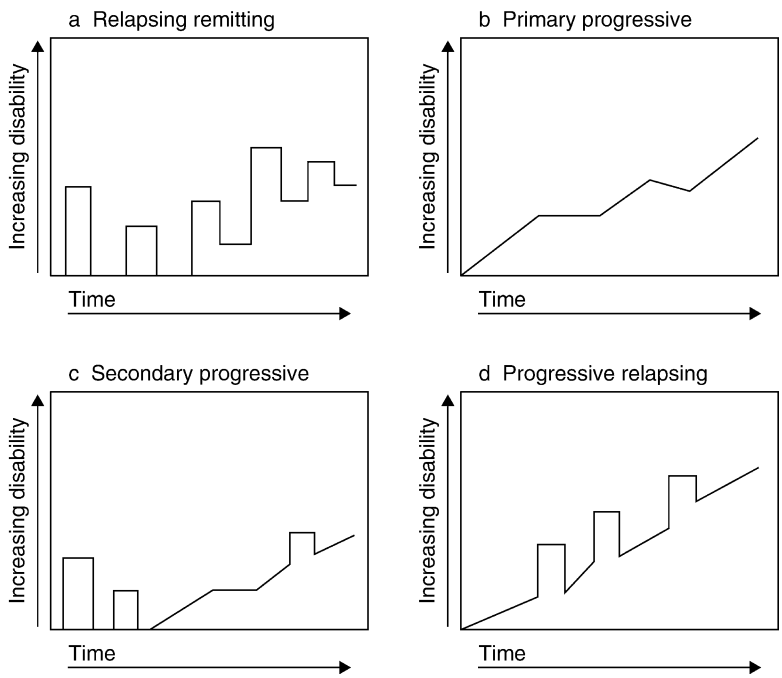
Because MS is thought to be predominantly a disease of white matter, inflammation and demyelination of myelinated tracts lead to common symptoms of sensory disturbances (paresthesias, numbness, dysesthesias), optic neuritis (usually unilateral), pyramidal symptoms, cerebellar symptoms (e.g. ataxia), or brainstem involvement (e.g. internuclear opthalmoplegia). Less common presentations are Lhermitte's sign (►Lhermitte's Symptom) (flexion of the neck produces electrical sensations or paresthesias along the spine or extremities), cortical symptoms or extrapyramidal syndromes. Bladder and bowel involvement is common (Table 1).

Symptoms which may also cause significant disability are fatigue, ►Uhthoff's phenomenon (symptoms exacerbated by increasing body temperature), primary pain syndromes (e.g. trigeminal neuralgia, flexor and extensor spasms, optic neuritis), spasticity, dementia, and mood disorders. Secondary pain syndromes may also occur such as hip or back pain from postural or gait abnormalities, decubital ulcers from skin breakdown, or compression palsies.

Attempts have been made to quantify neurologic impairment in MS to provide a current clinical description of the disease status of a patient as well as to follow disease course over time. The ►EDSS (Kurtzke Expanded Disability Status Score) and the Functional Status (FS) Score are used most commonly. Patients with EDSS scores <3.5 usually have RRMS and walk normally. Patients with EDSS scores >5.5 have symptom evolution indicative of progressive MS (SPMS or PPMS), are gait impaired and may be disabled [5].

Diagnosis

There is no single definitive test for MS. The diagnosis is based on clinical and paraclinical criteria of "dissemination in time and space." CDMS requires documentation of two or more distinct episodes of symptoms lasting at least 24 h and two or more exam signs indicative of neurologic dysfunction in different white matter tracts of the CNS. Paraclinical studies used



Multiple Sclerosis. Figure 1 Clinical course of MS. (a) Relapsing-remitting MS (RRMS) is characterized by acute attacks with full recovery or by a residual deficit after recovery. Times between relapses have no disease progression. (b) Primary progressive MS (PPMS) is characterized by progression of disease from the onset without periods of remission and no improvement in function. (c) Secondary progressive MS (SPMS) begins with an initial relapsing-remitting course followed by progression with or without relapses. (d) Progressive relapsing MS (PRMS) shows progression from the onset with superimposed relapses.

to diagnose MS include MRI, CSF findings and ►evoked potentials (EP) and may be useful to indicate disease activity even in the absence of any clinical activity.

MRI is 90–97% sensitive with typical lesions seen in periventricular white matter, corpus callosum, and juxtacortical white matter. Lesions are hyperintense on FLAIR and T2-weighted imaging (more useful than FLAIR for posterior fossa lesions), and may enhance with Gadolinium representing blood-brain barrier breakdown in acute disease activity. Chronic lesions may become hypointense on T1-weighted images (black holes) and other MRI findings of progressive disease are whole-brain atrophy, thinning of the corpus callosum and ex-vacuo dilation of the ventricles which correlate with cognitive impairment ([6]; Fig. 2).

CSF examination usually has a normal cell count or mild lymphocytosis, normal or slightly increased protein, and the presence of ►oligoclonal bands (OCBs) is highly sensitive (90–95%) for diagnosis, though they are not always present initially. There may be an increased IgG synthesis rate, IgG index and the presence of myelin basic protein [7].

Evoked potentials are most useful in patients with a history of optic neuritis and are abnormal in 90% of these patients. Visual, sensory or brainstem auditory evoked potentials are less sensitive (65–85%) and are usually unnecessary with the use of modern MRI imaging.

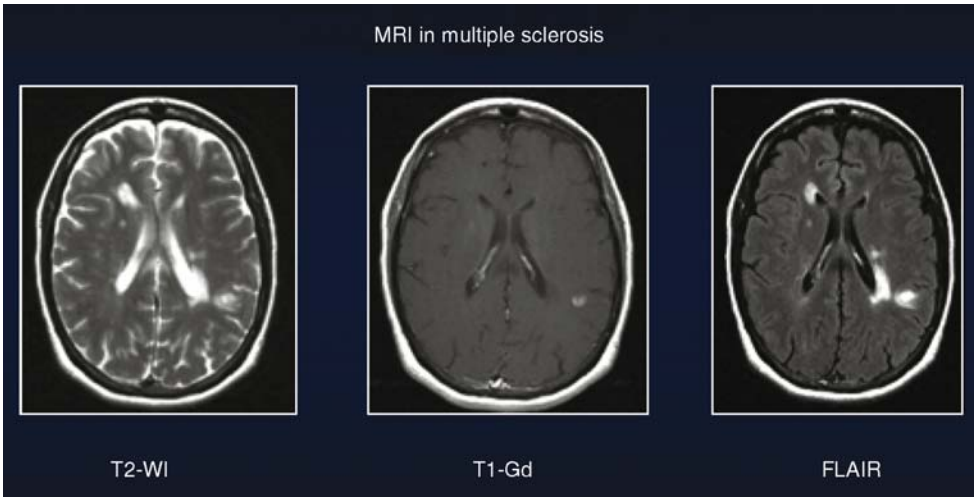
Pathophysiology

In the autoimmune hypothesis of MS, T lymphocytes become "activated" expressing receptors for myelin components in the central nervous system. They enter the CNS through the specialized endothelial blood-brain barrier, attacking target antigens and triggering an inflammatory cascade.

The entry of activated T lymphocytes is mediated by chemotactic cytokines and cell adhesion molecules (e.g., VCAM-1) displayed on the inner surface of CNS microvascular endothelial cells. Interaction between VLA-4 (integrin molecules expressed on T cell lymphocytes) and Vcam-1 leads to T cell production and secretion of gelatinases, which break up perivascular basal lamina and allow entry into CNS interstitial spaces.

In a process similar to immune surveillance, these auto-reactive T lymphocytes find their specific antigen and start the inflammatory process. There are two roles for these T cells, one as Th1 cells producing proinflammatory cytokines such as IFN-gamma and TNF alpha. Th2 cells produce anti-inflammatory cytokoines (IL-4, IL-5, IL10 and are regarded as having a role in downregulation of brain inflammation and may lead to myelin repair and/or oligodendrocyte precursor activation.

Evidence in favor of the autoimmune hypothesis comes from lesion pathology [8]. Early active lesions are characterized by perivascular round cell inflammation, and are similar to inflammatory pathology seen in models of experimentally induced autoimmune encephalomyelitis (EAE). Additionally, disease susceptibility is associated with the polymorphic major histocompatibility complex (MHC) genes whose class II products are required for antigen presentation by the T lymphocytes.



Multiple Sclerosis. Figure 2 MRI findings in a patient with relapsing-remitting multiple sclerosis. T2-weighted imaging (*left*) and FLAIR (*right*) imaging show several lesions in the periventricular white matter and juxtacortical areas. The T1 Gad image (*middle*) shows the left posterior lateral ventricular lesion enhancing with gadolinium indicative of an acute or active lesion.

The current working model of pathogenesis is based on evidence from human disease, EAE and other animal models of demyelination. This is a heterogeneous disorder with varying patterns of immune pathogenesis. In neuropathologic studies of MS lesions [9] four major patterns of demyelination are described. All patterns of these active MS lesions contain T lymphocytes and macrophages and though lesion patterns differ between patients, a given patient has a single lesion type. Patterns I and II (seen in 15% and 58% of patients, respectively) are characterized by oligodendrocyte survival and remyelination, with myelin appearing to be the principal target. Pattern I demyelination is probably mediated by macrophage toxins, whereas pattern II finds antibody deposition (Ig) and activated complement at sites of myelin destruction. Patterns III and IV (26 and 1% of patients, respectively) are characterized by oligodendrocyte loss and apoptosis with limited remyelination; oligodendrocytes appear to be the target of injury. Pattern III lesions show degeneration of distal oligodendrocyte processes with selective loss of myelin associated glycoprotein (MAG) and apoptosis. Pattern IV shows extensive oligodendrocyte degeneration in a small rim of periplacque white matter and no MAG loss or complement activation is present.

Treatment of Multiple Sclerosis

There is no cure for MS. However, the results of controlled clinical trials with immunomodulatory and immunosuppressive therapy suggest that the natural course of MS may be modified. Additionally, it is important that diligence in the recognition and satisfactory treatment of symptoms of MS may dramatically improve a patient's quality of life.

Treatment of MS falls into three categories: (i) treatment for the acute attacks or relapses of MS, (ii) disease-modifying therapies that may change the natural course and long-term disability of MS and (iii) treatment of the symptoms of MS.

High dose corticosteroid therapy is used to manage either an initial attack or an acute relapse (breakthrough disease). It may provide a short-term benefit by shortening an attack and decreasing its severity though it is generally thought not to affect the long-term outcome of the disease. Typical treatment for relapses is a 3–5 day course of intravenous methylprednisolone at 1 g/day which may be followed by a tapering dose of oral corticosteroids for 1–2 weeks. Plasma exchange may be useful in patients with severe attacks refractory to corticosteroid treatment.

Immunomodulatory treatment is available for the treatment of CIS and RRMS with interferons and glatiramer acetate which may be self-injected, and natalizumab which is delivered by intravenous infusion. Interferon beta-1A and interferon beta-1B have been shown to decrease relapse rate, accumulation of lesion volume, and to decrease the number of enhancing lesions on MRI compared to placebo treatment. Though mechanism of action is not well understood, interferons are thought to reduce cell trafficking through the blood-brain barrier, shift T-cell response from Th1 to Th2, increase IL-10 and IL-4 production, and decrease antigen presentation and T-cell proliferation. Glatiramer acetate (a random polymer mixture of four amino acids) may shift T-cell response from Th-1 to Th-2, induce antigen-specific suppressor T cells, and compete with myelin basic protein on MHC II sites. It has effects similar to the beta-interferons on exacerbation frequency, however effects on MRI lesions or disability progression are less well established. These therapies were studied in 2- or 3-year clinical trials and long-term benefit is still unknown [10].

Natalizumab is a humanized monoclonal antibody which binds to alpha/4-beta 1 integrin on T-cells preventing association with VCAM-1 receptors on CNS endothelium and inhibits trafficking of T-cells into the CNS. It is delivered by intravenous infusion every 30 days has been approved for treatment of relapsing forms of MS. Though not directly compared to the interferons or glatiramer acetate in head-to-head trials, it may be more effective than prior approved therapies in reducing relapses and MRI activity. Close attention to safety issues via a specialized educational and reporting process was instituted following two cases of progressive multifocal leukoencephalopthy (PML) seen in the clinical trial setting with long-term use of natalizumab in combination with an interferon.

Treatment with the immunosuppressant mitoxantrone has been approved for SPMS and worsening RRMS. Mitoxantrone inhibits T cell, B cell, and macrophage proliferation, antigen presentation, and increases T cell suppressor activity. Mitoxantrone is an analogue of doxorubicin and has a cumulative dose ceiling to limit risk of cardiotoxicity. Delivery is by intravenous route every 3 months. Echocardiograms or other tests of cardiac function are recommended prior to each dose.

The aim of symptomatic therapy is to give relief from symptoms which have negative impact on function or quality of life. For example, bladder dysfunction in MS is common. Most often seen is the condition of a neurogenic bladder, with urgency, frequency and occasional incontinence. This and other bladder dysfunction such as detrusor/sphincter dyssynergia may be evaluated with urodynamic testing. Medication such as oxybutinin, hyoscamine, tolteridine, solifenacin, or trospium is usually helpful.

Depression may be seen in up to 50% of patients with MS and can be treated with medication or psychotherapy. The selective serotonin reuptake inhibitors (e.g. fluoxetine), selective serotonin reuptake/

norepinephrine reuptake inhibitors (e.g. duloxetine), or bupropion are most often used.

Fatigue may be dramatic and is the symptom most often causing disability in the workplace. Besides behavioral strategies to conserve energy, medication such as amantadine, modafinil and CNS stimulants (methylphenidate or amphetamines) usually help.

Constipation is the most common bowel problem in MS. A bowel program is often necessary and may consist of high-fiber diet, fluid intake, and laxatives administered orally or by suppository.

Spasticity is often seen with brainstem or spinal cord involvement in MS. Disinhibition of motor systems can manifest as tone changes, jerking or twitching, or a stiff-legged spastic gait. Stretching and exercise may help, and baclofen, tizanidine or diazepam are often helpful, though may cause sedation. For severe spasticity, intrathecal pump delivery of baclofen has improved function.

Pain symptoms are under-recognized in MS and can be due to a primary central pain syndrome (neuropathic pain) or secondary to other causes such as decubital ulcers, poor biomechanics, or osteoporosis. Central pain syndromes may respond to anticonvulsant medication, tricyclic antidepressants (e.g. amitriptyline), or selective serotonin/norepinephrine reuptake inhibitors. The addition of nonsteroidal anti-inflammatories and opioids may be of benefit.

Prognosis

The clinical pattern or course of the disease is difficult to predict for an individual patient at disease onset. Certain patterns of disease are associated with slower progression and less disability. Optic neuritis or sensory symptoms at diagnosis, complete recovery between attacks, women and patients with one or two relapses in the first year of their MS will probably do better than those without these features. A progressive course has a worse prognosis for disability. Some patients have a more benign variant of MS and never develop disability. Mortality as a direct consequence of MS is highly uncommon. MRI has shown new or active lesions even in the absence of clinical disease. Known as "clinically silent lesions," these expressions of MS progression make it imperative that MS patients are followed with serial imaging studies as well as with office visits for clinical examination. If there is evidence of either clinical or radiological disease progression, more aggressive treatment to slow the course is likely to be of benefit. A comprehensive care approach to the treatment of MS by a caring, experienced physician can improve the quality of life for MS patients.

►Autoimmune Demyelinating Disorders: Stem Cell Therapy

References

1. Trapp BD, Peterson J, Ransohoff RM et al. (1998) Axonal transection in the lesions of multiple sclerosis. N Engl J Med 338:278–285
2. Weinshenker BG (1996) The epidemiology of multiple sclerosis. Neurol Clin 14:291
3. The Multiple Sclerosis Genetics Group (1996) A complete genome screen for multiple sclerosis underscores a role for the major histocompatibility complex. Nat Genet 13:469
4. Weinshenker BG, Bass B, Rice GP et al. (1989) The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 112:1419–1428
5. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
6. McDonald WI, Compston A, Edan G et al. (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annal Neurol 50:121–127
7. Freedman MS, Thompson EJ, Deisenhammer F, Giovanni G et al. (2005) Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. Arch Neurol 62:865–870
8. Pittock SJ, Lucchinetti CF (2007) The pathology of MS: new insights and potential clinical applications. Neurologist 13:45–56
9. Lassman H, Bruck W, Lucchinetti CF (2007) The immunopathology of multiple sclerosis: an overview. Brain Pathol 17:210–218
10. Goodin DS et al. (2002) Disease modifying therapies in multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 58:169

Multiple Sclerosis: Macrophages and Axonal Loss

Elly J. F. Vereyken, Christine D. Dijkstra, Charlotte E. Teunissen
Department of Molecular Cell Biology and Immunology, VUMC, Amsterdam, The Netherlands

Definition

►Multiple sclerosis is a disease of the central nervous system in which a progressive destruction of ►myelin, a fatty layer surrounding neurons, and transaction of neurons takes place. The mechanisms causing this destruction are largely unknown. ►Macrophages are thought to play a major role in the neuronal damage that occurs, through the release of inflammatory substances like ROS, ►cytokines and glutamate. Macrophages are not only detrimental in this disorder, but can also

be involved in axonal repair, e.g. by production of neutrophic factors.

Characteristics

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS) and the most common cause of neurological disability among young adults. The prevalence of MS is approximately 1.5 million people worldwide and women are affected more often compared to men [1]. Three major clinical courses are recognized: the relapsing-remitting (RR-MS), the secondary-progressive (SP-MS) and primary progressive (PP-MS) subtype. Approximately 80% of the cases start with the RR subtype, which is characterized by clinical attacks that are followed by a clinically silent period with almost complete recovery. After a period of 10–15 years most cases of the RR-MS subtype develop progressive neurological deterioration without apparent remission, the SP-MS subtype. The last subtype, PP-MS, is less common and is characterized by progressive neurological impairment without relapses or remissions.

The major neuropathological hallmarks of MS are demyelinating lesions associated with perivascular infiltrates containing macrophages and lymphocytes. Most lesions also have some degree of astrogliosis, which is hypertrophy of and an abnormal increase in the number of ►astrocytes. The animal model that is most often used to study MS is ►experimental allergic encephalomyelitis (EAE). EAE is an inflammatory demyelinating autoimmune disease. The symptoms of EAE can be characterized as either acute or chronic-relapsing. To induce EAE animals are injected with CNS homogenate, myelin proteins or parts of these myelin proteins in adjuvant. Adoptive transfer of autoreactive $CD4^+$ T-cells or autoantibodies can also induce EAE passively.

Historically, MS has been viewed as a primary demyelinating disease with relative axonal sparing, although early papers did describe axonal damage and loss [2]. However, the view that axonal damage is important in MS pathology is now being widely accepted.

Axonal Damage in MS

Demyelination has long been considered the main cause of disability in MS. However, more recent reports suggest that axonal injury is the correlate of irreversible clinical disability in MS patients. Early axonal damage may be either compensated for and/or repaired, but the continuous progression of axonal loss could ultimately lead to irreversible clinical dysfunction. A current hypothesis is that the transition from the RR to the SP subtype takes place once the loss of a critical number of ►axons is exceeded [2].

An indication that axonal damage might be important in MS pathology was that axonal transections are common in MS lesions, even in the periplaque white matter. It was most extensive in areas of active demyelination and inflammation. In chronic MS patients, axonal density was significantly decreased in both normal appearing white matter (NAWM) and lesions in the cervical spinal cord compared to controls. The decrease in axonal density was more extensive inside most lesions compared to the adjacent NAWM [2]. A marker for axonal injury is the amyloid precursor protein (APP). During acute injury anterograde axonal transport is interrupted causing APP to accumulate. In lesions with active demyelination APP accumulation was found, suggesting that axonal damage is a feature of early pathology and possibly associated with inflammation. In inactive lesions significant, though low-level axonal damage was observed associated with residual inflammation.

Magnetic resonance imaging (MRI) and spectroscopy (MRS) were used to visualize neuronal damage in living patients. Progressive brain atrophy was found to correlate with a decline in EDSS in MS patients. These findings suggest that brain atrophy leads to functional impairment. A more specific marker for axonal damage in MS is *N*-acetylaspartate (NAA), which can be detected *in vivo* in the brain using MRS. NAA is a mitochondrial amino acid that is primarily localized in neurons and neuronal processes, which means that a change in NAA signal reflects axonal injury and/or neuronal loss [2]. A relationship was observed between the decrease in NAA levels measured by MRS in MS lesions and the decrease in axonal density in corresponding biopsy specimens [2].

Changes in cerebrospinal fluid (CSF) concentrations of axon specific markers also point to a role of axonal damage in MS pathology and progression. In CSF of MS patients the NAA concentration was found to correlate with EDSS, a lower brain volume and a higher lesion load [3]. Other biomarkers for axonal damage in the CSF, as reviewed by our group, are proteins like Tau and neurofilament. The autoantibody index for the neurofilament-light chain has been found to correlate with atrophy [4].

All these data confirm the importance of axonal damage in MS pathology, which can already be observed early in the disease course. The mechanisms causing this damage are largely unknown. A hypothesis is that infiltrating macrophages might play a crucial role in axonal damage.

Macrophages in Axonal Damage

It is generally accepted that macrophages/►microglia are involved in the pathogenesis of MS and EAE, for example through the removal of myelin debris by phagocytosis. Some indirect evidence has been found supporting a role for macrophages in axonal damage. Several studies have found correlations between

macrophages and axonal damage in MS lesions. The first example is the correlation observed between the location of axonal damage and cellular infiltrates in both MS and EAE [2]. Secondly, a correlation between the number of infiltrating macrophages and axonal damage, as viewed with both APP and axonal transections, was observed. Finally, the elimination of infiltrating macrophages or resident microglia in the CNS has a suppressive effect on the clinical signs of EAE, indicating a direct effect of macrophages on axonal function [1].

Macrophage and microglial activation are associated with an upregulation of a plethora of inflammatory mediators that could mediate the acute damage seen in the axons. Many studies have shown increased concentrations of markers for oxidative stress, like oxidized proteins, lipids and DNA [1]. These markers have been found in the CNS of EAE animals and sera of MS patients. This oxidative stress is caused by both ROS, like superoxide and hydrogen peroxide, and nitric oxide (NO). Treatment with ROS scavengers and antioxidants reduced inflammation and axonal damage in acute EAE [1]. By activating nuclear transcription factor-kappa B, ROS can induce the transcription of many genes involved in the pathogenesis of EAE and MS such as tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase and intracellular adhesion molecule 1 [5]. The contribution of this pathway to the axonal damage in MS has not been investigated. ROS and NO could also lead to axonal damage by inducing oxidative stress in mitochondria. Axons are metabolically very active, especially due to impulse conduction and axonal transport. Mitochondria produce this energy and are therefore an intracellular source of ►reactive oxygen species (ROS). This makes them especially sensitive to exposure to extracellular ROS from macrophages. Mitochondrial dysfunction, due to the oxidative stress, leads to energy deficiency and can thereby lead to impairment of axonal transport and accumulation of APP. Impairment of axonal transport has been observed in many neurodegenerative disorders, like MS and Wallerian degeneration, indicating it plays an important role in axonal loss [6]. The precise mechanism behind decreased transport leading to axonal degeneration is not known. Reduced energy levels also cause increased sodium leakage into the axon and thereby reversal of the operation of the sodium-calcium exchanger and axonal swelling. This reversal of operation leads to increased intracellular calcium concentrations, bringing about the induction of apoptosis [6].

In CSF, blood and urine of MS-patients increased concentrations of markers of NO production, like peroxynitrite and 3-nitrotyrosine, have been observed. Peroxynitrite, which correlates with disease severity, is toxic and can damage both axons and myelin [1]. NO can induce a reversible conduction block in axons exposed to low frequency stimulation, while exposure to NO during higher frequency stimulation leads to axonal degeneration [7].

Both pro- and anti-inflammatory cytokines are upregulated, seemingly simultaneously as they are all detected in serum, CSF, and cultured mononuclear cells of MS patients. Cytokines have many different functions and in a complex disorder like MS it is not always clear whether they are beneficial or detrimental. For example moderate overexpression of TNF-α can lead to demyelination and axonal damage, very similar to that observed in EAE and MS [1]. However, no correlation was observed between axonal damage in MS patients and TNF-α expression in the CNS or serum levels, nor is treatment with TNF-α antibodies beneficial in MS. The same holds true for Interleukin-6 (IL-6), which has been implicated in induction of ►excitotoxicity, but also has been reported to have neuroprotective effects [1].

Glutamate is the most common excitatory neurotransmitter in the CNS. However, excessive concentrations of glutamate lead to excitotoxicity. Excitotoxicity is thought to play a role in MS since increased concentrations of glutamate have been observed in CSF of MS patients and this increase was found to be associated with the severity and course of the disease [1]. Treatment of EAE mice with an AMPA/kainate antagonist led to significant decrease in clinical scores, which corresponded pathologically to a reduction in axonal damage and oligodendrocyte loss [1].

Macrophages in CNS Regeneration and Repair

Recently, evidence has been found pointing to not only a detrimental but also a beneficial role of macrophages in axonal regeneration/repair. Several studies have found macrophages to be involved in axonal regenerative processes at different locations. At these different locations different macrophage derived mediators were implicated. For example, it was found that increased brain derived neurotrophic factor (BDNF) expression by macrophages could lead to locomoter recovery and axonal outgrowth [8]. Four weeks after a spinal cord compression injury, causing paraplegia in rats, an injection of granulocyte macrophages-colony stimulating factor (GM-CSF) promoted increased expression of BDNF by macrophages at the lesion site and thereby axonal regeneration. Also *in vitro* microglia activated by GM-CSF produced more BDNF, causing co-cultured neurons to generate more neurites. This effect could be blocked by anti-BDNF antibodies.

After optical nerve crush, lens injury induced pro-regenerative effects due to an influx of macrophages. Macrophage infiltration corresponded with an upregulation in growth-associated protein (GAP)-43 expression levels. GAP-43 is a marker for axonal growth and

synaptogenesis. Intraocular Zymosan injection, which also results in massive macrophage infiltration, led to increased GAP-43 expression and axonal regeneration in absence of lens injury. In vitro, medium from Zymosan stimulated macrophages was able to enhance axon regeneration, with the axon-promoting effects being mediated by oncomodulin [9].

Finally, macrophages could be positively involved in axonal outgrowth through expression of the axon guidance molecule EphrinB3 [10]. Macrophages recruited to the site of nerve crush express this axon guidance molecule EphrinB3, while injured retinal ganglion cells express the receptor for EphrinB3. This was further confirmed by the fact that a reduction of EphrinB3 function led to a greatly decreased retinal ganglion cell axon re-extension or sprouting, after optic nerve injury in EphrinB3 heterozygous and homozygous null mutants.

Subtypes of Macrophages

A current hypothesis poses that different activational subtypes of macrophages exist. These different macrophages have different functions in the immuneresponse and tissue repair. Interesting for the CNS could be the difference in their contribution to repair. The three main subtypes are: (i) the classically activated macrophages (CA-MΦ, also called M1), induced by IFN-γ and LPS; (ii) type II activated macrophages (MΦ-II), produced by exposure to IFN-γ in the presence of immunoglobulin G immunecomplexes; and the alternatively activated macrophages (AA-MΦ, also called M2), stimulated by IL-4 and/or glucocorticoids. The CA-MΦ is cytotoxic and secretes high amounts of NO and IL-12. The MΦ-II induces a Th2 response, through its release of IL-10. Finally, the AA-MΦ seems to be involved in immunosuppression and tissue repair, due to production of neurotrophic factors, extracellular matrix components and failure to produce NO [11]. Markers for the different types of macrophages are presented in Table 1. The most common used distinctive marker for AA-MΦ, in mice, is the higher expression and activity of arginase, leading to release of neurotrophic factors and extracellular matrix molecules [11]. Both CA-MΦ and MΦ-II are efficient antigen presenting cells, while AA-MΦ are not [11]. Until now, little research has been done about the presence and function of these different subsets of macrophages in neurodegenerative diseases like MS.

Macrophages and Axonal Repair in MS

Removal of myelin debris by macrophages is thought to be important for axonal repair/regrowth, since myelin debris have been found to be growth inhibiting. In MS lesions activated macrophages/microglia are a source of growth factors, neurotrophins and their receptors that actively promote axonal regrowth, such as BDNF and the receptor for NGF [30]. It has been shown that both *in vivo* and *in vitro* macrophages/microglia in the CNS express nerve growth factor, neurotrophin-3 and BDNF [30]. Furthermore, macrophages could contribute to the resolution of the inflammation in MS thereby inhibiting further injury to the axons. It was found that myelin-laden foamy macrophages in active lesions expressed anti-inflammatory molecules, with the exact molecules expressed depending on the precise location in the lesions, while pro-inflammatory molecules were not expressed in any of the lesion locations [31]. *In vitro*, myelin ingestion induced foamy macrophage morphology and expression of anti-inflammatory molecules and inhibited the response to pro-inflammatory stimuli. This indicated a strong immunosuppressive function for foamy macrophages [31]. These foamy macrophages displayed functions and activities that might put them in the category of AA-MΦ. Another study also indicated that foamy macrophages in MS lesions might be AA-MΦ, since they express CD163, although the expression of mannose receptor is low in these cells [32]. Furthermore, periventricular macrophages, which are located at the blood brain barrier, have an AA-MΦ phenotype, since they do express both CD163 and mannose receptor. This could be important since their location at the blood brain barrier means they occupy a strategic position to control innate and adaptive immune responses in the brain [32].

Another indication that macrophages could be involved in axonal repair was found in our studies showing that activated macrophages are present in the areas of increased GAP-43 expression [33]. Levels of GAP-43 were higher around lesions. Although no correlation was found between the intensity of GAP-43 staining and macrophage presence, their presence was consistently observed in areas of increased GAP-43 expression. Macrophages producing neurotrophic factors, like neurotrophic growth factor and BDNF could induce the increase in GAP-43 expression [33]. We are planning to investigate the phenotype of the macrophages present in the areas of GAP-43 expression.

