A

α_{2A} or α_{2C}-Adrenoceptor Agonists

▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

α_2-Adrenergic Agonists

▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

α-Agonists

▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

Aδ-mechanoreceptor

▶ Mechanonociceptors

A Afferent Fibers (Neurons)

Definition

These are types of sensory afferent nerve fibers that are myelinated (encased in a myelin sheath) and are classified according to their conduction velocity and sensory modality.

Aβ fibers are medium diameter afferent fibers with conduction velocities of 30–80 ms, and encode signals from non-noxious stimuli such as touch.

Aδ fibers are smaller caliber afferent fibers with conduction velocities of 5–30 ms, and principally encode signals from noxious stimuli. They are commonly thought to be responsible for the rapid sensation of "first pain" following injury.

It is often difficult to precisely identify the different classes of A fibers during development, as growth in fiber diameter and myelination occur slowly, so the eventual fate of fibers is not necessarily obvious at earlier stages of development.

Cross-References

▶ Infant Pain Mechanisms
▶ Insular Cortex, Neurophysiology, and Functional Imaging of Nociceptive Processing
▶ Magnetoencephalography in Assessment of Pain in Humans
▶ Nociceptor, Categorization
▶ Spinothalamic Tract Neurons, in Deep Dorsal Horn

A Delta(δ)-mechanoheat Receptor

▶ Polymodal Nociceptors, Heat Transduction

G.F. Gebhart, R.F. Schmidt (eds.), *Encyclopedia of Pain*, DOI 10.1007/978-3-642-28753-4,

A Fibers (A-Fibers)

Definition

The terminology refers to compound action potential deflections; A fibers are the most rapidly conducting category representing activity of myelinated fibers. Most A fibers are afferent nerve fibers that carry non-noxious somatosensory information.

Cross-References

- ▶ A Afferent Fibers (Neurons)
- ▶ Opiates During Development

AAV

- ▶ Adenoassociated Virus Vectors

Abacterial Meningitis

- ▶ Headache in Aseptic Meningitis

Abdominal Skin Reflex

Definition

A polysynaptic reflex triggered by stroking of the abdomen around the umbilicus. Excitation of low- and high-threshold mechanosensors induces a contraction of the abdominal muscles. The umbilicus moves toward the source of the stimulation. This reflex can be readily evoked in children but may have been lost in adult persons. The reflex action is tested in neurological examinations, e.g., for testing the integrity of spinal nerves. The interpretation as a "protective" reflex is plausible, but the reflex is not purely nocifensive.

Cross-References

- ▶ Mechanosensory Nociceptors
- ▶ Nocifensive

Abduction

Definition

It is the movement of a body part away from the midline of the body.

Cross-References

- ▶ Cancer Pain Management, Orthopedic Surgery

Aberrant Drug-Related Behaviors

Definition

Use of a prescription medication in a manner that violates expectations for responsible drug use. May be applied to verbal responses or actions. Occur on a continuum from relatively mild (e.g., unsanctioned dose escalation on one or two occasions) to severe (e.g., injecting oral formulations). Must be assessed to determine appropriate diagnosis (e.g., addiction, pseudoaddiction, and other psychiatric disorder).

Cross-References

- ▶ Cancer Pain, Evaluation of Relevant Comorbidities and Impact

Ablation

Definition

The basic definition of ablation is "elimination or removal." Medically, it is a procedure involving

destruction of brain tissue to decrease the activity of a brain structure or interrupt information transmitted along a specific tract.

Cross-References

- ▶ Facet Joint Pain
- ▶ Pain Treatment, Intracranial Ablative Procedures

Abnormal Illness Affirming States

Definition

A group of psychiatric disorders (conversion disorder, hypochondriasis, somatization, pain disorder, factitious disorder, and malingering), where primary and/or secondary gain is believed to be important to the production of some or all of the patient's symptoms. Primary gain refers to intrapersonal (e.g., anxiety reducing) benefits and secondary gain refers to interpersonal benefits. It is to be noted that for malingering, secondary gain is thought to operate on a conscious level, but at an unconscious level for the other illness affirming states.

Cross-References

- ▶ Abnormal Illness Behavior
- ▶ Malingering, Primary and Secondary Gain

Abnormal Illness Behavior

Definition

Refers to an inappropriate or maladaptive mode of perceiving and acting in relation to one's own state of health, despite the fact that the doctor has offered an accurate and lucid explanation about the illness based on an adequate assessment of all biological, psychological, social, and cultural factors.

Cross-References

- ▶ Abnormal Illness Affirming States
- ▶ Pain as a Cause of Psychiatric Illness
- ▶ Psychiatric Aspects of the Management of Cancer Pain

Abnormal Illness Behavior of the Unconsciously Motivated, Somatically Focussed Type

- ▶ Hypochondriasis, Somatoform Disorders, and Abnormal Illness Behavior

Abnormal Sensation

- ▶ Dysesthesia, Assessment

Abnormal Temporal Summation

Synonyms

Wind-up

Definition

Abnormal Temporal Summation ("wind-up"): Repeated stimuli (e.g., touch) delivered in rapid succession to the skin are normally felt individually, or as vibration. Patients with neuropathic pain sometimes report that light touch stimuli repeated about once per second cause a sensation that builds up abnormally into an intensely painful crescendo.

Cross-References

- ▶ Diagnosis and Assessment of Clinical Characteristics of Central Pain

Abnormal Ureteric Peristalsis in Stone Rats

Definition

A marked increase in amplitude of phasic contractions (such that the intraureter pressure reaches levels likely to be sufficient to activate ureteric nociceptors) associated with a decrease in rate of contractions, and a reduced basal tone compared to peristalsis seen in normal rats.

Cross-References

► Visceral Pain Model, Kidney Stone Pain

Abscess

Definition

An abscess is a circumscribed area of injury and inflammation in which considerable necrosis has occurred and a fluid containing dead tissue and bacteria has collected. It may drain and be relatively comfortable, but if closed, tissue distension results in pain.

Cross-References

► Dental Pain, Etiology, Pathogenesis, and Management

Absorption

Definition

The absorption of a drug begins with transport or diffusion from one compartment (e.g., the stomach) into another (e.g., the blood). Alternatively, after a drug dissolved in a vehicle is administered intravenously, absorption can refer to transport or diffusion from the blood into the site of action, for example, the brain parenchyma.

Cross-References

► NSAIDs, Pharmacokinetics

ACC

► Anterior Cingulate Cortex

Accelerated Recovery Programs

► Postoperative Pain, Importance of Mobilization

Acceleration-deceleration Injury

► Whiplash

Accelerometer

Definition

It is an instrument for measuring acceleration or change of velocity with respect to time.

www.ncbi.nlm.nih.gov/snp

Cross-References

► Assessment of Pain Behaviors

Acceptance

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Synonyms

Willingness

Definition

An ongoing quality of behavior that reflects a willingness to experience unwanted psychological experiences, such as pain, without defense, in the present moment.

Introduction

The word acceptance has philosophical and religious roots that span millennia. In more contemporary times, it appears within many varied approaches to psychological therapy and has become increasingly prominent (Williams and Lynn 2010–2011). Within the field of chronic pain, however, the term most frequently appears in association with the form of cognitive behavioral therapy called Acceptance and Commitment Therapy (ACT) where acceptance is one of six interconnected processes (Hayes et al. 2006; Hayes et al. 1999; Ruiz 2010). ACT is a contextual cognitive behavioral therapy and, in common with other approaches such as Mindfulness (Kabat-Zinn 1990) and Dialectical Behavior Therapy (Linehan 1993), it emphasizes behavior change and qualities of daily functioning rather than symptom reduction (Hayes et al. 2011). A key distinction in ACT and these other approaches is the difference between the form and the function of experienced events. From a "functional" perspective, psychological experiences, such as pain, are not seen as being problematic in their form alone but rather in the processes by which they influence an individual's behavior and, thus, their participation in life.

Pragmatic, functional, and contextual approaches, such as ACT, can be especially useful in working with long-term health conditions where consistent symptom reduction is often unobtainable. In such situations, moments spent wrestling for control over symptoms often have an ironic quality. In these moments, the influence of symptoms on behavior is actually increased and not decreased as intended, and a quality of connection with other goals or engagement in "normal life" can be lost. Acceptance can neutralize these ironic processes.

Characteristics

Expanded Definition

Similar to everyone, people experiencing chronic pain engage in behavior patterns that are natural and automatic given their circumstances. Many of these behaviors aim to avoid, control, reduce, or allow escape from unwanted experiences. This kind of behavior can take place in relation to physical sensations associated with pain as well as other psychological experiences such as thoughts, feelings, and memories that are painful. While entirely understandable, behavior of this kind is often unsuccessful in controlling experiences. In addition, such behavior often incurs additional costs. The dominance of avoiding unwanted experiences can narrow the range of behavior options, blocking other potentially more successful behavior and reducing quality of life. In fact, experimental and clinical evidence indicate that attempts to control the frequency or form of psychological experiences are difficult, *and* it can actually result in paradoxical increases in their occurrence and their impact (Hayes and Gifford 1997; Wenzlaff and Wegner 2000). Acceptance is at first an unusual and even counterintuitive approach to take toward pain and other distressing psychological experiences, and at the same time, it provides an alternative to the potential problems that emerge from the more

avoidant and control-focused behavior patterns highlighted above.

Acceptance is defined as an active, ongoing, purposeful, quality of behavior that involves a willingness to experience psychological experiences, in the present moment, and without defense. The term is notoriously easy to misunderstand, and a few distinctions can help. Acceptance is not a mental act. It does not reside in thoughts or beliefs. It is not a onetime act of saying, "I accept this." It is an act of the whole person. It involves ongoing moment-by-moment acts of openness to experiences that might otherwise invite resistance, defense, or refusal. Acceptance is typically found in the coordination of patterns of behavior around unwanted experiences. If what is coordinated is avoidance or struggling for control of these experiences, this is not acceptance. If what is coordinated is engagement in goals and normal life activities at the same time that unwanted experiences are being contacted, this is acceptance. In fact, it appears that the best way to consider acceptance is as having two components: one of these is *engaging* in activities while pain is present, and the other is *refraining* from attempts at avoidance (McCracken 2010).

Evidence for Acceptance

Over recent years, evidence for the utility of acceptance within chronic pain management has grown steadily in experimental research, clinical studies, and treatment outcome data. More detailed information on this body of work can be found in recent review papers and chapters (e.g., McCracken and Vowles 2006; Thompson and McCracken 2011; Vowles and Thompson 2011).

Experimental, laboratory-based, research in this area often involves healthy subjects without chronic pain. Here, participants may receive transient pain stimulation, for example, during cold-pressor tasks. In research of this kind, different experimental groups are given different instructions or brief training experiences while pain tolerance or task persistence is assessed. In some conditions, participants might be asked to distract themselves or to attempt to suppress or control the pain, while others are encouraged to respond with willingness to experience painful sensations. The growing body of work in this area suggests that acceptance-oriented instructions are more successful than distraction, suppression, or control techniques, particularly with respect to pain tolerance measures or persistence with experimental tasks.

In clinical settings, many studies have examined the relationships between measures of acceptance and reports of daily functioning in patients seeking treatment with chronic pain. Overall, results from these studies suggest that higher levels of acceptance are associated with lower levels of pain intensity, depression, pain-related anxiety, physical and psychosocial disability, higher levels of daily activity, and overall well-being. Recent research has also compared the utility of acceptance with other more traditional psychological variables thought to be important in this area such as attention, anxiety sensitivity, coping, and catastrophizing. Preliminary results suggest that levels of acceptance are better than most of these more traditional variables at predicting patient functioning. This suggests that research in these others areas might be enhanced by a closer understanding of the developing evidence base surrounding acceptance.

There is increasingly robust evidence for efficacy of acceptance-based treatment in the area of chronic pain. The first randomized trial was published in 2004 (Dahl et al. 2004). Results of treatment often include reductions in measures of disability, depression, pain-related anxiety, and distress along with improvements in measures of physical functioning and performance and reduced health care use. For example, one recent study suggested that 75.4 % of patients demonstrated reliable change in either disability, pain-related anxiety, or depression, while 61.4 % showed reliable change in two or more of these areas (Vowles and McCracken 2008). Notably, these treatments do not target acceptance alone but also the other processes from the ACT model, such as values, committed action, and others (see McCracken 2005 for more details). Research has been carried out in both adult and adolescent populations. While much of this research has

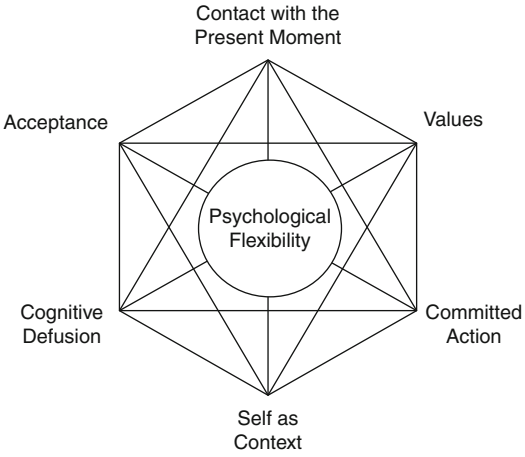
involved group-based interdisciplinary treatment with highly disabled individuals, there are also trials of treatment delivered individually and in the form of a self-help book with limited therapist support (Johnston et al. 2010). The status of this evidence base is now such that ACT is regarded as having "strong research support" by the Society of Clinical Psychology within the American Psychological Association (APA, Division 12; "Society of Clinical Psychology," 2011).

Wider Psychological Model

Acceptance is only one of six interrelated processes within the psychological model proposed by ACT. The other five processes are cognitive defusion, contact with the present moment, self as context, values, and committed action (see Fig. 1). Together, all six processes entail "psychological flexibility": an ability to be fully connected to the present moment and from there to be able to either maintain or change one's behavior to pursue one's goals and values according to what the situation directly affords. It is likely to be most useful to see acceptance within this wider context and not in isolation. Acceptance is not the complete answer to most behavior problems. It is also not an end in itself. It does, however, provide, in combination with other processes of behavior change, a pragmatic means for individuals with chronic pain to move toward the things which matter most to them in their lives. As mentioned, evidence for the wider set of processes, in combination with acceptance and by themselves, is growing (Thompson and McCracken 2011).

Measures of Acceptance

CPAQ: The Chronic Pain Acceptance Questionnaire is the measure most frequently used in the assessment of acceptance within chronic pain populations (McCracken et al. 2004). It is a 20-item scale consisting of two subscales: activity engagement and pain willingness. Activity engagement measures participation in activities with continuing pain (e.g., "I lead a full life even though I have chronic pain"), while pain willingness assesses an individual's capacity to have pain without attempts to avoid or control it (e.g., "Before I make any serious plans, I have to get some control over my pain"). A recent systematic review confirmed the status of the measures' internal consistency, construct validity, and reliability (Reneman et al. 2010). The CPAQ has been translated into a number of languages including Cantonese, German, Spanish, and Swedish. An adapted version of the measure for adolescent populations has also been developed (CPAQ-A; McCracken et al. 2010).



Acceptance, Fig. 1 The relationship between acceptance, psychological flexibility, and related processes

AAQ-II: The Acceptance and Action Questionnaire-II (Bond et al. 2011) is a broader measure of acceptance that explores an individual's relationship with thoughts, feelings, and other physical symptoms generally, not just those related to chronic pain. The AAQ-II contains seven items (e.g., "I'm afraid of my feelings") which relate to one factor. Higher scores indicate lower levels of acceptance and psychological flexibility. Research indicates that in studies involving both the CPAQ and the AAQ-II, the AAQ-II explains unique variance independent to that explained by the CPAQ (McCracken and Zhao-O'Brien 2010). Importantly, this suggests that it is both, willingness to experience psychological experiences not directly associated with chronic pain and willingness to experience pain, that facilitate healthy vital functioning.

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Acceptance-based Treatment

▶ Psychological Treatment of Pain in Children

Accommodation (of a Nerve Fiber)

Definition

Changes in the threshold for initiation of an action potential or in conduction velocity of a nerve fiber; for example, imposing a slow depolarizing stimulus on an axon will move the action potential threshold to a more depolarized potential, making it more difficult to initiate an action potential.

Cross-References

▶ Mechano-insensitive C-Fibers, Biophysics

Accuracy and Reliability of Memory

Definition

Reliability of memory of pain concerns the correlation for a group of patients between the report of pain at the time of its occurrence, for example, a score on a rating scale, and the estimate of that score at a later time (the remembered pain). Accuracy refers to the extent of agreement between records of the original event and the corresponding memory for an individual. According to this distinction, memories may be reliable but not accurate.

Cross-References

► Pain Memory

ACE Inhibitors, Beta(β)-Blockers

Definition

Drugs used to lower blood pressure and relieve heart failure.

Cross-References

► Postoperative Pain, Acute Pain Management Principles

Acetaminophen

► Paracetamol
► Pharmacology of Cyclooxygenase Inhibitors
► Postoperative Pain, Paracetamol
► Simple Analgesics

Acetylation

Definition

The acetyl group of acetylsalicylic acid (aspirin) binds to serine 530 in the active site of COX-1 or serine 516 in the active site of COX-2. This prevents the access of arachidonic acid to the catalytic site of the cyclooxygenase.

Cross-References

► Cyclooxygenases in Biology and Disease
► Pharmacology of Cyclooxygenase Inhibitors

Acetylcholine

Synonyms

ACh

Definition

Acetylcholine is a neurotransmitter synthesized from choline and acetyl coenzyme A. It is localized in large reticular formation neurons and is the chemical mediator in the synapse of a motor endplate. The electrical signal of the motor nerve terminal causes release of many packets of acetylcholine. The packets are released into the synaptic cleft, where receptors in the postjunctional membrane of the striated muscle fiber membrane convert the chemical signal to an electrical signal (a propagated action potential), which can produce muscle contractile activity. Normally, an occasional acetylcholine packet is released spontaneously by the nerve terminal without a nerve signal. Each packet produces a miniature endplate potential in the muscle fiber, but its amplitude is too small to be propagated. Myofascial trigger points are associated with excessive spontaneous release of acetylcholine packets in affected endplates.

Cross-References

- ▶ Myofascial Trigger Points
- ▶ Thalamic Neurotransmitters and Neuromodulators

Acetylcholine Receptors

Definition

Receptors for the neurotransmitter acetylcholine, which can be distinguished into muscarinergic (G protein-coupled) and nicotinergic (ion channel) receptors.

ACh

- ▶ Acetylcholine

Ache in First Trimester or in Early Gestation

- ▶ Pain in Early Pregnancy

Acidosis

Definition

Acidosis is the disturbance of the acid–base balance, characterized by acidity (decreased pH) by accumulation of protons, caused by injury, inflammation, or ischemia. Acidosis is an important source of pain. In humans, it produces nonadapting nociceptor excitation and contributes to hyperalgesia and allodynia in inflammation.

Cross-References

- ▶ Acid-Sensing Ion Channels
- ▶ TRPV1, Regulation by Protons

Acid-Sensing Ion Channels

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Synonyms

ASIC; ASIC1a; ASIC1b: ASICβ, BNaC2β; ASIC2a: mammalian degenerin 1 (MDEG1), brain sodium channel 1 (BNC1a, BNaC1a); ASIC2b: mammalian degenerin 2 (MDEG2), brain sodium channel 1 (BNaC1b); ASIC3: dorsal-root acid-sensing ion channel (DRASIC); ASICa, brain sodium channel 2 (BNC2, BNaC2a)

Definition

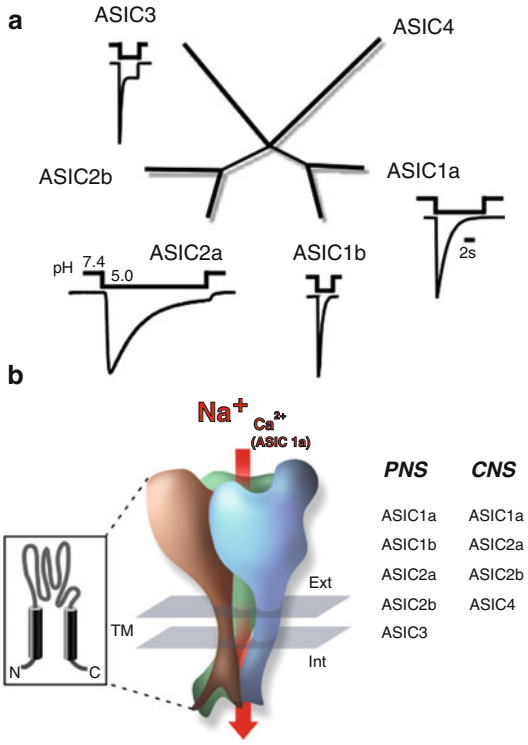
Acid-Sensing Ion Channels (ASICs) are membrane proteins that form depolarizing cation (principally sodium) channels. They are largely present on peripheral and central neurons. ASIC channels are opened by extracellular protons to produce a depolarization that can trigger action potential and/or modify neuronal excitability, depending on the amplitude and kinetics of pH change. Extracellular tissue acidosis is commonly associated with pain at the periphery in conditions like inflammation, ischemia, tumors, infections, lesions, or traumatic injuries. Peripheral ASICs have also been involved in cutaneous mechanical sensitivity and visceral mechanosensory function. In the central nervous system, these channels have been proposed to participate in the transmission and in the

modulation of nociceptive signals in the spinal cord, besides their contribution to fear, anxiety, depression, and neuronal degeneration.