Future Perspectives

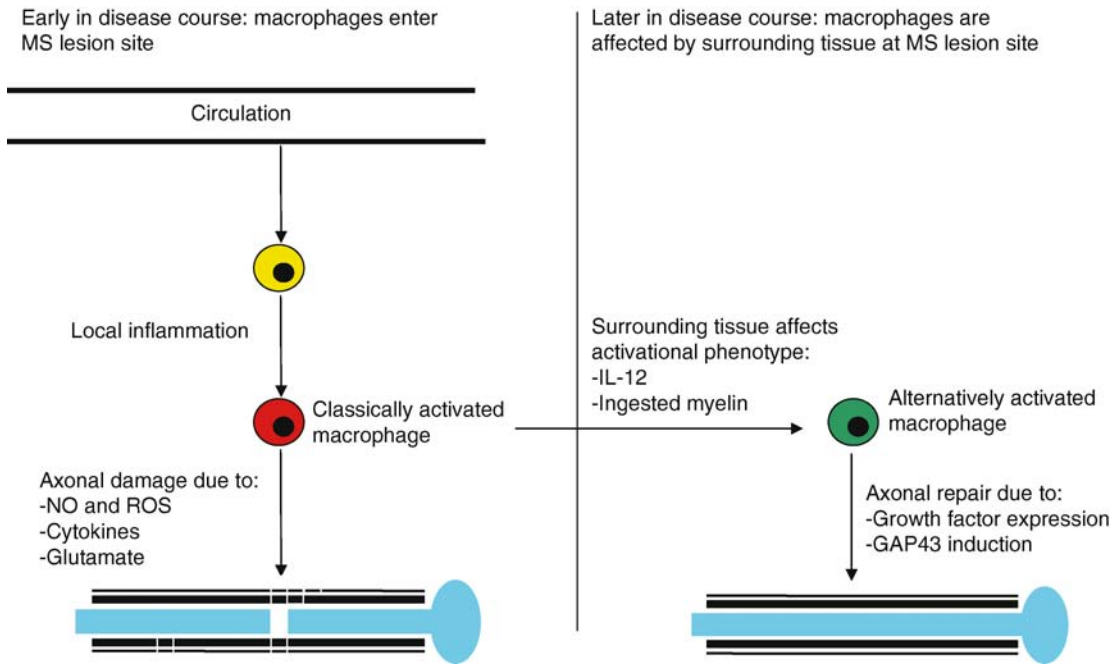
Our hypothesis is that alternatively activated macrophages and classically activated macrophages may be different phenotypic forms of macrophages during different phases of MS pathology. This is schematically represented in Fig. 1. Classically activated macrophages could play an important role in causing axonal damage early in lesion development, through the release of soluble mediators like NO, ROS and glutamate. When lesions develop further and macrophages are present in the tissue longer, our idea is that the classically activated macrophages change into alternatively activated macrophages. Alternatively activated macrophages can play a role in the resolution of inflammation due to their anti-inflammatory nature

Multiple Sclerosis: Macrophages and Axonal Loss. Table 1 Markers for the different macrophage subtypes

Marker	CA-MΦ	MΦ-II	AA-MΦ	Observed in	Reference
Enzymes					
iNOS mRNA expression	↑	↑	–	Mouse	[11]
iNOS activity					[12]
NO release					
Arginase mRNA expression	–	–	↑	Mouse	[11]
Arginase actvity					
SPHK1 mRNA	–	↑	–	Mouse	[11]
12,15-lipoxygenase	↓	?	↑	Human, mouse	[13]
Membrane receptor expression					
CD163 protein expression	–	–	↑	Human	[14]
CD163 mRNA	–	–	↑	Mouse	[11]
Mannose receptor protein expression	–	–	↑	Mouse	[15]
β-glucan receptor (Dectin-1)	–	–	↑	Mouse	[16]
MGL1/2 mRNA	–	?	↑	Human, mouse	[17]
MGL1/2 protein expression					
FcγR	↑	?	↓	Human	[18]
LIGHT mRNA	–	↑	–	Mouse	[11]
Antigen presentation					
MHC class II protein expression	↑	↑↑	↓	Human, mouse	[11]
CD86 protein expression	↑	↑	↓	Human, mouse	[11]
MS1-HMWP	↓	?	↑	Human	[19]
Cytokines					
IL-12 release	↑	–	–	Human, mouse	[11,20,21]
IL-12 mRNA	↑↑	↑	–		
IL-10 release	–	↑	–	Mouse	[11,21,22]
IL-10 mRNA	–	↑	–		
Ratio IL-10/IL-12	↓	↑	–	Mouse	[21,22]
IL-23 release	↑	–	–	Human	[23]
IL-6	↑	↑	↓	Mouse	[21]
TNF	↑	↑	↓	Human	[24]
IL-1Ra/IL-1 decoy receptor release	–	–	↑	Mouse	[19]
Chemokine					
AMAC-1 release	–	?	↑	Human	[25]
MIP-1a mRNA	↑	–	–	Human	[19,22]
MDC (CCL22) mRNA expression					
MDC release	–	–	↑	Human	[26]
TARC (CCL17)	↓	?	↑	Human, mouse	[27,28]
Secretory proteins					
FIZZ1 mRNA	–	–	↑	Mouse	[29]
YM1/2 mRNA	–	–	↑	Mouse	[29]

↑: an increase in expression/activity. –: no change in expression/activity. ↓: a decrease in expression/activity. ?: unknown

Abbreviations: AA-MΦ = alternatively activated macrophage; APP = amyloid precursor protein; BDNF = brain derived neurotrophic factor; CA-MΦ = classically activated macrophage; CNS = central nervous system; CSF = cerebrospinal fluid; EAE = experimental allergic encephalomyelitis; EDSS = expanded disability status scale; GAP-43 = growth-associated protein 43; GM-CSF = granulocyte macrophage colony-stimulating factor; MΦ-II = type II activated macrophage; MBP = myelin basic protein; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; MS = multiple sclerosis; NAA = *N*-acetylaspartate; NAWM = normal appearing white matter; NO = nitric oxide; PP-MS = primary progressive multiple sclerosis; ROS = reactive oxygen species; RR-MS = relapsing-remitting multiple sclerosis; SP-MS = secondary progressive- multiple sclerosis; TNF-α = tumor necrosis factor-alpha.



Multiple Sclerosis: Macrophages and Axonal Loss. Figure 1 Hypothesis of macrophage activation in MS lesions. As the macrophages enter the lesion site, they are classically activated due to the local inflammation. These classically activated macrophages induce axonal damage due to secreted factors like NO, pro- inflammatory cytokines and glutamate. The macrophages at the lesion site spent time in the CNS tissue. Slowly the surrounding tissue starts to affect the activational phenotype of the macrophages. Due to IL-12 secreted by astrocytes and ingestion of myelin, the macrophages take on an alternatively activated phenotype. These macrophages are involved in axonal repair due to the expression of growth factors, induction of GAP-43 expression in neurons and secretion of anti-inflammatory cytokines.

and axonal repair/regeneration through the release of neurotrophic factors.

It has been shown that classically activated macrophages can still become alternatively activated and vice versa [34]. The activational subtype of the macrophage is therefore not fixed and could be influenced by the surrounding environment, such as CNS cells like astrocytes. For example, the ingestion of myelin, which makes macrophages foamy, could induce an alternative phenotype in macrophages [31]. In Gaucher disease glycolipids also accumulate inside macrophages, which subsequently show an alternatively activated phenotype. This seems to implicate that glycolipids could induce alternative activation. It might be that accumulation of glycolipid constituents of myelin directs macrophage gene transcription to induce the alternatively activated phenotype in MS. However, it is still a question whether foamy macrophages, which have been shown to be anti-inflammatory [31], can be really characterized as alternatively activated. Another question is whether foamy macrophages are able to directly induce GAP-43 expression in axons and whether this also leads to functional repair. Furthermore, it has been shown that astrocytes secrete IL-12, which could influence the macrophage activational subtype and skew it more to the alternative side.

Future therapeutic interventions should aim at reducing activation of classically activated macrophages during early phases of lesion development, while stimulating the formation of alternatively activated macrophages. Since axonal damage occurs early during disease course, perhaps specifically blocking the activity of classically activated macrophages could be a candidate therapy. It may also be a good option to treat patients early during disease course with substances able to induce the alternative phenotype, thus reducing inflammation, axonal damage and consequently clinical dysfunction.

Acknowledgements

This research is sponsored by both the MS Research Foundation (grants 05-559 MS and 02-358b MS) and ZON-MW (veni grant).

References

1. Hendriks JJ, Teunissen CE, de Vries HE, Dijkstra CD (2005) Macrophages and neurodegeneration. Brain Res Brain Res Rev 48:185–195

2. Bjartmar C, Trapp BD (2001) Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. Curr Opin Neurol 14:271–278
3. Jasperse B, Jakobs C, Eikelenboom MJ, Dijkstra CD, Uitdehaag BM, Barkhof F, Polman CH, Teunissen CE. N-acetylaspartic acid in cerebrospinal fluid of multiple sclerosis patients determined by gas-chromatography-mass spectrometry. J Neurol 2007 May; 254(5):631–637
4. Teunissen CE, Dijkstra C, Polman C (2005) Biological markers in CSF and blood for axonal degeneration in multiple sclerosis. Lancet Neurol 4:32–41
5. Gilgun-Sherki Y, Melamed E, Offen D (2004) The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J Neurol 251:261–268
6. Coleman M (2005) Axon degeneration mechanisms: commonality amid diversity. Nat Rev Neurosci 6:889–898
7. Smith KJ, Lassmann H (2002) The role of nitric oxide in multiple sclerosis. Lancet Neurol 1:232–241
8. Bouhy D, Malgrange B, Multon S, Poirrier AL, Scholtes F, Schoenen J, Franzen R (2006) Delayed GM-CSF treatment stimulates axonal regeneration and functional recovery in paraplegic rats via an increased BDNF expression by endogenous macrophages. FASEB J 20:1239–1241
9. Yin Y, Henzl MT, Lorber B, Nakazawa T, Thomas TT, Jiang F, Langer R, Benowitz LI (2006) Oncomodulin is a macrophage-derived signal for axon regeneration in retinal ganglion cells. Nat Neurosci 9:843–852
10. Liu X, Hawkes E, Ishimaru T, Tran T, Sretavan DW (2006) EphB3: an endogenous mediator of adult axonal plasticity and regrowth after CNS injury. J Neurosci 26:3087–3101
11. Edwards JP, Zhang X, Frauwirth KA, Mosser DM (2006) Biochemical and functional characterization of three activated macrophage populations. J Leukoc Biol 80:1298–1307
12. Doyle AG, Herbein G, Montaner LJ, Minty AJ, Caput D, Ferrara P, Gordon S (1994) Interleukin-13 alters the activation state of murine macrophages *in vitro*: comparison with interleukin-4 and interferon-gamma. Eur J Immunol 24:1441–1445
13. Conrad DJ, Kuhn H, Mulkins M, Highland E, Sigal E (1992) Specific inflammatory cytokines regulate the expression of human monocyte 15-lipoxygenase. Proc Natl Acad Sci USA 89:217–221
14. Buechler C, Ritter M, Orso E, Langmann T, Klucken J, Schmitz G (2000) Regulation of scavenger receptor CD163 expression in human monocytes and macrophages by pro- and antiinflammatory stimuli. J Leukoc Biol 67:97–103
15. Stein M, Keshav S, Harris N, Gordon S (1992) Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J Exp Med 176:287–292
16. Willment JA, Lin HH, Reid DM, Taylor PR, Williams DL, Wong SY, Gordon S, Brown GD (2003) Dectin-1 expression and function are enhanced on alternatively activated and GM-CSF-treated macrophages and are negatively regulated by IL-10, dexamethasone, and lipopolysaccharide. J Immunol 171:4569–4573
17. Raes G, Brys L, Dahal BK, Brandt J, Grooten J, Brombacher F, Vanham G, Noel W, Bogaert P, Boonefaes T, Kindt A, Van den BR, Leenen PJ, De BP, Ghassabeh GH (2005) Macrophage galactose-type C-type lectins as novel markers for alternatively activated macrophages elicited by parasitic infections and allergic airway inflammation. J Leukoc Biol 77:321–327
18. te Velde AA, Huijbens RJ, De Vries JE, Figdor CG (1990) IL-4 decreases Fc gamma R membrane expression and Fc gamma R-mediated cytotoxic activity of human monocytes. J Immunol 144:3046–3051
19. Mosser DM (2003) The many faces of macrophage activation. J Leukoc Biol 73:209–212
20. Skeen MJ, Miller MA, Shinnick TM, Ziegler HK (1996) Regulation of murine macrophage IL-12 production. Activation of macrophages *in vivo*, restimulation *in vitro*, and modulation by other cytokines. J Immunol 156:1196–1206
21. Gerber JS, Mosser DM (2001) Reversing lipopolysaccharide toxicity by ligating the macrophage Fc gamma receptors. J Immunol 166:6861–6868
22. Anderson CF, Mosser DM (2002) A novel phenotype for an activated macrophage: the type 2 activated macrophage. J Leukoc Biol 72:101–106
23. Verreck FA, de BT, Langenberg DM, Hoeve MA, Kramer M, Vaisberg E, Kastelein R, Kolk A, de Waal-Malefyt R, Ottenhoff TH (2004) Human IL-23-producing type 1 macrophages promote but IL-10-producing type 2 macrophages subvert immunity to (myco)bacteria. Proc Natl Acad Sci USA 101:4560–4565
24. Hart PH, Vitti GF, Burgess DR, Whitty GA, Piccoli DS, Hamilton JA (1989) Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E2. Proc Natl Acad Sci USA 86:3803–3807
25. Kodelja V, Muller C, Politz O, Hakij N, Orfanos CE, Goerdt S (1998) Alternative macrophage activation-associated CC-chemokine-1, a novel structural homologue of macrophage inflammatory protein-1 alpha with a Th2-associated expression pattern. J Immunol 160:1411–1418
26. Bonecchi R, Sozzani S, Stine JT, Luini W, D'Amico G, Allavena P, Chantry D, Mantovani A (1998) Divergent effects of interleukin-4 and interferon-gamma on macrophage-derived chemokine production: an amplification circuit of polarized T helper 2 responses. Blood 92:2668–2671
27. Imai T, Nagira M, Takagi S, Kakizaki M, Nishimura M, Wang J, Gray PW, Matsushima K, Yoshie O (1999) Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. Int Immunol 11:81–88
28. Liddiard K, Welch JS, Lozach J, Heinz S, Glass CK, Greaves DR (2006) Interleukin-4 induction of the CC chemokine TARC (CCL17) in murine macrophages is mediated by multiple STAT6 sites in the TARC gene promoter. BMC Mol Biol 7:45
29. Raes G, De BP, Noel W, Beschin A, Brombacher F, Hassanzadeh GG (2002) Differential expression of FIZZ1 and Ym1 in alternatively versus classically activated macrophages. J Leukoc Biol 71:597–602
30. Kerschensteiner M, Stadelmann C, Dechant G, Wekerle H, Hohlfeld R (2003) Neurotrophic cross-talk between the nervous and immune systems: implications for neurological diseases. Ann Neurol 53:292–304

31. Boven LA, Van MM, Van ZM, Wierenga-Wolf A, Hintzen RQ, Boot RG, Aerts JM, Amor S, Nieuwenhuis EE, Laman JD (2006) Myelin-laden macrophages are anti-inflammatory, consistent with foam cells in multiple sclerosis. Brain 129:517–526
32. Fabriek BO, Van Haastert ES, Galea I, Polfliet MM, Dopp ED, Van Den Heuvel MM, Van Den Berg TK, De Groot CJ, Van DV, Dijkstra CD (2005) CD163-positive perivascular macrophages in the human CNS express molecules for antigen recognition and presentation. Glia 51:297–305
33. Teunissen CE, Dijkstra CD, Jasperse B, Barkhof F, Vanderstichele H, Vanmechelen E, Polman CH, Bo L (2006) Growth-associated protein 43 in lesions and cerebrospinal fluid in multiple sclerosis. Neuropathol Appl Neurobiol 32:318–331
34. Porcheray F, Viaud S, Rimaniol AC, Leone C, Samah B, reuddre-Bosquet N, Dormont D, Gras G (2005) Macrophage activation switching: an asset for the resolution of inflammation. Clin Exp Immunol 142:481–489

Multiple Sleep Latency Test

Definition

A standardized, objective, clinical and research tool used to assess physiologic sleepiness. The test is based on the idea that the sleepiness can be measured by the speed of falling asleep under controlled environmental conditions of lying in bed with the lights off. Polysomnographic recordings of electroencephalogram (EEG), electrocardiogram (EKG), chin electromyogram (EMG), and eye movements are analyzed for four to five 20-min nap opportunities provided every 2 h across the day (e.g., naps at 1000, 1200, 1400, 1600, 1800 h). The average time that it takes to fall asleep across naps is calculated. Average sleep latency below 5 min is considered to be indicative of pathological or excessive sleepiness. Average latencies of between 5 and 10 min are considered to be in the grey zone and average sleep latency above 10 min is considered to indicate a normal or low level of physiological sleepiness.

►Electroencephalography
►Electromyography
►Sleep – Motor Changes
►Sleep – Sensory Changes

Multiple System Atrophy

Definition

Distributed disease affecting many neuronal systems. Symptoms mostly start in the early fifties and include: signs of ►autonomic failure, ►Parkinsonism, ►cerebellar ataxia, and pyramidal signs, severe ►dysarthria, stridor, and occasionally contractures and ►dystonia. The major pathological changes include cell loss and gliosis in the ►basal ganglia, ►substantia nigra, ►locus coeruleus, ►inferior olives, ►pontine nuclei, cerebellar ►Purkinje cells, and intermediolateral cell columns of the spinal cord, and others.

►Ataxia
►Basal Ganglia
►Dysarthria
►Dystonia
►Locus Coeruleus
►Parkinsonism

Multipolar Neuron/Cellular

Definition

A multipolar neuron is a neuron with many processes and a variety of shapes. Common example is the motoneuron and stellate cells.

Multipotency

Definition

Multipotency is a word describing the ability of a progenitor cell or tissue stem cells to give rise to a limited number of cell types. If a progenitor cell of the central nervous system is capable of turning only into neurons, astrocytes, and oligodendrocytes, for example, the cell is said to be “multipotent.”

Multisensory

Definition

Refers to neurons that are capable of responding to stimuli from more than a single sensory modality and to the neural processes associated with these responses (e.g., multisensory integration).

►Multimodal Integration

Multisensory (Convergence, Integration)

Definition

Many neurons of the central nervous system outside the specific sensory nuclei respond to peripheral stimuli of more than one modality, e.g., visual, auditory, somatic. They display thus a property of multisensory convergence.

When presented simultaneously, stimuli of different modalities can produce stronger or weaker responses, as compared to the sum of responses to separate presentations of unimodal stimuli. Because interaction of modalities at the level of single neurons is far more complex than a simple summation, it is described by the term "multisensory integration." An example of multisensory integration is given by tectoreticulospinal neurons (TRSNs) which transmit motor command for a gaze shift and display, at the same time, a multisensory convergence.

►Multimodal Integration
►SC-Tectoreticulospinal neurons (TRSNs)

Multi-Track Disposition

Definition

A disposition whose manifestations can widely vary. e.g. the softness of an object can manifest itself in uncountable ways, whereas water-solubility is a single-track disposition which can only manifest itself by dissolving in water.

►Behaviorism
►Logical

Multi-Unit Recording

Definition

Simultaneous recording from multiple nerve, glia or muscle cells (units) by means of a single electrode or pair of electrodes.

►Extracellular Recording

Muscarinic Receptors

Definition

Muscarinic receptors are G-protein coupled receptors that respond to acetylcholine and muscarine, and that are blocked by atropine and related anti-muscarinic agents. They occur in five subtypes. Muscarinic M3 receptors have been considered to be an effector cell receptor, M1 a ganglionic, and M2 a presynaptic inhibitory one. In the peripheral nervous system, more than one type of the excitatory muscarinic M1, M3 and M5 receptors and of the inhibitory muscarinic M2 and M4 receptors may however co-occur on effector cells as well as on nerve fibers.

These receptors are expressed in smooth muscle, cardiac muscle and glands as well as in the peripheral and central nervous system. Muscarinic receptors mediate the excitatory effects of parasympathetic nerves in the urinary bladder.

►Acetylcholine
►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages
►Micturition, Neurogenic Control
►Parasympathetic Pathways

Muscle

C. J. Heckman, Eric Perreault, Thomas Sandercock, Huub Maas
Departments of Physiology, Physical Medicine and Rehabilitation, and Biomedical Engineering, Northwestern University, Sheridan Road Evanston, IL, USA

Introduction

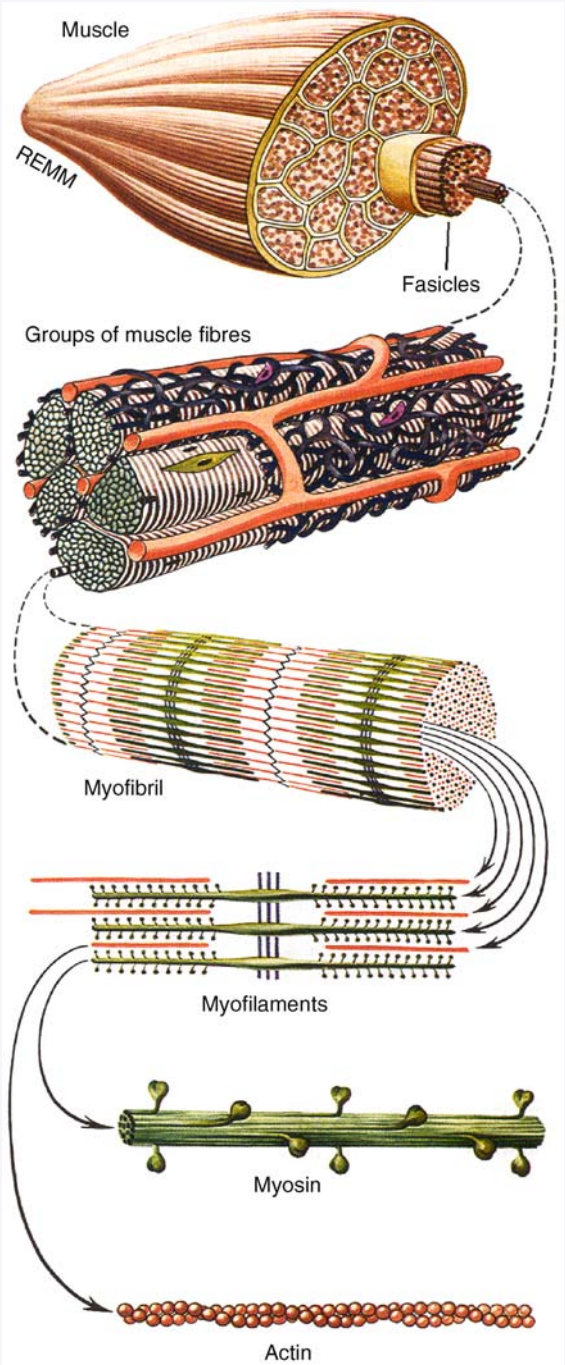
Skeletal muscle is the actuator for all vertebrate movements. As such, it has been the focus of scientific inquiry since the time of Erasistratus in the third century BC. While the earliest studies of muscle function focused on whole muscle properties, more recent investigations have been performed at levels ranging from mechanics within functional muscle groups down to the molecular interactions responsible for the active modulation of these mechanics. In accordance with the goals of this Encyclopedia, this section will focus on the role of muscle properties in the neural control of posture and movement. Hence, an emphasis will be

placed on the properties and control of individual motor units, the fundamental element of neural control, and how these units contribute to the regulation of whole muscle properties relevant to normal movement conditions. However, we also provide an overview of seminal findings across the spectrum of muscle research, from the molecular level to whole muscle behavior.

Muscle Structure

The macroscopic properties of muscle relevant to the neural control of movement arise from the underlying microstructure and corresponding molecular interactions involved in the chemical to mechanical energy conversion process known as muscle contraction. Each whole muscle is composed of many long thin cells, or muscle fibers, arranged parallel to each other (Fig. 1). Most fibers terminate in microtendons, which merge to form the aponeurosis and tendon that connect to the skeleton. Because of this parallel organization, the total force a muscle can produce is proportional to the summed cross-sectional area of all the fibers. The fibers are, in turn, composed of several thousand parallel myofibrils. Each myofibril is composed of repeating microscopic units (2–3 μm in length) called sarcomeres, which are the basic contractile units of muscle. Since sarcomeres within a fiber are linked in series and contract together, many key muscle properties, such as the maximum speed at which a muscle can shorten, are proportional to the length of the fiber. For this reason, muscle contractile properties are often normalized by both the muscle cross-sectional area and the fiber length (see essay ►Muscle: Tendon, Intramuscular Force Transmission).

The sarcomere is the basic contractile element (Fig. 1). It is composed of two sets of interdigitating protein filaments, called thin and thick filaments, which can slide by each other. The sarcomere is held together by large molecules that form the Z lines at each end and by the giant protein titin, which forms a spring between Z line and thick filament. Titin helps to maintain sarcomere shape as well as transmit force from the contractile proteins to the Z lines [1]. Each thick filament consists of a few hundred myosin molecules; the helix part of the myosin molecules aggregate to form the dominant part of the thick filament. A portion of the helix for each molecule extends out from the thick filament to form the myosin head, which has the capacity to swing up and attach to actin on the thin filament [2]. The myosin head and the portion of its helix that protrudes from the thick filament is known as a crossbridge. The thin filament is dominated by actin, but also includes the proteins tropomyosin and troponin, which regulate the interaction between actin and myosin. Actin monomers are connected end to end to form two fibrous strands that are wrapped around each other in a helical form. Tropomyosin is a chain structure that lies in the groove between the strands of actin, whereas troponin is a globular complex that binds to tropomyosin periodically (see essays ►Sarcomere structural proteins).



Muscle. Figure 1 Muscle structure. Diagram shows the organization of an idealized muscle. (from Gray's Anatomy, Warwick and Williams).

Muscle contraction occurs when calcium (Ca^{2+}) binds to troponin and causes a shift in the position of tropomyosin, uncovering binding sites for the myosin heads on actin. Depolarization of the muscle fiber via an action potential causes Ca^{2+} release from the sarcoplasmic reticulum where it is sequestered at rest (see below). Large populations of crossbridges on the thick filaments interact with receptor sites on the actin, to produce force and relative motion between the two sets of filaments. Adenosine triphosphate (ATP) is the energy source and is needed to detach the bridges and maintain movement. Several different substrates (e.g. glycogen, fat) are broken down via different biochemical pathways to provide the ATP for cross-bridge cycling. The forces thus produced between the two filaments are in a direction to cause each sarcomere to shorten. The actin and myosin filaments are approximately inextensible, and sarcomere shortening occurs because of the relative sliding of the filaments past each other (sliding filament theory) [3] (see essay ►Muscle: the molecular motor, ►Energy sensing and signal transduction in skeletal muscle).

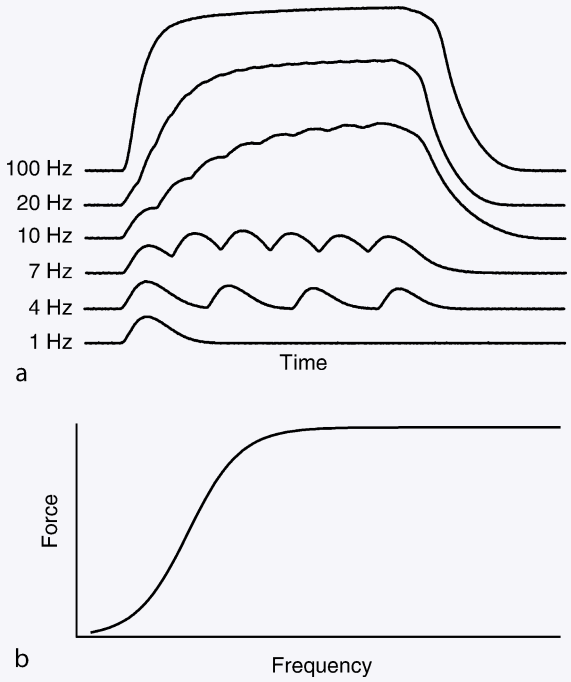
Muscle has specialized structures to allow a quick contraction following an action potential in the motor neuron. This complex process includes the following steps: release of acetylcholine at the neuromuscular junction in a response to the action potential, generation of a muscle fiber action potential, depolarization of the t-tubules that protrude into the muscle fiber, activation of ryanodine receptors, and release of Ca^{2+} from the sarcoplasmic reticulum. Pumps on the sarcoplasmic reticulum rapidly re-sequester Ca^{2+}, so that each action potential produces only a single pulse of Ca^{2+} and a single muscle twitch (see 1 Hz trace, Fig. 2a). The rate at which action potentials arrive at the muscle determine the sarcoplasmic level of Ca^{2+}, and hence, the strength of the contraction. This complete process is referred to as excitation contraction coupling (see essay ►Excitation Contraction Coupling).

Basic Muscle Properties

Muscle has four basic properties that are essential for understanding its control by the CNS (Figs. 2–4). These are: the force-frequency (F-f) relationship, the force-velocity (F-V) relationship, the length-tension (L-T) relationship, and muscle stiffness. Each will be discussed in the following paragraphs. Their fundamentals have been understood since the 1950s, but the details about the interaction between these properties, how they are used in normal movement, and how they relate to the properties of single motor units, are still incomplete.

Force-Frequency

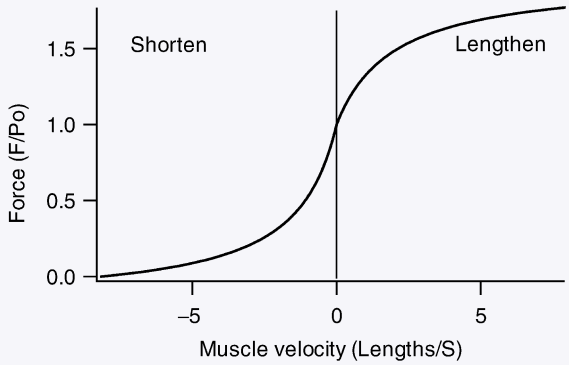
In general, a single muscle action potential does not produce full muscle force; rather, most actions require a sequence of action potentials. Summarizing the relation between an action potential train and the resulting muscle force has proven difficult. However, a useful steady state relationship can be determined by plotting action potential frequency against muscle force (Fig. 2). As the frequency is increased, single muscle twitches fuse and force increases (Fig. 2a). At high enough stimulus rates, which is dependent on the motor unit composition (see below), force is smooth. A further increase in action potential rate does not produce more force. This sigmoidal relation is shown in Fig. 2b. Stimulations rates and the details of the temporal pattern have important implications for the study of muscle function and its restoration following trauma or disease (see essay ►Force-Frequency; Muscle).



Muscle. Figure 2 Force-Frequency characteristics of a muscle (cat soleus). (a) shows the force waveforms produces when a muscle is held isometrically and stimulated at different frequencies (action potentials per second). (b) Sigmodial curve obtained when the mean force is plotted against the stimulation frequency. This relationship is, at best, a rough approximation and depends strongly on the exact experimental procedures to measure it.

Force-Velocity

The relationship between force and velocity is of fundamental importance when considering the power output and work performed by a muscle. Basically, when an active muscle shortens, it produces less force compared to that produced when it is held isometrically. A plot of the steady state relationship between

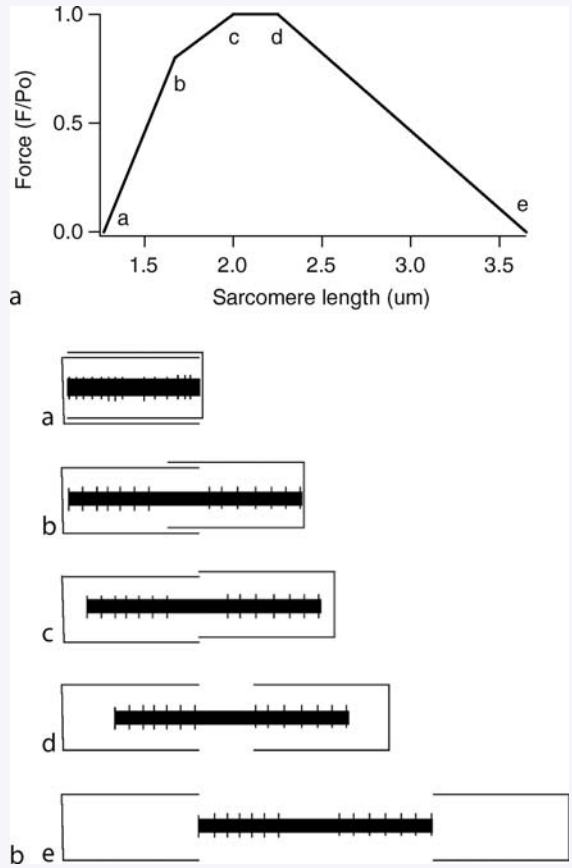


Muscle. Figure 3 Force-Velocity Relationship. When a muscle is activated and allowed to shorten against a load, it reaches a steady state velocity. When this relationship is plotted for different loads Hill's hyperbolic relationship is obtained (left side of plot). Similar measurements can be made using loads large enough to stretch the muscle (right side of plot). However, a true steady state is not reached during stretch and different results are obtained depending on whether a constant load or constant velocity is imposed on the muscle.

shortening velocity and muscle force results in a characteristic hyperbolic curve [4] that has been demonstrated in all skeletal muscles tested (Fig. 3). The maximum shortening velocity, Vmax, is the point where the muscle can no longer produce any force. Peak power is obtained from a muscle at a velocity between zero and Vmax. Huxley [3] showed this relationship can be explained using a probabilistic model of crossbridge dynamics. The relationship between force and velocity is more complex during lengthening contractions. A steady state relationship is never really achieved. The muscle may also be damaged by active stretch. An approximate relationship between stretch velocity and force shows force initially increases but soon a plateau is reached at moderate lengthening velocities [5] (see essay ►Force-Velocity Relationship of Skeletal Muscle).

Length-Tension

Muscle force is strongly affected by its length. During maximal stimulation the length-tension relationship (Fig. 4a) has a characteristic shape with an ascending limb, a plateau region of optimal force generation (defining an optimal length, L_O) and a descending limb. During tetanic stimulation the relationship is nicely explained by changing filament overlap within the sarcomere (Fig. 4b) [6]. However, the high frequencies used to induce a tetanic contraction in the laboratory are unlikely to be encountered during the physiological activation of motor units. At lower rates of activation, the length-tension relationship changes such that the peak shifts to longer lengths [7] (see essay ►Length-Tension).



Muscle. Figure 4 Active Length-Tension relationship during tetanic activation. Idealized length tension relationship (top) and the sarcomere position (bottom) believed to produce it. (Redrawn from [6]). Force from passive muscle structures are also important. They are not shown in this figure.

Muscle Stiffness

The CNS not only has to give commands to muscle to produce movement, but must also deal with stability of muscle in response to perturbations from the environment. The response of muscle to a perturbation, either lengthening or shortening, defines its stiffness (here we use "stiffness" in its most general form, to include all resistance to externally imposed displacements). For short perturbations muscle has a very linear spring-like response due to the spring-like behavior of the crossbridges. For larger perturbations, the response becomes complex and is determined by the L-T and F-V properties of sarcomeres. The passive structures within a muscle are also very important. The tendon and aponeurosis are connected in series with the muscle fibers and thus provide a series-elastic element (SEC). At long lengths, the passive molecules like titin that maintain the structure of the sarcomere also contribute substantially to total muscle stiffness [1]. These structures are in parallel with the force generated by

crossbridges and thus form the parallel elastic element (PEC). The PEC also includes the connective tissue surrounding muscle fibers as well as structures like the muscle fiber cell membrane. While the crossbridge dependent properties (L-T, F-V) are important determinants of stiffness at all lengths, tendon and other connective tissues are usually slack at short muscle lengths and the PEC does not contribute until muscle is stretched beyond its optimal length (see essays ►Muscular Stiffness, Tendon).

Muscle Models

Many different models of muscle force generation have been constructed. Perhaps the most widely used for the purposes of motor control is the Hill model. Originally, the Hill model contractile element consisted solely of the F-V function during shortening, which was placed in series with a spring representing tendon (i.e. the SEC) and in parallel with a spring representing the PEC. Recent models typically add the lengthening F-V function and use the L-T and F-f relationships to scale the F-V curve in order to account for more realistic behavior [8]. Also important are models based on crossbridge dynamics. Such a model was initially developed by Huxley [3] and models of this type are usually referred to as Huxley-type models or crossbridge models. These models can be modified to include reasonably detailed mathematical descriptions of Ca^{2+} dynamics to provide activation functions [9]. Muscle models face many tough challenges, primarily because the behavior of muscle is complicated. Thus far, we have only considered the "classic" muscle properties. Even these relatively simple muscle behaviors constitute a rather complicated mechanical interface: muscle force varies not only as a function of its neural activation but also as a function of its length and velocity. However, few studies have addressed the role of these and other complex properties in the neural control of movement. Recent studies attempting to assess muscle properties during normal movement conditions, including the use of advanced imaging techniques, hold much promise for both understanding muscle function and validating the models used to describe and predict that function (see essays ►Muscle Modeling; Muscle Imaging, Techniques: Computerized tomography, Magnetic resonance imaging, Ultrasound).

Complex Muscle Mechanical Behaviors

As mentioned above, attached crossbridges exhibit a spring-like response to small stretches, known as short range stiffness (SRS). For stretches greater than approximately 1–2% of fiber length, the attached crossbridges are broken causing a sudden drop in stiffness known as yielding [10]. Yielding is most pronounced in slow twitch muscle fibers because of their slow re-attachment rates. Although SRS varies with muscle fiber type, these differences do not appear to play a significant role at the whole muscle level [11]. The participation of crossbridges in the SRS means that it varies as a function of muscle activation: increased activation results in more attached crossbridges, higher muscle force and increased SRS. In addition, tendon itself exhibits increasing stiffness with increasing applied force.

Activation also plays a pivotal role in regulating F-V and L-T properties. This occurs in two ways. First, there exist interactions between the F-f, L-T and F-V functions. Perhaps the most important interaction is that between the F-f and L-T functions. [7] showed that as stimulation rate is reduced below that needed to achieve maximal force, the L_O point of the L-T function progressively shifts to longer lengths. Thus, the L-T function at low stimulation rates is not simply a scaled-down version of that at high rates. Interactions between the F-V and F-f functions are also important, especially during lengthening where, for example, yielding is greater at low stimulation rates [5]. There also exists an L-T/F-V interaction. At longer lengths, stretching at a given velocity produces more force [5]. A second important form of activation dependence is that F-V properties are very different in muscle fibers of different contraction speeds. These differences reflect both differences in the myosin ATPase on crossbridge heads and in the Ca^{2+} release system [12]. Thus as motor units of different speeds are recruited as force increases, F-V behavior changes (see the section on "Motor Units" below). Finally, it is important to realize that the activation of muscle in itself is affected by movement. That is, the Ca^{2+} system for control of crossbridge interactions is sensitive to both length and velocity [13]. Thus one reason that L_O shifts to longer lengths at lower stimulus rates is that Ca^{2+} release is length-dependent. In addition, movement may enhance Ca^{2+} release and thus speed the decay of force in a velocity dependent manner [14] (see essays ►Muscle Stiffness, ►Length-Tension, ►Force-Velocity Relationship of Skeletal Muscle, ►Force Potentiation in Skeletal Muscle).

Muscle also exhibits a number of behaviors that can be thought of as being history dependent, in that their occurrence depends on a particular sequence of events. Perhaps the F-f function is most influenced by muscle history because its shape is highly sensitive to the measurement protocol [15]. A simple change as reversing the order of the test frequencies has a profound effect. In addition, in isometric conditions, muscle force can be strongly potentiated by a brief high frequency activation (post-tetanic potentiation) or even by a single pair of closely spaced stimuli (doublet potentiation) [16]. Of course, if stimulation is prolonged, fatigue ensues. Fatigue is a complex

phenomenon acting at multiple locations within the muscle. These mechanisms are not yet fully understood, but it plays a key role in motor function. For example, the normal activation pattern of motor units appears to be designed to minimize the impact of fatigue (see below). Movement history also strongly influences muscle function. For example, muscle generates a greater isometric force (force enhancement) when it has been stretched during activation compared to when it has been stretched passively and then activated [17]. The converse phenomenon is also often seen: less isometric force following shortening of an active muscle (force depression) (see essays ►History-Dependent Properties of Skeletal Muscle).

Muscle Architecture

Provided the sarcomeres in a muscle are identical, and provided the fibers in a muscle are the same length and parallel to each other, the whole muscle can be viewed as a scaled version of the sarcomere. Few, if any, mammalian muscles fit the idealized profile above. Muscles come in a vast array of sizes and shapes and complex architecture is more the rule than the exception. Muscle fibers often lie at an angle to the direction in which the entire muscle changes length. This angle, called the angle of pennation, allows more muscle fibers to be arranged in parallel thus increase the force to weight ratio. Assuming the pennate fibers are attached to two bony surfaces that slide by, but do not approach each other, muscle force and length can be calculated by scaling fiber force and length by the cosine of the angle of pennation. This is the correction most models use to compensate for pennation. The true effects of pennation are more complex when the fibers are attached to connective tissue sheets, called aponeurosis, that show local deformation. Furthermore, connective tissues link adjacent muscles and, as a consequence, deformations in one muscle may influence force generation in another [18] (see essays ►Skeletal Muscle Architecture, ►Epimuscular Myofascial Force Transmission and Intermuscular).

Muscles are often composed of fibers of different lengths to accommodate for skeletal dimensions. Longer muscle fibers increase the maximum velocity of shortening by increasing the number of sarcomeres in-series. Recent studies have shown many seemingly long fibered muscles do not have fibers that run the length of the muscle (from tendon insertion to the tendon of origin), but rather are composed of fibers connected serially [19]. A portion of the force from these nonspanning muscle fibers must be transmitted to the tendon via myofascial pathways [20]. Serial fibers likely add to muscle compliance (see essays ►Intramuscular Myofascial Force Transmission, ►Epimuscular Myofascial Force Transmission and Intermuscular, ►Skeletal Muscle Architecture).

Motor Unit Types

The CNS controls not individual muscle fibers but motor units, which are the quantal elements of motor control. The motor unit consists of a motor neuron in the ventral horn of the spinal cord, its axon, and the muscle fibers that the axon innervates [21]. The muscle fibers belonging to a single motor unit are often termed the muscle unit. There exist a very wide range in both the electrical properties of motoneurons (see essay Motoneurons) and in the mechanical properties of their muscle units [21]. Slow twitch motor units exhibit not only slow contraction speeds but also low maximum forces and very high fatigue resistances. At the other end of the spectrum, the fastest contracting motor units generate the highest forces and have very little fatigue resistance. In between are fast contracting units with moderate forces and moderate fatigue resistances. These differences have been used to divide motor units into three or more types (S for slow, FR for fast fatigue resistant and FF for fast fatigable) [21], but it should be kept in mind that there is a more or less continuous distribution of contraction speeds, forces and fatigue resistances (see essay ►Motor Unit Types).

For the usage pattern of motor units, the most important factor is that the amount of synaptic current required to bring the motoneuron to threshold covaries with the mechanical properties of its muscle unit (see the Motoneuron section). Thus, the activation (recruitment) of motor units always begins with the small, slow twitch, low force units followed by recruitment of progressively faster and higher force units (i.e. S > FR > FF). As a result, overall contraction speed of the muscle increases as its activation level rises while fatigue resistance decreases. This recruitment-dependent behavior is rarely considered in muscle models.

Electromyography

Normally, a motoneuron action potential produces a corresponding action potential in each of the fibers of its muscle unit. Hence motoneuron firing patterns can be measured from muscle motor units in both humans and animals. Single fiber or single motor unit action potentials directly assess motoneuron firing patterns (motoneurons are the only CNS cells whose firing pattern can be individually measured in human subjects). Less selective electrodes measure the summed electrical activity of many motor units, the electromyogram (EMG). Both single fiber and whole muscle EMGs are valuable tools for assessing muscle and CNS function in normal and disease states (see essay ►Electromyography, ►Neuromuscular Junction).

Muscle Plasticity and Disease

Muscle is likely the most plastic tissue in the body. To support the metabolic costs of the protein synthesis

required for this adaptability, muscle fibers are multinucleate. In fact, small animal fibers of only 1–2 cm length have approximately 2000–5000 nuclei [22]. All of the major components of muscle fibers, including contractile machinery of the sarcomere, mitochondria, enyzmes for anaerobic energy production, and connective tissue, exhibit adaptations to exercise, disuse and injury. Thus motor units can adapt for either greater strength or fatigue resistance, but in exercise, the pattern of these adaptations are set by the orderly recruitment sequence mentioned in the previous section. For example, only types S motor units will exhibit increases in mitochondria in response to low intensity endurance training, while all motor units, S, FR, and FF, will exhibit hypertrophy in response to high resistance training.

Plasticity is also a hallmark of many muscle diseases and age related changes. There are a broad range of muscle diseases, or myopathies, many of which lead to or arise from structural and metabolic changes in the muscle such as fiber degeneration, mitochondrial dysfunction, fibrosis, nuclear abnormalities, fiber type reorganization and changes in fiber architecture to name a few. Muscle diseases can be acquired or inherited and can be classified broadly into primary diseases of the muscle or secondary diseases brought about via injury or dysfunction to the neural systems mediating muscle activity. Examples of the former include Myasthenia Gravis and the various forms of muscular dystrophy and myositis, while those of the latter include amyotrophic lateral sclerosis and other diseases or conditions that result in motorneuron damage and dysfunction (see essays ►Muscle: Duchenne Muscular Dystrophy, ►Muscle: Age Related Changes).

Which Muscle Properties are Most Important in Normal Movements?

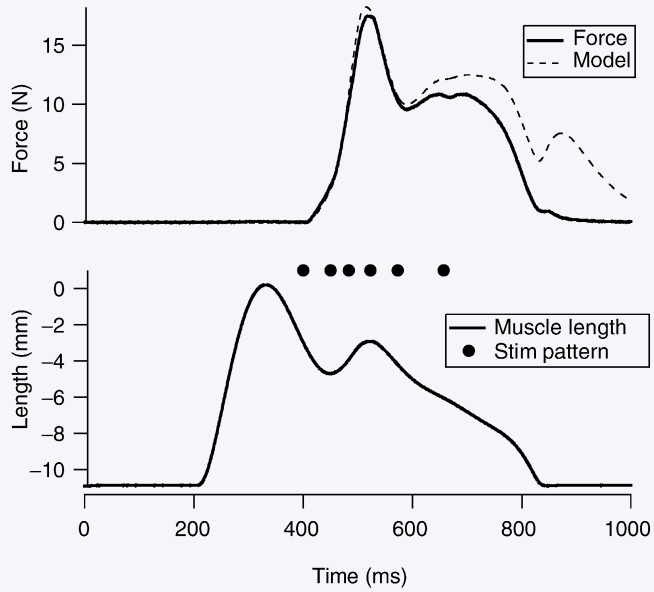
Although muscle exhibits an impressive array of properties in laboratory settings, the tightly controlled conditions so desirable for isolating specific properties often bear little relation to the highly dynamic conditions of normal movements. Consider first the normal neural activation pattern. Increasing neural activation produces a complex overlapping pattern of recruitment and rate modulation of a large population of motor units with very heterogeneous properties. This natural activation pattern stands in marked contrast to the usual techniques in the lab, such as activation of a single skinned muscle fiber via Ca^{2+} or stimulation of an entire muscle by electrical pulses applied to its nerve. At the same time, the muscle is often experiencing mechanical conditions that are highly dynamic. The primary measurement of muscle dynamics in the lab, the F-V relationship, is measured during constant activation and constant velocity conditions. In contrast, in a natural movement such as locomotion, both activation and velocity undergo dramatic and continuous variations [23].

The question of how muscle is used in normal movements has received considerable attention in the past 10–20 years. One fundamentally important issue is to identify the operating range for the basic properties of the F-f, L-T and F-V relations in normal movements. For the F-f relation, the fundamental question concerns the firing patterns of individual motor units. Studies in humans indicate that low threshold units (likely S) are not only recruited before high threshold (FR, FF) but also tend to exhibit higher firing rates (e.g. [24]). Presumably, at the highest forces, rates for FR and FF units eventually exceed those of S units [25], because the high contraction speeds of these units require higher firing rates to reach fusion [26]. Few studies have measured firing rate in dynamically moving muscles, but the same pattern of higher firing rates for lower threshold units does appear to occur [27].

Some animal studies suggest that muscle lengths remain near L_O [28]. However, other studies suggest that substantial force generation often occurs on either side of L_O - that is to say, on either the ascending or descending limbs of the L-T function. For example, the positions of the cat ankle extensor L-T functions in relation to the physiological range of motion is skewed, such that L_O occurs at a relatively long length [29]. While the peak force occurs during the stretch at the onset of the stance phase and is thus at a relatively long length near L_O, after this point, the ankle extensors exert substantial forces while rapidly shortening and most of this occurs on the ascending limb of the L-T function. In addition, studies of L-T functions in the hindlimbs of frogs suggest that much of the normal range of motion for thigh muscles can occur on the descending limb [30]. Finally, some specialized muscles operate over a very small range of the L-T function, serving primarily to transmit force and energy to the tendons connecting the muscle to the skeleton [31] (see ►Muscle and Tendon Energy Storage).

For the F-V functions, muscle velocities during locomotion have been estimated by inverse calculation from video records in numerous species (e.g. [32]) and from direct measurement in cats [33]. Clearly, even at the modest locomotor speeds associated with walking or slow running, the velocities reach peak values that result in substantial modulation of force due to the F-V relationship.

An approach that has great potential for delineating the role of various muscle properties in movement is to replicate the conditions of normal movements in isolated preparations, where the high degree of experimental control is highly advantageous for identifying the effect of each muscle property. An example from this type of experiment are shown in Fig. 5 [34]. A locomotor like movement was imposed on a cat



Muscle. Figure 5 Performance of a Hill model during a simulated locomotor movement in cat soleus. The experimentally measured force, and the force predicted by a Hill type model are shown in the top plot. The onset of the stance phase approximately corresponds with the onset of force generation. The lower plot shows the length imposed on the muscle and the time of the stimulus pulses. Note the largest error occurs during muscle relaxation.

ankle extensor muscle while it was stimulated with a locomotor-like frequency pattern. The resulting force was then compared to the output of a Hill-type model, which included both F-V and L-T effects as well as an accurate estimate of the activation function obtained during isometric conditions. The model prediction was remarkably good during the initial stance phase, but greatly overestimated force during the decay phase. In fact, the model predicted that force would last long after the push-off ended. Similar studies were carried out using random patterns of length changes and stimulation patterns [35]. The Hill-type model did a reasonable job predicting force at high activation levels with electrical stimulation but an extremely poor job during natural activation via a reflex, which generates relatively modest motor unit firing rates. Increasing muscle velocity also increased errors. In both the locomotor and random cases, it is likely that the model errors were due to the Hill model's inability to account for the coupling between muscle activation and force-velocity-length properties. Thus this coupling may be the most important factor to add to muscle models.

Summary

Muscle is a complex and adaptable organ. While great strides have been made toward understanding the molecular processes underlying muscle contraction, whole muscle function and its role in the neural control of movement remain an active and important area of research. New approaches that strive to link muscle ultrastructure to the whole muscle properties that emerge during the normal control of movement hold great promise for advancing our understanding of muscle and how it impacts the actions of the CNS controlling its function.

References

1. Granzier HL, Labeit S (2006) The giant muscle protein titin is an adjustable molecular spring. Exerc Sport Sci Rev 34:50–53
2. Rayment I, Holden HM, Whittaker M, Yohn CB, Lorenz M, Holmes KC, Milligan RA (1993) Structure of the actin-myosin complex and its implications for muscle contraction. Science 261:58–65
3. Huxley AF (1957) Muscle structure and theories of contraction. Prog Biophys Biophys Chem 7:257–318
4. Hill AV (1938) The heat of shortening and the dynamic constants of muscle. Proc Royal Soc Ser B 126:136–195
5. Joyce GC, Rack PMH, Westbury DR (1969) The mechanical properties of cat soleus muscle during controlled lengthening and shortening movements. J Physiol Lond 204:461–474
6. Gordon A, Huxley A, Julian F (1966) The variation in isometric tension with sarcomere length in vertebrate muscle fibres. J Physiol Lond 184:170–192
7. Rack PM, Westbury DR (1974) The short range stiffness of active mammalian muscle and its effect on mechanical properties. J Physiol 240:331–350
8. Zajac FE (1989) Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. Crit Rev Biomed Eng 17:359–411

9. Zahalak GI, Motabarzadeh I (1997) A re-examination of calcium activation in the Huxley cross-bridge model. J Biomech Eng 119:20–29
10. Rack PMH, Westbury DR (1969) The effects of length and stimulus rate on tension in the isometric cat soleus muscle. J Physiol Lond 204:443–460
11. Cui L, Perreault EJ, Sandercock TG (2007) Motor unit composition has little effect on the short-range stiffness of feline medial gastrocnemius muscle. J Appl Physiol 103:796–802
12. Close R (1972) Dynamic properties of mammalian skeletal muscles. Physiol Rev 52:129–197
13. Balnave CD, Allen DG (1996) The effect of muscle length on intracellular calcium and force in single fibres from mouse skeletal muscle. J Physiol 492:705–713
14. Caputo C, Edman KA, Lou F, Sun YB (1994) Variation in myoplasmic Ca2 + concentration during contraction and relaxation studied by the indicator fluo-3 in frog muscle fibres. J Physiol 478 (Pt 1):137–148
15. Binder-Macleod SA, Clamann HP (1989) Force output of cat motor units stimulated with trains of linearly varying frequency. J. Neurophysiol 61:208–217
16. Sandercock TG, Heckman CJ (1997a) Doublet potentiation during eccentric and concentric contractions of cat soleus muscle. J Appl Physiol 82:1219–1228
17. Herzog W, Lee EJ, Rassier DE (2006) Residual force enhancement in skeletal muscle. J Physiol 574:635–642
18. Huijing PA (2003) Muscular force transmission necessitates a multilevel integrative approach to the analysis of function of skeletal muscle. Exerc Sport Sci Rev 31:167–175
19. Trotter JA, Richmond FJR, Purslow PP (1995) Functional morphology and motor control of series-fibered muscle. Ex Sport Sci Rev 23:167–213
20. Street SF (1983) Lateral transmission of tension in frog myofibers: a myofibrillar network and transverse cytoskeletal connections are possible transmitters. J Cell Physiol 114:346–364
21. Burke RE (1981) Motor units: anatomy, physiology, and functional organization. In: Brooks VB (ed) Handbook of physiology, the nervous system, motor control, vol sect. 1 vol. II, Part 1. American Physiological Society, Bethesda, MD, pp 345–422
22. Tseng BS, Kasper CE, Edgerton VR (1994) Cytoplasm-to-myonucleus ratios and succinate dehydrogenase activities in adult rat slow and fast muscle fibers. Cell Tissue Res 275:39–49
23. Gregor RJ, Smith DW, Prilutsky BI (2006) Mechanics of slope walking in the cat: quantification of muscle load, length change, and ankle extensor EMG patterns. J Neurophysiol 95:1397–1409
24. De Luca CJ, LeFever RS, McCue MP, Xenakis AP (1982) Behavior of human motor units in different muscles during linearly varying contractions. J Physiol Lond 329:113–128
25. Bellemare F, Woods JJ, Johansson R, Bigland-Ritchie B (1983) Motor-unit discharge rates in maximal voluntary contractions of three human muscles. J Neurophysiol 50:1380–1392
26. Kernell D, Eerbeek O, Verhey BA (1983) Relation between isometric force and stimulus rate in cat's hindlimb motor units of different twitch contraction time. Exp Brain Res 50:220–227
27. Hoffer JA, Sugano N, Loeb GE, Marks WB, O'Donovan MJ, Pratt CA (1987) Cat hindlimb motoneurons during locomotion. II. Normal activity patterns. J Neurophysiol 57:530–553
28. Lutz GJ, Rome LC (1994) Built for jumping: the design of the frog muscular system. Science 263:370–372
29. Herzog W, Leonard TR, Renaud JM, Wallice J, Chaki G, Bornemisza S (1992) Force-length properties and functional demands of cat gastrocnemius, soleus and plantaris muscles. J. Biomech 25:1329–1335
30. Lieber RL, Boakes JL (1988) Sarcomere length and joint kinematics during torque production in the frog hindlimb. Am J Phyiol 254:C759–C768
31. Biewener AA, Konieczynski DD, Baudinette RV (1998) In vivo muscle force-length behavior during steady-speed hopping in tammar wallabies. J Exp Biol 201 (Pt 11):1681–1694
32. Goslow GE, Reinking RM, Stuart DG (1973) The cat step cycle: hindlimb joint angles and muscle lengths during unrestrained locomotion. J Morphol 141:1–42
33. Walmsley B, Hodgson JA, Burke RE (1978) Forces produced by medial gastrocnemius and soleus muscles during locomotion in freely moving cats. J Neurophysiol 41:1203–1216
34. Sandercock TG, Heckman CJ (1997b) Force from cat soleus muscle during imposed locomotor-like movements: experimental data versus Hill-type model predictions. J Neurophysiol 77:1538–1552
35. Perreault EJ, Heckman CJ, Sandercock TG (2003) Hill muscle model errors during movement are greatest within the physiologically relevant range of motor unit firing rates. J Biomech 36:211–218

Muscle: Age-related Changes

Jan Lexell
Department of Rehabilitation Medicine, Lund University Hospital, Lund, Sweden
Department of Clinical Science, Lund, Devision of Rehabilitation Medicine, Lund University, Lund, Sweden
Department of Health Sciences, Luleå University of Technology, Boden, Sweden

Synonyms

Sarcopenia

Definition

Age-related changes are those attributed primarily to increasing age. These changes are quantitative as well as qualitative and affect all parts of the ►motor unit, from the ►alpha motor neuron to the ►muscle fibers and various sub-cellular structures (►Muscle – ultrastructure and proteins). The main effects of increasing age are reductions in muscle mass and muscle strength and

alterations in the quality of the remaining muscle tissue, all referred to as sarcopenia. Sarcopenia leads to reduced functional capacity for the older individual, with an increased risk of falls, fractures, and dependency. The underlying mechanisms of these age-related changes are multifactorial (Fig. 1) and only partly known. Progressive ►resistance training (heavy-resistance strength training) (►Muscle: exercise adaptations) has become the most effective therapy to counteract the age-related changes in the skeletal muscle.