Characteristics

The three-dimensional structure of ASIC1 shows that three subunits, among the six characterized in rodents, need to assemble to form a channel (Fig. 1b). Four different genes encode these six subunits (ASIC1 to ASIC4, Fig. 1a), with two splice variants for ASIC1 (1a and 1b) and ASIC2 (2a and 2b) (Chen et al. 1998; Lingueglia et al. 1997; Waldmann et al. 1997a, b). Each subunit is 510–560 amino acids long, with two hydrophobic transmembrane regions flanking a large extracellular loop representing more than 50 % of the protein (Fig. 1b). The properties of ASIC channels (i.e., activation, inactivation and reactivation kinetics, pH sensitivity, ion selectivity, pharmacology) vary according to their subunit composition, which accounts for the large diversity of native ASIC-like currents observed in neurons (Krishtal and Pidoplichko 1980). ASIC channels are not voltage dependent and their $pH_{0.5}$ range from 4.0 to 6.8 with activation thresholds close to pH 7.0 for ASIC1 and ASIC3, i.e., well in the pathophysiological pH range (Table 1). They show steep pH dependence, making them very sensitive sensors of extracellular protons. Most ASIC channels are transiently activated and desensitize rapidly (within seconds). Moreover, ASIC3-containing channels have an additional slowly activating, sustained component that does not inactivate as long as the pH remains acidic (Fig. 1a). ASIC2b is not activated by acidic pH when expressed alone but can associate with other ASICs to modulate their properties and/or their regulation (Lingueglia et al. 1997).

Almost all ASIC isoforms are present in primary sensory neurons of the trigeminal, vagal, and dorsal root ganglia. ASIC1, ASIC2, and ASIC3 are expressed in nociceptors, including high-threshold mechanoreceptors. ASIC2 and



Acid-Sensing Ion Channels, Fig. 1 (**a**) Phylogenic tree of ASIC channels. There are four different genes encoding six isoforms in rodents, with two variants (a and b) for ASIC1 and ASIC2. Examples of current associated with each isoform and elicited by a change in external pH from 7.4 to 5.0 (indicated by the bar above the current traces) are represented. ASIC channels possess different properties (kinetics of activation, inactivation and reactivation, ionic selectivity, pH sensitivity) depending on the type of isoform and of their combination (see below). ASIC2b and ASIC4 are not activated by extracellular protons on their own, but can associate with other ASICs to modulate their properties and/or their expression. (**b**) Structure and expression in the nervous system. Functional Acid-Sensing Ion Channels (ASICs) are formed by the assembling of three identical subunits (homomers) or three different subunits (heteromers) (Jasti et al. 2007). The structure of one subunit is shown in inset. ASICs predominantly conduct Na^+ but homomeric ASIC1a also displays some calcium permeability. ASICs are largely expressed in the nervous system. Almost all subunits are present in the peripheral nervous system (PNS) with a strong expression of ASIC3. ASIC1a and ASIC2 (both variant a and b) are predominant in the central nervous system (CNS), including the spinal cord. ASIC4 is also present in the CNS but its exact function remains unknown

Acid-Sensing Ion Channels, Table 1 Properties of ASIC channels

Isoform	Tissue distribution	$pH_{0.5}$ activation	Inhibitors/ activators	Endogenous modulators	Physiology	Potential therapeutic implications
ASIC1a	Strong expression in PNS, brain, spinal cord, retina	6.2–6.8	Amiloride and derivatives benzamil and EIPA, NSAIDs (ibuprofen/ flurbiprofen), A-317567, diarylamidines, Psalmotoxin 1 (PcTx1), mambalgins	Arachidonic acid, lactate, NO, RFamide peptides, dynorphins	Central modulation of pain (alone or in association with ASIC2a or ASIC2b), central sensitization to pain in the spinal cord	*Inhibition:* pain, psychiatric disorders (anxiety, panic, depression), stroke, neurodegenerative diseases
	Also present in taste cells, peripheral and central auditory system, immune cells, lung epithelial cells, bone, vascular smooth muscle cells, gliomas		Potently activated by MitTx		Also involved in primary hyperalgesia in muscle, visceral but not cutaneous mechanosensation, possible implication in chemotransduction of low pH by carotid body	*Activation:* seizure treatment
					Important role in the CNS: synaptic transmission and plasticity, learning and memory, innate and conditioned fear, chemosensory function of the amygdala, depression, visual transduction	
ASIC1b	PNS, taste cells, cochlear hair cells, carotid body, immune cells	5.1–6.2	Amiloride, diarylamidines, mambalgins	NO	Nociception	Pain
			Potently activated by MitTx			
ASIC2a	PNS (including specialized cutaneous mechanosensory structures), brain, spinal cord, retina, peripheral and central auditory system, taste cells, bone, vascular smooth muscle cells, some expression in carotid body, gliomas	4.1–5.0	Amiloride, diarylamidines, A-317567, mambalgins (when associated with ASIC1a)	NO, Zn^{2+}	Modulation of ASIC1a in the CNS, central modulation of pain (in association with ASIC1a), visual transduction, cutaneous and visceral mechanosensation, noise susceptibility of hearing, baroreceptor reflex, may be involved in sour taste perception, vascular smooth muscle cell migration	Pain, control of blood pressure
			Response to H^+ enhanced by MitTx			

(*continued*)

Acid-Sensing Ion Channels, Table 1 (continued)

Isoform	Tissue distribution	$pH_{0.5}$ activation	Inhibitors/ activators	Endogenous modulators	Physiology	Potential therapeutic implications
ASIC2b	PNS, brain, spinal cord, retina, taste cells	n/a	PcTx1 and mambalgins (when associated with ASIC1a), APETx2, salicylic acid and diclofenac (when associated with ASIC3)		Modulate the properties of other ASICs (ASIC1a, ASIC2a, and ASIC3)	Presumably pain in association with ASIC3 or ASIC1a
ASIC3	PNS (including specialized cutaneous mechanosensory structures), retina, taste cells, carotid body, inner ear, testis, bone, lung epithelial cells, vascular smooth muscle cells, dendritic cells	6.2–6.7	Amiloride, NSAIDs (aspirin/ diclofenac), A-317567, diarylamidines, APETx2 Activated by MitTx and GMQ	Arachidonic acid, lactate, NO, agmatine, hypertonicity, RFamide peptides	Cutaneous acidic and primary inflammatory pain, secondary mechanical hyperalgesia in muscle and joints, cutaneous and visceral mechanosensation and mechanonociception, neuronal mechanosensor for pressure-induced vasodilation, acid sensing in gastroesophageal afferents, cardiac pain, maintenance of retinal integrity, hearing, testosterone homeostasis, possible implication in chemotransduction of low pH by carotid body and local vascular control in muscle	*Inhibition:* inflammation-related pain, postoperative pain, chronic muscular pain, angina, arthritis, gastritis, inflammatory and noninflammatory bowel disorders *Activation:* protection against pressure ulcers

n/a not applicable, *PNS* peripheral nervous system

ASIC3 have also been found in large non-nociceptive neurons that mostly correspond to low threshold mechanoreceptors. The proteins have been detected in the soma and in the peripheral nerve endings of DRG neurons, but their presence on central projections in the dorsal horn of the spinal cord is less clear. ASICs support most of the native proton-activated cation currents in sensory neurons, although a significant part of the sustained response to low pH (below pH 6.0) can be attributed to the capsaicin receptor TRPV1. However, the native ASIC-like responses are approximately tenfold more sensitive to changes in H^+ than the TRPV1 responses.

Peripheral ASIC channels are important for somatic and visceral pain. Their role in inflammatory pain is particularly noteworthy (Table 1). They display both an increase in expression and an upregulation of their activity by several

components of the "inflammatory soup." ASIC3 is particularly important in this regard as a pain sensor (Deval et al. 2008, 2010) that integrates responses to several molecular signals produced during inflammation or ischemia (protons, hypertonicity, lactic and arachidonic acid, ATP, NO, agmatine, bradykinin, serotonin) to contribute to peripheral sensitization of nociceptors. ASIC3 is also important for joint and muscle pain (Sluka et al. 2003). ASICs transduce acid sensation in gastric sensory nerve endings (Wultsch et al. 2008) and play a role in gastrointestinal mechanosensory function (Page et al. 2005). ASIC1a and ASIC2 (both variant a and b) are largely expressed in spinal second-order sensory neurons that receive primary afferent inputs. Their expression is upregulated during peripheral inflammation and they are probably playing a role in the processing of noxious stimuli and in the generation of hyperalgesia and allodynia in persistent pain (Baron et al. 2008; Duan et al. 2007). ASIC1a + ASIC2a heteromeric channels seem to be particularly important (Diochot et al. 2012). Some ASICs are also important for pain modulation since blocking of the ASIC1a homomeric channels, and possibly the ASIC1a + ASIC2b heteromeric channels, at the spinal and/or supraspinal level results in an activation of the endogenous enkephalin pathway and in increased levels of Met-enkephalin in the cerebrospinal fluid (Mazzuca et al. 2007), producing strong analgesic effects.

ASICs have been involved in mechanosensory function (Table 1). Interestingly, the general ASIC contribution to mechanoreceptor function in visceral fibers (Page et al. 2005) is much larger and significantly different than the one observed in skin, where studies of simple knockout mice showed only subtle contribution of ASIC2 and ASIC3 to normal touch sensation (Chen et al. 2002; Price et al. 2000, 2001). However, ASIC3 is an essential neuronal sensor for the skin vasodilation response to direct pressure in both humans and rodents, and for protecting against pressure ulcers in mice (Fromy et al. 2012).

ASIC currents are inhibited by amiloride, a potassium-sparing diuretic, which acts as a poorly selective, nondiscriminative pore blocker of ASICs at the micromolar range of concentrations (Waldmann et al. 1997b). Amiloride also has an additional paradoxical enhancing effect on the sustained current component of ASIC3. The amidine A-317567 has been described as a more specific although still nondiscriminative inhibitor of ASICs, with IC_{50} between 2 and 30 mM on native ASIC currents in DRG neurons (Dube et al. 2005). ASIC1a and ASIC3 are also directly inhibited by therapeutic concentrations of nonsteroidal anti-inflammatory drugs (NSAIDs) (flurbiprofen and ibuprofen for ASIC1a, salicylic acid, aspirin, and diclofenac for ASIC3, IC_{50}∼92–350 mM) (Voilley et al. 2001). Antiprotozoal diarylamidines (DAPI, diminazene, HSB, and pentamidine) have been reported to potently inhibit ASIC currents in primary cultures of hippocampal neurons with apparent affinities ranging from 300 nM to 38 μM (Chen et al. 2010).

Two small peptides that selectively and efficiently block ASICs in vitro and in vivo in a subtype-specific manner have been isolated from animal venoms (Diochot et al. 2007). The spider peptide Psalmotoxin 1 (PcTx1) blocks ASIC1a homomeric channel with an IC50 of ∼0.9 nM (Escoubas et al. 2000). The sea anemone peptide APETx2 blocks homomeric ASIC3 with an IC50 of ∼63 nM as well as ASIC3-containing heteromeric channels (IC50∼0.1–2 μM) (Diochot et al. 2004). Both PcTx1 and APETx2 evoke potent analgesic effects in rodents upon central and peripheral injection, respectively (Deval et al. 2008; Mazzuca et al. 2007). Mambalgins are peptides from black mamba venom that specifically inhibit all the channel subtypes expressed in the central nervous system (i.e., ASIC1a, ASIC1a + ASIC2a and ASIC1a + ASIC2b), as well as ASIC1b expressed in nociceptors (Diochot et al. 2012). Central injections of mambalgins evoke a naloxone-insensitive analgesia, which is different from the one produced by PcTx1 and operates through blockade of ASIC1a + ASIC2a channels, while the peripheral analgesic effect observed after intraplantar injection of mambalgins involves ASIC1b-containing channels. A Texas coral snake toxin that potently activates peripheral

ASICs in nociceptive neurons (and especially ASIC1a) has been shown to evoke pain in animals (Bohlen et al. 2011). Similarly, small molecules like the synthetic compound 2-guanidine-4-methylquinazoline (GMQ) or the endogenous arginine-metabolite agmatine (Yu et al. 2010) that act as nonproton activators and/or modulators of ASIC3 evoke pain-related behaviors in an ASIC3-dependent manner.

Neuropeptides can also modulate ASIC channels through direct interaction. FMRFamide, an invertebrate neuropeptide, and structurally related peptides present in the central nervous system of mammals, such as neuropeptide FF (NPFF, FLFQPQRFamide), potentiate H^+ gated currents of heterologously expressed ASIC1 and ASIC3, but not ASIC2a (EC50 ~ 10–50 μM; threshold ~1 μM) (Askwith et al. 2000; Catarsi et al. 2001; Deval et al. 2003). Dynorphin A and big dynorphin, two endogeneous opioid neuropeptides, have also been shown to enhance the ASIC1a channel activity (Sherwood and Askwith 2009).

Cross-References

► ASICs

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Acinar Cell Injury

▶ Visceral Pain Model, Pancreatic Pain

Acting-out

▶ Anger and Pain

Action Potential

Definition

Electrical potential actively generated by excitable cells. In nerve cells, the action potential is generated by a transient (less than 1 ms) increase in Na^+ and K^+ conductances, which brings the membrane potential to the equilibrium potential of Na^+. Immediately afterwards, the membrane repolarizes and becomes more negative than before, generating an afterhyperpolarization. In unmyelinated axons, the action potential propagates along the length of the axon through local depolarization of each neighboring patch of membrane. In myelinated axons, action potential is generated only in the Ranvier nodes and jumps rapidly between nodes increasing markedly the propagation speed.

Cross-References

▶ Demyelination
▶ Molecular Contributions to the Mechanism of Central Pain
▶ Nociceptor Generator Potential

Action Potential Conduction of C-Fibers

► Mechano-Insensitive C-Fibers, Biophysics

Actiq®

Definition

Actiq® is a transmucosal fentanyl system that provides significant pain relief for breakthrough cancer pain. It is also used for pain control in opioid-tolerant cancer patients.

Cross-References

► Postoperative Pain, Fentanyl

Actiq® Oral Transmucosal Fentanyl Citrate

► Postoperative Pain, Fentanyl

Activa®

Definition

It is the brand name (Medtronic, Minneapolis, USA) of a system of electrodes, connectors, and implantable pulse generators for the treatment of movement disorders, pain, and epilepsy, by stimulation of the basal ganglia, midbrain, and thalamus.

Cross-References

► Pain Treatment: Spinal Cord Stimulation

Activation/Reassurance

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Synonyms

Reassurance and activation

Definition

Activation and reassurance are interventions that have been used for the treatment of acute low back pain. They involve having the practitioner gain the patient's confidence that they do not have a serious cause of pain, and that remaining active, or restoring activity, is beneficial for their recovery.

Characteristics

Systematic reviews have shown that bed rest is neither appropriate nor effective for acute low back pain (Koes and van den Hoogen 1994; Waddell et al. 1997). Bed rest offers no therapeutic advantages, and is less effective than alternative treatments in terms of rate of recovery, relief of pain, return to daily activities, and time lost from work. By inference, these results support keeping patients active.

Nevertheless, patients may harbor fears or misconceptions about their pain, which may inhibit their resumption of activities. Explanation and reassurance are required to overcome these fears.

Evidence

The study of Indahl et al. (1995) constitutes a landmark in the management of nonspecific musculoskeletal conditions. It was the first rigorously controlled trial to demonstrate long-term efficacy for an intervention based on reassurance and activation, with no passive interventions.

Patients were provided with a biological model of their painful condition. They were

assured that light activity would not further injure the structures that were responsible for their pain, and was more likely to enhance the repair process. The link between emotions and musculoskeletal pain was explained as a muscular response. Patients were told that increased tension in the muscles for any reason would increase the pain and add to the problem. It was explained how long-standing pain and associated fear could create vicious cycles of muscular activity that caused pain to persist. It was strongly emphasized that the worst thing they could do would be to act in a guarded, overcautious way.

Regardless of clinical and radiographic findings, all patients were told to mobilize the affected parts by light, nonspecific exercise, within the limits of intense pain exacerbation. No fixed exercise goals were set, but patients were given guidelines and encouraged to set their own goals. Great emphasis was placed on the need to overcome fear about the condition and associated sickness behavior. Misunderstandings about musculoskeletal pain were dealt with.

The principal recommendation was to undertake light, normal activities, and move as flexibly as possible. Activities involving static work for the regional muscles were discouraged. No restrictions were placed on lifting, but twisting when bending was to be avoided. Acute episodes of pain in the affected region were to be treated as acute muscles spasm, with stretching and further light activity. Instruction was reinforced at 3 months and at 1 year.

The actively treated patients exhibited a clinically and statistically significant difference from the control group with respect to decrease in sickness leave. At 200 days, 60 % in the control group, but only 30 % in the intervention group, were still on sick leave. A 5-year follow-up demonstrated that these differences were maintained (Indahl et al. 1998). Only 19 % of the intervention group were still on sick leave at 5 years, compared with 34 % in the control group.

The results of Indahl et al. (1995) were corroborated by another study (McGuirk et al. 2001). The intervention was based on the principles set by Indahl, and focused on identifying the patient's fears, providing explanation, motivating patients to resume activities, and helping them maintain those activities. This approach achieved greater reductions in pain than did usual care, with fewer patients progressing to chronic pain, less use of other health care, and greater patient satisfaction.

Principles

Providing reassurance and motivating patients into activity are skills that have to be learnt. It is not enough to simply give information in the form of test results, diagnoses, prognoses, or proposed treatments. The manner of the consultation and the doctor's ability to empathize with the anxious patient is a prerequisite to any "motivational interview" (McDonald and Daly 2001). In order to develop empathy, a long consultation may be required. However, reassurance can, nevertheless, be achieved through a systematic series of shorter consultations (Roberts et al. 2002).

Interviewing techniques can be adapted to achieve an "educational outcome" (Arborelius and Bremberg 1994). The process of consulting or interviewing in a motivational way has been detailed (Kurtz et al. 2005), and is quite different from a normal medical interview that is geared toward collecting and collating information in as short a time as possible. Naturally, the educational (or motivational) interview demands more time from the practitioner. However, it is more effective in terms of changing behavior toward self-motivation (Miller and Rollnick 2002).

The doctor must establish an initial rapport with the patient. In general, one should greet each patient as if they were a friend of a friend, not a complete stranger. The doctor should not give the impression of rushing.

The concerns with which patients present can be encapsulated by Watson's quartet (Watson 1999): "I hurt," "I can't move," "I can't work," and "I'm scared." The latter can be expanded to encompass: What has happened? Why has it happened? Why me? Why now? What would happen if nothing were done about it? What should I do about it, and who should I consult for further help?

It is useful to ask patients what they think has caused their problems – the answers given to these questions are often surprising, and can sometimes hold the key to guiding patients through a complex biopsychosocial landscape.

There are no routine responses to these issues and questions. The practitioner must be prepared to respond in an informed, convincing, and caring manner. One example of an explanation might be:

> Well, we don't actually know why you have developed this but there are many reasons, and some of them come down to just bad luck. It might be related to an event or an injury, but these are often hard to track down. At the end of the day I can say that there doesn't seem to be anything that you could have avoided, and the problem is one that is not serious – it is painful, but not harmful. It might happen again and it might not.
>
> There are lots of people who will tell you that it's 'this' or 'that' which has caused it, but frankly this is speculation in most cases. Some people will tell you that it's because you have weak muscles, but you know that the fittest athletes in the world get injured from time to time, and there are many people out of condition who never get injuries. Others might say that it is your posture. But you have presumably not altered your posture in many years and you have never had the problem before. So trying to fix your posture in a major way might be pointless at this stage. I can say that there is no disease process going on and there are no broken bones or things that the surgeons have to fix. It's not something that you will pass onto your children and it will not shorten your lifespan. It might be that you will have to look at the type of work you do, but we will get more of an idea about that as time goes on.

This sort of explanation takes an enormous amount of time, but shortchanging the patient will result in a less-than-effective consultation. The paradox of appearing to have shortage of time will result in no change accomplished, whereas appearing to have "all day" often results in a change occurring in a matter of minutes (Miller and Rollnick 2002).

As the patient raises issues, their narrative should be expanded, with the use of phrases such as "tell me more about that." Terms and expressions used by the patient should be checked for meaning, so that the doctor understands what the patient is communicating.

Developing rapport relies on the appropriate use of eye contact, expressing concern and understanding, and dealing sensitively with the patient during the physical examination.

A thorough examination is a necessary prerequisite for gaining the satisfaction (and thus the confidence) of the patient (McCracken et al. 2002). The reasons for examination procedures should be explained.

The practitioner can reassure patients by developing an "educational enterprise" (Daltroy 1993). Printed material is an effective reinforcer of tuition (see ▶ Patient Education). Models and pictures serve to explain concepts about normal structure and pathology. The language used should be appropriate to the patient and understood by them. Alarming and distressing terms should be avoided.

When recommending exercises, those exercises should be demonstrated, and the patient's ability to reproduce them should be observed and confirmed. The same confirmation should be obtained when advice is given about how the patient will undertake their desired activities. Checking their understanding is what converts the consultation from one in which instructions are simply issued, to one in which the patient is confident about that instruction.