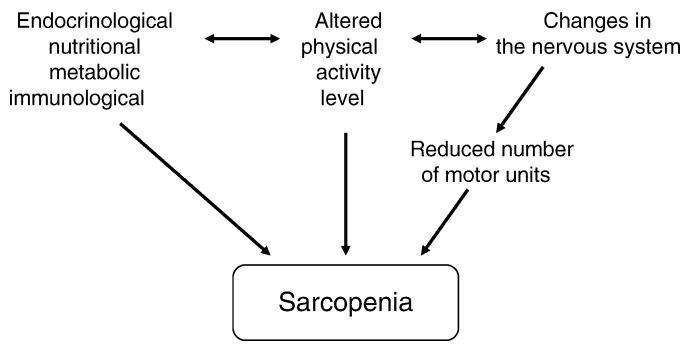
Characteristics

Higher Level Processes

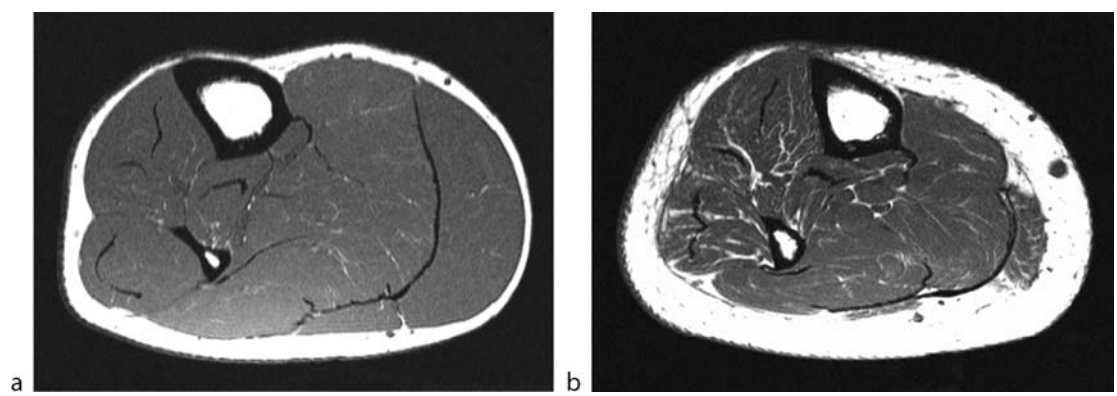
The reduction in muscle volume and muscle cross-sectional area is one of the most noticeable age-related muscle changes. With modern imaging techniques (►Muscle imaging), such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), muscle mass and muscle cross-sectional area can be assessed. With ultrasonography, a 25–35% reduction in the cross-sectional area of the quadriceps muscle in older compared to younger men and women has been found. CT has shown similar age-related reductions in the cross-sectional area of the psoas major and sacrospinalis muscles, the quadriceps muscle the brachial biceps and triceps muscles, and the plantarflexors. These CT studies have also shown increases in fat and connective tissue within the older muscle. MRI has confirmed these earlier studies, and also shown an age-related reduction in muscle cross-sectional area and an increase in non-contractile tissue, i.e. fat and connective tissue (Fig. 2), which can be more than twofold [1].

Direct assessments of the muscle cross-sectional area have been very limited, mainly due to the technical limitations in such analysis. Large cryomicrotomes and modified morphometric procedures have made it possible to study cross-sections of whole human (autopsied) muscles. The vastus lateralis of previously healthy men between 15 and 83 years of age have been analyzed [2], and the average reduction in muscle area between 20 and 80 years was 40% (Fig. 3).

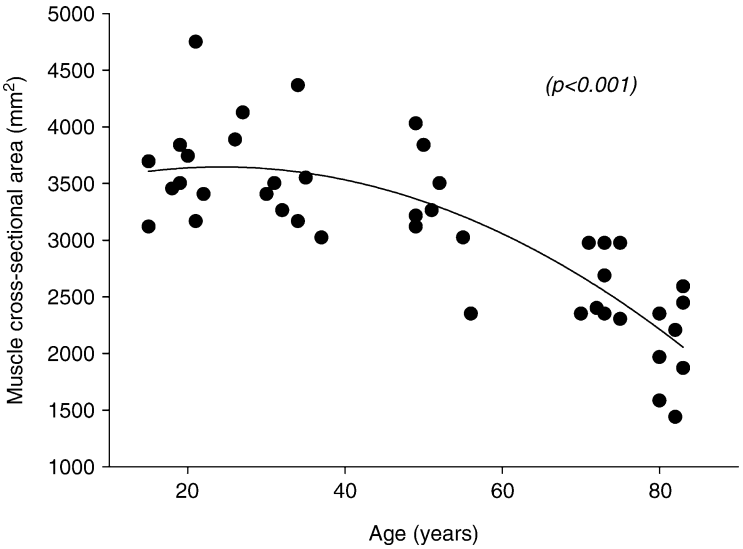
The reduction began as early as 25 years of age. By the age of 50 years, ~10% of the muscle area was lost, and thereafter the reduction accelerated. A majority



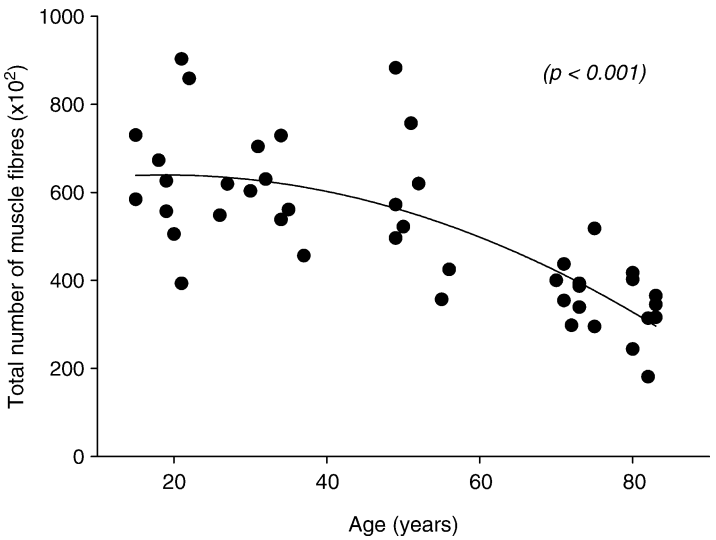
Muscle: Age-related Changes. Figure 1 Proposed mechanisms leading to sarcopenia, i.e. reductions in muscle mass and muscle strength and alterations in the quality of the remaining muscle tissue.



Muscle: Age-related Changes. Figure 2 Magnetic resonance image (MRI) of the lower leg of a healthy female, age 23 years (a), and healthy female, age 75 years (b). Note the reduced cross sectional areas of most muscles with an increase in non-contractile tissue.



Muscle: Age-related Changes. Figure 3 Relationship between age and muscle cross-sectional area.



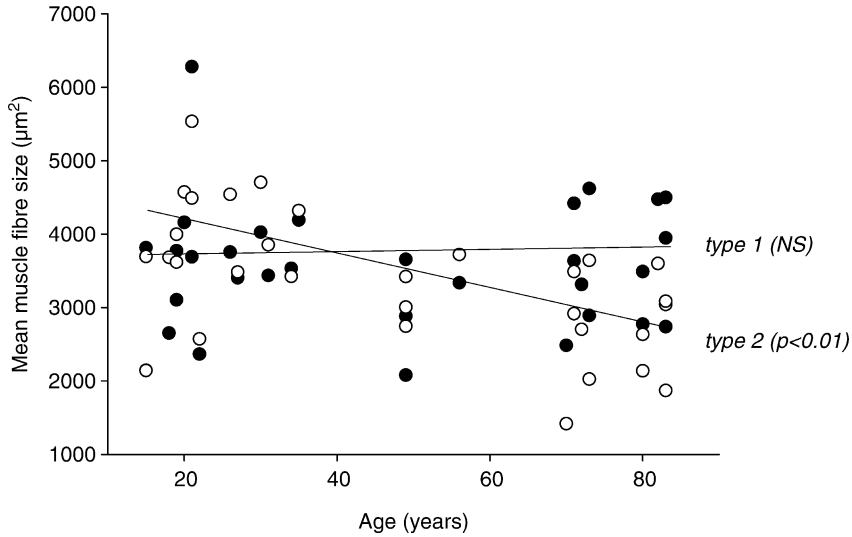
Muscle: Age-related Changes. Figure 4 Relationship between age and total numbers of fibers.

of studies on muscle mass have been performed on men, but data implies that increasing age affects muscle mass in women in a similar way.

Muscle biopsy studies of the vastus lateralis of the quadriceps muscle, and of the biceps brachii and the anterior tibial muscles, have consistently shown that the ►type II (fast-twitch) fiber size is reduced with increasing age, while the size of ►type I (slow-twitch) fibers are much less affected [3]. With techniques allowing assessments of whole muscles, it has been shown that the total number of fibers is significantly reduced with increasing age [2]. The reduction in muscle cross-sectional area of the vastus lateralis muscle was caused mainly by a loss of fibers and to a smaller extent by a reduction in the size of fibers, mainly of type 2 (Figs. 4 and 5).

This loss of fibers began as early as 25 years of age and thereafter accelerated. The age-related reduction in fiber number, at least in the vastus lateralis muscle, affected both types to the same extent. Overall, there is a decrease in the relative amount of type II fiber tissue, due to the combined reduction in the number and size of type II fibers [3]. Muscles other than the vastus lateralis have not been studied in any detail, nor have muscle biopsies from older individuals with different physical activity levels been compared.

As a result of the reduced muscle mass, increasing age leads to a significant decrease in muscle strength.



Muscle: Age-related Changes. Figure 5 Relationship between age and mean area of type 1 and type 2 fibers.

Studies of both upper and lower limb muscles have been compared between groups of young, middle-aged and older adults, showing that decreases in voluntary strength do not become readily apparent until after the age of 60 [4]. Small variations exist from muscle to muscle, but for all muscles in both men and women, the age-related reduction in strength tends to be curvilinear, with a relative plateau through the third, fourth and fifth decades. Most frequently studied has been the quadriceps femoris muscle group, measured extensively in test conditions involving all three actions of muscles: isometric, concentric and eccentric (►Isometric force; ►Contraction-concentric; ►Contraction-eccentric). Healthy people in the seventh and eighth decades score on average 20–40% less during isometric and concentric strength tests than young adults, and the very old show an even greater (50% or more) reduction. Differences between young and older groups of men and women are less for the eccentric type of muscle action than during either isometric or concentric.

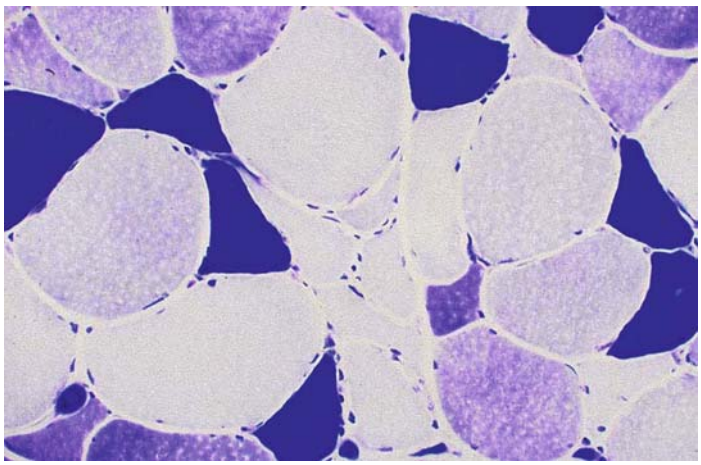
With regard to the volitional component of maximal strength tests, healthy older individuals are able to recruit and activate all their available motor units (►Motor unit – usage patterns) maximally or near maximal, indicating that the age-related declines in strength in healthy older people is due mainly to a decreased excitable muscle mass.

Tests of voluntary muscular effort, with variations in submaximal versus maximal contractions, and sustained versus intermittent efforts, have not found any age-related increase or decrease in ►muscle fatigue [5]. Despite the relatively greater proportion of type I fibers available, fatigue-resistance of aged muscle is not significantly enhanced.

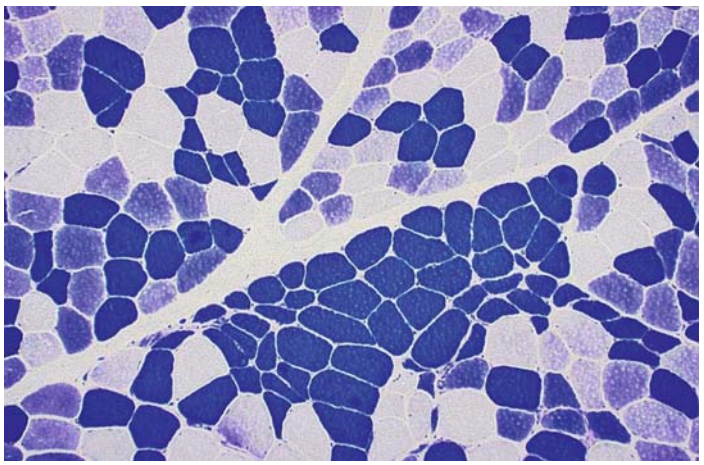
One of the factors leading to sarcopenia in old age is a progressive degeneration of the nervous system, particularly after the age of 60 years [6]. Studies have shown an age-related reduction in the number of functioning motor units with an increase in the size of remaining/surviving motor units, suggesting cycles of denervation followed by reinnervation that ultimately stems from death of motor neurons in the spinal cord and from irreparable damage to peripheral nerve axons. As a consequence, the muscle fibers innervated by these neurons will also be affected, which leads to changes in the function of aging muscles.

Quantitative ►electromyography (EMG) has shown changes in both duration and amplitude of motor unit action potentials (MUAP) with increasing age. It has also been shown that the axonal conduction velocity (CV) is slower with aging, an effect that could reflect a variety of changes in the nerve fibers, such as a dropout of the largest fibers, a segmental demyelination and a reduced internodal length. Assessment of the number of motor units have shown a reduced number of functioning motor units with increasing age, mainly after the age of 60 years. The estimated reduction in the number of motor units of older individuals has been reported to be as large as 50%, and this loss also seems to be greatest among the largest and fastest motor units, i.e. ►type II (fast) motor units.

Studies of the muscle fiber population have shown evidence of neuropathic changes, such as small angulated fibers and grouped atrophy, of old/very old individuals (Fig. 6). ►Fiber type grouping has also been found in muscles from individuals above the age of 70 years (Fig. 7). Macro EMG has confirmed these studies and shown an increase in motor unit size in the vastus lateralis, the tibialis anterior and the biceps



Muscle: Age-related Changes. Figure 6 Small part of a muscle biopsy from a healthy man, age 73 years. The biopsy is stained for toluidine blue mATPase. Type 1 (slow-twitch) fibers are darkly stained whereas type 2 (fast-twitch) fibers are lightly stained. Note the variability in fiber and the increase in angulated fibers.



Muscle: Age-related Changes. Figure 7 Small part of a muscle biopsy from a healthy man, age 73 years. The biopsy is stained for toluidine blue mATPase. Type 1 (slow-twitch) fibers are darkly stained whereas type 2 (fast-twitch) fibers are lightly stained. Note the increased occurrence of grouping of type 1 fibers.

brachii from subjects above the age of 60 years, indirectly indicating an increased number of muscle fibers per motor unit.

Lower Level Processes

Several other factors contribute to the age-related changes in muscle structure and function (cf. Fig. 1). Muscle biopsy studies of the tibialis anterior muscle has shown a reduction (40%) of muscle ►satellite cells [7]. As satellite cells are also considered to be skeletal muscle stem cells, they can generate daughter cells that become new satellite cells following myotrauma or exercise. It is possible that this age-related reduction in the satellite cell pool may impair the regenerative capacity of skeletal muscles, but evidence so far is insufficient to support this.

Studies of single muscle fibers from the vastus lateralis of older men and women have found a significant age-related reduction in shortening velocity of both type I and IIA fibers [8], which also contribute to the reduced muscle function in older individuals.

Several studies have found decreases in four major anabolic hormones – testosterone, growth hormone (GH), insulin-like growth hormone (IGF-1) and dehydroepiandrosterone (DHEA) – with increasing age [9]. The exact implications of these decreases and whether hormone supplementation is a feasible therapeutic strategy and prevention of sarcopenia remain to be

determined. So far, the long-term risks have not been well defined and the side-effects have been significant. Muscle protein synthesis rates have also been shown to decline with increasing age, whereas muscle protein breakdown seem to be less affected [9], which may contribute to the age-related loss of muscle mass.

Therapy

As a reduced neuromuscular capacity is related to limitations in activities of daily living, an important question has been whether muscles of older individuals can increase in size in response to resistance training, and to what extent resistance training can lead to motor learning or neural adaptations.

In 1988, Frontera and colleagues [10] presented strength and muscle biopsy results from a heavy-resistance training study in older men, and reported striking improvements in leg muscle strength, as well as significant increases in muscle fiber sizes. Since then, an increasing number of studies have documented the benefits of resistance training for older men and women, even above the age of 90 years [4]. Studies involving low intensity training in older adults report strength increases <20%, whereas high intensity training (>70% of one ►repetition maximum (RM)) has resulted in increases of up to 227% in one RM. Men are generally stronger than women, but there seems to be a remarkable similarity in their response to training. Moreover, ethnicity and previous experience of physical exercise do not seem to limit the response to heavy-resistance training; studies from North America and Scandinavia have yielded similar results.

Strength gains following heavy-resistance training in both young and older people may be explained by several factors. These include changes in muscle morphology, muscle/connective tissue biomechanics, central nervous system activation, motor skill coordination and motivation. Varying degrees of ►hypertrophy of both type 1 and type 2 fibers have been demonstrated following both short- and long-term heavy-resistance training in older individuals. When changes in fiber areas are minor and non-significant, they are consistent with small strength gains. Increases in fiber size as a result of strength training are generally small in comparison with the improvements in strength. Thus, the response to heavy-resistance training in older people can be mediated to some extent through hypertrophy of both fiber types, although the main part of the strength improvement, at least during the first 3 months of training, is caused by nervous system adaptation.

References

1. Kent-Braun JA, Ng AV, Young K (2000) Skeletal muscle contractile and non-contractile components in young and older women and men. J Appl Physiol 88:662–668
2. Lexell J, Taylor CC, Sjöström M (1988) What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci 84:275–294
3. Lexell J (1995) Human aging, muscle mass and fiber type composition. J Gerontol 50A(Special Issue):11–16
4. Porter MM, Vandervoort AA, Lexell J (1995) Ageing of human muscle: structure, function and adaptability. Scand J Med Sci Sports 5:1129–1142
5. Allman BL, Rice CL (2002) Neuromuscular fatigue and aging: central and peripheral factors. Muscle Nerve 25:785–796
6. Lexell J (1997) Evidence for nervous system degeneration with advancing age. J Nutr 127:1011S–1013S
7. Kadi F, Charifi N, Denis C, Lexell J (2004) Satellite cells and myonuclei in young and old women and men. Muscle Nerve 29:120–127
8. Krivickas LS, Suh D, Wilkins J, Hughes VA, Roubenoff R, Frontera WR (2001) Age- and gender-related differences in maximum shortening velocity of skeletal muscle fibers. Am J Phys Med Rehabil 80:447–455
9. Greenlund LJS, Nair KS (2003) Sarcopenia – consequences, mechanisms, and potential therapies. Mech Ageing Dev 124:287–299
10. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ (1988) Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol 64:1038–1044

Muscle and Tendon Energy Storage

Andrew A. Biewener
Concord Field Station, Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA, USA

Synonyms

Elastic energy savings; Muscle-tendon elasticity

Definition

Muscle and tendon energy storage refers to strain energy that is stored and elastically recovered within a muscle-tendon complex during each contractile cycle of a muscle.

Characteristics

Quantitative Description

Muscle and tendon energy storage represents the strain energy that is stored within a muscle-tendon complex as a muscle and tendon are stretched by the force developed by the muscle when it contracts. This energy may be subsequently recovered elastically when the muscle relaxes. The elastic elements of a muscle-tendon

complex are generally divided into "*parallel*" and "*series*" elastic elements, based on their role in force transmission relative to the muscle's force-generating cross-bridge elements. The interaction between a muscle's contractile elements – the cross-bridges formed between myosin and actin filaments – and its parallel and ►series elastic elements, determines the relationship between a muscle's force development and length change, as well as its elastic energy storage [1]. For parallel-fibered muscles that have little or no tendon in series with the muscle's fibers, elastic energy storage is limited to parallel and series elastic elements within the muscle, which include the cross-bridges themselves. For pinnate-fibered muscles that have a substantial tendon, considerably more energy is stored and recovered elastically within the tendon that is in series with the muscle's fibers. Consequently, elastic energy savings is greatest in pinnate muscles that attach to the skeleton via long tendons [2].

Mechanical Properties of Elastic and Viscoelastic Materials

Elastic materials are those that exhibit spring-like properties. When elastic materials are loaded, they store strain energy via deformation of their molecular bonds in combination with conformational changes in the protein's tertiary or quaternary structure. In the case of tendons and ligaments, this primarily results from the stretching of collagen. In the case of muscles, this involves additional elastic proteins, such as those within the cross-bridges (myosin I) and within the sarcomeres (titin), in addition to collagen. These proteins constitute the parallel and series elastic elements within a muscle, which are linked to a muscle's tendon as an external series elastic element [1]. During unloading, the stored strain energy is released and may be recovered to assist in mechanical movements of the body or limb segment, reducing the amount of work that the muscles must perform. The work performed by a muscle is the product of its force and its net length change (muscle shortening by definition corresponds to positive muscle work, whereas muscle lengthening corresponds to negative muscle work, or energy absorption). For pure elastic elements, all of the energy that is stored during loading is returned during unloading. However, most biological materials are non-linearly elastic and exhibit some degree of inelastic or viscous energy dissipation, which is ultimately lost as heat (Fig. 1c).

Due to this, materials like tendon are referred to as being "viscoelastic." The amount of strain energy that is elastically recovered relative to the amount of energy that is stored defines a material's resiliency. The resiliency of collagenous tendons is in the range of 90–94%, indicating that only 6–10% of the stored strain energy in a tendon is lost as heat during each contraction cycle of a muscle.

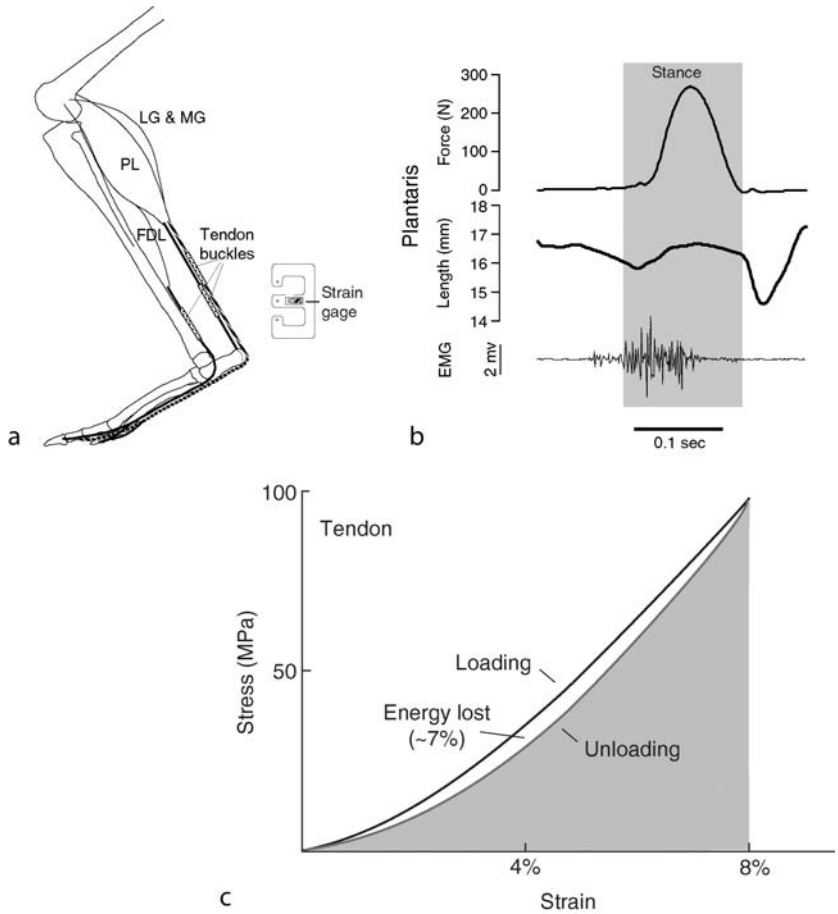
Elastic Energy Storage in Relation to the Force-Length Properties of a Muscle

The force that a muscle develops depends on its length, which specifically reflects the amount of overlap between its myosin (thick) and actin (thin) filaments [1]. This is most often measured as the isometric force that a muscle can develop when it is stimulated to contract at different lengths. The force that is measured can be separated into two components: the active force that is developed by the cross-bridges formed between myosin and actin, and the passive force that is developed when the muscle is stretched to longer lengths without being stimulated (Fig. 2).

The slope of a muscle's passive force versus length curve defines its ►passive stiffness. A muscle's passive stiffness increases as it is stretched to longer lengths, typically beyond the length that a muscle develops its maximal isometric force. Elastic energy that can be stored within a muscle when it contracts is generally associated with its passive force-length properties, because these depend on the amount of non-contractile connective tissue within the muscle. Muscles that are pinnate typically have more titin and collagenous connective tissue than parallel-fibered muscles and, as a result, display greater passive force when they are stretched. Consequently, pinnate muscles store more strain energy than parallel fibered muscles when force developed by cross-bridges is transmitted to the parallel and series elastic elements of the muscle. However, even for pinnate muscles, the strain energy stored in a muscle's tendon greatly exceeds that in the muscle's fibers [2,4].

Muscle-Tendon Design in Relation to Elastic Energy Storage

Muscle-tendon units with long thin tendons are most favorably designed for elastic energy savings. This is because strain energy varies with the square of tendon stress (force/area). Consequently, for a given muscle-tendon force, strain energy storage per unit mass (or volume) of tendon varies inversely in proportion to the square of the tendon's area ($\alpha\ 1/A^2$). The advantage of having slender tendons is evident in animals, such as antelope, horses and kangaroos, which have evolved particularly economical modes of locomotor transport [2]. The distal limb muscle-tendon units of these animals are often comprised of muscles with very short fibers and long tendons. The length of some tendons can exceed their muscle's fiber lengths by tenfold or more. As a result, the length change of the tendon, as it is stretched, may exceed the fibers' lengths in the muscle. The role of these muscle-tendon units, therefore, is mainly to facilitate elastic energy storage and recovery and to generate force economically, and not to do substantial mechanical work [5]. Even though the muscle's fibers may not perform much

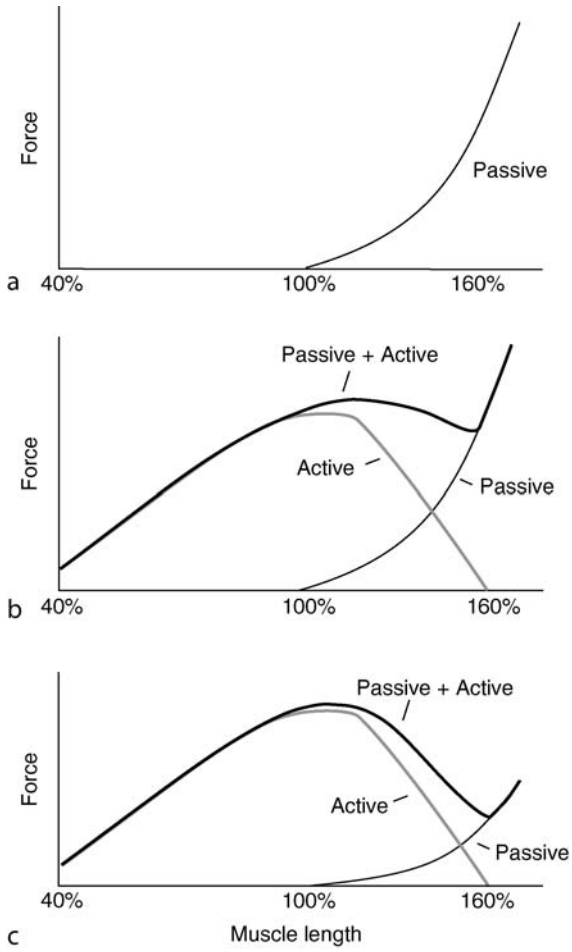


Muscle and Tendon Energy Storage. Figure 1 (a) Schematic drawing of the hind limb muscle-tendon units of a wallaby, comprising the lateral and medial gastrocnemius (LG + MG), the plantaris (PL), and the flexor digitorum longus (FDL). "E"-shaped force buckles are shown attached to the tendons of these three muscles, and were used in [3] to record in vivo muscle-tendon forces in relation to muscle fascicle length change and indwelling electromyographic (EMG) activation of the muscles. (b) Representative in vivo recordings of muscle-tendon force, muscle fascicle length change from sonomicrometry, and EMG of the plantaris muscle-tendon are shown for one hopping cycle. (c) Tendon stress-strain curve used to calculate the elastic energy storage and recovery within the tendon over a cycle of loading and unloading.

useful work, they may provide a means for dissipating energy associated with unwanted vibrations in the limb when it impacts the ground [6].

Measuring Elastic Energy Storage

Measurements of elastic energy storage and recovery depend on measurements of the material properties of muscle and tendon in combination with measurements of their structural dimensions and the forces that a muscle-tendon complex transmits during a given activity. Isolated in vitro or in situ force-length measurements allow the elastic and viscoelastic properties of a muscle and its tendon to be determined. The force-length properties of the muscle and tendon can then be normalized to muscle-tendon stress and strain (defined as their change in length/resting length). This allows a muscle's stiffness and a tendon's stiffness (ratio of force/length change) to be defined in terms of their elastic modulus (stress/strain). Whereas the (passive) force-length or stress-strain behavior of a muscle depends strongly on a muscle's architecture (i.e. whether or not a muscle is parallel- or more pinnate-fibered), the stress-strain behavior of various tendons in vertebrate animals is fairly uniform [2,4]. Consequently, the stress-strain behavior and elastic modulus of tendon can be generally characterized and used to



Muscle and Tendon Energy Storage. Figure 2 (a) Representative passive force-length properties of a pinnate muscle. (b) Active isometric force-length properties of the muscle when stimulated to generate force over different percentages of its resting length (100%) in relation to passive properties shown in A, yielding the overall active + passive properties of the muscle. (c) Representative comparison of passive and overall force-length properties of a parallel-fibered muscle that has similar normalized active properties, but exhibits less passive stiffness than the pinnate muscle shown in (b).

calculate the elastic strain energy that is stored in a tendon of a given size and shape.

To determine the amount of elastic energy stored and recovered in a muscle-tendon complex, the force that muscle and its tendon transmit and their structural dimensions must be known. It is generally difficult to determine with accuracy the amount of strain energy stored within a muscle and its aponeurosis versus that in its external tendon. Consequently, unless direct measurements are obtained, it is usually assumed that the large majority of elastic energy is stored within the in-series elastic elements of a muscle-tendon complex [4]. Nevertheless, it is likely that significant elastic energy is stored and recovered from the aponeurosis and internal elastic elements of pinnate muscles, such as the quadriceps, which act to extend the knee. Muscle-tendon forces can be either calculated indirectly based on kinetic analyses of limb and joint forces and moments [7], or measured directly using tendon buckle transducers [3,8] (Fig. 1a, b).

Indirect measurements of muscle-tendon forces are derived from measurements of external ground reaction forces, applied to the limb using a force platform in combination with a free-body analysis of joint forces and joint moments [2,7]. This approach depends on assumptions of muscle force distribution among muscle agonists in cases where more than one muscle-tendon unit transmits force across a joint, and when bi-articular muscles play a role in force and energy transmission between joints. This is typical of many limb muscles involved in elastic energy storage. Direct measurements of muscle-tendon forces depend on the tendon being sufficiently long to attach the transducer without disrupting normal function of the muscle-tendon unit and the animal (Fig. 1a). This approach is, therefore, generally limited to more distal muscle-tendon units in the limbs of animals.

The force transmitted by a muscle-tendon unit that is determined directly or indirectly can then be used to calculate the tendon's stress and resulting strain, based on the elastic modulus and resiliency of the tendon over the range of strain that the tendon operates. Knowing the structural dimensions of the tendon (overall length – L, average cross-sectional area – A, and total volume – V) allows the total strain energy stored and recovered in the tendon to be calculated for the level of force (F) that it transmits. As tendon is non-linearly elastic, this formally involves integrating over the stress-strain curve of the tendon and multiplying by the tendon's volume. However, in most cases, an average elastic modulus (E_{avg}) characteristic of the functional stress-strain range of the tendon can be used to simplify the equation for calculating tendon strain energy:

$$U_{elas} = 0.5\sigma\varepsilon VR = 0.5F\Delta LR$$

where σ is the tendon stress (= F/A), ε is tendon strain (=σ /E_{avg}), V is tendon volume, and R is the tendon's resiliency (typically 0.9–0.95), which equals the product of tendon force and total tendon length change (ΔL = ε L).

Role of Elastic Energy Storage in Locomotion and Movement Control

Elastic energy storage in muscle and tendon is important in at least three contexts (i) metabolic energy savings derived from reduced muscle work, (ii) amplification of muscle-tendon power during jumping, and (iii) stabilization of muscle-tendon force transmission for control of movement. Indirect [4,9] and direct [3] measurements show that elastic energy storage in tendons and ligaments is an important means of energy saving during running or trotting and galloping gaits, reducing the amount of work that muscles must perform to move the animal's body and to swing its limbs (Fig. 1b). Although some elastic energy is stored within the cross-bridges and ►parallel elastic elements of the muscle, this is generally considered to be quite small in comparison with that stored and recovered in the muscle's tendon and aponeurosis. In addition to horses and wallabies, tendon energy savings also serve to reduce the metabolic energy expenditure of running in humans and many other animals [2]. Like the distal tendons of cats, dogs, horses and kangaroos, the human Achilles tendon and ligaments in the foot have been estimated to contribute as much as a 30% saving of muscle work [9]. In hopping wallabies, elastic energy savings in leg tendons provide as much as a 100% saving of muscle work, reducing the metabolic cost of locomotion by 50% [3].

Elastic energy storage is also an important mechanism by which the work produced by a muscle in series with a tendon can be used to amplify the power output (work/time) of the muscle-tendon unit as a whole [4]. This allows muscle-tendon units to serve as catapults when an animal jumps or when a person throws a ball. The work done by a muscle to stretch its tendon and store elastic strain energy is limited by the rates of muscle activation and cross-bridge cycling as the muscle shortens. These generally occur much more slowly than the rate of strain energy release from the tendon when it recoils. Consequently, although the work done by the muscle can never exceed the work returned by elastic recoil, power output is amplified relative to power input because the energy return from stored strain energy in the tendon occurs over a much briefer period of time. Amplification of muscle power is an important mechanism in the jumping of many animals, and likely also humans, resulting in muscle-tendon power outputs that can exceed the maximum power output of the muscle alone by threefold or higher [10].

Compliance and elastic energy storage in a muscle's tendons can also play an important role in stabilizing force transmission and improving the control of position for fine scale motor tasks, such as those that involve finger movements, which underlie manipulation and gripping [4]. Although excessive compliance (tendon stretch/force transmitted) can compromise a muscle's ability to control for position, moderate compliance enables elastic energy stored in the tendon during a rise in force to be released as force declines, stabilizing the force output at a more steady level. This is achieved by introducing a time-delay between the induced stretch of the muscle spindles relative to small changes in muscle-tendon force, when the task is to hold force and finger position at a steady level. The time-delay introduced by the tendon's compliance improves the timing of force-feedback achieved via spindle Ia afferents to counter declining muscle force. The result is that a finger muscle can hold force at a steadier level and the finger's position is better controlled.

References

1. Herzog W, ed. (2000) Skeletal muscle mechanics: from mechanisms to function. Wiley, New York, p. 572
2. Biewener AA (2003) Animal locomotion. Oxford University Press, Oxford, p. 281
3. Biewener AA, Baudinette RV (1995) In vivo muscle force and elastic energy storage during steady-speed hopping of tammar wallabies (Macropus eugenii). J Exp Biol 198:1829–1841
4. Alexander RM (1988) Elastic mechanisms in animal movement. Cambridge University Press, Cambridge
5. Biewener AA, Roberts TJ (2000) Muscle and tendon contributions to force, work, and elastic energy savings: a comparative perspective. Exer Sport Sci Rev 28 (3):99–107
6. Wilson AM et al. (2001) Horses damp the spring in their step. Nature 414:895–899
7. Zajac FE, Zomlefer MR, Levine WS (1981) Hindlimb muscular activity, kinetics and kinematics of cats jumping to their maximum achievable heights. J Exp Biol 91:73–86
8. Gregor RJ, Abelew TA (1994) Tendon force measurements and movement control: a review. Med Sci Sports Exer 26(11):1359–1372
9. Ker RF et al. (1987) The spring in the arch of the human foot. Nature 325:147–149
10. Roberts TJ, Marsh RL (2003) Probing the limits to muscle-powered accelerations: lessons from jumping bullfrogs. J Exp Biol 206:2567–2580

Muscle Atonia

Definition

Muscle paralysis that occurs during rapid eye movement (REM) sleep resulting from active inhibition of motor neurons.

►Sleep – Motor Changes

Muscle Atrophy

Definition
Wasting away of formerly normal skeletal muscle (up to 70-80 percent of original muscle bulk), for example as a result of denervation.

Muscle Compartment

Definition
The working location of a group of agonistic muscles (with similar function) delimited by the general fascia, intermuscular septum, periost and interosseal membrane.

►Epimuscular Myofascial Force Transmission and Intermuscular Interaction
►Intramuscular Myofascial Force Transmission

Muscle Endplate

Definition
The region of the muscle fibers where the motor nerves terminate on each skeletal muscle fiber, is termed the muscle endplate. It is at this endplate that the perisynaptic Schwann cells are found interspaced between the nerve terminal and the muscle fiber. The muscle endplate is where the acetylcholine receptors are concentrated and bind the acetylcholine released from the activated nerve terminals to elicit muscle contraction.

►Acetylcholine
►Axonal Sprouting in Health and Disease
►Neuromuscular Junction (NMJ)

Muscle Fiber Conduction Velocity

Definition
Velocity with which the transmembrane action potential propagates along the muscle fiber.

►Action Potential
►Electromyography

Muscle Fiber End-Effect

Definition
Non-propagating component of the extracellular action potential waveform due to the extinction of the transmembrane action potential at the fiber termination.

Muscle Fiber Types

Definition
A constellation of coordinated biochemical, metabolic, structural, and mechanical characteristics of muscle fibers that differentiate them into a relatively small number of recognizable categories.

►Motor Units

Muscle Field

Definition
The set of muscles whose motoneurons have a relatively direct synaptic linkage to a particular corticospinal neuron. Muscles that are part of a neuron's muscle field are referred to as target muscles. The target muscles of corticospinal and other descending system neurons have been identified in alert monkeys using signal averaging methods to detect the synaptic effects of the neuron's excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) on motor unit firing probability.

►Corticospinal Neurons
►Motor Cortex: Output Properties and Organization

Muscle Hyperalgesia

Definition
Muscle hyperalgesia occurs when either noxious or ordinarily innocuous stimulation of muscle evokes a state of increased pain sensation.

►Hyperalgesia and Allodynia

Muscle Imaging Techniques: Computerized Tomography

Yasin Y. Dhaher
Department of Biomedical Engineering, McCormick School of Engineering, Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Senior Research Scientist, Sensory Motor Performance Program, The Rehabilitation Institute of Chicago, Chicago, IL, USA

Synonyms

CT

Definition

A CT scan is a computer aided imaging technique performed by subjecting the object of interest to a series of X-rays and measuring the attenuation along multiple projections using several detectors. With each projection, detectors measure X-ray absorption, which is used to construct cross-sectional images (tomograms) of the object.

Purpose

New developments in data-analysis techniques have facilitated the recent use of CT in the quantification of muscle cross-sectional area and volume [2,3]. For example, using a 345 mm^2 field of view and a 7 mm slice thickness CT scan, Mitsiopoulos et al. [3] showed that the computed muscle cross-sectional area strongly correlated with the muscle cross-sectional area obtained from actual cadavric measurements on the same muscle ($r < 0.99$; $p < 0.001$).

Principles

Subsequent tomograms consist of black–gray–white color scale picture elements. Each element of the picture is called a pixel and is characterized by a CT value or density value. These pictures are then combined using computer algorithms to reconstruct two- and three-dimensional images of the object. These algorithms include iterative solutions of simultaneous linear equations, Fourier transform techniques, and approaches that use a combination of back projection and deconvolution. Scan parameters are defined in terms of the size of the field of view and image thickness. For additional material on the mathematical basis of CT, the reader is referred to Shung et al. [1].

Advantages and Disadvantages

The use of CT in muscle imaging has been limited due to large estimation errors reported in early CT muscle imaging literature [4]. However, advances in post processing and reconstruction techniques, and recent developments in CT technology such as helical CT and multi-detector row helical CT, could further improve resolution in the estimation of muscular volumetric and cross-sectional geometries obtained from CT scans.

References

1. Shung KK, Smith MB, Tsui BMW (1992) Principles of medical imaging. Academic, San Diego
2. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R (1998) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 85(1):115–122 (see comment)
3. Tracy BL, Ivey FM, Jeffrey Metter E, Fleg JL, Siegel EL, Hurley BF (2003) A more efficient magnetic resonance imaging-based strategy for measuring quadriceps muscle volume. Med Sci Sports Exerc 35(3):425–433
4. Beneke R, Neuerburg J, Bohndorf K (1991) Muscle cross-section measurement by magnetic resonance imaging. Eur J Appl Physiol Occup Physiol 63(6):424–429

Muscle Imaging Techniques: Magnetic Resonance Imaging

Yasin Y. Dhaher
Department of Biomedical Engineering, McCormick School of Engineering, Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Senior Research Scientist, Sensory Motor Performance Program, The Rehabilitation Institute of Chicago, Chicago, IL, USA

Synonyms

MRI

Definition

MR imaging technique is based on the detection of the interactions between protons in liquid phase molecules (e.g., water and lipids) and the abilities of certain atomic nuclei, when exposed to a magnetic field, to absorb and release electromagnetic radiations at specific frequencies (Larmor frequency). These radiations are detected via receiving coils which are then used to construct the MR images of the object of interest. Computer integration and transformation of the signals detected by the receiving coils allows a two-dimensional map of proton density to be constructed, which can be visualized as a slice through the object (muscle).

Purpose

MRI imaging has been successfully used to measure stationary muscle volume and cross-sectional area (Tracy et al., 2003). Although both T2 and T1 weighted images have been used, T1 weighted imaging has been particularly successful for muscle tissues [2].

MRI has also been used to estimate muscle fiber direction. The estimation of fiber direction via MRI is based on the fact that muscle striations seen in MRI images are generated by fat that runs parallel to and between the muscle fascicles [3]. It is assumed that these striations represent the true fascicle orientation within the muscles. When the imaging planes are coplanar to the fascicle orientation, fascicle length and pennation angles can be computed [3]. However, the use of MRI is limited when fascicle orientation is difficult to identify, such as in complexly pennated muscles.

To circumvent this, a diffusion tensor magnetic resonance imaging technique (DT-MRI) has been used to estimate fiber direction. In DT-MRI, measurements are independent of the orientation of the image plane, and three-dimensional fiber directions can be obtained immediately. DT-MRI was introduced in 1988 by LeBihan [4]. It is based on the measurement of the apparent diffusion of water in a (biological) tissue. For muscle tissues, diffusion is not the same (isotropic) in all directions. Hence, applying diffusion sensitization in six independent directions on a series of diffusion-weighted images, a diffusion tensor can be calculated in each voxel [5]. The eigenvalues and eigenvectors of this tensor provide information about local tissue anisotropy. Anisotropic diffusion can be geometrically interpreted as an ellipsoid with its three axes oriented along these eigenvectors and with the three semi-axis lengths proportional to the square root of the eigenvalues of the tensor (mean diffusion distances). The geometric nature of the diffusion tensors can quantitatively characterize the local structure of the muscle. The eigenvector belonging to the largest eigenvalue of the diffusion tensor is assumed to coincide with the local muscle fiber direction in striated muscle [5,6]. DT-MRI based fiber orientation has been successfully verified against histological slices [6].

Van Donkelaar et al. [7] used DT-MRI to measure fiber orientation in the tibialis anterior muscle of the rat. Using a 0.6 mm slice thickness, a field of view of 70×35 mm^2 and a voxel size of 0.09 mm^3, they found that computed fiber orientations corresponded to fiber orientations obtained from actual longitudinal sections of the same muscle. More recently Damon et al. [8] provided a more quantitative validation study of fiber orientation estimates using DT-MRI. In the lateral gastrocnemius of Sprague-Dawley rats, Damon et al. [8] showed a strong correlation ($r = 0.89$) between DT-MRI based local fiber orientation estimates and the measured orientations obtained from direct anatomical inspection of the same muscle.

Cine Phase Contrast (Cine-PC) MRI, originally developed to measure blood flow and heart motion, initially showed promise as a non-invasive technique to also measure human muscle fiber velocity in vivo under dynamic conditions. At each time frame, the Cine-PC MRI produces a series of anatomic and velocity images of skeletal muscles synchronized with a periodic motion cycle in three orthogonal planes. The velocity images are then integrated to determine the position of the muscles in vivo. Cine-PC MRI has been shown to accurately measure skeletal muscle fiber velocity in vivo during a dynamic task [9]. Previous studies by the same authors have demonstrated that Cine-PC MRI tracks skeletal muscle motion with a root mean error of 1 mm [9]. However, conventional cine-PC MRI requires multiple cycles of motion; typically 60–120 repetitions are needed to acquire composite images representing one motion cycle. Image quality degrades significantly with small discrepancies among the consecutive motion cycles, resulting in a significant limitation for the use of the conventional Cine-PC MRI in musculoskeletal applications [10].

Principles

A background magnetic filed is used to align all atomic nuclei within the object of interest along the direction of the background field, producing a nuclei net longitudinal magnetic field. External energy is then applied using radiofrequency (RF) excitation pulses to change the direction of the nuclei net longitudinal magnetic field to point in a perpendicular direction to the background magnetic field and thus create what is known as transverse magnetization. Initially, all nuclei point along the same perpendicular direction representing the transverse magnetization in terms of one vector perpendicular to the direction of the background magnetic field. Because each nucleus has its own Larmor frequency, as time elapses, the transverse magnetization component eventually spans all directions, bringing the net nuclei magnetization component perpendicular to the background magnetic field to zero. T1 relaxation time is defined as the time the atomic nuclei needs to revert to equilibrium (regain their longitudinal mechanism) following the termination of the excitation pulses (RF). T2 (known as the spin echo relaxation time) is the time it takes for the net transverse magnetization to go to zero (decay). T2 (0.05–0.15 s) is always less than or equal to T1 (0.2–1.2 s) and both are intrinsic properties of tissues.

To obtain a successful imaging sequence, the technician defines a set of imaging parameters. These include: (i) repetition time (TR) or the time between two successive radio frequency (RF) excitation pulses measured in milliseconds; (ii) echo delay time (TE), or the time interval between RF pulse and the measurement

of the first echo measured in milliseconds; (iii) field of view (FOV) and slice thickness (interslice distance) both measured in millimeters and; (iv) receiver bandwidth measured in kHz. Tissues with short T1 have greater signal intensity than tissues with longer T1 at a given TR. TE on the other hand determines how much decay of the transverse magnetization is allowed to occur before the signal is read. The application of RF pulses at different TRs and the receiving of signals at different TEs produce variations in contrast of the MR images. For example, by selecting a relatively short TR (on the order of 300–600 ms generally) the image contrast will be primarily influenced by differences in the tissue's T1 relaxation times and hence T1-weigthed images are created. On the other hand, selecting a relatively long TE (on the order of 80–120 ms) will generate a T2-weighted image where the image contrast is primarily influenced by differences in tissue's T2 relaxation times. For further discussion on the underlying physics involved in MRI, the reader is referred to Buxton [1].

References

1. Buxton RB (2002) Introduction to functional magnetic resonance imaging: principles and techniques. Cambridge University Press, Cambridge
2. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R (1998) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 85(1):115–122 (see comment)
3. Scott SH, Engstrom CM, Loeb GE (1993) Morphometry of human thigh muscles. Determination of fascicle architecture by magnetic resonance imaging. J Anat 182(Pt 2):249–257
4. LeBihan D, Breton E, Lallemand D, Aubin M-L, Vignaud J, Laval-Jeantet M (1988) Separation of diffusion and prefusion in intravoxel incoherent motion MR imaging. Radiology 168:497–505
5. Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66 (1):259–267
6. Hsu EW, Muzikant AL, Matulevicius SA, Penland RC, Henriquez CS (1998) Magnetic resonance myocardial fiber-orientation mapping with direct histological correlation. Am J Physiol 274(5 Pt 2):H1627–H1634
7. Van Donkelaar CC, Kretzers LJ, Bovendeerd PH, Lataster LM, Nicolay K, Janssen JD, Drost MR (1999) Diffusion tensor imaging in biomechanical studies of skeletal muscle function. J Anat 194(Pt 1):79–88
8. Damon BM, Ding Z, Anderson AW, Freyer AS, Gore JC (2002) Validation of diffusion tensor MRI-based muscle fiber tracking. Magn Reson Med 48(1):97–104
9. Drace JE, Pelc NJ (1994) Skeletal muscle contraction: analysis with use of velocity distributions from phase-contrast MR imaging. Radiology 193(2):423–429
10. Asakawa DS, Nayak KS, Blemker SS, Delp SL, Pauly JM, Nishimura DG, Gold GE (2003) Real-time imaging of skeletal muscle velocity. J Magn Reson Imaging 18(6):734–739

Muscle Imaging Techniques: Ultrasound

Yasin Y. Dhaher
Department of Biomedical Engineering, McCormick School of Engineering, Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Senior Research Scientist, Sensory Motor Performance Program, The Rehabilitation Institute of Chicago, Chicago, IL, USA

Synonyms

ULT

Definition

Ultrasound or sonography is based on the application of high frequency sound pulses using an ultrasound transducer (probe; a transmitter and receiver) to a stationary (conventional ultrasound) or a moving (real-time ultrasonography) muscle and recording the echoes (reflections) returning from the muscle-tissue interface. The echoes are processed based on the location of origin and amplitude. From this information, two-dimensional gray scale images are constructed. These images can be analyzed to obtain quantitative structural and functional information from the muscle of interest.

Purpose

Several studies have used ultrasonography techniques to quantify muscle fiber length and direction under static conditions [3] and dynamic [4]. Under static conditions, measurements obtained by ultrasound were consistent with direct anatomical measurements on cadavers [3]. Under dynamic conditions, several studies have tested the effectiveness of real-time ultrasonography in estimating changes in human muscle architecture in vivo during muscle contractions [4]. However, direct validation studies on the use of ultrasonography under dynamic conditions are warranted.

Principles

The fundamental principle of ultrasound is based on the idea that sound waves are transmitted though soft tissue relative to the acoustic impedance of each tissue. Sound wave frequencies used in ultrasound technology are in the 2–10 MHz range. The acoustic impedance of a particular tissue is the product of the transmission velocity of sound and the tissue density. For example, the wave velocity in pure fat is approximately 1,450 m/s whereas the velocity through muscle tissue is approximately 1,580 m/s. When two

tissues with different densities/wave velocities are located next to each other, an acoustic impedance mismatch is created and sound waves are reflected by the mismatch. For example, muscle imaging via ultrasound is possible because muscle fascia is a highly echoic structure (provides a significant acoustic mismatch), allowing for muscle differentiation. Scans used to estimate muscle fiber length and directions identify echoes from fascicle interspaces.

Image resolution is divided into spatial and temporal components (important when imaging moving muscles; real-time ultrasonography). The spatial component (the ability to differentiate between two adjacent tissues) consists of axial (the smallest axial distance that must be resolved) and lateral resolution. Axial resolution is dependent on sound wave pulse width and frequency. Two structures will be seen as separate structures only if the pulse length is shorter than the distance between the structures. Also, higher frequency sound waves have shorter pulse lengths and generally greater axial resolution. Lateral resolution is dependent on beam width and sound wave frequency. Narrower beam width and higher frequencies provide greater lateral resolution. Hence, in mapping small structures like muscle fibers, high frequency (>7 MHz) ultrasounds are commonly used. It is important to note, however, that as a wave propagates through a material, the signal amplitude is attenuated. Attenuation within a tissue increases with increasing wave frequency. For example, a 5-MHz transducer will generally image to a depth of 12–15 cm, but a 10-MHz transducer may image to a depth of only 3–4 cm. Thus improving image resolution comes with the loss of distal information when scanning deeper structures.

The temporal resolution of ultrasound is determined by the number of image frames that can be acquired per second. For real-time ultrasonography, images are obtained at a pre-specified rate, usually 65 images per second, during the dynamic task [1]. For more on the underlying physics and the image processing techniques involved in ULT, the reader is referred to Shung et al. [2].

Advantages and Disadvantages

Improvement in image resolution in an attempt to scan small structures or differentiate between structures with close acoustic impedances limits the field of view hence hindering the ability to scan deep muscles. In addition, muscle architectural properties such as fiber length and angle obtained using ultrasonography are calculated from a two-dimensional image and thus represent the projection of these values on that plane. Recent developments in three-dimensional ultrasonography may prove useful in addressing this limitation of the two-dimensional ultrasonography.

References

1. Martinson H, Stokes MJ (1991) Measurement of anterior tibial muscle size using real-time ultrasound imaging. Eur J Appl Physiol Occup Physiol 63(3–4):250–254
2. Shung KK, Smith MB, Tsui BMW (1992) Principles of medical imaging. Academic, San Diego
3. Narici MV, Binzoni T, Hiltbrand E, Fasel J, Terrier F, Cerretelli P (1996) In vivo human gastrocnemius architecture with changing joint angle at rest and during graded isometric contraction. J Physiol (Lond) 496(Pt 1):287–297
4. Ichinose Y, Kawakami Y, Ito M, Kanehisa H, Fukunaga T (2000) In vivo estimation of contraction velocity of human vastus lateralis muscle during "isokinetic" action. J Appl Physiol 88(3):851–856
5. Fukunaga T, Miyatani M, Tachi M, Kouzaki M, Kawakami Y, Kanehisa H (2001) Muscle volume is a major determinant of joint torque in humans. Acta Physiol Scand 172(4):249–255
6. Tracy BL, Ivey FM, Jeffrey Metter E, Fleg JL, Siegel EL, Hurley BF (2003) A more efficient magnetic resonance imaging-based strategy for measuring quadriceps muscle volume. Med Sci Sports Exerc 35(3):425–433
7. Van Donkelaar CC, Kretzers LJ, Bovendeerd PH, Lataster LM, Nicolay K, Janssen JD, Drost MR (1999) Diffusion tensor imaging in biomechanical studies of skeletal muscle function. J Anat 194(Pt 1):79–88

M

Muscle Modeling

Eric J. Perreault
Department of Biomedical Engineering, Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, IL, USA

Definition

For the purposes of this essay, a muscle model is defined as a set of mathematical equations that can be used to predict the whole muscle forces generated in response to changes in muscle activation and external loading.

Purpose

The use of muscle models can be categorized broadly into two domains. The first focuses on the properties and function of individual muscles. These applications are often designed to test the limits of our knowledge with respect to how muscle functions. By developing quantitative descriptions of the physiological processes contributing to muscle function, it should be possible to assemble these descriptions into a model describing whole muscle behavior. Comparing the results of such models against experimental data allows the accuracy of the mechanistic descriptions and the assumptions

contained within to be evaluated, a process that can assist in guiding future experimentation.

The second class of applications falls into the category of musculoskeletal modeling. Such applications typically incorporate multiple muscle models to study how muscle properties contribute to the control of movement and posture. The goals of this class again may be to examine the limits of our understanding by comparing experimental data to that predicted by the model, or to predict muscle function in applications where direct measurements are difficult or unfeasible. Examples include investigating how specific muscle activation patterns influence joint contact forces, how different neural control strategies alter movement production or predicting the outcomes of specific surgical interventions.

Principles

Contractile Properties

Muscle contracts and realistic models of muscle force generation need to describe this contractile process. There are two different approaches to describing the contractile machinery. Mechanistic models attempt to describe the physiological mechanisms underlying muscle force generation. In contrast, phenomenological models use empirical descriptions to describe how force is generated under a range of conditions.

Mechanistic Models

Most current mechanistic models stem from the work of Huxley [1]. In his seminal paper, Huxley described the contractile properties of muscle in terms of the number of currently attached cross-bridges. Each cross-bridge was assumed to be elastically linked to the myosin filament and to move randomly about a neutral equilibrium point due to thermal agitation, as depicted in Fig. 1a.

Further, it was assumed that cross-bridges could be in one of two states, either attached or detached to an actin binding site, and that there were no interactions between neighboring cross-bridges. Under these conditions, the rate equation for cross-bridge attachment is given by Equation 1, where $n(x,t)$ is the fraction of attached cross-bridges at time t and displacement x from the equilibrium point, $f(x)$ is the rate at which cross-bridges attach and $g(x)$ is the rate at which they detach.

$$\frac{\partial n(x,t)}{\partial t} = f(x)(1-n(x,t)) - g(x)n(x,t) + v(t)\frac{\partial n(x,t)}{\partial x} \quad (1)$$

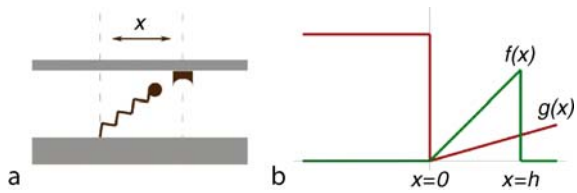
$$F(t) = k\int n(x,t)x\,dx \quad (2)$$

Fig. 1b illustrates the shape of the rate functions originally proposed by Huxley; the asymmetry of these functions leads to muscle shortening. Each cross-bridge is assumed to be elastic. Hence, when attached, a cross-bridge produces a force proportional to its distance from the equilibrium point. The total force generated is given by Equation 2, in which k is defined as the cross-bridge stiffness.

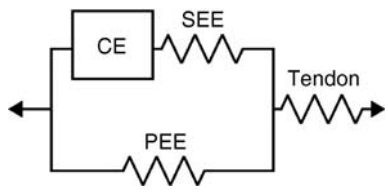
Since Huxley's original work, a variety of extensions have been made to his proposed model including the incorporation of length-tension properties, changes in the attachment and detachment rate functions, the addition of intermediary states between cross-bridge attachment and detachment and the allowance for cooperativity between neighboring cross-bridges.

Phenomenological Models

A number of linear and nonlinear phenomenological muscle models have been proposed. The most widely used of these stem from the work of A.V. Hill [2], and the modifications outlined by Zajac [3]. These Hill-type models have a structure as shown in Fig. 2. The parallel elastic element (PEE) is often ignored, as it contributes little force within the working range of most muscles and the stiffness of the series elastic element (SEE) is combined with that of the tendon. The contractile element (CE) of a Hill-type model is described in terms of the instantaneous force-length, force-velocity and activation properties of muscle. Many Hill-type models assume that these properties are independent (see Winters [4] for discussion), and that the contractile element force, F_{CE}, can be characterized by Equation 3, where $\tilde{A}(t)$ is the normalized muscle activation, $\tilde{F}_{FL}$ is the normalized tetanic force-length relationship, and



Muscle Modeling. Figure 1 Schematic of original Huxley model. (a) Assumed mechanism. (b) Proposed rate functions.



Muscle Modeling. Figure 2 Schematic of a typical Hill model.

$\widetilde{F}_{FV}$ is the normalized tetanic force-velocity relationship, measured at the muscle length corresponding to the peak of force-length curve. Alternative formulations assume that the maximum shortening velocity varies with muscle length and activation, requiring that $\widetilde{F}_{FV}$ be dependent upon instantaneous muscle velocity and activation.

$$F_{CE}(t) = F_{\max} \cdot \widetilde{A}(t) \cdot \widetilde{F}_{FL}(L(t)) \cdot \widetilde{F}_{FV}(V(t)) \quad (3)$$

The above descriptions outline the elements common to all Hill-type models. However, a number of extensions to this model have been developed. These include incorporating geometrical parameters to account for changes in muscle architecture, allowing for significant coupling between the $\widetilde{F}_{FV}$ and $\widetilde{F}_{FL}$ properties and acknowledging the fact that these properties do not scale simply with changes in activation level. Each of these modifications has been shown to improve model performance for specific experimental conditions, although head-to-head comparisons of these modified models have not been performed yet, and there is no consensus as to which is most appropriate for a specific application.

Activation Dynamics

Both mechanistic and phenomenological models need to account for the scaling of muscle force with changes in neural input. This is accomplished through the use of an activation function, which characterizes the processes triggered by the occurrence of a muscle fiber action potential and ending with the binding of calcium to troponin. A number of activation functions have been proposed, ranging from the first-order activation dynamics often incorporated into Hill-type muscle models [3], to detailed descriptions that attempt to account for the physiological processes underlying calcium release and reabsorption [5]. Between these extremes are the many phenomenological descriptions that use the activation function to account for activation-dependent muscle responses such as fatigue, nonlinear summation of neural inputs and movement-related history dependence. A good example of this approach is provided by the work of Brown and Loeb [6].