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Active Inhibition

Definition

Active inhibition implies that nociceptive processing is suppressed by specific inhibitory mechanisms, as opposed to simply reflecting the absence of excitatory input.

Cross-References

► Formalin Test

Active Myofascial Trigger Point

Definition

An active trigger point is a myofascial trigger point that is causing, or contributing to, a clinical pain complaint. When it is compressed, the individual recognizes the induced referred pain as familiar and recently experienced.

Cross-References

► Dry Needling
► Myofascial Trigger Points

ActiveLocus

Synonyms

EPN locus

Definition

The motor component of a Myofascial Trigger Point is the active locus, or endplate-noisy locus (EPN locus). From this locus, spontaneous electrical activity, known as endplate noise (EPN), can be recorded. It is related to taut band formation in skeletal muscle fibers.

Cross-References

► Dry Needling

Activities of Daily Living

Definition

Activity: The execution of a task or action by an individual. Activities of daily living refer to normal physical activities, such as getting out of bed, walking (initially with support), sitting, and personal toileting.

Cross-References

► Physical Medicine and Rehabilitation, Team-Oriented Approach
► Postoperative Pain, Importance of Mobilization

Activity

Definition

Activity is described as the execution of a task or action by an individual. It represents the individual perspective of functioning. Difficulties an individual may have in executing activities are activity limitations.

Cross-References

► Functioning and Disability Definitions

Activity Limitation

► Impairment, Pain-Related

Activity Limitations

Definition

Difficulties an individual may have in executing activities.

Cross-References

► Impairment, Pain-Related
► Physical Medicine and Rehabilitation, Team-Oriented Approach

Activity Measurement

Definition

A measure of personal activities of daily living (e.g., showering, dressing, toileting, and feeding), independent activities of daily living (e.g., cleaning, cooking, shopping, and banking), and discretionary activities of daily living (e.g., driving, visiting, and leisure activities). This also includes the automated assessment of motor activity.

Cross-References

► Pain Assessment in the Elderly

Activity Mobilization

Definition

Strategies aimed at maximizing a chronic pain patient's participation in activities of daily living.

Cross-References

► Catastrophizing

Activity-dependent Slowing

► Nociceptors and Activity-Dependent Changes in Axonal Conduction Velocity

Acupuncture

Definition

A system of healing that is part of traditional Chinese medicine, also containing herbal therapy and tuina (a kind of massage). Acupuncture consists of the insertion and twirling of thin solid needles into specific points on the body that lie along the so-called channels or meridians, in order to treat different, usually chronic, symptoms. The needles are usually inserted into muscles but may also be inserted superficially into the skin. Neither the acupuncture points nor the meridians have been unequivocally verified

in a biological sense but are considered of importance by most practitioners of acupuncture.

Cross-References

- ▶ Acupuncture Efficacy
- ▶ Acupuncture Mechanisms
- ▶ Alternative Medicine in Neuropathic Pain

Acupuncture Efficacy

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Definition

▶ Acupuncture can be defined as the insertion of needles into the skin and underlying tissues at specific sites (acupuncture points) for therapeutic or preventative purposes (Ernst et al. 2001). Sometimes other forms of point stimulation are used: electrical current (electroacupuncture), pressure (acupressure), heat (moxibustion), or laser light (laser acupuncture). Acupuncture is part of the ancient Chinese medical tradition. In recent years, a new style (Western acupuncture) has emerged, which no longer adheres to the Taoist philosophies underpinning Chinese acupuncture but seeks explanations for its mode of action from modern concepts of neurophysiology and other branches of medical science.

Characteristics

The evidence for or against the efficacy (or effectiveness) of acupuncture is highly heterogeneous and often contradictory. Thus, single trials, even of good quality, may not provide a representative picture of the current evidence. The following section is therefore exclusively based on systematic reviews of controlled clinical trials, i.e., on the totality of the available trial data rather than on a possibly biased selection of it. Whenever more than one such publication is available, the most up-to-date one was chosen.

Any Chronic Pain

One landmark paper summarized the results of 51 randomized clinical trials testing the efficacy of acupuncture as a treatment of all forms of chronic pain (Ezzo et al. 2000). Any type of acupuncture was considered. The studies were rated for methodological rigor using the Jadad score (Jadad et al. 1996). The results revealed a significant association between lower-quality studies and positive outcomes. There was no clear evidence to demonstrate that acupuncture is superior to sham acupuncture or to standard treatment. Good evidence emerged that it is better than waiting list (i.e., no acupuncture). The quality of the review was rated "good" by independent assessors (Tait et al. 2002). Depending on one's viewpoint, one can interpret these findings differently. Acupuncture "fans" would claim that they demonstrate acupuncture to be as good as standard treatments, while skeptics would point out that the data suggest that acupuncture has no more than a placebo effect. Pooling the data for all types of chronic pain is perhaps an approach too insensitive to tease out effects on more defined types of pain. Other systematic reviews have therefore focussed on more specific targets.

Dental Pain

Sixteen controlled trials were available, 11 of which were randomized (Ernst and Pittler 1998). All studies of manual or electroacupuncture were included. Their methodological quality was assessed using the Jadad score (Jadad et al. 1996). The collective evidence suggested that acupuncture can alleviate dental pain, even when compared against sham acupuncture. The strength of the conclusion was, however, limited through the often low quality of the primary data. The quality of the review was rated by independent assessors as "satisfactory" (Tait et al. 2002). Since effective and safe methods for relieving dental pain exist, the clinical relevance of acupuncture for dental pain may be limited.

Headache

A Cochrane Review summarized the evidence from 26 randomized or quasi-randomized trials of any type of acupuncture (Linde et al. 2001). Their methodological quality was assessed using the Jadad score (Jadad et al. 1996). The overall results support the role of acupuncture for recurrent headaches but not for migraine or other types of headache. The conclusions were limited through the often low methodological quality of the primary studies. The review was independently rated to be of good quality (Tait et al. 2002).

Neck Pain

Fourteen randomized clinical trials of all types of acupuncture were included in a systematic review (White and Ernst 1999). Their rigor was evaluated using the Jadad score (Jadad et al. 1996) and found to be mixed. About half of the trials generated a positive result, while the other half could not confirm such a finding. Thus, the efficacy of acupuncture was not deemed to be established. The quality of the review was rated "good" (Tait et al. 2002).

Back Pain

A Cochrane Review assessed the effectiveness of manual acupuncture or electroacupuncture for nonspecific back pain (van Tulder et al. 2001). Eleven randomized trials were included and evaluated according to the Cochrane Back Review Group criteria. The results were mixed, but overall acupuncture was not found to be of proven effectiveness, not least because the quality of the primary studies was found to be wanting. This review was rated as of good quality (Tait et al. 2002). Other systematic reviews of these data have drawn different conclusions, e.g., Ernst and White (1998). An updated review on the subject including many new studies is now being conducted.

Fibromyalgia

A systematic review included four cohort studies and three randomized clinical trials of any type of acupuncture (Berman et al. 1999). Their methodological quality as assessed using the Jadad score (Jadad et al. 1996) was mixed, but in some cases good. The notion that acupuncture alleviates the pain of fibromyalgia patients was mainly based on one high-quality study and thus not fully convincing. The quality of the review was rated as "satisfactory" (Tait et al. 2002).

Osteoarthritis

A systematic review of controlled acupuncture trials for osteoarthritis of any joint included 13 studies (Ernst 1997). Their methodological quality was evaluated using the Jadad score (Jadad et al. 1996) and found to be highly variable. The methodologically sound studies tended to yield negative results. Sham acupuncture turned out to be as effective as real acupuncture in reducing pain. Thus, it was concluded that acupuncture has a powerful placebo effect. Whether or not it generates specific therapeutic effects was deemed uncertain.

Conclusion

These systematic reviews collectively provide tantalizing but not convincing evidence for acupuncture's pain reducing effects. The evidence is limited primarily by the paucity of studies and their often low methodological quality. The scarcity of research funds in this area is likely to perpetuate these problems. Since acupuncture is a relatively safe therapy (Ernst and White 2001), it deserves to be investigated in more detail and with more scientific rigor, e.g., using the novel sham needle devices (Park et al. 2002; Streitberger and Kleinhenz 1998) that have recently become available.

Cross-References

► Acupuncture Mechanisms

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Acupuncture Mechanisms

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Definition

► Acupuncture is a traditional Chinese therapeutic method for the treatment of different symptoms including pain. Thin, solid needles are inserted into proposed specific points on the body, called acupuncture points. The needles are inserted through the skin to varying depths, often into the underlying musculature. The needles are often twirled slowly for a short time, 30–60 s and may be left in place for a varying time, 2–30 min. Many modifications of the method have been described, and the concept of acupuncture is not well defined. The method of applying electrical stimulation via acupuncture needles, ► Electro-acupuncture (EA), was introduced in 1958.

The treatments are usually applied in series of 8–12 sessions, each treatment lasting 20–30 min and separated by 1/2–2 weeks. Needling is often performed with some needles near the source of pain (called local points) and some other needles on the forearms and lower legs (called distal points).

Common Clinical Observations Concerning Therapeutic Acupuncture for Chronic Pain

After the first few acupuncture treatments there may be some hours of pain relief or nothing at all happens. Often pain relief starts 1–2 days after treatment. Some patients even get worse and have a temporary aggravation of their symptoms for some days before they start to improve. This aggravation can be seen for 2–3 days or even for a week. For those responding to acupuncture, usually both the degree and duration of the pain relief increase after each treatment, a clinical observation that has gained some experimental support (Price et al. 1984).

Acupuncture is a Form of Sensory Afferent Stimulation

As acupuncture needles are inserted into the tissue and mostly down to the muscular layer, they excite receptors and nerve fibers, that is, the needles mechanically activate somatic afferents. Other forms of afferent sensory stimulation are trigger point needling or dry needling and transcutaneous electrical nerve stimulation (► TENS) as well as vibration. These methods may share some common features concerning mechanisms of action. A special method is painful sensory stimulation, which has been used through the centuries, an idea that a short but very painful stimulus would reduce pain. These

methods have been called "► counter irritation" or "► hyperstimulation analgesia," and acupuncture is sometimes regarded as such. However, it is important to know that most patients who are treated with acupuncture describe the procedure as relaxing and pleasant but not painful.

The term acupuncture analgesia (AA) was used for electro-acupuncture (EA) used to get powerful and immediate pain relief during surgery, first used in China in 1958 but not described until 1973 (Foreign Languages Press 1973). A success rate of 90 % was claimed among those selected for the method. However, it soon became clear that only a minority of patients could develop so strong an analgesia as to tolerate surgery. Less than 10 % of the patients showed a satisfactory response in acupuncture trials (Bonica 1974). Among these 10 %, only one-third had acceptable analgesia according to Western standards. Even so, patient selection and psychological preparations were crucial, and often combinations with local anesthetics or other drugs were used.

Felix Mann (1974) reported 100 observations on patients receiving AA. In only 10 % of the experiments was the resulting analgesia considered adequate for surgery. He emphasized that in ► therapeutic acupuncture (TA) to treat different symptoms, a mild stimulus was all that was usually required. This was in contrast to that needed to obtain AA where the stimulation had to be continued for at least 20 min and had to be painful to the maximum level the patient could tolerate. He concluded that usually, the stimulus required to achieve AA was so intense that the resulting pain would be unacceptable to most Western patients. For the main differences between AA and TA, see Table 1.

Acupuncture Mechanisms, Table 1 Differences between acupuncture analgesia and therapeutic acupuncture

Acupuncture analgesia	Therapeutic acupuncture
Immediate and strong hypoalgesia is the goal	Immediate hypoalgesia is not the goal
Fast onset (minutes)	Slowly induced symptom relief after a number of treatments
	The effects gradually increase after additional treatments
Short term = minutes	Long term = days-weeks-months
The stimulation is felt very strongly. It is often painful and uncomfortable	The stimulation is felt rather weakly. It is rarely painful and often relaxing.
Used most often in different physiological experiments and for surgical hypoalgesia	Used for clinical pain relief and other symptom relief
Often electroacupuncture and pain threshold experiments on humans or animals	Most often manual acupuncture but can also be electroacupuncture

Characteristics

The proposed AA effect on surgical pain initiated physiological research where the goal was to find an explanation for immediate and very strong analgesia. Consequently, physiological research during the last 25–35 years has concentrated on explaining a phenomenon that may only exist in about 3–10 % of the population and that may have little in common with therapeutic acupuncture.

The experimental acupuncture research has concentrated on very short-term effects (after a single treatment of EA) where pain thresholds and/or central neurochemicals (mostly endorphins) have been measured. The research groups have mostly used conscious animals where no special care has been taken to rule out stress-induced analgesia (► SIA) (Akil et al. 1984). In some studies it is explicitly noted that the animals showing obvious signs of discomfort during EA also had pain threshold elevations, but that this was not the case for those who were not distressed (e.g., Bossut and Mayer 1991; Galeano et al. 1979; Wang et al. 1992).

Conclusions from the Existing Acupuncture Experimental Data

Most acupuncture research on animals has been performed using (strong) EA, even though human therapeutic acupuncture is most often performed with gentle manual acupuncture. Much of the

animal research on acupuncture probably only shows the consequences of nociceptive stimulation and the activation of ▶ SIA and ▶ Diffuse Noxious Inhibitory Control (DNIC). When manual acupuncture has been used in animal research, no pain threshold elevation has been described.

Pain threshold elevation in humans only seems to occur if the stimulation is painful and does not correspond at all with the clinical outcome after therapeutic acupuncture. Endorphins are partially involved in acupuncture analgesia in humans. Thus, AA in humans is believed to rely both on opioid and non-opioid mechanisms. However, whether endorphins are involved both locally (in the tissues) and within the central nervous system is not known (Price and Mayer 1995). Thus, the hitherto performed experimental acupuncture mechanism research is really only valid for acupuncture analgesia and not for therapeutic acupuncture.

Acupuncture Mechanisms: The Standard Neurophysiological Model

Several physiological mechanisms have been suggested to account for the pain-relieving effect of acupuncture. Spinal and supraspinal endorphin release has been proposed, as has the activation of diffuse noxious inhibitory control (DNIC) through bulbospinal paths. The involvement of neurochemicals like serotonin, noradrenalin, and different endorphins as well as hormones like Adrenocorticotrophic hormone (ACTH) and cortisone has been studied in detail.

Acupuncture physiology is often summarized in the following manner (Han 1987; Pomeranz 2000):
For acupuncture needles inserted within the segment of pain:

- Spinal gate-control mechanism

For extrasegmental acupuncture:

- Activation of midbrain structures Periaqueductal Grey (PAG) and the descending pain-relieving system (involving endorphins, serotonin, and noradrenaline).
- Diffuse noxious inhibitory control (DNIC) is sometimes claimed to be involved.
- Activation of the hypothalamic pituitary adrenal axis (HPA) with increased levels (in the blood) of β-endorphin and ACTH/cortisone.

Problems with the Standard Neurophysiological Model to Explain Clinical Observations

The model can only explain very short-term pain relief after each stimulation period. The gate-control mechanism is only active during stimulation and the descending inhibitory system for up to perhaps 8 h.

The model cannot explain why, in some patients, pain relief starts some days after the treatment whether the patient is first worse or not. The gate control does not start some days after the stimulation and that does not hold for the descending pain-inhibitory systems either. The model cannot explain why there seems to be more prolonged pain relief after additional treatments and why there seems to be long-term pain relief after a course of 8–12 treatments in at least some patients. From clinical research, in which the author has been involved, the conclusion has been drawn that clinically relevant long-term (>6 months) pain relief from acupuncture can be seen in a proportion of patients with chronic nociceptive pain (Carlsson and Sjölund 1994; Carlsson and Sjölund 2001). Probably, the standard neurophysiological model can explain AA, but even so it should be realized that AA is mostly a painful stimulation – and if the gate-control mechanisms are implicated, then the stimulation should be non-painful.

For a summary of probable acupuncture mechanisms for both TA and AA, see below. For a full reference list to all of this section, see (Carlsson 2002).

Hypothesis on Different Mechanisms for Acupuncture

Acupuncture Induces Peripheral Events

These events might improve tissue function and induce local pain relief. These events are induced from all local needles in the tissue and not only from traditional acupuncture points.

Axon Reflexes, Neuropeptides, and Dichotomizing Nerve Fibers Just the insertion of a needle in the tissue induces changes close to the needle (in all different tissues penetrated) and through axon reflexes. The flare reaction

(reddening, vasodilatation) is often seen locally around the acupuncture needles. This vasodilatation in the skin due to axon reflexes has been recognized for a very long time, and the mechanisms have been clarified in detail. The stimulation of Ad or C fibers releases vasoactive and pro-inflammatory neuropeptides (e.g., Calcitonin Gen Related Polypeptide (CGRP), Substance P (SP), Neurokinin A (NKA), opioids, galanin, somatostatin, and Vasoactive Intestinal Polypeptide (VIP)). The profound and prolonged vasodilatation is probably mediated mostly by CGRP. EA (and TENS) produces peripheral vasodilatation, in skin and muscle, both experimentally and clinically, that probably is caused by this neuropeptide release.

Remarkably, CGRP is pro-inflammatory, but it has also been shown that CGRP in low doses has a potent anti-inflammatory action. Thus, it seems like a form of balance exists between anti-inflammatory and pro-inflammatory effects (low dose or high dose of CGRP) in the tissue. This may have a practical consequence – strong stimulation leads to more damage in the tissue and thus more pain through higher levels of CGRP, while careful stimulation leads to smaller amounts of CGRP release and thus an anti-inflammatory, pain-relieving effect. This is a practical observed phenomenon when working a lot with acupuncture.

The identification of dichotomizing spinal nerves having branches to two different types of tissues might be relevant here for influences (through axon reflexes) on deeper tissues than only skin and muscles. For example, stimulation to the saphenous nerve gives rise to vasodilatation around the sciatic nerve, and nerve fibers to the intervertebral disc do also supply the groin skin. So, these dichotomizing nerve fibers may explain why sometimes effects in deeper tissues can be observed.

Neuropeptides and Trophic Effects Acupuncture can improve salivary flow, long term, for patients with xerostomia of different causes. Manual acupuncture has been shown to significantly increase the blood flow in the area overlying the parotid glands. Moreover, the concentration of the neuropeptides VIP and CGRP in saliva from xerostomic patients has been shown to increase after acupuncture. It is also known that neuropeptides like SP, VIP, and CGRP have a trophic effect on glandular tissues (leading to regeneration). A possible explanation for the long-term effects of acupuncture might be that the release of these neuropeptides induces regeneration of traumatized glandular tissue.

Local Endorphins Local endorphins and their different receptors have been found on nociceptive afferents in inflammatory conditions. The different endorphins are secreted from inflammatory cells in the tissue after an injury. A synthesis of endorphin receptors from the dorsal root ganglion starts as a response to the nociceptive input to the dorsal horn. The endorphins and receptors accumulate at the injury site after a few days. This accumulation may lead to a peripheral opioid analgesia some days after an injury. The penetration of acupuncture needles induces small tissue injuries; thus, there may, in some instances, be an increase in local endorphins after some days. This could be one explanation for pain relief coming 2–3 days after a treatment session and a possible reason why it appears to be so useful to use many local acupuncture needles.

Changes in Nociceptor Density in the Tissue Some pain conditions, tendinosis, seem to have an increased density of nociceptors peripherally in the tender painful area (e.g., Achilles tendinosis). It has been shown that there is an ingrowth of new nerves, nociceptors, in the area. Thus, the density of nociceptors is increased. That may be one explanation of these chronic pain conditions. The author has been involved in one study where we investigated the peripheral innervation before and after a series of very local subcutaneous acupuncture needlings. It was then shown, very surprisingly, that the number of peripheral nerve endings was reduced. Especially there was a reduction in the number of CGRP-containing nerve fibers. Thus, perhaps there are in the periphery a plastic downregulation of nociceptor density as a partial explanation for pain relief (Carlsson et al. 2006).

Spinal Mechanisms

These mechanisms can be stimulated from regional, segmental and extrasegmental needles, not only from traditional acupuncture points.

Gate Control The inhibition produced through this mechanism works fast and short term, with effects occurring mainly during stimulation. Thus, this mechanism only explains pain relief during the non-painful stimulation period and perhaps some hours afterwards.

Long-Term Potentiation (LTP) and Long-Term Depression (LTD) in the Dorsal Horn Long-term potentiation (LTP) is a form of synaptic plasticity where the synaptic strength increases. Long-term depression (LTD) is the opposite – a synaptic plasticity where the synaptic strength decreases. The LTP phenomenon is probably one background to central sensitization and memories in the pain transmission system. Central sensitization can occur within the Central Nervous System (CNS) from the dorsal horn level up to the thalamus and perhaps even to the cortex and is probably involved in some forms of chronic pain.

A long-term depression of C-fibre evoked mono- or polysynaptic excitatory postsynaptic potentials in the superficial spinal dorsal horn has been found upon low-frequency stimulation of afferent Ad-fibers (mildly painful) in the same segment. At least in awake animals, this LTD may last for days and weeks and might thus explain pain relief with a little longer duration, than the gate-control mechanism does.