Structural Properties

Intramuscular Structure

There are wide variations in muscle structure and these variations significantly impact muscle function. Hence, whole muscle models must take structural variations into account. Fiber length, cross-sectional area and pennation angle are the factors most often considered. At a minimum, these can be used to scale model parameters such as maximal isometric force and shortening velocity. More involved approaches consider how these factors vary and influence force generation throughout the physiological range. This has been attempted using both 2D and 3D models of muscle architecture. Recent studies have used finite element approaches to investigate and model how these architectural features influence force generation during normal movement conditions [7]. This approach may also prove to be useful for assessing the role of passive mechanical structures such as tendons and aponeuroses. Currently, these are modeled most often as elastic elements in series with the contractile machinery (e.g. SEE in Fig. 2).

Intermuscular Structure

Significant force can also be transmitted between muscles via myofascial structures. Such transmission poses enormous challenges for the modeling of multiple muscle systems and is ignored in most musculoskeletal models. The essay by Huijing, *Epimuscular Myofascial Force Transmission and Intermuscular Interaction*, covers this topic in detail. It should be noted, however, that most studies demonstrating significant intermuscular force transmission have examined this phenomenon by disrupting the normal transmission pathways. Recent data from out laboratory suggests that intermuscular transmission is less than 5% between muscles with intact tendons and intermuscular linkages. Hence, the problem of intermuscular transmission may be most important when modeling injuries or surgical interventions in which the normal transmission pathways are disrupted.

Advantages and Disadvantages

There are many choices to be made when choosing or designing a muscle model for a particular application. The advantages and disadvantages of each are driven at least as much by the application as by the model. As always in modeling, there is a tradeoff between physical realism and computational efficiency. A related issue is the ability to estimate appropriate model parameters, for even an accurately modeled system will produce inaccurate results if the parameters cannot be set appropriately. In reviewing the relative merits of the available modeling approaches, we focus on three common applications.

Mechanisms of Muscle Contraction

Models designed to investigate the mechanisms underlying muscle contraction are typically derived from the Huxley models presented above. Such models are attractive because they have the ability to link macroscopic phenomena, such as force-velocity properties, yielding and short-range stiffness, to the underlying microscopic structure of muscle. As a result, they are the models of choice for muscle biophysicists, and represent an enticing structure upon which to incorporate additional physiological information as it becomes available. A limitation of Huxley-type models is the

difficulty associated with measuring model parameters and choosing appropriate forms for the rate functions. Indeed, many rate functions and parameter estimates have been proposed to match different sets of experimental data. These models are also computationally intensive, which has limited their use in studies of multiple muscle systems as well as those assessing the impact of structure on function, although a reformulation of the Huxley equations by Zahalak and colleagues [8] has a reduced computational cost and helped bridge the gap between mechanistic and phenomenological models.

Muscle Mechanics

The mechanical properties of muscle describe the dynamic relationship between imposed displacements and the corresponding changes in muscle force. These properties, which are influenced by the contractile properties and passive structures, are critical for understanding the role of muscle in the control of posture and movement. Some mechanical responses, such as yielding and short-range stiffness, appear to be cross-bridge phenomena and are characterized well by Huxley-type mechanistic models. However, a number of phenomena, such as movement history-dependent changes in muscle force, cannot be attributed to cross-bridge dynamics alone.

Hill-type models describe the forces generated during isovelocity movements reasonably well, since they specifically incorporate force-velocity characteristics, but are less capable of describing the forces generated in response to more complex movements, especially at non-tetanic levels of activation [9]. A number of groups have proposed modifications to the Hill model that broaden the range of mechanical responses that can be predicted [6,10]. Often, these modifications rely on coupling the contractile properties of muscle to the activation dynamics. A process that may also be useful for extending the utility of Huxley-type models.

Realistic representations of muscle architecture and the passive structures responsible for transmitting muscle force are essential for modeling muscle mechanics. Currently, finite element models represent the best opportunity for assessing how these structural features impact whole muscle mechanics. The current drawbacks of these methods include the computational demands required for simulation and the lack of reliable parameter estimates for the material properties of muscle.

Multiple Muscle Systems

In neuroscience, muscle models often are incorporated into multiple muscle systems used to study the neural control of movement. Under these circumstances, computational efficiency becomes a primary concern. As a result, most simulations of multiple muscle systems rely on Hill-type muscle models or even linear visco-elastic models. As discussed above, these models are known to be inaccurate. However, these inaccuracies for predicting the details of muscle force generation may become less important when these forces are filtered by the musculoskeletal system. In contrast, errors may be magnified when such models are used to estimate the activation patterns required to generate an observed set of movements. The difficulties associated with such inverse problems are well described by Hatze [11].

The inability to estimate muscle activation accurately is a major limitation in the use of multiple muscle models for studying the neural control of movement. During physiological conditions, muscle force is graded via changes in motor unit recruitment and firing rate, and it is currently not possible to obtain reliable estimates of these processes during the control of voluntary movement. As an alternative, the whole muscle electromyograms (EMGs) are often used to approximate muscle activation and as inputs to the muscle models in a multiple muscle system. Rectified EMG can be a good predictor of isometric muscle force. However, this relationship is muscle specific. In addition, the EMG-force relationship for a given muscle depends upon recording electrode placements and movement of the electrodes with respect to the muscle. Hence, the use of EMG as an approximation of muscle activation is problematic, and multiple muscle models that rely on EMGs need to assess how these limitations impact model performance.

References

1. Huxley AF (1957) Muscle structure and theories of contraction. Prog Biophys Mol Biol 18:257–318
2. Hill AV (1938) The heat of shortening and the dynamic constants of muscle. Proc R Soc (London) B126:136–195
3. Zajac FE (1989) Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. Crit Rev Biomed Engl 17:359–411
4. Winters JM (1990) Hill-based muscle models: a systems engineering perspective. In: Winters JM, Woo SL (eds) Multiple muscle systems: biomechanics and movement organization. Springer, Berlin Heidelberg New York, pp 69–93
5. Cannell MB, Allen DG (1984) Model of calcium movements during activation in the sarcomere of frog skeletal muscle. Biophys J 45:913–925
6. Brown IE, Loeb GE (2000) Measured and modeled properties of mammalian skeletal muscle: IV. dynamics of activation and deactivation. J Muscle Res Cell Motil 21:33–47
7. Johansson T, Meier P, Blickhan R (2000) A finite-element model for the mechanical analysis of skeletal muscles. J Theor Biol 206:131–149
8. Zahalak G (1981) A distribution-moment approximation for kinetic theories of muscular contraction. Math Biosci 55:89–114

9. Perreault EJ, Heckman CJ, Sandercock TG (2003) Hill muscle model errors during movement are greatest within the physiologically relevant range of motor unit firing rates. J Biomech 36:211–218
10. Shue GH, Crago PE (1998) Muscle-tendon model with length history-dependent activation-velocity coupling. Ann Biomed Engl 26:369–380
11. Hatze H (2002) The fundamental problem of myoskeletal inverse dynamics and its implications. J Biomech 35:109–115

Muscle Moment Arm

Definition
The distance from the line of action of a muscle to the center of rotation of a joint.

►Impedance Control

Muscle/Muscle Fiber Stiffness

Definition
Muscle and muscle fiber stiffness are typically evaluated by quick stretch experiments or sinusoidal oscillations of the preparation. Stiffness is then evaluated as the resistance to stretch (for example, as the instantaneous slope of the force elongation curve during stretch). Muscle stiffness has played an important role in muscle physiology and mechanics as it has been viewed as a measure of the proportion of attached cross-bridges.

►Cross-bridge Theory
►Force Depression/Enhancement in Skeletal Muscles
►Muscular Stiffness

Muscle Nociceptors

Definition
Free nerve-endings on small-diameter myelinated (Group III) or unmyelinated (Group IV) muscle afferent nerve fibers. Group IV corresponds to cutaneous C fibers and group III to Aδ-fibers. Conduction velocities for cat muscle afferent fibers are below 2.5 m/s for group IV and 2.5–30 m/s for group III fibers [7].

►Muscle Pain Including Fibromyalgia
►Nociceptors and Characteristics

Muscle Pain, Including Fibromyalgia

Lars Arendt-Nielsen,
Thomas Graven-Nielsen
Center for Sensory-Motor Interaction (SMI),
Department of Health Science and Technology,
Aalborg University, Aalborg, Denmark

Synonyms
Musculoskeletal pain; Myofascial Pain; Deep somatic pain

Definition
Pain from deep somatic structures.

Characteristics
Musculoskeletal pain is an important factor in many disorders, including chronic pain conditions, work related disorders, injuries, degenerative diseases, and cancer, but the peripheral and central mechanisms underlying musculoskeletal pain are still poorly understood. The typical characteristics are drilling, aching pain often referred to other somatic structures. Musculoskeletal disorders can be classified as articular (e.g., rheumatoid arthritis, osteoarthritis (see ►Immune system and pain) or non-articular (e.g., myofascial pain syndrome, fibromyalgia (FM). This essay will present manifestations and methods for assessment of human non-articular pain with focus on muscle pain.

Manifestations of Selected Painful, Musculoskeletal Disorders
Myofascial pain syndromes are regional muscle pain disorders characterised by localized tenderness in muscles (trigger points), leading to persistent, regional pain such as back pain, neck pain, shoulder pain, headaches, and orofacial pain. The affected muscles often display an increased fatigability, stiffness, subjective weakness, pain in movement, and slight restricted range of motion unrelated to joint restrictions. The exact etiology of myofascial pain syndromes is unclear.

Widespread pain is defined as pain lasting for more than three months present as follows: (i) Pain in both

sides of the body, pain above and below the waist, (ii) Axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back pain) must be present. Widespread pain includes classes of syndromes such as FM, fatigue syndrome, exposure syndromes (e.g., Gulf War illnesses). FM is a chronic, painful musculoskeletal disorder of unknown etiology and defined by chronic widespread pain, involving three or more segments of the body plus the finding of at least 11 out of 18 designated tender points often developing after localised pain problems. However, not all people with chronic, localized or regional muscle pain develop FM. Hereditary factors might be important. Serotonin- and dopamine-related genes have been suggested to be involved in the development of FM. Studies of the endocrine profile of FM patients have indicated elevated activity of corticotropin releasing hormone (CRH) neurones which may not only explain some symptoms of FM, but may also cause alterations observed in the hormonal axes [1]. Hypothalamic CRH neurones may play a role not only in resetting various endocrine loops, but possibly also for nociceptive and psychological mechanisms as well.

FM patients show differentiated ►hyperalgesia to different sensory stimuli indicating that only specific parts of the sensory and nociceptive systems are influenced and that the sensory disturbances are accentuated as the syndrome progresses [2].

Myalgia can be related to a variety of medical conditions, and common terms for the symptom are stiffness, soreness, aching, spasms, or cramps. The associated pain is often described as having a dull, aching quality and can be exacerbated by muscle contractions. The manifestation of pain in some of the myalgias, however, is not the most prominent problem.

For example, in myositis (e.g., polymyositis and dermatomyositis) muscle weakness is often the prominent feature.

Muscle pain of neurogenic origin can be difficult to dissociate from other manifestations of ►neuropathic pain. Examples include cervical radiculopathy with pain radiating into the myotomal distribution of the roots or nerve compressions (e.g., carpal tunnel syndrome), where the pain radiates into muscles in the region. Little is known about muscle sensitization in relation to neuropathic pain as normally only the cutaneous manifestations of neuropathic pain (allodynia, hyperalgesia) are investigated.

Musculoskeletal disorders and pain are more prevalent in females than males, with female predominance in painful musculoskeletal syndromes such as widespread pain, temporomandibular disorders, neck pain, shoulder pain, back pain, joint pain, FM, whiplash, and headache. High rates of comorbidity, particularly in women, have been reported between temporomandibular dysfunctions and other clinical musculoskeletal disorders (e.g., FM). Fluctuations in hormonal levels have been implicated in symptom severity in women with rheumatoid arthritis, temporomandibular disorders, and FM. The many symptoms of FM could be explained by the fact that there are bidirectional connections between the nociceptive system and the immune, sleep regulating and the stress regulating systems. Furthermore, it has recently been described that descending facilitatory pathways may cause widespread hypersensitivity [3]. One mechanism by which hormones may affect ►muscle nociceptor sensitization could be related to nerve growth factor (NGF) and one of its high-affinity receptors (trkA). TrkA receptor expression is influenced by gonadal hormones. Injection of NGF into muscle causes muscle tenderness to pressure which lasts for weeks. There has been some speculation that hormone replacement therapy may increase a woman's risk of developing musculoskeletal pain.

Fundamentals of Musculoskeletal Pain

The manifestations of musculoskeletal pain include spread of pain and ►referred pain, somatosensory changes in referred pain areas, and interaction with the motor system (e.g., muscle coordination and activation, postural stability, movement initiation, and reflex pathways) [4].

Localization of pain is poor in skeletal muscles, and it is difficult to differentiate pain arising from tendons, ligaments, and bones as well as from joints and their capsules. Referred muscle pain is typically described as a sensation from deep structures in contrast to referred visceral pain, which is described as located both superficially and deeply. The characteristic pattern of referred muscle pain was initially observed by Kellgren in the late 1930s, who injected hypertonic saline into skeletal muscles and ligaments and characterised the referred pain. Similar characterization has been performed clinically when activating trigger points in various muscles [5].

It is obviously important to distinguish the painful tissue, but it may be very difficult due to poor localization and referred pain. Examples can be pain from an arthritic hip, which may refer to the thigh muscles or knee joint, carpal tunnel syndrome, which may refer to forearm muscles, and cervical spondylosis, which may refer to arm muscles. Pain from joints and their capsules tends to be more localised than myalgia, and arthralgia is often worsened by passive joint movements. Capsular pain may be present only in specific joint positions. Bone pain also tends to be poorly localized but, unlike myalgia, usually worse at night and tends to be unaffected by either movement or muscle activity.

Referred muscle pain has been known and described for more than a century and is used extensively as a diagnostic tool. The pattern of referred pain frequently follows the distribution of sclerotomes (muscle, fascia, and bone) rather than the classical dermatomes. A clear distinction between spread of pain and referred pain is not possible, and these phenomena may also share common pathophysiological mechanisms. Firm neurophysiologically-based explanations for referred pain do not exist, but it has been shown that wide dynamic range and nociceptive specific neurons in the spinal cord and brain stem of animals receive convergent afferent input from the mucosa, skin, muscles, joints, and viscera. This may cause a misinterpretation of the afferent information coming from muscle afferents and reaching high levels in the central nervous system, and hence be one reason for the diffuse and referred characteristics of muscle pain. Referred pain is a combination of central processing and peripheral input [6] as it is possible to induce referred pain to limbs with complete sensory loss due to an anesthetic block. However, the involvement of peripheral input from the referred pain area is not clear because anesthetizing this area shows inhibitory or no effects on the intensity of the referred pain. ►Central sensitization may be involved in the mechanism of referred pain. A complex network of extensive collateral synaptic connections for each muscle afferent fiber onto multiple dorsal horn neurons is assumed [7]. Under normal conditions, afferent fibers have fully functional synaptic connections with dorsal horn neurons as well as latent synaptic connections to other neurons within the same region of the spinal cord. Following ongoing strong noxious input, latent synaptic connections become operational, thereby allowing for convergence of input from more than one source. Animal studies show development of new and/or expansion of existing receptive fields after a noxious muscle stimulus. For example, recordings from a dorsal horn neuron with a receptive field located in the biceps femoris muscle show new receptive fields in the tibialis anterior muscle and at the foot after noxious stimulation of the tibialis anterior muscle [7]. In the context of referred pain, the unmasking of new receptive fields due to central sensitization could mediate referred pain [4]. The area of the referred pain is correlated with the intensity and duration of the muscle pain, and the appearance of referred pain is delayed (20–40 s) compared with the local muscle pain, indicating that a time-dependent process, like the unmasking of new synaptic connections (see above), is involved in the neural mediation of referred pain. Recently it has been emphasised that referred pain and central sensitization are closely related [4].

The pattern and size of referral seem to be changed in chronic musculoskeletal pain conditions. For example, FM patients experience greater pain and larger areas of referral after experimental muscle pain compared with matched controls [4]. Interestingly, these manifestations were present in lower limb muscles where the patients typically do not experience ongoing pain. Normally, pain from the tibialis anterior is projected distally to the ankle and only rarely is it projected proximally. In FM patients, substantial proximal spread of experimentally-induced referred pain was found. Enlarged areas of referred pain in pain patients suggest that the efficacy of central processing is increased (central sensitization). Moreover, the expansion in the area of referred pain in FM patients is partly inhibited by ketamine (an *N*-methyl-d-aspartate (NMDA) receptor antagonist) targeting central sensitization. Extended areas of referred pain from the tibialis anterior muscle, indicating central sensitization, have also been shown in patients suffering from other chronic musculoskeletal pain conditions such as whiplash, low back pain, and osteoarthritis.

Somatosensory changes in areas of referred muscle pain have been reported, and it seems that the duration and intensity of pain are important for such manifestations. As well as hypoalgesia, hyperalgesia has been reported in areas of referred muscle pain. Referred muscle hyperalgesia can also be a result of visceral pain due to viscero-somatic convergence. This may occur for example in gastrointestinal, gynaecological/urological, or in chronic visceral painful conditions without known etiology (e.g., irritable bowel syndrome, endometriosis). The degree of referred muscle hyperalgesia is related to the severity of the visceral pathology and hence the degree of visceral pain. Persistent referred muscle hyperalgesia can be manifested not only by chronic conditions, but also after recurrent painful visceral attacks such as in dysmenorrheic women, where lumbar muscles are hyperalgesic to pressure, or after colic attacks following calculosis of the upper urinary tract, where hyperalgesia to pressure is found in muscles in the left lumbar region [8].

Assessment of Muscle Pain in Experimental and Clinical Studies with Focus on FM

Several methods exist to assess pain sensitivity of musculoskeletal structures. The methods are based on application or induction of standardized pain to musculoskeletal structures to evaluate how sensitive the structure is to that specific stimulus modality. Such procedures can be applied to healthy volunteers in the laboratory for basic experimental studies or to patients for clinical examinations [4].

Pressure algometry is the most commonly used technique to induce muscle pain and hence assess tenderness in myofascial tissues and joints (e.g., tender points, FM, work-related myalgia, myofascial pain, strain injuries, myositis, chronic fatigue syndrome, arthritis/

orthroses, and other musculoskeletal inflammatory conditions). The American College of Rheumatology's classification criteria for FM requires 11 or more tender points to pressure out of 18 specified anatomical sites. Widespread hypersensitivity in chronic musculoskeletal pain conditions means general reduction in pressure pain thresholds assessed from many sites.

Another way to experimentally assess pain sensitivity is to apply repetitive painful pulses and investigate temporal integration/summation and the involvment of central NMDA receptors. ►Temporal summation means that repetitive, identical stimulation at frequencies lower than 5 Hz give rise to gradually increasing pain responses. FM patients show increased and prolonged responses to repetitive stimulation and ketamine (an antagonist of the NMDA receptor) can inhibit this.

Referred pain can be assessed experimentally from muscles by injection of various chemical substances such as hypertonic saline, capsaicin, and glutamate [4].

The balance between descending inhibition and facilitation can be assessed experimentally.

The phenomenon of descending inhibition, in which "muscle pain inhibits pain," has been extensively investigated and the heterotopic character demonstrated in many human studies (for references see [4]). Painful heterotopic conditioning stimuli (thermal, mechanical, electrical, or chemical) decrease pain perception induced by phasic noxious stimulation given elsewhere in the body. Recent data have shown that endogenous pain modulation in FM is impaired [9]. Descending facilitatory pathways originating in frontal cortical areas can contribute to generalized, increased neuronal responses along the neuraxis, suggesting that emotions such as fear may drive the development of wide spread pain and sensitization [3].

Muscle blood flow impairment during and post contractions, resulting in ischemia, has been suggested as contributing to FM pain. Other studies support that decreased relaxation between contractions, which has been found in patients with FM, means that not only static, but also dynamic muscle contractions might cause ischemic pain.

Muscle pain and musculoskeletal pain have implications on many aspects in daily life, and questionnaires for assessment of different dimensions have been developed for general and regional (e.g., back pain and neck pain) pain problems (General Function Score, Roland and Morris Disability Scale, Oswestry Pain Disability Index, West Haven-Yale Multidimensional Pain Inventory, Bournemouth questionnaire, fear avoidance beliefs, life satisfaction) [10].

Verbal assessments of musculoskeletal pain intensity and other subjective characteristics of the pain are obviously needed in clinical and experimental muscle pain studies. Visual analog scales (VAS), verbal descriptor scales (VDS), the McGill Pain Questionnaire (MPQ), and similar scales and questionnaires may be very helpful for the assessment of perceived pain intensity and quality [10]. Musculoskeletal pain is most frequently characterised by descriptors as: "drilling," "aching," "boring," and "taut."

The intensity of musculoskeletal pain is easily measured using VAS. However, this is only a one-dimensional aspect of the pain experienced, and additional VAS should be applied to monitor unpleasantness and soreness for example. Word descriptors on the VAS are important as muscle tenderness and muscle pain may not reflect the same mechanisms. In addition to verbal assessments, psychophysical tests are valuable adjuncts for the examination of musculoskeletal pain [10].

Summary

A significant part of the manifestations of muscle and myofascial pain (e.g., tenderness and referred pain) in chronic musculoskeletal disorders may be the result of peripheral and central sensitization. Reliable methods for quantitative induction and assessment of muscle sensitization, referred pain and muscle sensitivity are available. Sensory assessment procedures can provide complementary clinical information and give qualified clues to revise and optimize treatment regimes.

References

1. Adler GK, Geenen R (2005) Hypothalamic-pituitary-adrenal and autonomic nervous system functioning in fibromyalgia. Rheum Dis Clin North Am 31:187–202, xi
2. Carli G, Suman AL, Biasi G, Marcolongo R (2002) Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain. Pain 100:259–269
3. Suzuki R, Rygh LJ, Dickenson AH (2004) Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol Sci 25:613–617
4. Graven-Nielsen T (2006) Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. Scand J Rheumatol 35 (Suppl 122):1–43
5. Simons DG, Travell JG, Simons L (1999) Myofascial pain and dysfunction. The trigger point manual. Lippincott Williams and Wilkins, Philadelphia
6. Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds.) 2008 Fundamentals of Musculoskeletal pain. IASP Press
7. Mense S, Simons DG (2001) Muscle pain. Understanding its nature, diagnosis, and treatment. Lippincott Williams and Wilkins, Philadelphia
8. Giamberardino MA (1999) Recent and forgotten aspects of visceral pain. Eur J Pain 3:77–92
9. Julien N, Goffaux P, Arsenault P, Marchand S (2005) Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295–302
10. Turk DC, Melzack R (1992) Handbook of pain assessment. Guilford, New York

Muscle-specific Receptor Tyrosine Kinase (MuSK)

Definition

In the development of the neuromuscular junction (NMJ), acetylcholine clustering at endplates depends on MuSK as knockout mice fail to form NMJs and die at birth. MuSK may mediate acetylcholine receptor (AchR) pre-patterning by agrin-dependent and -independent activation pathways.

►Agrin
►Acetylcholine
►Neuromuscular Junction (NMJ)
►Synapse Formation: Neuromuscular Junction Versus Central Nervous System

Muscle Spindle

Definition

A stretch-sensitive muscle receptor. The mammalian muscle spindle is 2–6 mm long and is attached at each end to the (extrafusal) skeletal muscle fibers that envelop it. Two or more sensory endings are located within a capsule near the middle of the spindle. When extrafusal muscle fibers lengthen and shorten, the spindles stretch and shorten too, which modulates the firing rates of their sensory endings. Much of the spindle comprises intrafusal muscle fibers whose sole function is to alter the stretch-sensitivity of the spindle's sensory endings. These muscles fibers are activated by γ-motoneurons (also known as fusimotor neurons). There are typically 100–200 muscle spindles in a medium-sized muscle, each innervated by up to 6 sensory afferents (group Ia and II afferents) and 10 fusimotor neurons.

►Feedback Control of Movement
►Motoneuron
►Proprioception: Role of Muscle Receptors

Muscle Sympathetic Nervous Activity

Definition

Muscle sympathetic nervous activity (MSNA) refers to neural traffic of sympathetic nerves that innervate skeletal muscles, regulating vascular resistance in skeletal muscles and controlling systemic blood pressure.

►Autonomic Function in Space
►Sympathetic Pathways

Muscle Synergies

Andrea d'Avella
Department of Neuromotor Physiology, Santa Lucia Foundation, Rome, Italy

Definition

The term "synergy" literally "working together," has been used in the motor control literature with various meanings. Here a muscle synergy is defined as the coordinated recruitment of a group of muscles with specific activation balances or specific activation waveforms. Recent experiments have indicated that many motor behaviors are controlled through the flexible combination of a small number of muscle synergies. This mechanism is believed to simplify the selection of the appropriate muscle commands for a given behavioral goal.

Characteristics

To control goal-directed movements the central nervous system (CNS) must map sensory input into motor output. For example, ►reaching movements usually require selecting the appropriate muscle activation patterns to move the arm to visually specified targets. This transformation is thought to be performed by an ►internal model implemented in the neural circuits. However, given the complexity of the computations required to select the appropriate activation waveforms of many muscles acting on many articulated body segments, it is not clear what mechanisms allow for an efficient implementation of an internal model. One possibility is that this mapping is simplified by a low-dimensional representation of the motor output. The key idea is that, if all useful muscle patterns can be constructed by the combination of a small number of basic elements, selecting the appropriate muscle pattern for a given goal requires only determining how these elements are combined.

Two Types of Synergies

Muscle synergies are suitable basic elements for constructing a low-dimensional representation of the motor output because they capture a set of features

shared by a variety of muscle patterns. Such features can be identified in the spatial domain and in the temporal domain. In the spatial domain, i.e. across muscles, a muscle synergy captures a specific relationship in the muscle activation amplitudes. Considering a set of D muscles, a muscle synergy can be expressed as a D-dimensional vector $\boldsymbol{w}$ of weighting coefficients that specify the activation balance among the muscles (Fig. 1a).

Different levels of activation may be generated by a single muscle synergy by scaling in amplitude the entire vector:

$$\mathbf{m} = c\,\mathbf{w} \tag{1}$$

where $\boldsymbol{m}$ is a D-dimensional vector that specifies the recruitment level of each muscle and c is a scaling coefficient (Fig. 1b, *columns* 1–3). More generally, a set of N synergies, $\{\boldsymbol{w}_i\}_{i\,=\,1\ldots N}$, can generate many distinct muscle patterns by linear combination:

$$\mathbf{m} = c_1\mathbf{w}_1 + c_2\mathbf{w}_2 + \cdots + c_N\mathbf{w}_N = \sum_{i=1}^{N} c_i\ \mathbf{w}_i \tag{2}$$

where c_i is the scaling coefficient for the i-th synergy (Fig. 1b, *rows* 4–6).

Since the muscle activation vectors involved in most behaviors are time-dependent, synergistic relationships may also be found in the temporal domain. With respect to time, a synergy may be time-invariant or time-varying. A synergy is time-invariant if the same muscle activation balance, expressed by a vector $\boldsymbol{w}$, holds at all times, i.e. for all the time-varying activation vectors comprising a muscle patterns. If all the synergies are time-invariant, eq. 2 can be written, taking time into account, as:

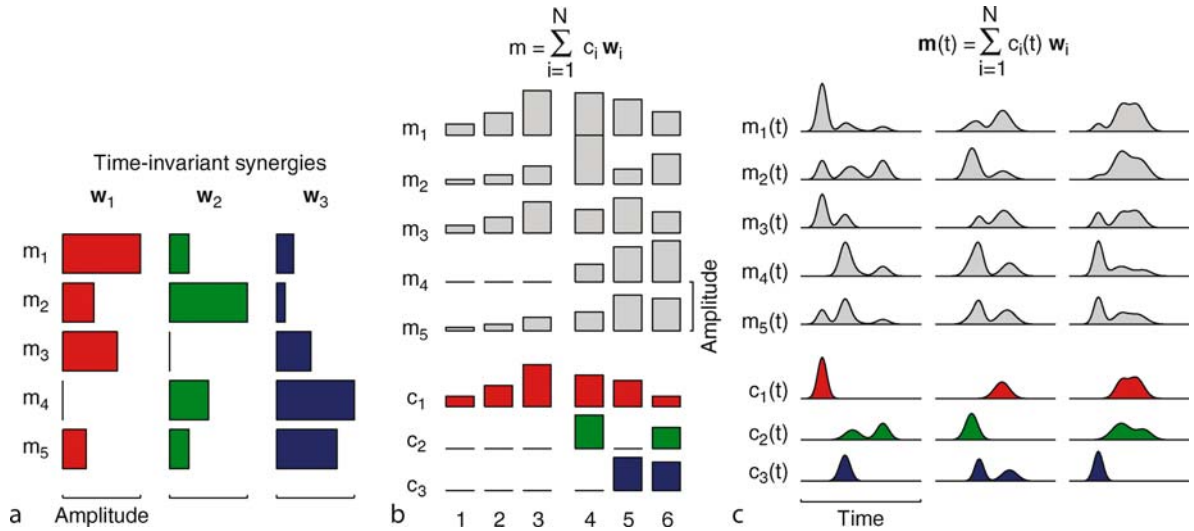
$$\mathbf{m}(t) = \sum_{i=1}^{N} c_i(t)\,\mathbf{w}_i \tag{3}$$

where $\boldsymbol{m}(t)$ is the muscle activation at time t and $c_i(t)$ is the scaling coefficient for the i-th synergy at time t (Fig. 1c). Since each time-invariant synergy contributes to the waveform of different muscles with the same $c_i(t)$ waveform, the muscle waveforms associated with each synergy are synchronous. In contrast, a time-varying synergy is comprised by a collection of waveforms, each one specific for a muscle, and thus not necessarily synchronous (Fig. 2a).