It is usual to note, clinically, that there is a great variability within and between patients even if the same stimulation parameters are used. This may depend on the balance that seems to exist between LTP and LTD. The result of an Aδ stimulation period appears to be dependent on the initial resting membrane potential of the WDR cells. If the WDR cell was hyperpolarized (e.g., activity in the segmental inhibitory system and/or descending inhibitory systems), the result of the stimulation was a LTD. If instead the cell was a little depolarized (e.g., ongoing pain, descending excitatory influences), then the result was a LTP. Thus, the same stimulation parameter sometimes induces LTP (with more pain) and sometimes LTD (with less pain), just dependent on the initial condition of the WDR cells.

Propriospinal Pain Inhibition (Extrasegmental Needles) Sandkuhler has pointed out that numerous propriospinal intersegmental systems exist to be involved in pain inhibition. These propriospinal neurons may be activated by afferent stimulation or by supraspinal pathways. With superperfusion techniques, it has been shown that axons from thoracic, cervical, or sacral levels can induce a lumbar antinociceptive effect. The efficacy of this propriospinal inhibition has been shown to be similar to the inhibition produced by stimulation of PAG. Thus, the propriospinal antinociceptive neurons may constitute a third component of endogenous antinociception in addition to segmental and supraspinal descending inhibition.

Supraspinal Mechanisms

These mechanisms can be stimulated from needles distributed all over the body, not only from traditional acupuncture points.

The Descending Pain-Inhibitory Systems This well-known descending pain-inhibitory system is best activated by noxious and/or stressful events.

As direct electrical stimulation to PAG only gives rise to short-term pain relief, it does not seems very realistic that acupuncture could give rise to long-term effects through this system. However, probably this system is involved in AA.

The DNIC System The DNIC gives only an extremely short-lasting pain-inhibitory effect activated by painful stimulation applied outside the segment of pain. Thus, this system, also, might be involved in AA.

The Sympathetic Nervous System and the HPA axis Low-intensity stimulation gives rise to reduced sympathetic outflow and reduced amount of adrenaline/noradrenaline from the

Acupuncture Mechanisms, Table 2 Probable acupuncture mechanisms

Summary of probable mechanisms for acupuncture	Therapeutic acupuncture: mostly gentle manual. Usual clinical use	Acupuncture analgesia: high-intensity electroacupuncture Physiological experiments and surgical analgesia
Local events in the tissue (**Local needles**)	Axon reflexes in the tissue around needles and deeper through dichotomizing fibers giving increased circulation and neuropeptide release	Tissue trauma around the needles giving rise to more local pain (CGRP in higher doses has pro-inflammatory actions)
	These can act as trophic factors (e.g., regeneration of glands). They can also have anti-inflammatory effects (like low dose of CGRP)	Increased local pain for some days
	Release of local endorphins to local receptors	
	Perhaps a downregulation of nociceptive afferents in the tissue surrounding the needles	
Segmental mechanisms and somato-autonomous reflexes (Regional needles)	Gate mechanism and perhaps long-term depression (LTD)	Gate mechanism and perhaps LTD
	Sympathetic inhibition with increased segmental circulation	Sympathetic stimulation with decreased segmental circulation
Central mechanisms (Distal, regional, and some local needles)	Sympathetic inhibition. Decreased levels of stress hormones, adrenaline, and cortisone in plasma.	Sympathetic stimulation. Increased levels of the stress hormones, ACTH, adrenaline, and cortisone in plasma
	Perhaps oxytocin is involved and induces long-term antistress-like effects	DNIC is activated. Descending pain inhibition from PAG with endorphins, serotonin, and noradrenaline

adrenals, while strong (noxious) stimulation gives rise to the opposite. ACTH/cortisone increases after painful or stressful acupuncture but not after non-painful or non-stressful. Thus, the intensity of stimulation seems to be very important for what system is activated.

Oxytocin Research has indicated that oxytocin probably is secreted in response to non-noxious sensory stimulation. This hormone seems to give rise to long-term effects, of an antistress nature, that resemble those after acupuncture. Indeed, in humans, intrathecal oxytocin has been shown to induce pain relief in lumbar pain. It has also been shown that different kinds of sensory stimulation (2Hz EA, thermal stimulation, massage, or vibration) increased oxytocin in plasma and CSF. Further, oxytocin has given rise to anxiolysis and sedation. Thus, oxytocin might be a candidate for inducing long-term effects after therapeutic acupuncture.

Cortical, Psychological, and Placebo Mechanisms (From the Treatment Sessions)

Since the mid-1990s different brain-imaging techniques (e.g., PET and fMRI) have been performed. These have shown the involvement of many brain areas after acupuncture. However, the picture is very complex. It seems like some areas are activated and some areas are deactivated. It seems like a broad network of areas are affected of acupuncture stimulation. These areas belong to the somatosensory cortex as well as areas involved in affective and cognitive processing. How the different results shall be interpreted is not clear at this time. Many areas involved after acupuncture are also involved in the pain processing as well as in the processing of placebo mechanisms. For details, see, for example, Huang et al. 2012.

Of course, acupuncture, like all other treatments, might have a placebo effect. This has also been proposed from the brain-imaging

studies. Therapeutic acupuncture involves regular visits to a therapist for about 6–12 sessions. These sessions do not only consist of needle insertions but also discussions about possible changes, alternative diagnosis, and perhaps therapeutic alternatives. If there is a good patient-therapist relation, these regular visits will probably lead to advice (counseling) and reassurances, which probably reduce the anxiety. In support of this, it has been shown that among compared physical therapies (including placebos), those involving more time with the therapist or more treatments had a significant tendency for the best outcome. Thus, acupuncture treatment involves counseling and reassurance. This probably gives rise to anxiety reduction and thereby improves some different symptoms.

Summary

The mechanisms of therapeutic acupuncture are probably a mixture of physiological events from the most peripheral needling area to the spinal cord interactions and further to the brainstem pain processing areas as well as placebo and other mechanisms at the cortical level. For a summary, see also Table 2 below.

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Acupuncture-Like TENS

Definition

The delivery of acupuncture-like TENS is to generate activity in small-diameter group III muscle afferents, leading to the release of opioid peptides in a similar manner to that suggested for acupuncture. TENS is administered using low-frequency train (1–4 Hz) bursts (5–8 pulses at 100 Hz) at a high, but non-painful, intensity to stimulate selectively large-diameter muscle afferents. This results in a "strong but comfortable" muscle twitch that elicits group III muscle afferent activity. The stimulation should

go on for 30 min to provide temporary analgesia for 3–6 h. At variance with classical acupuncture, there is no long-term effect.

Cross-References

- ▶ Transcutaneous Electrical Nerve Stimulation (TENS) in Treatment of Muscle Pain
- ▶ Transcutaneous Electrical Nerve Stimulation Outcomes

Acute Backache

▶ Lower Back Pain, Acute

Acute Experimental Monoarthritis

▶ Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee)

Acute Experimental Synovitis

▶ Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee)

Acute Idiopathic Demyelinating Polyneuropathy

▶ Guillain-Barré Syndrome

Acute Idiopathic Demyelinating Polyradiculoneuropathy

▶ Guillain-Barré Syndrome

Acute Ischemia Test

▶ Tourniquet Test

Acute Knee Joint Inflammation

▶ Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee)

Acute Lumbago

▶ Lower Back Pain, Acute

Acute Pain

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Characteristics

Why Should We Aim to Optimize the Management of Acute Pain?

Postoperative pain is a major marker of perioperative morbidity and mortality and its effective treatment should be a goal in every hospital and institution. We should all aim to control pain, not only for humanitarian reasons, but also to attenuate the psychological and physiological stress with which it is associated following trauma or surgery. While it is now recognized that adequate pain control alone is not sufficient to reduce surgical morbidity, it remains an important variable and one that is perhaps more readily controlled (Kehlet and Holte 2001).

Adequate management of postoperative pain is vital to attenuate the stress response to surgery and the accompanying pathophysiological changes in metabolism, respiratory, cardiac,

sympathetic nervous system, and neuroendocrine functions. These effects (summarized in Neuroendocrine and metabolic responses to surgery after NH&MRC 1999) are wide ranging and have significant impact on homeostasis. Effects on the respiratory system are most prominent, as persistent pain will result in a reduction in respiratory effort that then leads to hypoxemia from significant ventilation/perfusion mismatching. Continuing hypoventilation predisposes to collapse of lung segments and the supervening infection that follows carries significant morbidity. Psychological and behavioral changes (e.g., yellow flags) also accompany pain states and may need to be recognized and managed. Not only will proper management of postoperative pain result in greater patient comfort and earlier discharge home, but the improved earlier mobilization and return to function will also reduce serious postoperative complications such as venous thromboembolism.

Neuroendocrine and Metabolic Responses to Surgery

Endocrine

- Catabolic – due to increase in ACTH, cortisol, ADH, GH, catecholamines, renin, angiotensin II, aldosterone, glucagon, interleukin-1 (After Macintyre et al. 2010)
- Anabolic – due to decrease in insulin, testosterone

Metabolic

- Carbohydrate – hyperglycemia, glucose intolerance, insulin resistance
- Due to increase in hepatic glycogenolysis (epinephrine, glucagon) and gluconeogenesis (cortisol, glucagon, growth hormone, epinephrine, free fatty acids)
- Due to decrease in insulin secretion/action
- Protein – muscle protein catabolism, increased synthesis of acute-phase proteins
- Due to increase in cortisol, epinephrine, glucagon, interleukin-1
- Fat – increased lipolysis and oxidation
- Due to increase in catecholamines, cortisol, glucagon, growth hormone
- Water and electrolyte flux – retention of H_2O and Na^+, increased excretion of K^+, decreased functional extracellular fluid with shifts to intracellular compartments
- Due to increase in catecholamines, aldosterone, ADH, cortisol, angiotensin II, prostaglandins, and other factors

However, despite the emergence of pain management as a specialty and the availability of a wide range of guidelines and templates for effective analgesia, pain continues to be poorly managed. Why this should be the case is a difficult question to answer, although there is clearly a wide range of possibilities (Cousins and Phillips 1986; Macintyre and Ready 1996).

As can be seen from "Reasons for ineffective analgesia (after NH&MRC 1999)," in some cases it may be simply the result of inadequate knowledge or equipment, but sometimes there can be more disturbing reasons. Macintyre (2001) has pointed out that some health service personnel are still concerned that pain relief can be "too efficacious" and thereby mask postoperative complications such as urinary retention, compartment syndrome, or even myocardial infarction. Another barrier to providing effective analgesia is a view held in some quarters that maintaining the patient in pain is somehow a useful way to aid diagnosis – a concept with no valid scientific basis (Attard et al. 1992; Zolte and Cust 1986).

Reasons for Ineffective Analgesia

- The common idea that pain is merely a symptom and not harmful in itself (After Macintyre et al. 2010)
- The mistaken impression that analgesia makes accurate diagnosis difficult or impossible
- Fear of the potential for addiction to opioids
- Concerns about respiratory depression and other opioid-related side effects such as nausea and vomiting
- The lack of understanding of the pharmacokinetics of various agents
- The lack of appreciation of variability in analgesic response to opioids
- Prescriptions for opioids, which include the use of inappropriate doses and/or dose intervals

- Misinterpretation of doctor's orders by nursing staff, including the use of lower ranges of opioid doses and delaying opioid administration
- The mistaken belief that patient weight is the best predictor of opioid requirement
- The mistaken belief that opioids must not be given more often than 4 hourly
- Patients' difficulties in communicating their need for analgesia

Mechanisms in Acute Pain

The manner in which pain signals are processed and modulated is a complex topic that is covered in detail elsewhere. However, the following brief overview is provided as a background to the sections that follow.

The traditional view of the processing of pain inputs is that they are first detected through nonspecific polymodal nociceptors that respond to a range of stimuli, including thermal, chemical, and mechanical alterations. It is a process designed to alert us to tissue damage. These inputs are then transmitted by A delta and C-type fibers to the spinal cord at speeds of between 2 m/s in the case of the C-type fibers and 10 m/s in the myelinated A delta fibers.

These peripheral nerves terminate in the dorsal horn of the spinal cord where they undergo considerable modulation both via neurotransmitters present at that site and through the action of descending tracts from higher centers, which usually have an inhibitory role. Following modulation, the nociceptive impulse is finally transmitted through tracts to supraspinal sites. Although a number of links are involved, the spinothalamic tract is perhaps the most prominent.

Having given this outline, it is now accepted that our nervous system is a "plastic" environment where stimuli or trauma in any one part of the body can invoke change within other body systems, especially that of the nervous system (Cousins and Power 1999). Changes in nerve function are particularly important and this plasticity can lead nerve fibers whose physiological role is not normally to transmit pain signals to act as nociceptors. For example, while A delta and C fibers are traditionally seen as primary nociceptive fibers, A beta fibers can become nociceptive under certain circumstances.

Coincident with this is the development of peripheral sensitization. Trauma or other noxious stimuli to tissue result in a neurogenic inflammatory response that in turn leads to vasodilation, increased nerve excitability, and the eventual release of a range of inflammatory mediators such as serotonin, substance P, histamine, and cytokines – the so-called sensitizing soup. This altered environment leads to a modification in the way that input signals are processed with innocuous stimuli being sensed as noxious or painful stimuli, leading to the phenomena of ▶ hyperalgesia.

The Scope of Acute Pain Management

Acute pain management has developed into a subspecialty in its own right during the last decade with an ever-increasing range of activities. In the hospital setting, the major role of the acute pain team is in the area of postoperative pain management in the surgical patient, although their involvement must not be limited to these patients. In patients with burns, appropriate pain management will help in optimizing pain control both in the early stages where skin grafting and debridement are being carried out and later when the patient requires assistance to undergo physiotherapy. In the patient with spinal cord injury, the initial phase following the injury is often complicated by acute neuropathic pain where early intervention is critical, while in the oncology patient, acute pain can complicate therapy, as in the patient who develops mucositis as a complication of treatment.

Providing Comprehensive Acute Pain Management

Acute and postoperative pain is best managed by an acute pain team and there are a number of structural models of how these are best set up and operated (Rawall and Allvin 1996). While many are headed by consultant anesthetists, this is not always the case and often the day-to-day running of the team is managed by a specialist pain nurse, with medical staff used only for

backup when necessary. Acute pain teams need to have clearly defined guidelines and major goals, which will be dictated in part by their institution and circumstances (see Clinical practice guidelines for Acute Pain teams, Cousins and Power 1999). Irrespective of how the team is organized, there must be an efficient method of referral of patients either from the operating theater or from the various surgical teams.

Clinical Practice Guidelines for Acute Pain Teams

Guidelines

- A collaborative, interdisciplinary approach to pain control, including all members of the healthcare team and input from the patient and the patient's family, when appropriate. An individualized proactive pain control plan developed preoperatively by patients and practitioners (since pain is easier to prevent than to treat) (Cousins and Power 1999)
- Assessment and frequent reassessment of the patients' pain
- The use of both drug and nondrug therapies to control and/or prevent pain
- A formal, institutional approach, with clear lines of responsibility

Major Goals

- Reduce the incidence and severity of patients' postoperative or post-traumatic pain
- Educate patients about the need to communicate regarding unrelieved pain, so they can receive prompt evaluation and effective treatment
- Enhance patient comfort and satisfaction
- Contribute to fewer postoperative complications and, in some cases, shorter stays after surgical procedures

Where possible, the pain team should also be involved in ▶ preoperative education of the elective surgical patient. At such a meeting, the patients' fears and anxieties about pain should be addressed, as there is considerable evidence to suggest that patients who have the opportunity to speak about their concerns about postoperative pain prior to surgery do better and use less medication than control groups. A number of studies have consistently pointed out that pain is usually the major fear of patients undergoing surgery. During preoperative assessment, at least in the elective patient, it is important to obtain a full medication history especially in relation to use of analgesic agents and the duration of such therapy. Tolerance to opioids can develop quickly and identifying patients who attend for surgery with a history of oral opioid use is important, as they will most likely have different analgesic requirements when compared to the opioid-naïve individual.

The acute pain team also needs to be responsible for the overall postoperative management of the patient. This includes ensuring that regular monitoring and recording of physiological parameters occurs. Details such as oxygen saturation, respiratory rate, and pain status need to be recorded regularly and reviewed. Pain scores can be recorded either numerically or by descriptors. It is important to record pain levels both at rest and on movement, since treatment strategies for these problems will differ. Movement pain in particular is better treated with adjuvant agents rather than opioids.

Accurate recording of physiological data in patients being treated for acute pain is mandatory. Sedation scores and respiratory rate are important in reducing the incidence of opioid-induced toxicity. Pain management records or electronic data apparatus should also allow for the recording of any associated ▶ adverse events (such as nausea and vomiting) and record data in a form allowing regular or ongoing ▶ audit. Such audits of acute pain patients should, where possible, allow not only for examination of the parameters already described but also for ▶ outcome measures. The acute pain team should supervise the transition from a parenteral to an oral analgesic regime. Likewise, members of the acute pain service must recognize when a patient might be suffering a ▶ persistent acute pain state or undergoing transition from an acute to a chronic pain state and need referral to chronic pain specialists.

Postoperative care also involves being alert for warning signs, so-called ▶ red flags that might indicate developing complications of the

surgery or trauma. In patients previously well controlled using a particular analgesic regime, continuing episodes of unexpected pain requiring increasing doses of medication should alert the practitioner. Under these circumstances, an investigation should be made to elicit the cause of these events, which might be a result of complications of surgery or trauma. This should be diagnosed and treated directly, rather than merely increasing doses of analgesic drugs (Cousins and Phillips 1986).

Preemptive Analgesia Much has been made of the usefulness of ▶ preemptive or preventive analgesia. The concept of providing analgesia prior to a surgical stimulus and thus reducing ▶ central sensitization seems to be a logical and useful proposition and generated a great deal of initial enthusiasm (Dahl and Kehlet 1993; Woolf and Chong 1993). Unfortunately, subsequent controlled trials have failed to consistently demonstrate that any of the commonly used strategies are effective in reducing postoperative pain or analgesic use. These include the preoperative administration of opioids, nonsteroidal anti-inflammatory drugs, and the provision of local analgesic neural blockade (Gill et al. 2001; Podder et al. 2000; Uzunkoy et al. 2001). Much research has been conducted in an effort to ascertain the reasons for this (Charlton 2002; Kehlet 1998; Kissin 1996). Some hypotheses that have been advanced include the suggestion that when local anesthesia is employed in a preemptive setting, any failure to provide complete blockade will still allow sensitization to occur (Lund et al. 1987). Another possibility is that the timing between placement of the blockade and the commencement of surgery is critical, with a time interval of at least 30 min being required between drug administration and surgery (Senturk et al. 2002). One question that has not been fully answered is whether the use of preemptive analgesia might lead to a reduction in the number of patients progressing from acute to chronic pain states. Early studies such as that of Bach et al. (1998) suggested that this may well be the case, and this has been supported by more recent reports (Obata et al. 1999).

Treatment Strategies: General The principles of management of acute nociceptive pain are generally ▶ multimodal. This implies using a number of agents, sometimes given by different routes, to maximize pain control. While pain control after some minor procedures can be controlled by non-opioids alone, opioids remain the main stay of moderate to severe pain management. The use of combinations of ▶ adjuvant analgesics, also known as ▶ balanced analgesia, allows for a reduction in opioid dosage and thus side effects, which can be useful in managing some aspects of pain that can be less responsive to opioids alone.

With regard to the selection of a route of drug administration, while the use of the oral route might initially seem easiest, it is rarely used in the first instance. The variable bioavailability of oral products coupled with postoperative attenuation of gastrointestinal function and the possibility of superimposed vomiting makes this route a poor choice initially. Parenteral administration is usually called for and the intravenous route is the preferred route of administration, often using ▶ patient-controlled analgesia (PCA) devices.

Patient-Controlled Analgesia PCA as a means of drug administration has to a degree revolutionized modern pain management. Although purchase of the devices represents a significant financial outlay, there are savings to be made in terms of medical and nursing staff time, as well as less tangible benefits, such as reducing the number of needle stick injuries. Importantly, patients generally feel positive about using PCAs (Chumbley et al. 1999), with most studies suggesting that the feeling of "being in control" was the most common reason for the high level of satisfaction (Albert and Talbott 1988). However, despite a number of inbuilt safety mechanisms, overdosage can still occur with these devices, and strict postoperative monitoring is imperative (Macintyre 2001). While the intramuscular route can be used for intermittent analgesia, the pharmacokinetics is often unattractive, requiring repeated injections. Furthermore, intramuscular analgesia is most often prescribed on a p.r.n. or "as required" basis, which perforce implies that

the patient must be in a pain state before they request the medication – a situation that should be avoided. Finally, every intramuscular (or indeed subcutaneous) injection given presents a possibility for a needlestick injury to occur – another situation best avoided.

Epidural Analgesia Much has been written about the risks and benefits associated with the use of epidural analgesia in the postoperative period, and interpreting the results of these myriad studies conducted under varying circumstances is extremely difficult. There is no doubt that epidural analgesia provides a number of real advantages. It allows the use of drug combinations, which can be delivered close to appropriate receptor sites in the spinal cord (Schmid and Sandler 2000), it reduces the requirements of opioid analgesics (Niemi and Breivik 1998), and it generally allows for a faster return of physiological function, especially gastrointestinal and respiratory status in the postoperative period. The degree to which this occurs appears to be dependent, at least in part, on the nature of surgery performed (Young Park et al. 2001).