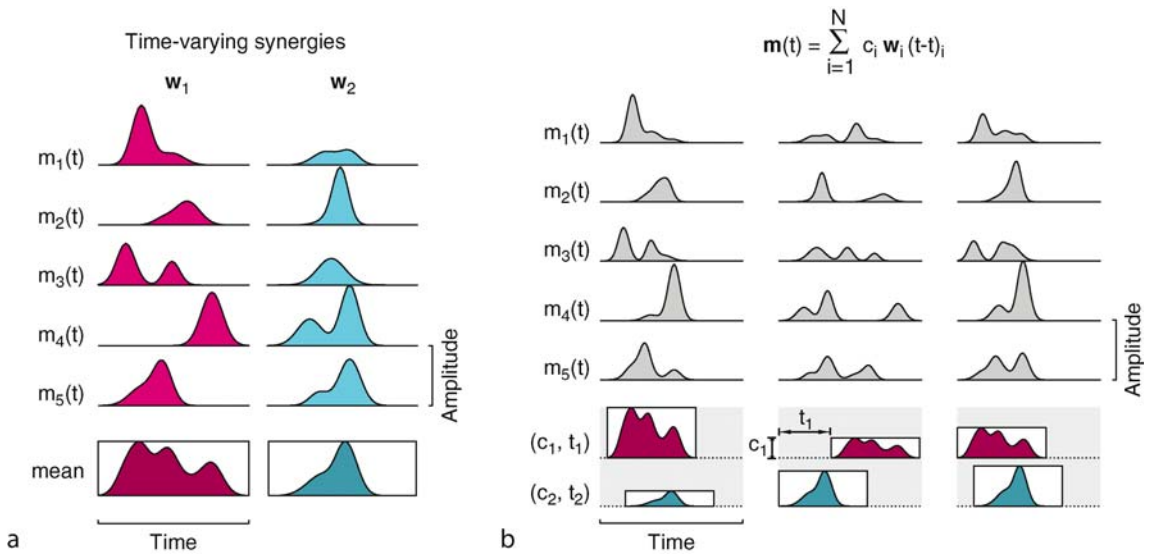
These waveforms can be expressed by a time-varying synergy vector $\boldsymbol{w}(t)$ and eq. 2 can be written as:

$$\mathbf{m}(t) = \sum_{i=1}^{N} c_i\ \mathbf{w}_i(t - t_i) \tag{4}$$

with one scaling coefficient (c_i) and one time delay (t_i) for each synergy. In this case, the time dependence of the muscle activation waveforms is captured by the temporal structure of the synergies and by their relative delays (Fig. 2b). Time-varying synergies represent parsimoniously the motor output because, once the



Muscle Synergies. Figure 1 Generation of muscle patterns by combination of time-invariant synergies. (a) Three different activation balances among five muscles are expressed by three vectors (w_i), whose components are represented by horizontal bars of different lengths. (b) Different muscle patterns (1–6) are generated by multiplying the three vectors by three scaling coefficients (c_i) and summing them together. (c) A time-varying muscle pattern ($m(t)$) is generated by combining the synergies with time-varying scaling coefficients ($c_i(t)$). Different patterns can be obtained by changing the scaling coefficient waveforms.



Muscle Synergies. Figure 2 Generation of muscle patterns by combination of time-varying synergies. (a) Each one of the two synergies illustrated is composed by a collection of muscle activation waveforms. The profile inside the rectangle below each synergy represents the mean activation waveform for that synergy. (b) A time-varying muscle patterns ($m(t)$) is generated by multiplying all waveforms of each synergy by a single scaling coefficient (c_i), shifting them in time by a single delay (t_i), and summing them together. In this example, different patterns are obtained by changing two scaling coefficients and two delays.

synergies are given, a few scaling and delay coefficients are sufficient to specify many muscle patterns.

Muscle Synergy Identification

Muscle synergies provide a useful representation of the motor output if they can generate all muscle patterns observed during the performance of either a task in variety of conditions or multiple tasks. Thus, to test the validity of a synergy model it is necessary to identify a set of synergies from the observed muscle patterns and to show that they capture most of the variability in the data.

The identification of the synergies according to a model that allows for the simultaneous recruitment and combination of multiple synergies (eq. 2) requires a multivariate decomposition algorithm. For time-invariant synergies, the identification of the combination coefficients and synergies of eq. 3 can be obtained with a number of decomposition algorithm such as Principal Component Analysis (PCA), Factor Analysis (FA), Independent Component Analysis (ICA), and Non-negative Matrix Factorization (NMF) [1]. The number of synergies (N) is a free parameter for each decomposition algorithm. While the selection of this parameter is performed with different criteria for each algorithm, in general the goal is to determine the minimum number of synergies that explain all the structured variation in the data, interpreting the remaining unstructured variation as noise. Often this minimum number is determined by inspecting a plot of the reconstruction error as a function of the number of synergies. As the number of synergies increases the reconstruction error decreases and the number at which the error curve changes slope, indicating that additional synergies only explain a small additional amount of variation due to noise, is usually taken as correct number of synergies. The identification of time-varying synergies, according to the model of eq. 4, can be accomplished with the same methods used for time-invariant synergies if the simplifying assumption that the synergies are not time-shifted relatively to each other is introduced [2]. More generally, to identify a set of time-varying synergies that can be time-shifted with respect to each other, it is possible to use an iterative optimization algorithm [3].

Experimental Evidence

Qualitative observations of stereotyped muscle activity patterns in specific tasks, suggestive of a synergistic organization, have long been reported. However, whether muscle synergies are fixed or require task-dependent flexible adjustment has been a controversial issue. Recently, systematic investigations and quantitative analyses of the muscle synergies according to synergy combination models have addressed this issue with a new perspective. Studies conducted on frogs, cats, and humans have provided evidence that the CNS flexibly combines fixed muscle synergies for generating the muscle patterns necessary to perform many motor tasks and behaviors.

Electromyographycal (EMG) activity recorded from many hindlimb muscles of spinalized frogs during withdrawal reflexes [4], decerebrated frogs during spontaneous behavior [5], and intact frogs during defensive kicking [3] and locomotion, has revealed a synergistic organization. These studies have shown that a variety of muscle patterns used in different behaviors are generated by the combination of a small number of time-invariant and time-varying synergies. For example, 90% of the variability in the EMG responses associated with the withdrawal reflexes evoked by skin stimulation at a variety of sites on the frog limb is explained by the combination of four time-invariant synergies.

The study of postural control in cats and humans has also provided evidence for muscle synergies. The activations of cat hindlimb muscles during postural responses to perturbations of the support surface (translations and rotations in multiple directions) are captured by the combination of a five time-invariant synergies [6]. These muscle synergies are associated with specific force vectors applied by the paw against the support, suggesting that they encode task-level biomechanical variables. In humans, the muscle patterns used for shifting the center of pressure during balancing while standing are constructed by combinations of three time-invariant synergies [7].

The muscle patterns in leg and trunk muscles during human locomotion at different speeds and with different fractions of the body weight supported by a harness are accounted by the combination of five time-invariant synergies [8]. The time-varying amplitude scaling coefficients, once the muscle patterns are time-normalized to equal gait cycle duration, have similar waveforms across conditions.

Time-varying muscle synergies have been identified in the patterns of activation of extrinsic and intrinsic hand muscles during fingerspelling [2]. The synergy, identified with PCA, which explains the largest fraction of the data variation has asynchronous waveforms with activity waves unfolding in time across muscles.

Finally, there is evidence that the combinations of time-varying muscle synergies are used for controlling reaching movements in humans [9]. The phasic EMG patterns recorded in arm and shoulder muscles during fast reaching movements to targets arranged in different directions on two vertical planes are generated scaling in amplitude and shifting in time four or five time-varying muscle synergies. The amplitude modulation of the synergy has a simple dependence on the direction of movement, well captured by a cosine function.

In summary, a growing number of studies are unveiling the existence of regularities in the spatiotemporal organization of the muscle patterns observed during the performance of a variety of tasks in many conditions. These regularities are well described by a synergy combination model suggesting that the CNS uses a low-dimensional representation of the motor output and simple combination rules for mastering the complex task of selecting the appropriate muscle pattern for achieving a desired goal.

►Postural Synergies

References

1. Tresch MC, Cheung VC, d'Avella A (2006) Matrix factorization algorithms for the identification of muscle synergies: evaluation on simulated and experimental data sets. J Neurophysiol 95(4):2199–2212
2. Klein Breteler MD, Simura KJ, Flanders M (2007) Timing of muscle activation in a hand movement sequence. Cereb Cortex 17(4):803–815
3. d'Avella A, Saltiel P, Bizzi E (2003) Combinations of muscle synergies in the construction of a natural motor behavior. Nat Neurosci 6(3):300–308
4. Tresch MC, Saltiel P, Bizzi E (1999) The construction of movement by the spinal cord. Nat Neurosci 2(2):162–167
5. Hart CB, Giszter SF (2004) Modular premotor drives and unit bursts as primitives for frog motor behaviors. J Neurosci 24(22):5269–5282
6. Torres-Oviedo G, Macpherson JM, Ting LH (2006) Muscle synergy organization is robust across a variety of postural perturbations. J Neurophysiol 96(3):1530–1546
7. Krishnamoorthy V, Goodman S, Zatsiorsky V, Latash ML (2003) Muscle synergies during shifts of the center of pressure by standing persons: identification of muscle modes. Biol Cybern 89(2):152–161
8. Ivanenko YP, Poppele RE, Lacquaniti F (2004) Five basic muscle activation patterns account for muscle activity during human locomotion. J Physiol 556(Pt 1):267–282
9. d'Avella A, Portone A, Fernandez L, Lacquaniti F (2006) Control of fast-reaching movements by muscle synergy combinations. J Neurosci 26(30):7791–7810

Muscle-tendon Elasticity

►Muscle and Tendon Energy Storage

Muscle-tendon Unit

►Tendon

Muscle: The Molecular Motor

C. J. Heckman
Department of Physiology and Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Definition

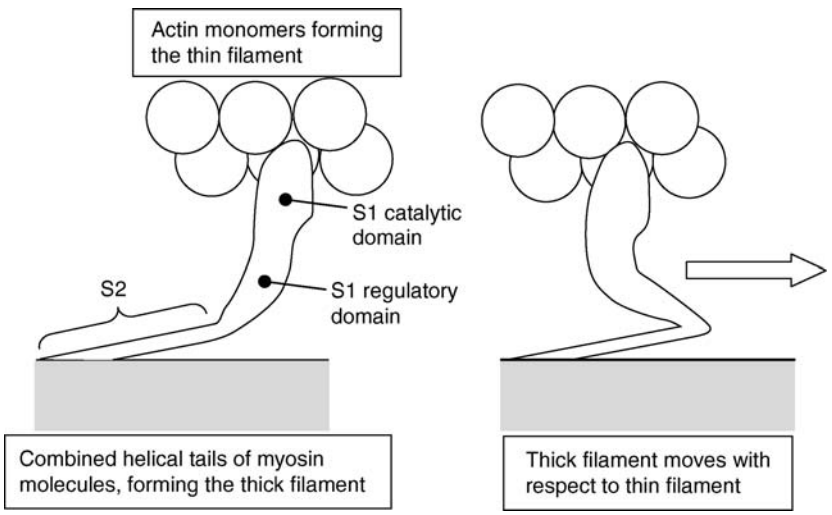
Muscle consists of an exceedingly complex array of molecules. The exertion of force and the production of movements thus rely on the summation of forces and movements of many molecules. The sarcomere provides the basic structural organization of a muscle fiber (see Fig. 1 in ►Muscle). From the perspective of the molecular motor, the sarcomere structure can be divided into three components: the thick filaments (made of up myosin molecules), the thin filaments (made of actin molecules), and the structural proteins that transmit forces to the ends of the sarcomere and among sarcomeres. The primary basis of the molecular motor for movement consists of a configuration change in myosin. This configuration change, however, does not produce movement or force unless the myosin is attached to actin; the forces so produced are transmitted via the structure of the sarcomere to neighboring sarcomeres and so on through to the tendon (see ►Length-Tension) and even to other muscles (see ►Intramuscular myofascial force transmission and Epimuscular Myofascial Force Transmission and Intermuscular Interaction).

Characteristics

Quantitative Description

The myosin in muscle is one of a large set of molecular motors consisting of various families of myosins, kinesins and dyneins. Myosins move along actin filaments; kinesins and dyneins along microtubules [1]. These motors provide functions such as moving substrates within the cell. The myosin II family in muscle is unique in being part of the structure of the sarcomere, and produces summed movements that generate the huge forces that muscles are capable of producing. Muscle myosin contains a long helix, which with other myosin molecules, forms the thick filament of the sarcomere. A portion of this helix (called the S2 subfragment) protrudes from the thick filament and connects to a head region (S1 subfragment). For some years, it was assumed that the configuration change in myosin that generated movement involved rotation of the S1 head with respect to actin at the attachment site between these two molecules. However, studies from a number of labs have now demonstrated that the angle between the attached part of the S1 head and actin stays constant during force generation [2,3–5]. Instead, the configuration change occurs within the S1 head. The S1 head comprises of two distinct regions: a regulatory domain that contains the myosin light chains and a catalytic domain for hydrolysis of ATP to ADP + Pi. Force is generated when the angle between the regulatory domain and the catalytic domain changes. The regulatory domain rotates with respect to the catalytic domain, as shown by the cartoon in Fig. 1.

This is known as the "lever arm" hypothesis, with the lever arm being the regulatory domain of S1.



Muscle: The Molecular Motor. Figure 1

The hydrolysis of ATP is of course essential for this configuration change. The basic features of how the steps of hydrolysis of ATP are related to the contraction cycle is as follows: (i) binding of ATP to S1 catalytic domain: unbinding of actin and myosin; (ii) hydrolysis of ATP to ADP and Pi: S1 lever arm straightens, moving S1 head to next attachment site; and (iii) release of ADP and Pi from the S1 head: lever arm bends to produce movement of thin versus thick filaments (this is the step illustrated in Fig. 1) [2,5]. Myosin is only tightly bound to actin for about 5% of the total crossbridge cycle; the rest of the cycle involves either weak binding or the unbound state [5]. Speed of the crossbridge cycle is related both to the various subforms of the myosin ATPase, as well as to differences in the myosin light chains. Immunohistochemical techniques to identify these subtypes are the basis of the standard identification of type I (slow), IIa and IIb (both fast) muscle fibers.

Higher Level Structures
Myofilament, myofibril, muscle fiber, muscle.

Higher Level Processes
Forces are also transmitted between muscles (see ►Epimuscular Myofascial Force Transmission and Intermuscular Interaction).

Process Regulation
The interaction of actin and myosin is dependent on calcium; release of calcium is controlled via action potentials from motoneurons (see ►Neuromuscular Junction).

Function
The function of the molecular motor is clear: generation of movement.

Pathology
Genetic mutations in the molecular machinery produce severe pathological deficits. Nemaline myopathies can be produced by genetic defects in action, tropomyosin and other sarcomere proteins.

References

1. Schliwa M, Woehlke G (2003) Molecular motors. Nature 422(6933):759–765
2. Geeves MA, Holmes KC (1999) Structural mechanism of muscle contraction. Annu Rev Biochem 68:687–728
3. Highsmith S (1999) Lever arm model of force generation by actin-myosin-ATP. Biochemistry 38(31):9791–9797
4. Tyska MJ, Warshaw DM (2002) The myosin power stroke. Cell Motil Cytoskeleton 51(1):1–15
5. Spudich JA (2001) The myosin swinging cross-bridge model. Nat Rev Mol Cell Biol 2(5):387–392

Muscle Tone

Definition
Muscle tone is defined as the resistance that a relaxed muscle opposes to passive stretch.

►Postural Muscle Tone

Muscle Torque

Definition
The product of muscle force and muscle moment arm.

►Impedance Control

Muscle Twitch

Definition
An action potential in a skeletal or oculomotor motoneuron axon produces, after neuromuscular synaptic transmission, a propagating action potential in the innervated muscle fibers followed by an increase in intracellular calcium. The calcium activates the actin-myosin cross-bridges and the buildup of force (a process called excitation-contraction coupling). Force peaks at a characteristic "twitch time" that is dependent on the rate of calcium release (fast in most skeletal and extraocular muscles) and the interaction between the muscle's series elastic component (embodied in the connective tissue and muscle proteins) and the force-velocity relationship. In the initial part of the twitch, the muscle contracts rapidly internally as the series elastic component stretches, so less force is produced. Force declines slowly after the peak due to the re-sequestering of calcium. The time course of the contraction depends on the muscle fiber type (type-I, type-II, and subtypes) to the extent that the terms "slow-twitch" and "fast-twitch" fibers are also used as synonyms of type-I and type-II respectively.

►Actin
►Cross-bridge Theory
►Excitation-contraction Coupling
►Force-velocity Relationship of Skeletal Muscle
►Myosin

Muscle Unit

Definition

The set of striated muscle fibers in a specific anatomical muscle that receives innervation from a single motoneuron.

►Motor Units

Muscular Dystrophy

Definition

A group of ~40 inherited heterogeneous disorders that result in progressive muscle weakness and muscle wasting.

►Duchenne Muscular Dystrophy

Muscular Stiffness

T. Richard Nichols,
Clotilde M. J. I. Huyghues-Despointes
Department of Physiology, Emory University, Atlanta, GA, USA

Synonyms

Elasticity; Impedance; Stretch resistance

Definition

Muscular stiffness is defined as the change in force divided by the corresponding change in length, when the length change is imposed by an external agent or by a change in the external load on the muscle. In the present context, stiffness is time-varying and therefore has dynamic attributes. Classically, stiffness refers only to the elastic, and therefore static, component of impedance. However, muscular properties are nonlinear, and therefore muscular impedance cannot easily be partitioned into components corresponding to the derivatives of position. Researchers in motor systems have chosen to retain the term "stiffness" to describe the resistance of muscle to length change.

Characteristics

Quantitative Description

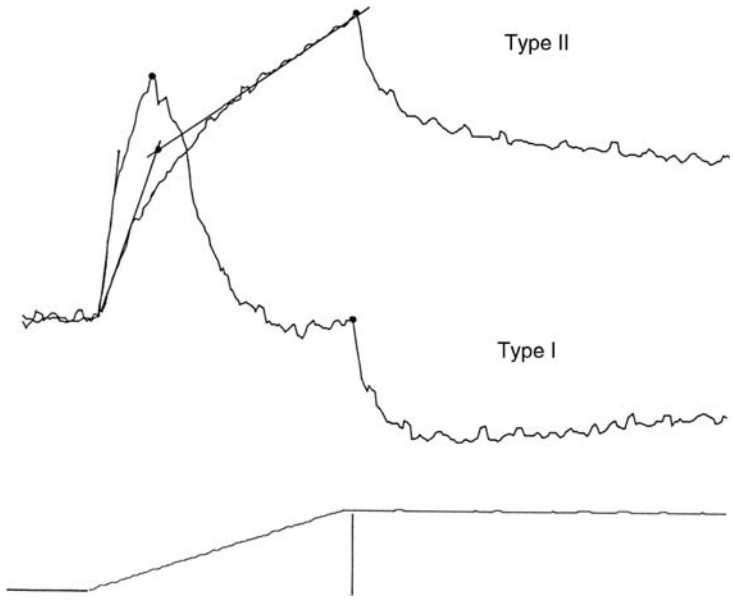
Stiffness of Inactive Muscle

The stiffness of inactive skeletal muscle is dominated by the elastic properties in-parallel and in-series connective tissue. This stiffness increases at long muscle lengths and can effectively limit extreme joint angles, but is normally low enough through the physiological range of the muscle so as not to offer significant resistance to joint motion. However, inactive muscle can offer some resistance for small disturbances. Evidence does exist that some cross-bridges that cycle either slowly or not at all remain attached at rest. The additional stiffness contributed by these cross-bridges is reduced by stretching the muscle beyond the working range of the cross-bridges or by prior activation of the muscle. These non-cycling cross-bridges can reform over a period of seconds, and re-establish elevated stiffness for small (1% of muscle length) amplitudes of stretch. These "thixotropic" properties of inactive muscle have been observed in experiments on animals and human subjects [1], and may be important during the maintenance of steady postures.

Stiffness of Active Muscle

When a muscle is activated, the stiffness becomes considerably larger through the physiological range of joint angles. The magnitude of this stiffness, which is intrinsic to the contracting muscle, depends on a number of factors, including the level of motor unit recruitment, length and force, and movement history. The stiffness of actively contracting muscle is thought to arise from the mechanical properties of cycling cross-bridges. Cross-bridges are believed to have spring-like properties, so they contribute to muscular stiffness when attached. In a muscle fiber with a population of cycling cross-bridges, the stiffness of the fiber depends on the average number of attached cross-bridges and the rate of turnover. The contribution of a given cross-bridge to the stiffness of the muscle fiber increases with the length change over which it is attached. For a given rate of stretch, this contribution will decrease with an increase in the rate of turnover. These basic principles can be used to explain how muscular stiffness changes under different contractile conditions and how it depends on the fiber type composition of the muscle.

If, after a period of isometric contraction, a muscle fiber is stretched by a small amount so that the length change remains within the working range of the attached cross-bridges, the muscle fiber exhibits spring-like behavior known as *short-range stiffness*. If the disturbance carries the muscle fiber beyond the working range of cross-bridges, then stiffness abruptly declines as cross-bridges are mechanically disrupted [2] (Fig. 1).



Muscular Stiffness. Figure 1 Responses of chemically-skinned muscle fibers to constant velocity stretch. The fibers were submaximally activated to the same background force levels in solutions containing calcium and ATP. Stretches lasting 100 ms and 0.05 muscle lengths in amplitude were delivered after periods of isometric contraction in activating solutions. The type II fiber was obtained from the lateral gastrocnemius muscle and the type I fiber from the soleus muscle of the cat. Both fibers show short-range stiffness followed by yielding, but the short range stiffness (indicated by the initial *fitted lines*) and yield were both greater in the type I fibers. This figure was modified from Fig. 2 of [3].

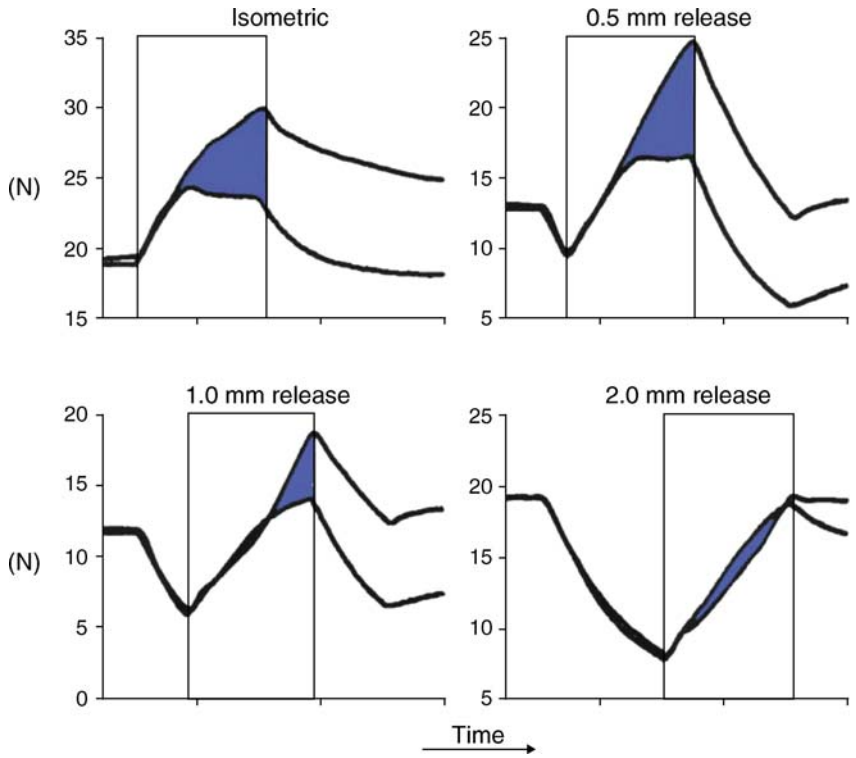
The extent of this decline, or yield, and short-range stiffness depend on the rate of stretch and on the rate of cross-bridge turnover. Increasing the rate of stretch can lead to an increase in short-range stiffness, since the cross-bridges remain attached over a larger change in length [3]. Yield can also increase since there is more synchronous detachment and a decrease in the time for reattachment relative to the rate of stretch. An increase in the rate of turnover would lead to a small decrease in stiffness since cross-bridges remain attached for shorter periods of time and a decrease in yield occurs due to the more rapid reattachment. Therefore, a previously isometric muscle responds to forcible lengthening with short-range stiffness followed by a yield that in some cases can result in a transient reduction in force (Fig. 1). One way to summarize this behavior is that active muscle shows significant damping [4], albeit nonlinear damping, which can have a stabilizing influence on the musculoskeletal system. If the muscle is allowed to shorten instead, force declines throughout the shortening, but the stiffness is also greater over the short range. When the responses to lengthening and shortening are compared, stiffness is greater during shortening [5].

If the muscle fiber is perturbed after a period of motion, its mechanical properties are different from those described above. Constant motion leads to increased turnover and a tendency for cross-bridges to be in positions of lower stress than in the isometric state. As might be expected, the yield decreases and the short range is extended. As a result, the responses of the muscle to length change more closely resemble those of linear springs with some damping [6] than the highly nonlinear behavior described above (Fig. 2).

Under conditions of quiet standing, stability is achieved in part by intrinsic mechanical properties of muscle, including thixotropic properties of inactive muscle, and short-range stiffness and damping of active muscle. During ongoing movements, muscular stiffness is less dependent on amplitude of the perturbation, and thixotropy in inactive muscles is greatly reduced, in keeping with the requirements of a wide dynamic range of joint motion.

Dependence of Muscular Stiffness on Motor Unit Composition and Recruitment

Muscular stiffness is strongly dependent on the motor unit composition of a muscle and the level of recruitment in the muscle. For muscles that are used for standing or braking and that are rich in slow twitch muscle fibers, the cycling rate of cross-bridges tends to be lower. Consequently, these predominantly slow-twitch muscles exhibit higher short range stiffness and yield to a greater extent than muscles with substantial



Muscular Stiffness. Figure 2 Dependence of muscular stiffness on movement history. Reflexive and areflexive soleus muscles from a decerebrate cat were subjected to 2 mm ramp stretches following releases of progressively larger amplitude, from 0 to 2 mm. In each panel, the lower trace corresponds to the areflexive muscle. The portions of the responses obtained during the 2 mm stretch are denoted by the rectangles. Note that the yields of the intrinsic responses become progressively small and more delayed as the prior release increases. Reflex action also becomes reduced and delayed, until there is no contribution from the reflex with the largest prior release. This figure is modified from Fig. 1a of [6].

populations of fast-twitch muscle fibers (see Fig. 1). As motor units are recruited into activity, force and stiffness both increase. A dependence of stiffness on force contrasts with the property of a linear spring that stiffness is constant with force. Intrinsic muscular force and stiffness increase together with recruitment, but not in exact proportion (Fig. 3).

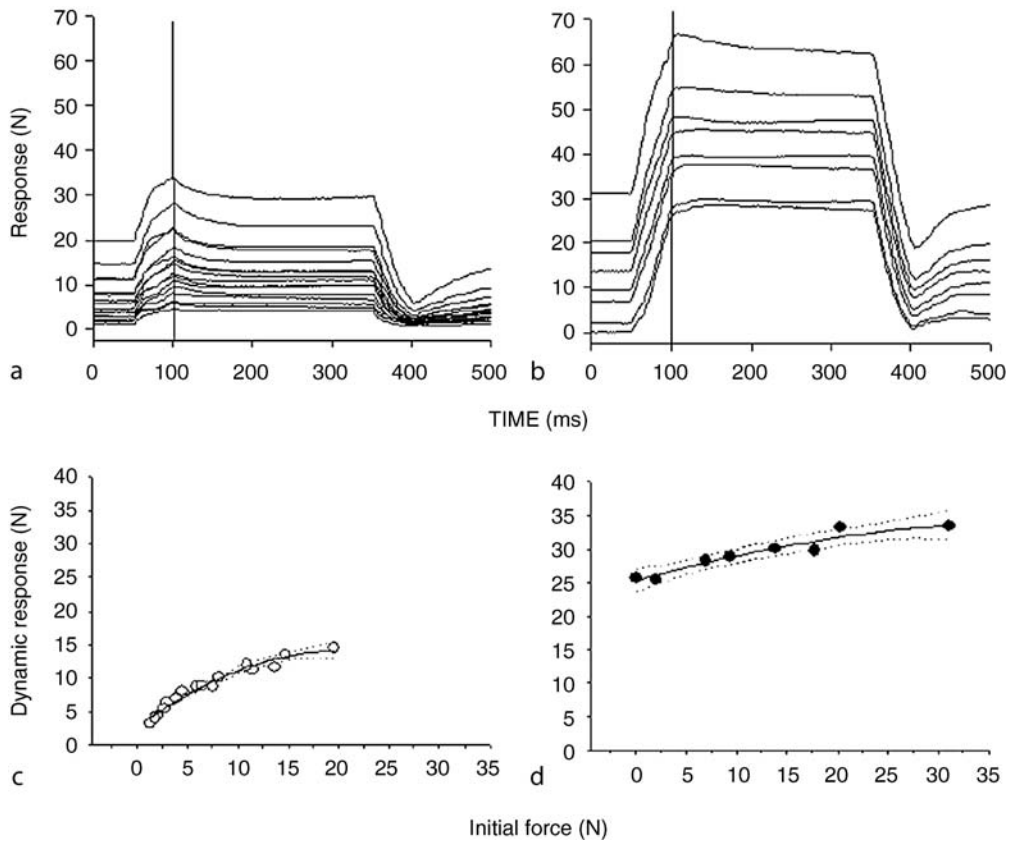
Stiffness increases slightly less rapidly than force due to the presence of series elastic elements [7,8]. The consequence of these nonlinear properties is that high intrinsic stiffness can only be achieved by recruiting many motor units. Co-contraction is one strategy for increasing the stiffness of a joint. Under these conditions, agonist and antagonistic muscles are activated together to provide high joint stiffness with no net joint torque. At low background activity, such as occurs during quiet standing, intrinsic muscular stiffness is low.