However, more recently, despite the fact that there are considerable benefits associated with the use of epidural infusions, attention has focussed on the nature and incidence of complications associated with epidural infusions (Horlocker and Wedel 2000; Rigg et al. 2002; Wheatley et al. 2001). These complications can range from local or systemic infection through to hematoma formation and local or permanent neurological sequelae. The rates of the most serious complications of permanent nerve defects or paraplegia are quoted as between 0.005 % and 0.03 % (Aromaa et al. 1997; Dahlgren and Tornebrandt 1995). Again analysis of these data is difficult because of the number of variables involved. For example, there is growing evidence that those people who develop epidural neurological complications frequently have significant preexisting pathologies, which may predispose them to such complications. Lastly, there has been considerable debate about the guidelines for epidural placement and removal in patients undergoing perioperative anticoagulation. This is especially so when fractionated or low molecular weight heparin products are employed, because of the possibility of increased risk of development of epidural hematoma under these circumstances. Again, the evidence is conflicting (Bergqvist et al. 1992; Horlocker and Wedel 1998). Patient-controlled epidural analgesia is a means of pain management that combines the efficacy of epidurally administered drugs with the convenience of patient control. In many countries the use of epidural analgesia, especially for the control of postoperative pain, has declined, on account of the potentially serious adverse effects associated with its use, coupled with the increased use of targeted peripheral nerve blocks that provide specific areas of regional anesthesia (Grossi and Urmey 2003).

Intrathecal Analgesia The intrathecal route of drug administration can be useful both as a means of providing anesthesia and for postoperative analgesia. Both opioids and local anesthetic agents have been administered by this route. While the use of low doses of less lipophilic agents such as morphine is popular and gives prolonged postoperative care, the use of this route is not without risk, as there has been a rise in the number of cases of transient neurological symptoms following lignocaine use (Johnson 2000). Recent reviews have suggested that the use of intrathecal morphine for postoperative pain is efficacious, but that certain types of surgery are more responsive than others to the type of management (Eandi et al. 2003; Meylan et al. 2009).

Pharmacotherapies

Opioids With regard to the ▶ opioids, there has been an increase both in the range of drugs available and in their routes of administration. The traditional range of opioids such as morphine, pethidine, and fentanyl has been augmented by drugs such as ▶ oxycodone, dihydrocodeine, and ▶ hydromorphone. None of these drugs are actually "new," having been synthesized in some cases almost 100 years ago, but rather they have been rediscovered by a new generation of prescribers. Oxycodone in particular is

available in a sustained-release form that exhibits a useful biphasic pharmacokinetic profile. The role of pethidine (meperidine) in modern pain management continues to be problematic. While it still has a place under certain circumstances, it should be avoided as an agent for longer-term use, owing to its apparently increased abuse potential and the risk of accumulation of the excitatory metabolite norpethidine (Pattullo and MacPherson 2011). Codeine (when used alone) is also a drug of limited utility. Although it has good oral bioavailability, it is a poor analgesic, has a high degree of constipation, and is influenced by genetic polymorphism. The increased opioid armamentarium has also given scope for ▶ opioid rotation. Although this is a strategy primarily associated with chronic pain management, patients can develop a degree of tolerance to opioids even after a few days. Where continued opioid treatment is needed for whatever reason, switching opioids often results in enhanced pain control, often together with a reduction in dosage. Methadone is an interesting drug, which has generated some recent interest. Its unusual pharmacokinetic profile, with a long and unpredictable half-life of up to 72 h, makes it impracticable for use in the very early stages of acute pain. However, it can be used in later stages where a long-acting oral product is preferable. That the drug has activity at the NMDA receptor as well as the mu opioid receptor is well known. However, it has always been difficult to assess to what, if any, extent this contributes to its analgesic effect and the fact that it has been shown to be of benefit in the treatment of other pain states such as phantom limb pain (Bergmans et al. 2002).

Non-Opioids The non-opioids are a diverse group of drugs with differing modes of action and means of administration. Most show clear synergism with the opioids. Members of this group include tramadol, the nonsteroidal anti-inflammatory drugs (NSAIDS), COX-2 inhibitors, and ketamine.

Paracetamol ▶ Paracetamol should be almost the universal basis of acute and postoperative pain control. A number of well-controlled trials have clearly demonstrated that regular paracetamol, when given in a dose of 1 g q.i.d., clearly reduces opioid requirements by up to 30 %. Side effects are minimal and the drug is very well tolerated. In most countries it is available in both oral and rectal forms, and in a small number, a parenteral prodrug propacetamol is also available.

The only real contraindication to the prescribing of paracetamol is impaired hepatic function, where the drug is probably best avoided. Much work has also been done on the efficacy of other drugs given in combination with paracetamol. In general, the analysis of trial data suggests that while the combination of codeine phosphate (60 mg) has benefits over paracetamol alone, the use of paracetamol with lower quantities seems to confer little benefit. Parenteral paracetamol has now been available for some years and, although more expensive than oral or rectal products, now provides a convenient parenteral form of administration. It has no specific advantages over the oral form and should be ceased as soon as the patient is able to commence enteral feeding. Although paracetamol generally offers a very favorable adverse effect profile, the dose must be reduced in elderly or cachectic patients, and a close monitor kept on liver function tests. Adverse effects to paracetamol use have still been reported when the drug has been used at "therapeutic" dosage.

Tramadol Tramadol is unique among analgesic agents in having a dual action. Its main activity probably lies in enhancing the action of noradrenaline and 5-hydroxytryptamine at the spinal cord level, while it also has a very weak agonist activity at the mu receptor at supraspinal sites. Tramadol is a very useful drug for the management of mild to moderate pain, and the fact that it can be given orally or by the intravenous or intramuscular routes further adds to its versatility.

A recent review of tramadol use in acute pain has confirmed its effectiveness in both nociceptive and neuropathic pain, making it a useful agent in cases of mixed pain or where the diagnosis is unclear (Duehmke et al. 2006; Moore and McQuay 1997).

Its low addiction potential makes it a good choice for long-term use. Because of the risk of precipitating serotonin syndrome, tramadol is probably best avoided in combination with many of the different antidepressant medications, especially the SSRIs, although in clinical practice the real risk seems quite low. Recent studies have confirmed that it possesses significant synergy when combined with paracetamol, and indeed a combination product is now available in some countries (Fricke et al. 2002). There are few studies available on the usefulness of combination of tramadol with opioids, although initial results appear encouraging (Webb et al. 2002).

Tramadol is also attractive because of its low abuse potential. Certainly in comparison to strong opioids, the incidence of abuse, dependence, and withdrawal is considerably lower (Cicero et al. 1999). However, a number of such cases have been reported, almost all of which were in patients with a preexisting history of drug or substance abuse (Brinker et al. 2002; Lange-Asschenfeldt et al. 2002).

In the management of postoperative pain, all efforts should be made to reduce the incidence of postoperative nausea and vomiting, which is not only uncomfortable for the patient but can also lead to fluid imbalance, impaired respiratory function, and electrolyte disturbances. In this regard the use of tramadol is somewhat problematic, as the incidence of nausea and vomiting is at least as high as with opioids (Silvasti et al. 2000; Stamer et al. 1997). However, some strategies have been suggested to attenuate this response including administration of an intraoperative loading dose (Pang et al. 2000) and slow IV administration (Petrone et al. 1999). Should management of tramadol-induced nausea and vomiting require pharmacological intervention, recent studies suggest that members of the butyrophenone class such as droperidol might be a better choice than 5HT3 antagonists such as ondansetron, which might not only be less effective but also antagonize tramadol's analgesic effects.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs (▶ NSAIDs, Survey) are widely used in acute pain management (Merry and Power 1995). While they may be used as the sole agent in mild pain, they are primarily employed as adjunctive medications in combination with opioids in moderate to severe pain states. Here their action both at central and peripheral sites complements opioid activity, and they are especially useful in the management of pain associated with movement. There have always been concerns associated with the use of NSAIDs in the surgical patient because of the risk of the development of serious complications, especially renal impairment. However, careful patient selection and monitoring, the use of a product with a short half-life, and restricting the duration of treatment to about 3 days greatly reduce the danger.

The discovery of the two isoforms of the cyclooxygenase (COX) enzyme has more recently led to the development of COX-2-specific inhibitors such as celecoxib and rofecoxib, with the aim of developing potent NSAIDs without significant associated gastrointestinal side effects. The majority of studies on these drugs have been conducted in outpatient populations, and whether they offer any advantage over traditional NSAIDs in the management of postoperative pain is unclear. Even more recently, a parenteral COX-2 inhibitor (parecoxib) has been developed specifically for the management of postoperative pain, and initial results of studies are encouraging.

Unfortunately, the cardiovascular safety of these products has recently come under scrutiny resulting in the removal of some products from the marketplace, owing to an increase in thromboembolic events associated with its use (Solomon et al. 2004). There were initial concerns that this might have been a class effect of COX-2 inhibitors, but it now appears to be agent specific. Although the analgesia offered by these agents is not superior to that seen with conventional NSAIDS, nevertheless in long-term use they almost certainly offer improved safety over conventional NSAIDs (Tramèr et al. 2000).

Gabapentin and Pregabalin These antiepileptic agents have been used for some time in the management of neuropathic pain with excellent results. However, in recent times, there have

been a number of studies involving their use in acute postoperative pain. What is interesting is that it appears that gabapentin administration, even for a few days in the perioperative period, can improve quality of analgesia and reduce opioid use. Clearly more work is needed in this area, but a recent systematic review certainly suggests that the perioperative use of either gabapentin or pregabalin improves the quality of postoperative analgesia and reduces opioid use (Elina et al. 2007).

► Ketamine is an important second-line drug in the pain physician's armamentarium. Well known as an anesthetic agent, it has in the last decade or so found use as an analgesic product when used in sub-anesthetic doses. The drug has some useful N-methyl-D-aspartate (NMDA) receptor antagonist activity and can also augment the action of opioids in the treatment of nociceptive pain. The usual psychomimetic effects of the drug are not usually a problem in the dosages employed, although the development and release of the S(+) might signal a resurgence in the interest of this drug. The clinical applications of ketamine have recently been briefly reviewed by Persson (2010), while an earlier paper by Elia (2005) has undertaken a systematic review of ketamine use in postoperative pain.

Neuropathic Pain Comprehensive acute pain management also entails the recognition and management of ► acute neuropathic pain. Neuropathic pain is most frequently seen as a sequela of long-term pathological states such as diabetes or herpes zoster infection (Bowsher 1991). However, this is not always the case and acute neuropathic pain can be seen immediately following surgical procedures where peripheral nerves have been disrupted, such as in the ► post-thoracotomy syndrome following specific events such as acute spinal cord injury or as evidenced by ► phantom limb pain following amputation. It is important to be alert for the signs or symptoms of neuropathic pain in the acute or postoperative phase (see Features suggestive of neuropathic pain after NH&MRC 1999). Failure to diagnose such a condition will result not only in prolonged pain but also most probably in the patient being given increasing doses of opioid medication in a futile effort to control the condition (Hayes and Molloy 1997).

Features Suggestive of Neuropathic Pain

- Pain can be related to an event causing nerve damage (After Macintyre et al. 2010).
- Pain unrelated to ongoing tissue damage.
- Sometimes a delay between event and pain onset:
  - The pain is described as burning, stabbing, pulsing, or electric-shock-like.
  - Hyperalgesia.
  - Allodynia (indicative of central sensitization).
  - Dysesthesia.
- Poor response to opioids.
- The pain is usually paroxysmal and often worse at night.
- Pain persists in spite of the absence of ongoing tissue damage.

The management of neuropathic pain can be complex and much has been written on the usefulness of various pain strategies. A wide range of drugs with differing pharmacological targets such as ► anticonvulsant medications, notably ► gabapentin and carbamazepine; ► antidepressants; and ► membrane stabilizing agents such as ► mexiletine/Mexitil have all been employed with varying success. Local anesthetics such as lignocaine have all been found to be useful, especially in the acute case, where they can be administered as a subcutaneous infusion.

Specific Acute Pain States

There are some acute pain states that have been subject to more extensive research and whose symptomatology and pathogenesis follow recognized patterns. These include acute lower back pain, pain following chest trauma or thoracic surgery, compartment syndrome, and the acute presentation of ► complex regional pain syndrome. There have also been significant advances in our understanding of ► acute pain mechanisms and the differentiation between visceral and somatic (deep or superficial) pain.

Summary

There have been a number of significant improvements in the management of acute and postoperative pain management during the past decade. To some degree, this has been helped by the emergence of new drugs or, in some cases, whole new drug groups. However, in the main, advances in acute and postoperative pain management have come about by recognizing how to manage pain better with existing drugs, focussing on the use of drug combinations to maximize outcomes. There has also been a greater appreciation of the importance of diagnosing acute neuropathic pain, requiring a different approach. Those involved in pain management have embarked on a virtual crusade in an effort to convince health professionals that acute and postoperative pain can be and must be appropriately and successfully managed. Perhaps the most important lesson of all is an appreciation that all chronic pain must start as acute pain. Appropriate management of acute pain will therefore have the additional bonus of eventually reducing the worldwide burden of patients having to suffer debilitating chronic pain states.

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Acute Pain Database

► Postoperative Pain, Data Gathering and Auditing

Acute Pain in Children, Postoperative

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Synonyms

Acute postoperative pain in children; Pediatric postsurgical pain

Definition

Surgical trauma from tissue destruction and musculoskeletal strain causes inflammatory and neurohumoral responses with release of vaso- and immunoreactive substrates (cytokines, complement, arachidonic acid, metabolites, nitric oxide, free oxygen radicals) that promote inflammation, vascular hyperpermeability, and pain.

The duration of postoperative pain that is considered acute is not clearly defined and is dependent on the amount of tissue trauma and the time taken for healing. In the perioperative setting, pain that persists after healing has occurred could be considered persistent pain.

Introduction

Despite advances in the safety of perioperative care, pain remains a problem for many children after surgery. Moderate-to-severe pain occurs in almost half of children hospitalized after an operation and is not limited to any specific surgeries with fairly similar rates occurring after orthopedic; general; ear, nose, and throat; and neuro- and plastic surgeries (Groenewald et al. 2012). Teenagers are more at risk than children, with males and females being equally affected. Moderate-to-severe pain in pediatric patients, once present, is difficult to treat and tends to persist in subsequent

days, contributing to delayed recovery. Poorly controlled postoperative pain may also predispose patients to developing chronic pain syndromes (Macrae 2008).

Characteristics

Causes and Risk Factors

Pain occurs after surgery for a number of reasons. Direct trauma to tissue from incisions and handling, stretch from retraction, and insufflation for laparoscopy causes somatic and referred pain. Musculoskeletal pain may also occur from prolonged positioning. In addition, children may have pain from tissue ischemia, inflammation, and gastrointestinal disturbance (distension or spasms). Pain from complications, for example, compartment syndrome, must always be considered and ruled out. Children may also have pain from the underlying disease process or comorbid conditions and from painful procedures in the postoperative period (venipuncture, dressing changes, and continuous passive motion machine).

Several biological, psychological, and social processes have been identified as determinants of acute and chronic pain in children. In the context of surgery, psychological processes, particularly preoperative levels of anxiety, have been identified as an important risk factor for acute postoperative pain in children (Kain et al. 2006; Kotzer 2000). Postoperative sleep quality in children has also been shown to be linked to acute postoperative pain (Kain et al. 2002), but the relationships between sleep and pain in children after surgery are not yet clear. Moderate-to-severe pain present several days into the hospitalization tends to persist through the hospitalization (Groenewald et al. 2012). Risk factors for more severe and persistent postoperative pain in children are active areas of investigation.

Importance of Effective Management of Postoperative Pain

Postoperative pain has significant immediate and long-lasting effects and delays overall recovery. Pain has deleterious effects on pulmonary, cardiovascular, endocrine, immunologic, coagulation, gastrointestinal, and musculoskeletal systems, delays mobilization, and is also associated with impaired wound healing. Pain is central in the surgical stress response which contributes to postoperative morbidity (Kehlet 1997). Fatigue and sleep disturbance are also contributory to the stress response and are also exacerbated by pain.

Pain is one of the main outcomes affecting quality of life in children after major surgery (Jacobsen et al. 2010). Moreover, inadequately treated pain can lead to central sensitization and further pain problems in the future. Pain is also one of the main factors affecting both the child's and their parents' satisfaction with their perioperative care (Bull and Grogan 2010; Cucchiaro et al. 2006b; Wagner et al. 2007).

On the other hand, many pharmacologic pain management strategies also have deleterious short- and long-term effects. All analgesic medications have potential side effects and complications, for example, opioid-induced nausea and vomiting, sedation, and ileus which delay postoperative recovery. In addition, opioid escalation may lead to tolerance and opioid-induced hyperalgesia (Lee et al. 2011). It is, therefore, important that a balanced multimodal approach to postoperative analgesia is used to enhance postoperative recovery (Kehlet and Dahl 1993).

Assessment Tools

Effective pain assessment requires measurement tools that are reliable (reproducible over time), valid (accurately measure pain), responsive (track changes in pain over time), and clearly interpretable and feasible (easy to use). In addition, pain measurements should be frequent, at minimum every 4 h, before and after pain relief interventions and as medically indicated. Pain measurement during activity is a better indicator of effective pain control and postoperative outcome than measurement at rest only (Kehlet and Dahl 1993). Various pediatric pain scales have been developed based on the child's age, developmental status, and verbal ability, and these can be broadly classified as being either observational (nonverbal children) or self-report (children able to report pain in terms of the scale used).

To standardize pain measurement tools for research trials the Ped-IMMPACT group (Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) commissioned two systematic reviews in 2005 aimed at evaluating the use of existing pain measurement tools in children (McGrath et al. 2008; Stinson et al. 2006; von Baeyer and Spagrud 2007). Stinson et al. identified three age-specific self-report scales validated for acute postoperative pain measurement: The Poker Chip Tool for ages 3–4 years, the Faces Pain Scale-Revised for ages 4–12 years, and the Visual Analog Scale for ages 8 years and beyond (Stinson et al. 2006). All three are well established in both research and clinical practice and have been extensively validated and found reliable. Interestingly at the time of Stinson's review, the numerical rating scale (NRS), a widely used pain scale in clinical practice had not yet been adequately studied; however, its use for acute postoperative pain assessment was recently validated (Page et al. 2012). Observational pain scores are needed for children unable to self-report due to being too young, cognitively impaired, or critically ill. Von Baeyer and Spagrud reviewed all published reports of observational measures in patients 1–18 years of age (von Baeyer and Spagrud 2007). They recommend the Face, Legs, Arms, Cry, Consolability (FLACC) and Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) pain scales for acute postoperative pain assessment in nonverbal children older than 1 year of age. Both of these have been extensively used in clinical research and have excellent reliability and responsiveness. For pain assessment at home by parents the Parents' Postoperative Pain Measure (PPPM) was recommended. The only pain measurement recommended for critically ill children is the COMFORT scale. The Ped-IMMPACT Group did not publish guidelines for the assessment of pain intensity in children younger than age 1 or for those cognitive disabilities; however, scales validated postoperatively for children younger than 1 year include the Neonatal Pain, Agitation and Sedation Scale (NPASS) for term neonates (Hummel et al. 2008) and the Premature Infant Pain Profile (PIPP) for preterm and term infants (Stevens et al. 2010).

Obstacles to adequate assessment of pain in children include communication and language barriers, unwillingness to participate, and disruptive behaviors (frustration, annoyance). In the postoperative setting, additional barriers include sedation, intubation, and difficulty differentiating pain from agitation or from discomfort from other sources (e.g., orthopedic casts, urinary catheter, intravenous lines, etc.). Differentiating behaviors, distress and pain is particularly difficult as pain itself has both emotional and sensory components (Blount and Loiselle 2009).

Strategies for Postoperative Pain Management

Multimodal opioid sparing analgesia is an important part of "fast-track" approaches to enhance postoperative function and recovery (Kehlet and Dahl 1993). Strategies target multiple levels of the nociceptive pathways to achieve effective analgesia through additive or synergistic effects of different analgesics, with fewer side effects.

Painful nociceptive stimuli from the site of tissue injury are conducted via peripheral nerves to the spinal cord where first-order neurons synapse in the dorsal horn. Ascending spinothalamic tract fibers travel to the cerebral cortex where the perception of pain is then further influenced by emotional factors, the memory of previous pain, and behavioral experiences. Descending inhibitory pathways then modulate pain conduction pathways at the spinal level. The practice of providing pain control by targeting several of these levels is termed multimodal or balanced analgesia. For example, pain can be treated at the local site of surgical trauma with local anesthetic agents and anti-inflammatory drugs, while at the spinal cord level it may be treated by opioids and local anesthetic agents and at the cortical level with opioids, acetaminophen, α2-agonists, and non-pharmacological behavioral therapies. The goal of effective multimodal analgesia is the achievement of additive or synergistic effects among different analgesics thereby reducing the total dosing of individual medications, particularly opioids, with concomitant decreasing of side effects. The objective of multimodal postoperative analgesia is to hasten convalescence,

improve surgical outcomes, and prevent postsurgical hypersensitization and persistent pain (Kehlet 1997; Kehlet and Dahl 1993).

The introduction of preemptive analgesia, that is, the amelioration of postoperative pain by preemptive administration of opioids or local anesthetics prior to surgical trauma, has remained popular in anesthetic practice. However, this technique remains controversial as there is no scientific evidence to support it (Dahl and Kehlet 2011).

Preventive analgesia, that is, the treatment of pain to prevent central sensitization and persistent postoperative pain, is separate from preemptive analgesia and is currently a focus of research (Dahl and Kehlet 2011).

Pharmacological Treatment of Postoperative Pain

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in managing mild-to-moderate postoperative pain. Acetaminophen is available in oral, rectal, and intravenous forms. The oral and intravenous doses are 10–15 mg/kg every 4–6 h, while the rectal dosing is 40 mg/kg, with repeated dosing 20 mg/kg every 6 h in children and every 12 h in neonates. Acetaminophen is remarkably safe when used within these dosing limitations; however, accidental overdose may lead to hepatic necrosis. Postoperatively due to restricted oral intake or nausea and vomiting, many children are unable to tolerate oral acetaminophen, and therefore, the recently introduced intravenous formulation of the drug is gaining popularity. Acetaminophen is efficacious in children of all ages, including infants; however, the dose should be reduced in neonates with unconjugated hyperbilirubinemia (Palmer et al. 2008). Acetaminophen is often combined with NSAIDs for superior postoperative analgesia. NSAIDs act via inhibition of the COX-system to reduce prostaglandin synthesis, thus reducing both pain and inflammation at the surgical site; unfortunately, the same mechanism may lead to significant side effects, including gastric ulceration, bleeding, and impaired renal function (Lynn et al. 2007). Contraindications to NSAIDs used in the postoperative setting include hypovolemia, acute renal impairment, thrombocytopenia, coagulopathy, and active hemorrhage. These conditions are fairly prevalent in hospitalized children and may be one of the reasons why NSAIDS are not routinely prescribed to all postoperative patients (Groenewald et al. 2012).

Opioids remain the mainstay of management of moderate-to-severe acute postoperative pain. Opioid agonists commonly used postoperatively include morphine, hydromorphone, fentanyl, methadone, codeine, hydrocodone, and oxycodone. These exert their analgesic action through μ1 receptors located in the central nervous system, and can be administered via various routes including enteral, intravenous, intrathecal, epidural, transmucosal, and transdermal routes. The agonist-antagonist opiates, such as nalbuphine and pentazocine, which are also used to treat moderate-to-severe pain, provide analgesia mainly by κ receptor-mediated interactions. Morphine has well-established pharmacokinetics in children (Duedahl and Hansen 2007); however, it has a 50 % incidence of side effects, including respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention, ileus, and constipation. The presence of these side effects makes morphine and other opioid agonists undesirable for unimodal analgesia. Scheduled or as needed intravenous bolus doses of opioids may be sufficient to treat intermittent pain; however, for patients experiencing continuous and/or moderate-to-severe pain, opioids should be given as a continuous intravenous infusion or as patient controlled analgesia (PCA). Opioids should be tapered as recovery occurs and pain improves.

Local anesthetic agents can be administered as single agents or in combination with additives at the level of the neuraxis, the peripheral nerve or the surgical site as continuous infusions or single shot injections. Administration for postoperative pain in children is usually done while under anesthesia for the surgical procedure. Regional anesthesia is an integral part of postoperative pain management in adults and is gaining popularity in children. Many blocks have been extrapolated from adult practice and currently data is being collected from large numbers of children in both

Europe (French Language Societies of Pediatric Anesthesiologists or ADARPEF) and the USA (Pediatric Regional Anesthesia Network or PRAN). Information from these databases will hopefully resolve the many controversial issues in this area and provide evidence-based support for routine regional anesthesia in children undergoing surgery.

The most commonly performed neuraxial block is the caudal block. It is inserted with relative ease in children up to about age 5 and landmarks are readily palpable. Epidural infusions are commonly used for extensive lower extremity orthopedic surgery, abdominal surgery, and thoracic surgery. At the level of the neuraxis, the addition of opioids acts synergistically to improve analgesia; however, these can also be administered intravenously. Using clonidine as an additive in epidural anesthesia enhances the duration of the block (Cucchiaro et al. 2006a). Neonates have pharmacokinetic differences in local anesthetics and, therefore, should receive lower infusion rates and shorter acting drugs. In a national pediatric continuous epidural audit in Great Britain and Ireland, there were approximately 1 in 2,000 serious incidents, 1 in 1,100 intermediate severity incidents, and 1 in 189 low severity incidents. Residual effects from a grade 1 incident 12 months after surgery occurred in one out of the total of 10,633 cases (Llewellyn and Moriarty 2007), a similar rate to that reported in opioid infusions (Morton and Errera 2010).

Data from ADARPEF and PRAN show an increase in use of peripheral nerve blocks and declining neuraxial blocks since the advent of ultrasound guidance (Bosenberg 2012). Continuous peripheral nerve blockade has been shown to be equally effective for orthopedic surgeries as continuous epidural anesthesia, with some additional advantages (Ganesh et al. 2007). Peripheral techniques have the benefits of avoiding potential neuraxial complications, having fewer technical failures, reducing incidence of postoperative nausea and vomiting, avoiding bladder catheterization, interfering less with ambulation, and offering prolonged analgesia for outpatients. Truncal blocks (transversus abdominis plane block, rectus sheath block) are commonly used for analgesia after smaller abdominal procedures.

Ketamine is a potent anesthetic and analgesic that is particularly useful in treating acute postoperative pain in opioid-tolerant patients. Ketamine acts via inhibition of the *N*-methyl-D-aspartate receptor complex (NMDA) which plays a central role in pain sensitization (Himmelseher and Durieux 2005). Primary concerns for the use of ketamine include adverse neurocognitive effects (e.g., hallucinations) which are commonly seen when used at anesthetic doses (1–2 mg/kg). However, when used in the subanesthetic doses for perioperative pain management (0.1–0.15 mg/kg), there is a lower incidence of unpleasant side effects associated with ketamine. To effectively decrease postoperative pain and opioid requirements ketamine should be administered continuously during the perioperative period. Single doses prior to nociceptive stimulation have not been shown to improve pain management; however, anecdotally a single postoperative dose of ketamine (0.1 mg/kg) may significantly reduce analgesic requirements in opioid-resistant patients.

Gabapentin may be a useful adjunct to postoperative pain management. The perioperative administration of oral gabapentin has been found to decrease postoperative morphine requirements and reduce early pain scores in the immediate postoperative period in children and adolescents undergoing scoliosis repair surgery (Rusy et al. 2010). Despite these promising results, data on the perioperative benefits and use of gabapentin and pregabalin are still lacking and they are consequently not recommended as a standard component of multimodal analgesia.

Clonidine, an α_2-receptor agonist, is associated with many beneficial analgesic properties. Given orally it decreases postoperative pain and analgesia requirements, while it may also prolong and improve neuraxial and peripheral nerve blocks when co-administered with local anesthetics block (Cucchiaro et al. 2006a). Dexmedetomidine, a centrally acting α_2-receptor antagonist that is given intravenously, shares some of the same analgesic characteristics as clonidine and in addition provides excellent sedation (Kraemer and Rose 2009).

Summary

Postsurgical pain remains challenging to manage in children. This population has a high prevalence of moderate-to-severe pain. Accurate pain assessment requires the use of age and developmentally appropriate pain scales. The adequate management of acute pain is particularly important in the postsurgical population as uncontrolled pain may, in addition to unnecessary suffering, result in a variety of adverse consequences. Multimodal pain management techniques, the pharmacological targeting of multiple components of the pain conduction pathways, are superior to unimodal treatment strategies and enhance postoperative function and recovery.

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Acute Pain in Children, Procedural

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Synonyms

Acute procedural pain in children; Pediatric pharmacological interventions; Pediatric psychological interventions

Definition

Acute procedural pain refers to the relatively brief pain that infants and children experience as a result of necessary ▶ invasive preventative, diagnostic, and therapeutic medical procedures. Procedural pain management is the pharmacological, psychological, and physical interventions used to prevent, reduce, or eliminate the affective and sensory components of pain that accompany many acute medical procedures.

Characteristics

Acute procedural pain can be defined as the affective and sensory distress that accompanies a brief but invasive medical event. This includes routine (e.g., venous access, immunization injections) and specialized (e.g., bone marrow aspiration, urethral catheterization, burn debridement) procedures. Pain is not a necessary part of the medical intervention, and this aversive affective and sensory side effect is often untreated, especially in children (Finley et al. 2005). A growing body of literature suggests that acute procedural pain in children can have significant negative effects in the short- and long-term both for the pediatric patient as well as the family (e.g., Taddio 1999). These and other concerns (e.g., social and economic) likely contributed to the Joint Commission on Accreditation of Healthcare

Organizations directing that pain be considered the "fifth vital sign" (Phillips 2000) and the International Association of the Study of Pain and the World Health Organization stating that "the relief of pain should be a human right" (see Brennan and Cousins 2004).

The aims of acute procedural pain management are to minimize the affective and sensory distress that occurs prior to, during, and immediately following the procedure. In addition to these immediate aspects of the procedure, acute procedural pain management efforts might target long-term effects (e.g., attitudes, memories, adherence) and self-efficacy (e.g., enhance coping with stressors) (e.g., Cohen et al. 2008b).

Invasive Procedures in Children

Starting soon after birth, children face a number of routine and specialized acute medical procedures. The most common routine procedures are vaccinations with children undergoing several dozen immunizations in their first 2 years of life, with most being administered via intramuscular injection. Some developing countries, such as those in northern Africa, require 15 immunizations within the first 24 months of life; Europe requires 19 within that period; and the United States requires 25 (World Health Organization 2011). Children who are born prematurely, who have been diagnosed with a disease, or who experience accidents or injuries will undergo additional acute painful procedures. Stevens et al. (2004) estimate that neonates born between 27 and 31 weeks of age undergo an average of 134 painful procedures within the first 2 weeks of their lives. For the 10 % of newborns at the lowest birth weights, Stevens et al. found that they receive an average of more than 300 painful procedures within the same period of time. Preterm infants are also at risk for increased pain sensitivity (for a review, see Beggs and Fitzgerald 2007) and this continued exposure to painful stimuli may lead to functional changes in pain and stress processing systems in the brain (Grunau et al. 2005; Slater et al. 2010).

Factors that Affect Procedural Pain in Children

There is significant variability in children's reaction to acute procedures with some children sleeping or showing little reaction, with others vomiting, panicking, or fainting. Clearly, some of the variance can be explained by the nature of the procedures – venipuncture is arguably qualitatively and quantitatively less painful than burn debridement. Individual differences also account for some of the differences in procedural pain; for example, age, gender, prior experience, culture, and temperament have been linked to pain response (e.g., Bustos et al. 2008; Chen et al. 2000; Fillingim et al. 2009; Kim et al. 2004; Lamberg 1998; Miller and Newton 2006; Piira et al. 2007; Ranger and Campbell-Yeo 2008; Sweet et al. 1999). Environmental factors (e.g., child-friendly atmosphere; e.g., Zempsky et al. 2004), physical positioning (e.g., Lacey et al. 2008; Sparks et al. 2007; Stephens et al. 1999), and other aspects of the procedure (e.g., needle gauge) have been shown to influence children's procedural response. Adult behavior has received significant attention given that it explains approximately 25–50 % of the variance in child acute procedural distress (Cohen et al. 2002; Frank et al. 1995). Cohen et al. (2008b) outlined the Stimulus-Response Model of Pain as well as a modified version of the Social Ecological Model (Bronfenbrenner 1979) to detail some of the important contextual variables influencing children's acute procedural pain. Given the complexity in children's response to acute procedures, an evidence-based practice perspective – integrating the best available research evidence; patient characteristics, preferences, and values; and clinical expertise of the health-care staff – should provide an optimal framework for approaching acute procedural pain in children.

Assessment of Procedural Pain in Children

The assessment of acute pain is challenging given that pain is a personal and thus subjective experience. This is complicated in children with unsophisticated vocabularies for describing their internal experiences. The accurate assessment of children's pain is vital for diagnosis and guiding

interventions. Fortunately, there are a number of well-validated and reliable self-report, adult proxy-report, and behavior observational tools to assess pediatric acute pain (for reviews, see Cohen et al. 2006, 2008a; von Baeyer and Spagrud 2007).

Pharmacological Interventions for Procedural Pain in Children

Routine Medical Procedures

Data indicate that pharmacological interventions can provide some relief for children's routine needle pain (for reviews, see Baxter and Cohen 2009; Schechter et al. 2007; Zempsky 2008). The most common pharmacological agents are topical anesthetics (e.g., prilocaine, lidocaine, tetracaine), which provide brief dermal anesthesia. Although the literature generally support the pain relieving qualities of these agents, predominately for venous access (e.g., Zempsky 2008), there are downsides including cost and time of onset (e.g., 20–60 min for analgesia). There is mixed support for the use of quick-onset of vapocoolant spray (Cohen et al. 2009; Schechter et al. 2007; Shah et al. 2009). Recent advances in healthcare have focused on decreasing the time of onset of activation via technological methods (e.g., carbon dioxide to transmit buffered lidocaine; Luhmann et al. 2004) and needle-free options (e.g., Zempsky et al. 2008).

Specialized Medical Procedures

Procedures that are more severe (e.g., bone marrow aspirations, burn debridement) will require a wider array of pharmacological approaches to manage children's pain. Some pharmacological agents for the affective and sensory pain accompanying specialized medical procedures include topical anesthetics, nerve blocks, opioids, ketamine, nitrous oxide, and anxiolytics (Finley 2001). For example, pain management for pediatric cancer lumbar punctures might include lidocaine in addition to deep sedation or general anesthesia (Gorchynski and McLaughlin 2011; Iannalfi et al. 2005). However, there are risks that should be considered with sedation, anesthesia, and other pharmacologic approaches to pediatric pain management for specialized procedures (Finley 2001).

Psychological Interventions for Procedural Pain in Children

Routine Medical Procedures

Psychological interventions for routine procedures include relaxation, deep breathing, praise of appropriate behavior, and distraction (Blount et al. 2009; Pillai Riddell et al. 2011; Powers 1999). The most widely documented psychological intervention for routine pediatric procedural pain is distraction. Distraction functions via diverting the child's attention away from negative sensory stimuli (e.g., needles) toward more positive and engaging stimuli (e.g., cartoon movies; Cohen 2008; DeMore and Cohen 2005). Data support the efficacy of distraction for pediatric immunization pain relief in infants (Cohen 2002; Cohen et al. 2006), preschoolers (Berberich and Landman 2009), and preadolescents (Cohen et al. 1999). Distraction stimuli include movies, nonprocedural talk, imagery, toys, and music, with some data suggesting that the most effective approaches engage the child in multiple modalities (DeMore and Cohen 2005). A systematic review of randomized controlled trials for pediatric immunizations concluded that both child-directed (e.g., cartoons, music) and nurse-led (e.g., trained to provide distraction with movies or toys) distraction effectively reduce pain and distress, the benefits of parent-led distraction (e.g., trained to distract with movies or toys) remain inconclusive (Chambers et al. 2009; Uman et al. 2010). Despite the effectiveness of many studies using multifaceted distraction techniques, it is challenging to determine which components of the intervention are contributing the strongest effects (Cohen 2010). Combined cognitive-behavioral interventions and breathing exercises have also demonstrated reductions in children's self-reported pain during immunization (Chambers et al. 2009). Data equally support the benefit of distraction for children undergoing venous access (e.g., MacLaren and Cohen 2005; Bellieni et al. 2006; Wang et al. 2008; Yoo et al. 2011). In addition to directly targeting the child, data suggest that providing distraction education for parents prior to venous access procedures is beneficial (Kleiber et al. 2001).

Specialized Medical Procedures

Given that pharmacological approaches do not adequately address all of the pain associated with specialized procedures, such as burn care and psychological approaches are necessary (e.g., de Jong et al. 2007; Hoffman et al. 2004; for a review, see Morris et al. 2009). Due to the severity of pain, more engaging interventions have been deemed most effective in decreasing pain during dressing changes and burn treatment, including multimodal distraction in the form of a handheld device, "augmented reality" (using overlays of virtual images onto the actual world), and immersive virtual reality (Miller et al. 2010; Mott et al. 2008; Schmitt et al. 2011; Das et al. 2005). Unfortunately, cost and portability are current barriers to widespread dissemination of these approaches (Hoffman et al. 2011). Psychological approaches for pediatric oncology procedures include hypnosis and imagery techniques (Liossi et al. 2009; Richardson et al. 2006) as well as virtual and standard distraction (Gershon et al. 2004; Windich-Biermeier et al. 2007) and music distraction (Nguyen et al. 2010).

Summary

Pain is an unfortunate and common side effect of routine and specialized acute procedures that can result in negative short- and long-term consequences. Regardless of health status, it is likely that children will undergo numerous potentially painful procedures. Given that children's acute medical pain is often predictable, practitioners can be prepared to minimize, assess, and treat this negative emotional and physical event. Fortunately, there are a range of validated assessment tools available that can be used to quantify the experience and guide intervention approaches. The extant literature not only provides data to support a range of pharmacological and psychological methods to provide children with pain relief, but also provides suggestions on how to effectively combine and tailor these techniques to particular procedures and populations.

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Acute Pain Management in Infants

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Synonyms

Infant pain reduction/therapy/treatment; Infant pain therapy; Infant pain treatment; Pain management in infants

Definition

Infant pain management is defined as any strategy or technique administered to an infant experiencing pain with the intention to lessen pain sensation and/or perception. Pain management strategies include drugs and various nonpharmacological strategies (contextual, cognitive, and behavioral) interventions described in this entry. Pain management during infancy has been almost exclusively focused on acute procedural (including postoperative) pain, thus the emphasis throughout this entry will be on pain reduction strategies for procedural pain. A recent in-depth meta-analysis was conducted by examining 13 different nonpharmacological strategies for infant pain management, which will serve as a key reference for this entry (Pillai Riddell et al. 2011).

Characteristics

Developmental Considerations

A sensitive appreciation of the infant in pain and their complete reliance on their caregiver is a fundamental starting point for approaching infant pain management (Als et al. 1994; Pillai Riddell and Racine 2009). Aside from the caregiver context, infants are also different from other stages due to: (a) greater sensitivity to noxious stimuli due to immature nervous system pathways, (b) immature cognitive ability to comprehend the purpose or predict the end of a painful procedure, (c) limited developmental motor competency to manage their pain, and (d) minimal communication abilities to alert a caregiver who can alleviate their pain. Complicating this issue is that even within infancy, there is a steep development trajectory that impacts the effectiveness and/or appropriateness of certain nonpharmacological interventions.

A recent Cochrane Review of nonpharmacological interventions for infant procedural pain purported that different intervention strategies may be differentially efficacious for infants of different ages (Pillai Riddell et al. 2011). From an age vantage point, the data suggested potential developmental trends of different strategies across the infant/early child stage. For example, while sufficient evidence showed that kangaroo care was one of the most efficacious strategies for preterm infants, limited evidence suggested this was not the case for neonates, and the impact on infants older than 1 month remains unknown. The age of the infant should be considered when selecting the most appropriate intervention for pain management.

An Integrated Approach to Acute Pain Management

Pain management during infancy should be multifaceted and integrated within every step of the

decision-making process, from deciding whether a particular procedure is warranted to determining the least painful methods of undertaking the procedure to selecting the best pain management strategy. An informed understanding of drug therapies (e.g., topical anesthetics, sucrose) and nonpharmacological strategies are a crucial facet of integrated pain management.

Limit Exposure to Pain-Inducing Procedures

Often the routine care of an ill infant necessarily includes the infliction of pain for diagnostic or therapeutic purposes. However, recent guidelines recommend that health care providers attempt to limit the number of painful procedures performed on infants (Joint Fetus and Newborn Committee of the Canadian Paediatric Society and American Academy of Pediatrics 2000). The number and frequency of painful procedures, particularly those often repeated during an infant's hospitalization (e.g., heel lance), should be carefully considered within the developmental stage and health status of the infant. Before subjecting an infant to a painful procedure, caregivers should determine whether the procedure is warranted in relation to the potential benefit to the child's health status. Unnecessary procedures should be avoided and alternative nonpainful or less painful options should always be explored.

Select the Least Painful Diagnostic or Therapeutic Method

If a painful procedure is unavoidable, conducting the procedure in the least painful manner should be considered.

For example, venipuncture is recommended as less painful than heel lance for blood sampling in newborns (Shah and Ohlsson 2011). Another example may be found in the circumcision context. In addition to dorsal penile nerve blocks, the specific clamp used to hold the foreskin (i.e., Mogen) can moderate pain and distress by shortening procedure time (Brady-Fryer et al. 2009). For immunization, using the anterolateral thigh as the injection site, performing intramuscular injections rapidly without prior aspiration, using the least painful injectate formulation, and injecting the most painful vaccine last when multiple vaccines are administered have all been shown to result in a less painful experience for infants (Taddio et al. 2010).

Nonpharmacological Strategies for Management of Infant Acute Pain

In addition to selecting the least distressing procedure possible, it is crucial to try to moderate the pain experience through direct pain management strategies – both pharmacological and nonpharmacological. The following is a review of key nonpharmacological strategies.