Structural Regulation

Muscular stiffness is influenced by the architecture of the muscle. Stiffness increases with the cross-sectional area of muscle and decreases with length, according to the in-parallel and in-series arrangement of sarcomeres, respectively.

Process Regulation

The mechanical properties of muscle are subject to local control by reflex circuits in the spinal cord. The initial response of a muscle, and therefore the musculoskeletal system, to a mechanical perturbation depends on the intrinsic mechanical properties described above. After a brief delay, feedback from muscle spindle receptors can increase or decrease the recruitment of motor units as well as influence firing rate modulation in response to muscle lengthening or shortening, respectively, through the monosynaptic (stretch) reflex. Muscle spindle receptors, which contain specialized muscle fibers (intrafusal muscle fibers), signal length changes and the dynamics of length change. Due to the high sensitivity of the primary receptors of the muscle spindle, the monosynaptic reflex can recruit substantial numbers of motor units even at low forces, making the stiffness



Muscular Stiffness. Figure 3 Dependence of muscular stiffness on initial force. Reflexive and areflexive gastrocnemius muscles of a decerebrate cat were subjected to ramp-and-hold stretches. (a) Responses of muscles in which reflexes were disrupted by prior reinnervation of the muscle obtained at different initial forces. Dynamic responses were computed by subtracting the initial (pre-stretch) force for each trace from the corresponding force measured at the time of ramp completion denoted by the vertical line. These responses are shown plotted against initial force in (c). (b) Responses of untreated contralateral muscles with intact reflexes. Note the greater magnitude and less abrupt yielding of these responses compared to those shown in (a). The dynamic responses are shown plotted against initial force in (d). The amplitude of the ramps was 2 mm, so dynamic stiffness (N/mm) can be computed by dividing the dynamic responses by 2. These plots indicate that intrinsic muscular stiffness increases with force. In the presence of reflexes, stiffness is larger and less dependent on force. This figure is modified from Fig. 3 of [7]. Further experimental details can be found in this paper.

of the muscle-reflex system less dependent on background force than intrinsic muscular stiffness (Fig. 3). As stiffness remains force-dependent to some extent, however, co-contraction still results in an increase in the stiffness of the joint.

Due to the filtering properties of the intrafusal muscle fibers, the length signals are subject to similar history-dependent properties as found in extrafusal muscle fibers as described above [9]. The monosynaptic reflex compensates for muscular yield through recruitment of additional motor units, but compensates less during ongoing motion when the yield is less [6] (Fig. 2). In these ways, the stretch reflex can regulate muscular stiffness over a wide range of forces and movement histories, and therefore reduce the computational burden on the central nervous system.

Function

The initial response of a muscle to length change is determined by the intrinsic stiffness of the muscle. Reflex pathways then regulate the response after a brief delay. These intrinsic and extrinsic mechanisms regulate the mechanical response properties of joints in a three-dimensional manner according to the attachments of the muscles crossing the joint. For a given axis or rotation, the stiffness of synergistic and antagonistic muscles add together to determine the stiffness of the joint. Muscular stiffness influences interjoint coordination by virtue of the regulation of individual joints, as well as by the mechanical coupling of multi-articular muscles. These intrinsic and extrinsic mechanisms therefore influence the endpoint stiffness of the limb and coordination of the component joints.

Pathology

Muscular growth and maintenance are strongly influenced by muscular load and length [10]. In disorders that involve prolonged shortening, such as spastic diplegia, muscle fibers may become shortened with the consequent equine posture. In addition, the tendon will account for a greater proportion of total muscle length. The shortened muscle fibers will consequently have reduced shortening velocity, increased active stiffness, and increased overall stiffness.

References

1. Proske U, Morgan DL, Gregory JE (1993) Thixotropy in skeletal muscle and in muscle spindles: a review. Prog Neurobiol 41:705–721
2. Joyce GC, Rack PMH, Westbury DR (1969) The mechanical properties of cat soleus muscle during controlled lengthening and shortening movements. J Physiol 204:461–474
3. Malamud JG, Godt RE, Nichols TR (1996) Relationship between short-range stiffness and yielding in type-identified, chemically skinned muscle fibers from the cat triceps surae muscles. J Neurophysiol 76:2280–2289
4. Lin DC, Rymer WZ (1993) Mechanical properties of cat soleus muscle elicited by sequential ramp stretches: implications for control of muscle. J Neurophysiol 70:997–1008
5. Nichols TR, Houk JC (1976) The improvement in linearity and regulation of stiffness that results from action of the stretch reflex. J Neurophysiol 39:119–142
6. Huyghues-Despointes CM, Cope TC, Nichols TR (2003b) Intrinsic properties and reflex compensation in reinnervated triceps surae muscles of the cat: effect of movement history. J Neurophysiol 90:1547–1555
7. Huyghues-Despointes CM, Cope TC, Nichols TR (2003a) Intrinsic properties and reflex compensation in reinnervated triceps surae muscles of the cat: effect of activation level. J Neurophysiol 90:1537–1546
8. Sandercock TG (2000) Nonlinear summation of force in cat soleus muscle results primarily from stretch of the common-elastic elements. J Appl Physiol 89:2206–2214
9. Haftel VK, Bichler EK, Nichols TR, Pinter MJ, Cope TC (2004) Movement reduces the dynamic response of muscle spindle afferents and motoneuron synaptic potentials in rat. J Neurophysiol 91:2164–2171
10. Burkholder TJ (2003) Permeability of C2C12 myotube membranes is influenced by stretch velocity Biochem Biophys Res Commun 305:266–270

Musculoskeletal Pain

►Muscle Pain, Including Fibromyalgia

MuSK

Definition

►Muscle-specific Receptor Tyrosine Kinase (MuSK)

Mutagenesis, Structure-Function

Definition

The process by which selective changes to the amino acid sequence of a protein are made and the functional consequences of such mutations then determined. This process is used to identify functionally important parts of proteins (e.g. ion channels, enzymes), and thus provides insight into the molecular mechanisms by which these proteins function. Such changes are usually made to a cDNA clone of the target protein using recombinant DNA techniques. The choice of which residues to alter is often guided by predictive models of the protein as made by hydropathy or secondary structure analysis of the primary amino acid sequence. Assessment of the functional consequences of such mutations is usually done by expressing the protein in a cell type that is null for this protein.

►Heterologous Expression

Mutual Information Maximization

Definition

A principle of feature extraction and dimension reduction of multi-dimensional data from multiple information sources. Effective low dimension features are obtained by transforming data to maximize mutual information between them.

Myasthenia Gravis

Masaharu Takamori
Neurological Center, Kanazawa-Nishi Hospital and Kanazawa University, Kanazawa, Japan

Definition

Myasthenia gravis (MG) is a disease of neuromuscular transmission, with clinical features of weakness and

fatigue that is mainly caused by an autoimmune response to the nicotinic ►acetylcholine receptor (AChR) in skeletal muscle (Fig. 1).

Anti-AChR antibodies directed against the specific sites of AChR molecular structure, depending on their pathogenic actions, are detected in the sera of 80–90% of generalized MG patients.

The remaining 10–20% of MG patients lack anti-AChR antibodies in sera, termed "seronegative MG (►Seronegative Myasthenia Gravis)", but have a humorally mediated disorder, as evidenced by that their Sera, passively transferred to mice, results in neuromuscular weakness. The seronegative MG could therefore be caused by non-AChR antibodies. The search for non-AChR pathogenic antigens has recently been focused on ►muscle-specific tyrosine kinase (MuSK) (Fig. 1).

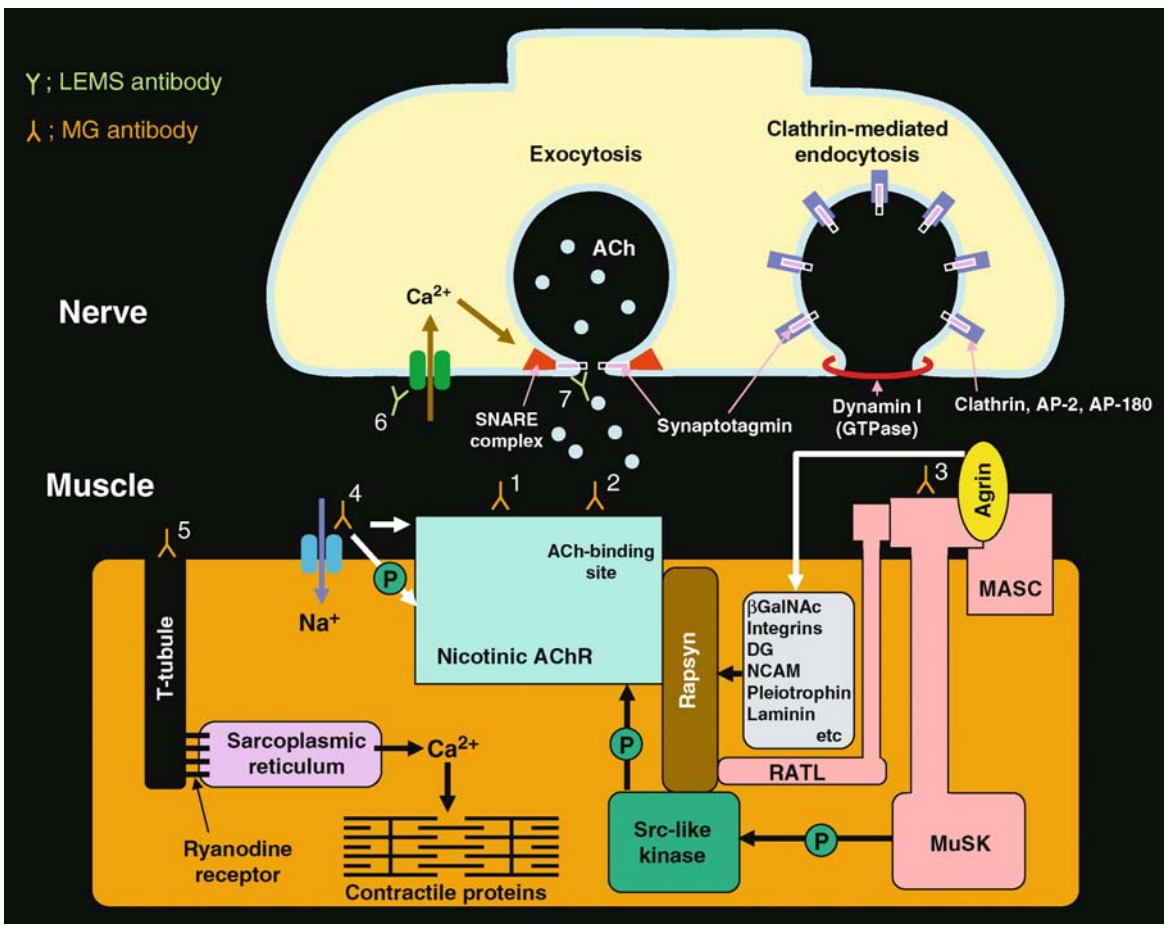
Characteristics

Seropositive (Anti-AChR-Positive) Myasthenia Gravis

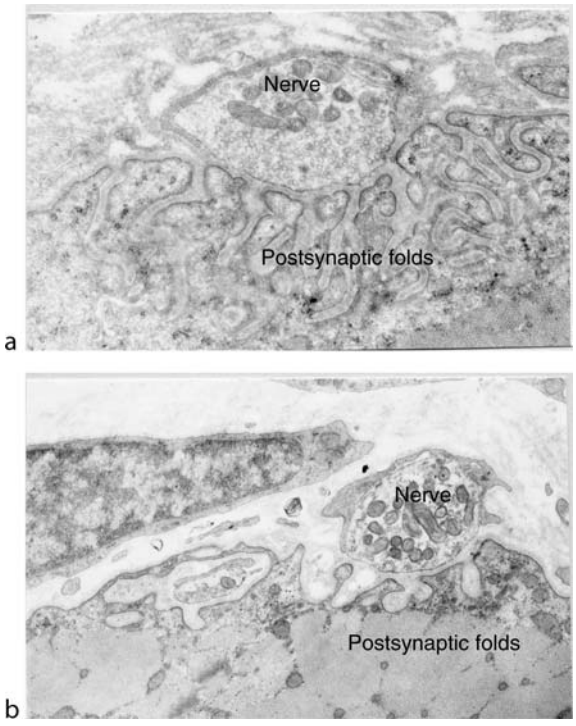
Pathogenesis: Antibodies to AChR

Anti-AChR antibodies cause the accelerated degradation of AChR, complement-mediated destruction of postsynaptic membrane, and blockade of ACh-binding to AChR resulting in impairment of neuromuscular transmission (Fig. 2).

The search for epitopes bearing on AChR, which are implicated as targets for myasthenic antibodies, has developed through the information about the AChR primary structure comprising of four homologous polypeptide subunits. Based on this, myasthenic domains are localized at the segment alpha 67–76 [1] and alpha 125–147 [2] as the sites recognized by antibodies causing the accelerated AChR degradation and the complement-mediated destruction of postsynaptic



Myasthenia Gravis. Figure 1 Schematic representation of neuromuscular synapse. Myasthenia gravis (MG) is caused by antibodies to the acetylcholine receptor (AChR) (antibodies-1 and 2), and modified by those to muscle-specific tyrosine kinase (MuSK) (antibody-3), muscle membrane sodium channel (antibody-4) and ryanodine receptor (antibody-5). The antibody-4 (non-IgG) also provides an AChR desensitization through cGMP-mediated protein kinase G or allosteric inhibition. Antibodies numbered 6 and 7 are referred to the section of Lambert-Eaton myasthenic syndrome (LEMS).

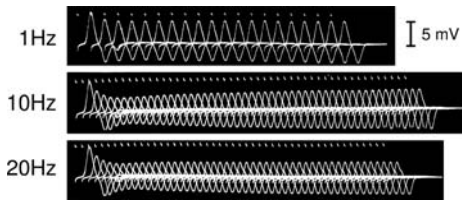


Myasthenia Gravis. Figure 2 Ultrastructure of neuromuscular junction. Postsynaptic folds are richly developed in normal skeletal muscle (a). In myasthenia gravis, in which anti-AChR antibodies cause the complement-mediated destruction of postsynaptic membrane, the folding becomes less dense than that of the mature configuration in normal muscle, resulting in the AChR loss leading to transmission failure; the synaptic gap becomes widened (b). No abnormality is seen in the nerve terminal.

membrane (Fig. 1, antibody-1), and the segment alpha 183–200 as the site recognized by antibodies preventing the ACh-binding to AChR (Fig. 1, antibody-2) [3]. The factors involved in the initiation or induction of autoimmune MG are unknown. However, MG is associated with other immune system abnormalities, particularly in the ►thymus (thymoma or thymic hyperplasia).

Clinical Features, Diagnosis and Treatments

Only the motor system is impaired with the cardinal features of weakness and fatigability in skeletal muscles. Frequently involved are extraocular muscles, neck extensors, facial and bulbar muscles, and proximal limb muscles. When the muscles concerning swallowing and respiration are involved, the intubation for artificial respirator and feeding is emergently required. There is usually a history of fluctuation of symptoms and fatigability (worse with repeated activity, improved by rest). In women, weakness may worsen in relation to the menstrual cycle. Transient weakness of an infant born to a



Myasthenia Gravis. Figure 3 Muscle action potentials evoked by repetitive nerve stimulation at rates of 1, 10 and 20 Hz. The initial response is normal in size; during repetitive stimulation, muscle responses show an early rundown (1st–4th responses) even with a slow rate such as 1 Hz, followed by a maintained plateau or partial recovery in amplitude. These phenomena are provided by a narrow safety margin of neuromuscular transmission due to the AChR loss caused by myasthenic antibodies.

myasthenic mother may occur in 15%. Approximately 75% of patients have thymic abnormalities including thymoma (15%). The diagnostic test is (i) muscle responses to repetitive peripheral nerve stimulation (Fig. 3), (ii) ►single-fiber electromyography, (iii) edrophonium (anti-cholinesterase) injection, and (iv) anti-AChR antibody radioimmunoassay [4].

Anti-cholinesterase agents (pyridostigmine bromide etc.) are used as symptomatic management. The long-term immune-directed treatment includes immunosuppressive drugs such as corticosteroids, azathioprine, cyclosporine A, tacrolimus and mycophenorate mofetil. In thymoma-associated MG, thymectomy is indicated universally, occasionally followed by postoperative radiation. In non-thymomatous generalized MG, thymectomy is advocated empirically and possibly reduces the long-term exposure to immunosuppressive drugs, but requires up to 2–5 years for demonstrable efficacy; this estimation is based on data from nonrandomized studies, however. The short-term immune-directed treatment to overcome severe myasthenic states such as respiratory crisis includes ►plasmapheresis and intravenous human immunoglobulin; their effect is short-lasting but tends to be prolonged with the concomitant immunosuppressive drugs [5].

Seronegative (Anti-AChR-Negative) Myasthenia Gravis

Pathogenesis: Antibodies to MuSK

AChR is clustered to effectively receive the ACh-derived information from the nerve through a pathway in which agrin is a critical nerve-derived signal; MuSK is a key component of the postsynaptic agrin receptor, and rapsyn is a cross-linker of AChR [6] (Fig. 1). The z-site spliced isoform of agrin specifically clusters AChR and is, independently of it, required for neuromuscular junctional differentiation. Jointly with the co-receptor (muscle-associated specificity component, MASC), agrin binds to the first of four Ig-like domains

of MuSK [7]. The fourth Ig-like domain of MuSK is required for interaction with rapsyn through the rapsyn-associated transmembrane linker (RATL) [7]. The MuSK intracellular domain (kinase domain) activates AChR phosphorylation but is not sufficient for AChR clustering; the MuSK ectodomain plays a required role for the clustering process, perhaps by helping to recruit neuromuscular junctional components to a MuSK-based scaffold. Although anti-MuSK antibodies (Fig. 1, antibody-3) inhibit agrin-induced clustering of AChR in cultured muscle cells, the pathogenic role of the anti-MuSK IgG antibody is not clear. The non-IgG fraction, probably including the IgM antibody which blocks the sodium channel, from anti-MuSK-positive and anti-MuSK-negative seronegative (anti-AChR-negative) MG patient sera exerts an inhibitory effect on AChR function [8] (Fig. 1, antibody-4). There is the MuSK-independent agrin-rapsin signal transduction pathway including integrins, beta-linked N-acetylgalactosamine, alpha-dystroglycan, neuronal cell adhesion molecule, heparin-binding growth-associated molecule, beta-2 laminins and heparan sulfate proteoglycan [7] (Fig. 1). Also, antibodies raised against the extrajunctional component, which conducts a signal into the sarcoplasmic reticulum [►ryanodine receptor (RyR)], can be found in some of ►myasthenia gravis patients, often those with thymoma [9] (Fig. 1, antibody-5). These suggest a research direction to search for non-AChR, non-MuSK antibodies pathogenic to the disease.

Clinical Features, Diagnosis and Treatments

Forty to 70% of seronegative MG patients are positive for anti-MuSK antibodies and clinically characterized by a relative prevalence of female patients, the age at onset ranging from 3 to 68 years, prevalent involvement of cranial, bulbar and neck muscles, high incidence of respiratory crisis; wasting of facial and bulbar muscles is evident in some patients [10]. Unlike seropositive MG, the ►repetitive nerve stimulation and edrophonium tests are not necessarily diagnostic; the single-fiber electromyography is only reliable for diagnosis [10]. No satisfactory benefit is provided by ►anti-cholinesterase drugs, conventional immunosuppressive therapy and thymectomy [10]; a short-term response to plasmapheresis can be striking [10]. Thymic histology is reportedly normal. However, the clinical features reported by a recent series do not clearly distinguish MuSK antibody-positive from MuSK antibody-negative serotypes.

References

1. Tzartos SJ, Kokla A, Walgrave SL, Conti-Tronconi EM (1988) Localization of the main immunogenic region of human muscle acetylcholine receptor to residues 67–76 of the alpha subunit. Proc Natl Acad Sci USA 85:2899–2903
2. Lennon VA, McCormick DJ, Lambert EH, Griesmann GE, Atassi MZ (1985) Region of peptide 125–147 of acetylcholine receptor alpha-subunit is exposed at neuromuscular junction and induces experimental autoimmune myasthenia gravis, T-cell immunity, and modulating autoantibodies. Proc Natl Acad Sci USA 82:8805–8809
3. Takamori M, Okumura S, Nagata N, Yoshikawa H (1988) Myasthenogenic significance of synthetic alpha-subunit 183–200 of Torpedo californica and human acetylcholine receptor. J Neurol Sci 85:121–129
4. Drachman DB (1994) Myasthenia gravis. N Engl J Med 330:1797–1810
5. Richman DP, Agius MA (2003) Treatment of autoimmune myasthenia gravis. Neurology 61:1652–1661
6. Gautam M, DeChiara TM, Glass DJ, Yancopoulos GD, Sanes JR (1999) Distinct phenotypes of mutant mice lacking agrin, MuSK, or rapsyn. Dev Brain Res 114:171–178
7. Liyanage Y, Hoch W, Beeson D, Vincent A (2002) The agrin/muscle-specific kinase pathway: new target for autoimmune and genetic disorders at the neuromuscular junction. Muscle Nerve 25:4–16
8. Plested CP, Tang T, Spreadburg I, Littleton ET, Kishore U, Vincent A (2002) AChR phosphorylation and indirect inhibition of AChR function in seronegative MG. Neurology 59:1682–1688
9. Takamori M, Motomura M, Kawaguchi N, Nemoto Y, Hattori T, Yoshikawa H, Otsuka K (2004) Anti-ryanodine receptor antibodies and FK506 in myasthenia gravis. Neurology 62:1894–1896
10. Vincent A, Bowen J, Newsom-Davis J, McConville J (2003) Seronegative generalized myasthenia gravis: clinical features, antibodies, and their targets. Lancet Neurol 2:99–106

Mydriasis

Definition

Pupillary dilation, particularly when the pupil approaches maximum dimensions.

►Neural Regulation of the Pupil

Myelencephalon

Synonyms

►Medulla oblongata

Definition
The lowest portion of the brainstem. Here in the transition region to the spinal cord are important nuclear regions (olive, pyramid, gracile nucleus, cuneate nucleus), the cranial nerve nuclei of nerves V-XII as well as the centers of respiratory control. Important pathways are the medial lemniscus (somatosensory), lateral lemniscus (auditory) and vestibulospinal tract.

Myelin

Definition
CNS myelin consists of many layers of tightly wound membranes formed from the cytoplasmic extensions of oligodendrocytes. Myelin forms regular patches around axons, called the *internode*. The space between the internodes is the *Node of Ranvier*. The size of the internode and the thickness of the myelin sheath depend on the diameter of the axon it is associated with. The main role of myelin is to insulate the axonal membrane and thus speed the rate of conduction of the action potential, which jumps for one node to the next, a process called *saltatory conduction*. Myelin also contains molecules that can inhibit axon growth and regeneration. Myelin is composed of lipids (about 70%) and proteins (about 30%) such as myelin basic proteins, myelin-associated glycoprotein, proteolipid PLP.

►Inhibitory Molecules in Regeneration
►Node of Ranvier
►Schwann Cell

Myelin Basic Protein

Definition
Myelin basic protein (MBP) is the second most abundant protein in central nervous system (CNS) myelin, comprising about 30% of the myelin proteins. It is localized to the cytosolic surface of the cell membranes of oligodendrocytes, which are the cells that produce myelin in the CNS. It mediates adhesion to the cytosolic surface of the adjacent oligodendrocyte membrane that results in compaction of the myelin sheath. MBP can undergo a variety of post-translational modifications, such as phosphorylation, methylation, and deimination. Modifications such as phosphorylation and methylation promote the compaction of myelin, protect MBP from proteolysis, and serves to maintain the integrity of myelin. Deimination of MBP on the other hand makes it more susceptible to proteolysis and induces myelin breakdown. MBP therefore plays a crucial role in the formation and maintenance of the myelin sheath, and imbalance in its normal post-translational modification states may lead to myelin pathology and disease.

►Inhibitory Molecules in Regeneration

Myelin Stain

Definition
Myelin stains (such as the Weil or Weigert stains) are those that react with the lipoprotein sheath of myelinated axons making them dark.

Myelin-associated Glycoprotein (MAG)

Definition
A glycoprotein found on central nervous system (CNS) myelin which inhibits axon growth.

►Regeneration

Myelinated Axons

Definition
Axons surrounded by a compact spiraled sheet of Schwann cell plasma membrane are called myelinated axons.

►Schwann Cell

Myelination

Definition
Myelination is the process by which glial cells wrap axons with an insulating sheath. This is done by the

oligodendrocyte in the central nervous system, and by the Schwann cell in the peripheral nervous system.

Myelitis

Definition

Myelitis is an inflammation of the spinal cord. One group of diseases is named according to whether primarily white matter or gray matter is affected (see leukomyelitis and poliomyelitis); another group is defined by whether there is coexistent disease of the meninges (►meningomyelitis) or the brain (►encephalomyelitis). In practice, the term is also used to denote non-inflammatory lesions of the ►myelin sheath of the spinal cord.

Myeloencephalitis

Definition

Inflammation of the spinal cord and brain (also called ►encephalomyelitis).

Myelomalacia

Definition

A process of tissue softening within the spinal cord. It may result from a stroke, trauma or a degenerative process.

►Gliomas
►Stroke

Myelopathy

Definition

Disease of the spinal cord or the bone marrow.

Myeloperoxidase

Definition

It is a peroxidase enzyme, a lysosomal protein stored in the azurophilic granules, abundantly present in neutrophil granulocytes. It is also detected in the macrophages.

Myenteric Plexus

Definition

The myenteric plexus is a plexus of small groups of nerve cells (ganglia) and connecting nerve fiber bundles that lies between the longitudinal and circular muscle layers of the gut wall and forms a continuous network from the upper esophagus to the internal anal sphincter.

►Enteric Nervous System

Myocardium

Definition

The heart muscle that makes up the walls surrounding the heart ventricles.

►Cardiovascular Mechanics

Myoclonus

Definition

Involuntary, abrupt, brief, rapid jerks of limbs or trunk, which may occur spontaneously at rest, in response to sensory stimuli or with voluntary movements. Myoclonus occurs in a variety of generalized metabolic and neurological disorders.

Myofascial Force Transmission

Definition

Transmission of force between muscle fibers and surrounding connective tissue fascia.

►Intramuscular Myofascial Force Transmission

Myofascial Pain

►Muscle Pain, Including Fibromyalgia

Myofibril

Definition

Multiprotein complex in striated muscle cells, in which the contractile proteins actin and myosin are organized into a paracrystalline fashion.

►Actin
►Myosin
►Sarcomere Structural Proteins

Myofibrillogenesis

Definition

Process of the assembly of myofibrils during embryonic development.

►Myofibril
►Sarcomere Structural Proteins

Myogenic Musculature

Definition

Myogenic musculature refers to the spontaneous generation of electrical and contractile activity by the musculature itself, independent of nerves, hormones or other signaling mechansims.

Myoglobinuria

Definition

Appearance of myoglobin (O_2 carrier in skeletal muscle) in urine, for example in ►mitochondrial myopathies.

Myopathies

Definition

Myopathies can be inherited (►Duchenne muscular dystrophy, ►fascioscapulohumeral dystrophy, ►limb-girdle dystrophy, ►myotonic dystrophy) or acquired (►dermatomyositis, ►polymyositis syndrome, ►endocrine myopathies, ►myoglobinurias).

►Dermatomyositis
►Duchenne Muscular Dystrophy
►Facioscapulohumeral Dystrophy
►Limb-girdle Muscular Dystrophy (LGMD)
►Myoglobinuria
►Myotonic Dystrophy
►Polymyositis Syndrome

Myosin

Definition

Myosin (sometimes also referred to as the thick filament) is the second contractile protein in muscle. Myosin contains the cross-bridge heads that interact with actin to produce contraction. The cross-bridges are arranged uniformly on the myosin filament, they contain a binding site for actin and an enzymatic site that catalyzes the hydrolysis of ATP, which is needed for muscle contraction.

►Sliding Filament Theory

Myosin Motor

Definition

Myosin motor is a protein that acts as a motor to move along a surface, such as microtubules. The energy for such movement comes from the hydrolysis of ATP. A myosin motor often functions in the active transport of proteins and vesicles in the cytoplasm.

Myositis

Definition

Myositis means muscle inflammation.

Myotendinous Force Transmission

Definition

Transmission of force between muscle fibers and its microtendon, made up of aligned collagen fibers. The site of such a transmission of each fiber is called the myotendinous junction.

►Intramuscular Myofascial Force Transmission

Myotendinous Junction

Definition

The specialized region where fingerlike extensions of the sarcolemma at the ends of muscle fibers interdigitate with similar extensions of the connective tissue of the tendon. This is one region for force transmission.

►Skeletal Muscle Architecture

Myotonia

Definition

Muscle stiffness, in which muscle relaxation after voluntary contraction is impaired. Myotonic diseases are hereditary muscle diseases falling into two large groups: ►myotonic dystrophies and ►non-dystrophic myotonias.

Myotonia Congenita

Definition

►Non-dystrophic Myotonias

Myotonic Dystrophy

Definition

Group of hereditary muscle diseases inherited via a dominant mutant gene on chromosome 19. There are three groups: Myotonic dystrophy type 1 (DM-1), proximal myotonic myopathy/myotonic dystrophy type 2 (PROMM/DM-2), and proximal myotonic dystrophy (variant of DM-2). The disease may be so mild as to be nearly asymptomatic or so severe as to appear in early life. In addition to weakness in limb and cranial muscles, characteristic symptoms are ►myotonia, which is a delayed relaxation of muscle after strong voluntary contraction or electrical stimulation, and often cataracts, baldness and testicular atrophy in men.