Contextual Strategies to Manage Infant Pain The context in which a painful procedure is conducted modifies behavioral and physiological aspects of infant pain. Context can refer to (a) the personal context of the infant, specifically that pain responses of infants are significantly increased with a history of numerous painful procedures and (b) the environmental context, most often the presence of stressful elements such as significant handling, unpredictable noises, multiple caregivers, and bright lights. Limiting and moderating painful experiences for the individual infant in the present may help prevent maladaptive pain experiences in the future (Taddio et al. 2010).

In terms of environmental context, evidence from a recent review (Pillai Riddell et al. 2011) suggests environmental modification techniques (i.e., low noise and lighting, clustering procedures to avoid overhandling, exposure to maternal voice) for preterms have equivocal efficacy, while exposing a preterm or neonate to calming and familiar smells may be efficacious but more methodologically rigorous trials must be conducted. With older infants, simply allowing the parent to be present and very basic parental coaching strategies have not been found to be efficacious in reducing infant pain. More developmentally informed parent management research is needed. In a separate review, the efficacy of music for pain relief in infants was presented as equivocal (Cepeda et al. 2010).

Cognitive Strategies Despite extensive evidence of the value of inhibitory mechanisms in

pain control with older children and adults, researchers have only begun to consider the inhibitory cognitive capabilities of the infant in relation to pain (e.g., distraction). Any intervention that is suspected to have a mechanism of action that impacts an infant's abilities to perceive the pain experience is considered a cognitive strategy. The main intervention falling under this category is distraction. Two types of distractions were reviewed (Pillai Riddell et al. 2011) for older infants with toy-mediated distraction showing no efficacy and video-mediated distraction suggesting promise as a pain management technique for older infants.

Behavioral Strategies Most of the interventional pain research on infants has been conducted within this domain. These strategies involve either direct (e.g., rocking) or indirect (e.g., nonnutritive sucking) manipulation of the infant's body by a caregiver. Common strategies involve nonnutritive sucking (NNS, e.g., pacifiers), skin-to-skin contact (e.g., kangaroo care), swaddling or facilitative tucking, rocking/holding, touch/massage, or some combination of the above.

While the synergistic effect of sucrose and NNS has been demonstrated in a review on sucrose (Stevens et al. 2010), research has also simply investigated the nonpharmacological impact of nonnutritive sucking. Pillai Riddell et al. (2011) demonstrated that there is sufficient evidence to support the use of nonnutritive sucking for pain behaviors in preterm infants and neonates. Another behavioral strategy sharing the sucking mechanism would be breastfeeding. While the research on breast milk alone is equivocal, a recent review on the topic (Shah et al. 2009) concluded that, for term and pre-term neonates, breastfeeding is efficacious for reducing procedural pain.

In the Pillai Riddell et al. (2011) review, skin-to-skin contact (also known as kangaroo care) was noted to have received substantial research attention with preterm infants and was deemed efficacious in reducing pain reactivity and improving pain regulation. Another group of pain management strategies that were reviewed also related to the positioning or containing of the infant during painful procedures. Swaddling and facilitative tucking appear to have sufficient evidence to support efficacy on their own for preterm infants, and emerging evidence suggests preliminary efficacy in neonates.

The effects of rocking, holding, or both were also reviewed for their effect on infant pain-related distress. Rocking is efficacious in improving the regulation of pain-related distress in neonates, but not the initial pain reactivity immediately after the painful stimuli for neonates or older infants. There is also evidence to suggest that simulated rocking and water are inefficacious in reducing pain for preterm infants. Other physical techniques, such as touch and massage, which provide counter-stimulation to the nociceptive input, have shown preliminary evidence suggesting inefficacy across infant stages (i.e. preterm born infants, neonates, and older infants).

Summary

Understanding that unrelieved pain during infancy can alter an individual's pain sensation and perception underscores the importance of infant caregivers' responsibility for being cognizant of the vast array of empirically supported nonpharmacological strategies available to appropriately manage infant pain. Infant age should be taken into consideration when selecting strategies to reduce pain.

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Acute Pain Mechanisms

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Definition

Acute pain is defined as "pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease" (Ready and Edwards 1992). The perception of acute pain requires transduction of noxious mechanical, thermal, or chemical stimuli by nociceptive neurons, integration, and modulation at the level of the spinal cord and ultimately transmission to cortical centers.

Characteristics

Peripheral Nociception

▶ Nociceptors in the skin and other deeper somatic tissues such as periosteum are morphologically free nerve endings or simple receptor structures. A ▶ noxious stimulus activates the nociceptor depolarizing the membrane *via* a variety of stimulus–specific transduction mechanisms. C polymodal nociceptors are the most numerous of somatic nociceptors and respond to a full range of mechanical, chemical, and thermal noxious stimuli. Polymodal nociceptors are coupled to unmyelinated C fibers. Electrophysiological activity in these slow conduction C fibers is characteristically perceived as dull, burning pain. Faster conducting Aδ fibers are coupled to more selective thermal and mechanothermal receptors considered responsible for the perception of sharp or "stabbing" pain (Julius and Basbaum 2001).

Inflammatory–Induced Peripheral Sensitization

A complex interaction of molecules produced during the inflammation acting on nociceptors results in functional, morphological, and electrophysiological changes causing "primary hyperalgesia." Nociceptors are sensitized due to changes in the absolute numbers of Na^+ and K^+ channels and their relative "open-closed" kinetics. This results in neuronal activation in response to innocuous stimuli and spontaneous ectopic discharges. Inflammatory mediators also act to increase the activity of "silent" nociceptors normally unresponsive to even noxious stimuli. There is an increase in many ion channel subtypes, (particularly the ▶ tetrodotoxin (TTX)-resistant Na^+ channel) both on the axon and also in the dorsal root ganglion (DRG) (Kidd and Urban 2001). There is upregulation of receptor expression, including substance P and brain–derived growth factor (BDGF). Morphological changes including sprouting of unmyelinated nerve fibers have also been identified.

Spinal Cord Integration

The majority of somatic nociceptive neurons enter the dorsal horn spinal cord at their segmental level. A proportion of fibers pass either rostrally or caudally in ▶ Lissauer's tract. Somatic primary afferent fibers terminate predominantly in laminas I (marginal zone) and II (substantia gelatinosa) of the dorsal horn where they synapse with projection neurons and excitatory/inhibitory interneurons. Some Aδ fibres penetrate more deeply into lamina V. Projection neurons are of three types classified as nociceptive specific (NS), low threshold (LT), and wide dynamic range (WDR) neurons. The NS neurons are located predominantly in lamina I and respond exclusively to noxious stimuli. They are characterized by a small receptive field. LT neurons, which are located in laminae III and IV, respond to innocuous stimuli only. WDR neurons predominate in lamina V (also in I), display a large receptive field, and receive input from wide range of sensory afferents (C, Aβ) (Parent 1996).

Spinal Modulation and Central Sensitization

Glutamate and aspartate are the primary neurotransmitters involved in spinal excitatory transmission. Fast post-synaptic potentials generated *via* the action of glutamate on AMPA receptors are primarily involved in nociceptive transmission (Smullen et al. 1990). Prolonged C-fiber activation facilitates glutamate-mediated activation of ▶ NMDA receptors and subsequent prolonged depolarization of the WDR neuron (termed "▶ wind-up"). This is associated with removal of a Mg^+ plug from the NMDA-gated ion channel. The activation of this voltage-gated Ca^+ channel is associated with an increase in intracellular Ca^+ and upregulated neurotransmission (McBain and Mayer 1994). The peptidergic neurotransmitters substance P and calcitonin G-related peptide (CGRP) are co-produced in glutaminergic neurons and released with afferent stimulation. These transmitters appear to play a neuromodulatory role, facilitating the action of excitatory amino acids. A number of other molecules including glycine, GABA, somatostatin, endogenous opioids, and ▶ endocannabinoids play modulatory roles in spinal nociceptive transmission (Fürst 1999).

Projection Pathways

Nociceptive somatic input is relayed to higher cerebral centers *via* three main ascending pathways, the spinothalamic, spinoreticular, and spinomesencephalic tracts (Basbaum and Jessel 2000). The spinothalamic path originates in laminae I and V–VII and is composed of NS and WDR neuron axons. It projects to thalamus *via* lateral (▶ neospinothalamic tract), and medial or ▶ paleospinothalamic tracts. The lateral tract passes to the ventro-postero-medial nucleus and subserves discriminative components of pain, while the medial tract is responsible for the autonomic and emotional components of pain. Additional fibers pass to reticular activating system, where they are associated with the arousal response to pain and the periaqueductal gray matter (PAG) where ascending inputs interact with descending modulatory fibers. The spinoreticular pathway originates in laminae VII and VIII and terminates on the medial medullary reticular formation. The spinomesencephalic tract originates in laminae I and V and terminates in the superior colliculus. Additional projections pass to the mesencephalic PAG. It appears that this pathway is not essential for pain perception but plays an important role in the modulation of afferent inputs.

Cortical Representation

Multiple cortical areas are activated by nociceptive afferent input including the primary and secondary somatosensory cortex, the insula, the anterior cingulate cortex and the prefrontal cortex. Pain is a multidimensional experience with sensory-discriminative and affective-motivational components. Advances in functional brain imaging have allowed further understanding of the putative role of cortical structures in the pain experience (Treede et al. 1999).

Localization
1. Primary somatosensory cortex
2. Secondary somatosensory cortex
3. Insula

Intensity
1. Prefrontal cortex
2. Right posterior cingulate cortex
3. Brain stem
4. Periventricular gray matter

Affective Component
1. Left anterior cingulate cortex

Threshold
1. Cingulate cortex
2. Left thalamus
3. Frontal inferior cortex

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Acute Pain Service

Synonyms

APS

Definition

Poor perioperative pain management is remedied not so much in the development of new techniques but by the development of Acute Pain Services (APS) to exploit existing expertise. APSs have been established in many countries. Most are headed up by anesthesiologists. An APS consists of anesthesiologist-supervised pain nurses and an ongoing educational program for patients and all health personnel involved in the care of surgical patients. The benefits of an APS include increased patient satisfaction and improved outcome after surgery. It raises the standards of pain management throughout the hospital. Optimal use of basic pharmacological analgesia improves the relief of postoperative pain for most surgical patients. More advanced approaches, such as well-tailored epidural analgesia, are used to relieve severe dynamic pain (e.g., when coughing). This may markedly reduce risks of complications in patients at high risk of developing postoperative respiratory infections and cardiac ischemic events. Chronic pain is common after surgery. Better acute pain relief offered by an APS may reduce this distressing long-term complication of surgery.

Cross-References

▶ Multimodal Analgesia in Postoperative Pain

Acute Pain Team

Synonyms

APT

Definition

A team of nurse(s) and doctors (usually anesthesiologist(s)) that specializes in preventing and

treating acute pain after surgery, trauma, due to medical conditions, and in some hospitals also labor pain.

Cross-References

- ▶ Postoperative Pain, Acute Pain Management Principles
- ▶ Postoperative Pain, Acute Pain Team

Acute Pain Therapy

Definition

Acute pain therapy is the therapy of acute pain and best defined as "pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease" (Ready and Edwards 1992).

The most common manifestation of acute pain in the medical setting is postoperative pain.

Acute pain therapy is aimed at rapid pain relief and increasingly performed by acute pain services (Macintyre and Scott 2009). The management is guided by guidelines published in a number of countries (Macintyre et al. 2010; Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management 2012).

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Acute Pain, Subacute Pain, and Chronic Pain

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Synonyms

Pain of recent origin; Persisting pain

Definition

Acute pain is pain that has been present for less than 3 months (Merskey 1979; Merskey and Bogduk 1994). Chronic pain is pain that has been present for more than 3 months (Merskey 1979; Merskey and Bogduk 1994). Subacute pain is a subset of acute pain: It is pain that has been present for at least 6 weeks but less than 3 months (van Tulder et al. 1997).

Characteristics

Acute pain, **subacute** pain, and **chronic** pain are defined by units of time, but the concepts on which they are based are more fundamentally related to causation and prognosis. This entry discusses what the definitions imply and the clinical significance of classifying pain into these categories.

Acute pain was first defined by Bonica, in his textbook published in 1953, as "a complex constellation of unpleasant sensory, perceptual and emotional experiences and certain associated autonomic, physiologic, emotional and

behavioural responses" (Bonica 1953). Bonica went on to say "invariably, acute pain and these associated responses are provoked by . . . injury and/or disease . . . or abnormal function." Thus, acute pain was originally defined as a combination of biological and psychological phenomena resulting from bodily impairment. Pain was recognized as playing the important physiological role of making an individual aware of impairment so that they can respond appropriately. Responses include withdrawal from the stimulus causing the pain, to avoid further impairment, and behaviors that minimize the impact of the impairment and facilitate recovery. For example, if a person suffers from a fracture, the resultant pain warns them so that they can limit activities that further deform the injured part. In this way, acute pain is fundamentally associated with the early stage of a condition and with the healing process. It can be expected to last for as long as the healing process takes to restore the impaired tissue.

Chronic pain was originally defined by Bonica as "pain that persists a month beyond the usual course of an acute disease or . . . time for an injury to heal or that is associated with a chronic pathologic process." The implication was that if pain persists beyond the time in which an impaired tissue usually heals, the condition involves more than a simple insult to the tissue. Possible biological explanations for persistent pain would be (1) that the original insult caused damage beyond the capacity of the natural healing process to repair, (2) that the insult was repetitive, causing a series of impairments with sequential healing times, (3) that the condition involved a chronic pathological process which continued to impair tissue over a long period, or (4) that the biological impairment was prolonged by the application of inappropriate interventions. Possible psychological explanations for persistent pain invoke endogenous factors such as cognitions and behaviors that inhibit recovery. Recognition of these endogenous factors led Engel to develop the biopsychosocial model of chronic pain (Engel 1977), recognizing the interplay of prognostic risk factors that influence the duration of pain.

The time factor ascribed by Bonica, 1 month longer than the usual time of recovery, would vary from condition to condition. In order to standardize the definitions of acute and chronic pain, attempts were made to ascribe finite durations to them. In 1974, Sternbach (1974) suggested 6 months as an arbitrary limit, so pain present for up to 6 months would be classed as acute and that present for more than 6 months would be deemed chronic. Others felt 6 months was too long, and discussion ensued. The International Association for the Study of Pain (I.A.S.P.) formed a committee chaired by Merskey to consider such issues and it determined, in 1979 in a publication defining pain terms, that "three months is the most convenient point of division. . ." (Merskey 1979).

Thus, we have the current definitions of acute and chronic pain as pain present for less than, and more than, 3 months. The 3-month period is arbitrary, but it operationalizes the definitions so that pains can be classified readily and systematically as acute or chronic.

The definition of subacute pain has not been addressed so deliberately. The term "subacute" evolved to describe longer-lasting acute pain and has been quoted in the literature (van Tulder et al. 1997; Hippocrates. Of the epidemics) as pain present for between 6 weeks and 3 months. As such, it forms a subset of acute pain. The main division between acute and chronic pain remains at 3 months.

The pragmatism of the time-based definitions should not be allowed to obscure the concept, from which they were derived, that different types of condition give rise to acute and chronic pain. Acute pain should be considered primarily as pain due to a condition that is likely to resolve spontaneously by natural healing. Chronic pain should be considered as signifying a condition unlikely to resolve spontaneously by natural healing. The clinical significance of the categories of pain flows from the implicit likelihood of spontaneous recovery which is crucial to management and prognosis.

The rational management of acute pain is clear when the condition is understood as likely to resolve within a short time by natural healing.

No therapeutic intervention is necessary for recovery, by definition, so rational management involves helping the patient understand the situation, reassuring them, and simply allowing natural healing to proceed. The only active intervention that might be needed is something to ease the pain while healing occurs, and the least invasive measure for that purpose is to be preferred. Such an approach carries the least risk of iatrogenic disturbance of the healing process. It fits nicely with Hippocrates's aphorism of "first, do no harm," (Cochrane 1977) to which doctors have subscribed for centuries. Cochrane promoted this approach in his farsighted work that led to the formal development of evidence-based medicine; he wrote of "the relative unimportance of therapy in comparison with the recuperative power of the human body" (Indahl et al. 1995) and wondered "how many things are done in modern medicine because they can be, rather than because they should be" (Indahl et al. 1995). The effectiveness of the approach has been shown by Indahl et al. (Hippocrates. Of the epidemics) in the management of subacute low back pain and by McGuirk et al. (2001) in the management of acute low back pain.

The rational management of chronic pain is quite different. As the conditions giving rise to chronic pain will not resolve spontaneously, intervention is indicated in virtually every case. The key to the problem is valid diagnosis. Psychosocial factors are important in chronic pain, but their roles are usually secondary to what began and often persists as a biological impairment. If the treating clinician can identify an underlying biological mechanism (a causative injury or disease), many chronic conditions have specific treatments that will control the pain effectively (Lord et al. 1996; Govind et al. 2003). Psychosocial factors must always be considered too and addressed if necessary in the management of the condition, but not to the exclusion of the fundamental (biological) cause. Pursuing the diagnosis of a disorder so as to address its cause seems obvious and is standard practice in other fields of medicine but for some reason is controversial in pain medicine. Chronic low back pain and chronic neck pain in particular are often managed as if precise diagnosis is impossible, which in these days is untrue in the majority of cases (Bogduk 2004). If specific treatment is applied and the pain controlled, associated psychosocial problems can also be expected to remit; there is sound evidence (Wallis et al. 1997) to show this happens and no sound evidence to show that when pain is controlled effectively, pain-related psychosocial problems persist.

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Acute Painful Diabetic Neuropathy

▶ Diabetic Neuropathies

Acute Pelvic Pain

▶ Gynecological Pain and Sexual Functioning

Acute Phase Protein

Definition

Liver proteins whose synthesis increases in inflammation and trauma.

Cross-References

▶ Pain Control in Children with Burns

Acute Postinfectious Polyradiculoneuropathy

▶ Guillain-Barré Syndrome

Acute Postoperative Pain in Children

▶ Acute Pain in Children, Postoperative

Acute Postoperative Pain Therapy

▶ Postoperative Pain, Thoracic and Cardiac Surgery

Acute Procedural Pain in Children

▶ Acute Pain in Children, Procedural

Acute Salpingitis

▶ Chronic Pelvic Pain, Pelvic Inflammatory Disease and Adhesions

Acute Sciatica

▶ Lower Back Pain, Acute

Acute Stress Disorder

Definition

A psychiatric disorder whose onset is within 1 month of exposure to trauma, and whose symptoms are similar to posttraumatic distress disorder. They include reexperiencing the event as with flashbacks and nightmares, dissociative symptoms like numbing, avoidance of any reminder of the trauma, and hyperarousal or increased generalized anxiety.

Cross-References

▶ Pain Control in Children with Burns

Acute-Recurrent Pain

► Chronic Postsurgical Pain (CPSP)

Adaptation

Definition

Adaptation refers to a decrease in the firing rate of action potentials in the face of continuing excitation.

Cross-References

► Coping and Pain
► Mechanonociceptors

Adaptation Phase

Definition

A phase of the psychophysiological assessment designed to permit patients to become acclimated.

Cross-References

► Psychophysiological Assessment of Pain

ADD Protocol

► Assessment of Discomfort in Dementia Protocol

Addiction

Definition

Addiction is a biopsychosocial disease, with a strong genetic component, characterized by the maladaptive use of a substance in a manner that reflects: (1) loss of control over use; (2) compulsive use; (3) continued use despite physical, psychological, or social harm; and (4) craving. Although the word "dependence" often is used as a synonym for addiction, it is imprecise; physical dependence, a phenomenon defined by the occurrence of withdrawal following abrupt discontinuation or dose reduction, or administration of an antagonist, is not addiction, but a physiological phenomenon. Tolerance also is a physiological response, defined by the need for a higher dose to obtain the same effect.

Cross-References

► Cancer Pain, Evaluation of Relevant Comorbidities and Impact
► Cancer Pain Management
► Opioids, Clinical Opioid Tolerance
► Opioid Receptors
► Opioid Therapy in Cancer Patients with Substance Abuse Disorders, Management
► Postoperative Pain, Opioids
► Psychiatric Aspects of the Management of Cancer Pain

Adduction

Definition

Movement of a body part toward the midline of the body.

Cross-References

► Cancer Pain Management, Orthopedic Surgery

Adenoassociated Virus Vectors

Synonyms

AAV

Definition

Adenoassociated virus (AAV)-based vectors are derived from a nonpathogenic parvovirus. AAVs are thought to be naturally defective, because of their requirement for coinfection with a helper virus, such as Ad or HSV, for a productive infection. The single-stranded 4.7-kB DNA genome is packaged in a 20-nm particle. AAV is not associated with any known disease and induces very little immune reaction when used as a vector. For applications requiring a relatively small transgene, AAV vectors are very attractive, but the small insert capacity limits their utility for applications requiring a large transgene.

Cross-References

► Opioids and Gene Therapy

Adenoma

Definition

Adenoma is a benign growth starting in the glandular tissue. Adenomas can originate from many organs including the colon, adrenal, and thyroid. In the majority of cases, these neoplasms stay benign, but some transform to malignancy over time.

Cross-References

► NSAIDs and Cancer

Adenomyosis

Definition

The growth of endometrial glands and stroma into the uterine myometrium, to a depth of at least 2.5 mm from the basalis layer of the endometrium.

Cross-References

► Dyspareunia and Vaginismus
► Gynecological Pain, Neural Mechanisms

Adenomyosis Model

► Visceral Pain Models, Female Reproductive Organ Pain

Adenosine 5′ Triphosphate

Synonyms

ATP

Definition

ATP is one of the five nucleotides that serve as building blocks of nucleic acids. Structurally, adenine and guanine nucleotides are purines, whereas cytosine, thymine, and uracil are pyrimidines. ATP is also the main energy source for cells. More recently it has been recognized that ATP, some of its metabolites, as well as some other nucleotides play a role as extracellular signaling molecules by activating specific cell surface receptors.

Cross-References

► Purine Receptor Targets in the Treatment of Neuropathic Pain

Adenoviral Vectors

Definition

Adenoviral (Ad) vectors are based on a relatively nonpathogenic virus that causes

respiratory infections. The 36 kb linear, double-stranded Ad DNA is packaged in a 100-nm-diameter capsid. In first-generation Ad vectors, the early region 1 (E1) gene was deleted to generate a replication-defective vector and to create space for an inserted gene coding for a marker or therapeutic protein. A cell line that complements the E1 gene deletion allows propagation of the viral vector in cultured cells. These first-generation Ad vectors can accommodate up to approximately 8 kb of insert DNA. In high-capacity Ad vectors, the entire Ad vector genome is "gutted" (hence the alternative name "gutted Ad vector"), removing all viral genes and providing 30 kb of insert cloning capacity.

Cross-References

► Opioids and Gene Therapy

Adequate Stimulus

Definition

A term coined by Sherrington in the 1890s to define the optimal stimulus for the activation of a particular nervous system structure. For nociceptive systems in humans, it is simply defined as "a pain-producing stimulus"; for animal studies it has been defined as a stimulus that produces, or threatens to produce, tissue damage. This is valid for studies of skin sensation, but may not be valid for deep tissues such as viscera.

Cross-References

► Nocifensive Behaviors of the Urinary Bladder
► Visceral Pain Model, Urinary Bladder Pain (Irritants or Distension)

Adherence

Definition

The active, voluntary, collaborative involvement of a patient in a mutually acceptable course of behavior to produce a desired therapeutic result.

Cross-References

► Multidisciplinary Pain Centers, Rehabilitation

Adhesion Molecules

Definition

Circulating leukocytes migrate to injured tissue and the classical steps of rolling, firm adhesion, and chemotaxis depend on a class of cell surface molecules that are known as adhesion molecules. The major families of cell adhesion molecules include the selectins, the immunoglobulin superfamily, and the integrins. The selectins are important for leukocyte homing to particular tissues. Selectins can be expressed on leukocytes (L-selectin (CD62L)), vascular endothelium (P-selectin (CD62P) and E-selectin (CD62E)), and platelets (P-selectin). The initial step of leukocyte migration, rolling, is mediated by selectins on leukocytes (L-selectin) and endothelium (P- and E-selectin). The immunoglobulin superfamily includes intercellular cell adhesion molecule-1 (ICAM-1), ICAM-2, and vascular cell adhesion molecule-1 (VCAM-1). Integrins are a large family of proteins that mediate cell adhesion, migration, activation, embryogenesis, growth, and differentiation by interacting with immunoglobulin superfamily members such as intercellular adhesion molecule-1. Leukocytes migrate through the vessel wall, directed by platelet-endothelial cell adhesion molecule-1 and other immunoglobulin ligands. Many cell–cell interactions are dependent on adhesion and signal

transduction via adhesion molecules, in particular the integrins. Interruption of this cascade can block immunocyte extravasation.

Cross-References

► Opioids in the Periphery and Analgesia

Adjunctive Drugs

Definition

Adjunctive drugs are medications that may be used to manage the side effects of analgesics or potentiate analgesic effects.

Cross-References

► Analgesic Guidelines for Infants and Children

Adjusted Odds Ratio

Definition

"Adjusted Odds Ratio" is the expression of probability after taking into account possible confounding variables.

Cross-References

► Psychiatric Aspects of the Epidemiology of Pain

Adjustment Disorder

Definition

Adjustment disorder, defined by DSM-IV, includes significant depressive symptoms or anxiety symptoms after an identifiable stress, for example, a painful illness, injury, or hospitalization that do not meet severity or duration criteria for a mood or anxiety disorder.

Cross-References

► Somatization

Adjuvant

Definition

An add-on intervention that is used to enhance the benefit of an existing therapy.

Cross-References

► Cancer Pain Management, Adjuvant Analgesics in Management of Pain due to Bowel Obstruction

Adjuvant Analgesic

Definition

Drugs that are added to a traditional analgesic, such as an opioid, to enhance the analgesic effects, or alternatively, drugs that have a primary indication other than pain, but are analgesic in some painful conditions. Examples include some antidepressants and anticonvulsants.

Cross-References

► Analgesic Guidelines for Infants and Children
► Cancer Pain Management, Adjuvant Analgesics in Management of Pain Due to Bowel Obstruction

- ▶ Cancer Pain Management, Nonopioid Analgesics
- ▶ Cancer Pain Management, Principles of Opioid Therapy, Drug Selection
- ▶ Opioid Rotation in Cancer Pain Management

Adjuvant Analgesics in Management of Cancer-Related Bone Pain

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Synonyms

Boney pain; Cancer-related bone pain; Malignant bone pain

Definition

▶ Adjuvant ▶ analgesics in the management of cancer-related bone pain are supplemental treatments that are added to the primary analgesics, usually NSAIDs and opioids. These additional analgesic interventions include radiation, using either palliative ▶ radiotherapy or ▶ radiopharmaceuticals, and two classes of medications, ▶ bisphosphonates and steroids.

Characteristics

Normal bone undergoes constant remodeling in which resorption or formation of bone occurs. The cells involved in these processes are ▶ osteoblasts and ▶ osteoclasts, respectively. These cells respond to signals from several types of mediators, including hormones, prostaglandins, and ▶ cytokines. Tumor cells invade bone and interrupt the balance between osteoblastic and osteoclastic activity, alter bone integrity, and produce pain (Mercadante 1997).

Boney cancers can be exquisitely painful. The severity of pain does not always correlate with radiographic findings. Primary and metastatic bone tumors produce severe pain in about 90 % of patients who develop such tumors. Therefore, aggressive and effective treatment of boney cancer pain is important to maintain patients' quality of life.

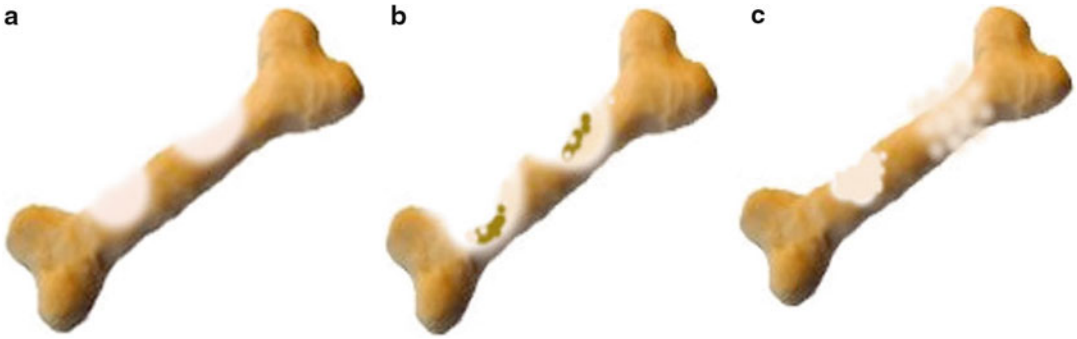
Boney metastases occur in approximately 60–85 % of patients who develop metastatic disease from some of the more common cancers, e.g., bredast, prostate, and lung. Bone is one of the most common metastatic sites. There are also primary bone cancers, e.g., myeloma, osteosarcoma, and Ewing's sarcoma (Mercadante 1997).

When tumors metastasize to bone, they can either be osteolytic, causing boney destruction, or osteoblastic, producing sclerotic boney changes (1). Figure 1 illustrates bone changes in cancer. Examples of these processes are prostatic cancer stimulating osteoblasts to lay down boney material and breast cancer causing osteolysis from stimulation of osteoclasts. Mixed osteoblastic-osteoclastic states also can occur.

Chemical mediators, most notably prostaglandins and cytokines, are released in areas of tumor infiltration. These mediators stimulate osteoclasts or osteoblasts and nociceptors (Payne 1997). When tumor invasion occurs, the highly innervated periosteum that surrounds bone is disturbed, and microfractures may occur within the trabeculae (Payne 1997). Nerve entrapment can also occur as disease progresses, due either to direct tumor effects or to collapse of the skeletal structure (Mercadante 1997; Payne 1997; Benjamin 2002).

Radiopharmaceuticals and bisphosphonates are very effective at treating boney pain; some clinicians consider these first-line therapies. The combination of the two may be additive or synergistic in the treatment of bone pain and dose sparing to lessen dose-related complications of opioid therapy (Hoskin 2003).

Radiotherapy and radiopharmaceuticals are often underutilized therapies for treating bone pain. These two methods of delivering



Adjuvant Analgesics in Management of Cancer-Related Bone Pain, Fig. 1 Cancer effects on bone. (**a**) Normal bone (balance between formation and remodeling). (**b**) Osteolytic bone (unbalanced – increase in osteoclastic activity). (**c**) Osteoblastic bone (unbalanced – increase in bone formation)

radionuclides have comparable efficacy as analgesics. A systematic review of 20 trials (12 using external field radiation and 8 using radioisotopes) showed that 1 in 4 patients received complete pain relief in 1 month and 1 in 3 patients achieved at least 50 % pain relief. For radiotherapy, no differences in efficacy or adverse events were reported with single or multiple fractional dosing in the external field trials. Radiotherapy has been reported to be up to 80 % effective for the treatment of boney pain (McQuay et al. 2000). Radiation can be delivered by localized or widespread external beam radiation and also by systemic bone-seeking radioisotopes. For widespread painful boney metastases, external ▶ hemibody radiation may be administered. With radiation administered above the diaphragm, pneumonitis is a risk (Mercadante 1997). Below the diaphragm administration commonly causes nausea, vomiting, and diarrhea. If whole body radiation is the goal, a period of 4–6 weeks between treatments must occur to allow bone marrow recovery.

An alternative to systemic delivery is the use of radioisotopes that target bone. There are four such agents available: ^{89}strontium (^{89}Sr), ^{32}phosphorous (^{32}P), ^{186}rhenium (^{186}Re), and ^{153}samarium (^{153}Sm). ^{89}Sr is the most commonly used due to its greater specificity for bone. All of these agents target osteoblastic activity. They emit beta particles and are associated with less systemic toxicity than hemibody radiation. However, bone marrow suppression is still a risk. Use of these radiopharmaceuticals is limited due to the expense of the drugs and by storage and disposal requirements (Hoskin 2003). Current radioisotope research is focusing on low-energy electron emitters over the current energetic β emitters to produce therapeutic benefit without bone marrow suppression (Bouchet et al. 2000).

Local irradiation is the treatment of choice for localized bone pain because this method is associated with a low incidence of local toxicity and virtually no systemic toxicity. Radiotherapy often provides relatively prompt pain relief, which is probably due to reduced effects of local inflammatory cells responsible for the release of inflammatory mediators, not tumor regression alone.

Bisphosphonates are another form of systemic treatment for bone pain. A recent meta-analysis of 30 randomized controlled trials, to evaluate relief of pain from bone metastases, supports the use of bisphosphonates as adjunct therapy when primary analgesics and/or radiotherapy is inadequate to treat the pain (Wong and Wiffen 2002). Evidence is lacking for the use of bisphosphonates as first-line therapy for immediate relief of bone pain.

Two bisphosphonates are currently approved for the treatment of painful boney metastasis in the United States: pamidronate and zoledronic acid. Both are intravenous preparations. Doses

of 90 mg pamidronate administered over 2–4 h and 4 mg zoledronic acid administered over 15 min every 3–4 weeks have comparable effectiveness in reducing the need for radiotherapy, decreasing the occurrence of fractures, and reducing pain scores (Lucas and Lipman 2002). The most common adverse effects of both agents include bone pain, anorexia, nausea, myalgia, fever, and injection site reaction. Bisphosphonates have been associated with renal toxicity. Bisphosphonates bind strongly to the bone surface and are taken up by osteoclasts during bone resorption. The osteoclasts are then inhibited and apoptosis is induced. The reduction in the number of osteoclasts inhibits boney metastasis. The bisphosphonates also have an antitumor effect, possibly due to drug uptake in tumor cells (Green and Clezardin 2002).

Although NSAIDs are generally considered first-line drugs for mild cancer pain, their specific role in boney pain is currently being investigated. A recent study in mice evaluated a cycloxygenase-2 (COX-2) selective NSAID on movement-evoked cancer bone pain and tumor burden. A decrease of ongoing and movement-evoked pain was seen in acutely treated mice (day 14 post-tumor implantation), and the same decrease in pain was expressed as well as decreased tumor burden, osteoclastogenesis, and bone destruction, by 50 % of chronically treated mice (day 6 post-tumor implantation) (Sabino et al. 2002). Tumors that invade bone express COX-2, possibly as a mechanism for implantation. This work supports the inhibition of prostaglandin synthesis as being the mechanism of action of the drugs in cancer-related bone pain.

Systemic steroids can also be useful adjuvants in cancer-related bone pain due to their broad-spectrum anti-inflammatory properties. They are most commonly used for spinal cord compression due to collapse of vertebrae or pressure by the tumor itself. Approximately 90 % of prostatic metastases involve the spine, with the lumbar region most commonly affected. Early diagnosis of spinal cord compression is critical. It presents as localized back pain in 90–95 % of patients; muscle weakness, autonomic dysfunction, and sensory loss will follow if untreated (Benjamin 2002). Intravenous dexamethasone is a steroid of choice due to its high potency, low mineralocorticoid activity, and low cost.

When primary analgesics, i.e., nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, no longer control boney pain adequately, adjuvants should be considered. Local radiation should be used when pain is localized, and fractures are ruled out. Pain due to solid tumors tends to respond greater to radiotherapy than bisphosphonates. Generally, as the disease progresses, patients will have received both of these modalities. The role of their use together has yet to be evaluated. To forestall neurological complications of spinal cord compression, steroids are indicated and should be started promptly upon suspicion.

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Adjuvant Analgesics in Management of Cancer-Related Neuropathic Pain

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Definition

An adjuvant analgesic (see "► Adjuvant Analgesic") is any drug that has a primary indication other than pain but is analgesic in some painful conditions.

Characteristics

Although numerous barriers may lead to undertreatment (Van den Beuken-van Everdingen et al. 2007), opioid-based therapy is widely accepted as the first-line strategy for moderate or severe chronic pain due to active cancer and usually is considered to be a second-line approach for those with limited or remote disease. Other categories of analgesic drugs, which include the nonopioids (e.g., the NSAIDs) and the so-called adjuvant analgesics, can be combined with opioid therapy or used independently in selected patients.

Historically, the term "adjuvant analgesic" has referred to a drug that has a primary indication other than pain but may be analgesic in specific painful conditions (Deandrea et al. 2008). This definition is likely to evolve, however, as more of these drugs are used as primary analgesics for various types of pain. When combined with opioid therapy, these drugs collectively may be termed "coanalgesics."

In the treatment of pain related to active cancer, adjuvant analgesics usually are added to opioid therapy after the opioid dose has been titrated to optimize the balance between analgesics and side effects. The occurrence of troublesome side effects before satisfactory analgesia occurs characterizes the pain as "poorly responsive" to the specific opioid and route of administration, and a trial of one or more of these drugs is a common strategy to address this scenario (Lussier and Portenoy 2010).

The decision to offer a trial of an adjuvant analgesic to address poor opioid responsiveness must be based on the findings of a comprehensive assessment of the pain and the patient (Saarto and Wiffen 2007). Rational decisions require an understanding of the nature of the pain, status of the underlying disease and its treatment, salient medical and psychiatric comorbidities, psychosocial factors, and the values and preferences of the patient and family. All this information informs the clinical recommendations and the goals that are pursued.

Types of Adjuvant Analgesics

There have been few studies of the adjuvant analgesics in populations with cancer pain and their use has been based largely on data obtained from studies in other populations and clinical experience (Lussier and Portenoy 2010). Based on this information, some drug classes appear to have potential utility in heterogeneous painful conditions and have been described as "multipurpose" adjuvant analgesics. The drugs in this category are usually combined with opioid therapy to treat patients with opioid-refractory neuropathic pain. The most important groups are the corticosteroids and the analgesic antidepressants. Other adjuvant analgesics only have evidence of efficacy in neuropathic pain and are used in cancer populations for this purpose. The most prominent are anticonvulsants. Other groups of adjuvant analgesics are used to treat bone pain, musculoskeletal pain, or pain and other symptoms in bowel obstruction (Lussier and Portenoy 2010).

First-Line Adjuvant Analgesics in Cancer Pain

Corticosteroids. In populations with advanced cancer, corticosteroids have been widely used for symptoms such as pain, nausea, fatigue, poor appetite, malaise (Loblaw et al. 2005). Although evidence from adequate clinical trials is lacking, there is extensive clinical experience

that suggests benefit for varied pain syndromes, including neuropathic pain resulting from nerve compression, bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. The mechanism of action is unknown, but may relateto the reduction of peritumoral edema, anti-inflammatory effects, and direct effects on nociceptive neural systems.

Although many clinicians favor dexamethasone, presumably because of its relatively low mineralocorticoid effects, there are no comparative trials of the drugs in this class. Prednisone and methylprednisolone are acceptable alternatives. Based on clinical experience in the treatment of emergent spinal cord compression (Loblaw et al. 2005), a high-dose dexamethasone regimen has been used to treat very severe and escalating pain (sometimes called "pain emergencies"). The more common low-dose regimen comprises 1–2 mg per day, with dose escalation as needed to obtain symptom control.

Antidepressants. Analgesic efficacy is best established for some of the tricyclic compounds and the serotonin-norepinephrine reuptake inhibitors (SNRIs). The analgesic mode of action presumably relates to the enhanced availability of monoamines at synapses in pathways that are part of the descending pain modulating system (Saarto and Wiffen 2007).

The tricyclic antidepressants include tertiary amine compounds, such as amitriptyline, imipramine, and doxepin, and secondary amine compounds, such as nortriptyline and desipramine. The latter drugs are less anticholinergic and sedating and generally are preferred for use in patients with cancer. All the tricyclic compounds are relatively contraindicated in patients with serious heart disease, severe prostatic hypertrophy, and narrow-angle glaucoma.

The SNRIs include duloxetine, minalcipran, venlafaxine, and desvenlafaxine. Evidence of analgesic efficacy is best for duloxetine (Arnold et al. 2005; Wernicke et al. 2006), but like other drugs, trials in cancer pain are lacking. The risk profile of the SNRIs is more favorable than that of the tricyclic antidepressants, and clinicians commonly initiate a trial of an analgesic antidepressant with one of these drugs. The SNRIs side effects include nausea, sexual dysfunction, and somnolence or mental clouding.With the exception of bupropion and two SSRIs (paroxetine and citalopram), analgesic efficacy has not been demonstrated for other antidepressants (Semenchuk et al. 2001; Sindrup et al. 1990, 1992). Bupropion, which is a dopamine and norepinephrine reuptake blocker, is distinguished by its tendency to be activating. Patients with pain complicated by fatigue or somnolence may be considered for a trial of this drug.

Anticonvulsants. The gabapentinoids, gabapentin and pregabalin, often are considered first-line therapy for neuropathic pain of diverse types in patients without major depression (Dworkin et al. 2007). They are usually considered after an antidepressant trial if pain is complicated by depressed mood. In the cancer population, these drugs are first-line co-analgesics, along with the corticosteroids and antidepressants.

Both gabapentin and pregabalin act by binding to the alpha-2 delta protein modulator of the N-type, voltage-gated calcium channel. Binding to this protein reduces calcium influx into the neuron and lessens the likelihood of depolarization. The main difference between the drugs is pharmacokinetic. Absorption of gabapentin is facilitated by a saturable transporter in the small bowel and central nervous system. At relatively higher doses (approximately 1,800 mg per day), kinetics becomes nonlinear and less absorption occurs with each dose increase. This means that gabapentin has a pharmacokinetic ceiling, which coexists with a possible pharmacodynamic ceiling of the type observed with all adjuvant analgesics. Pregabalin has linear kinetics, which simplify dose titration.

Gabapentin and pregabalin have a relatively good safety profile. They do not require hepatic metabolism and there are no known drug-drug interactions. They are renally excreted and the dose must be adjusted in the setting of renal failure. Their common side effects are mental clouding, dizziness, somnolence, and peripheral edema.

In the medically frail cancer patient, gabapentin often is initiated at a dose of approximately of 100–300 mg per day. The dose is gradually escalated while monitoring analgesia and side effects. If pain relief does not occur, dose escalation in the absence of an analgesic ceiling or adverse effects typically extends to 3,600 mg per day and sometimes higher. The starting dose of pregabalin is usually 50–75 mg per day (or lower, 25 mg, in those with advanced age or frailty) and escalation to the usual effective dose of 150–300 mg twice daily typically is accomplished in 2–3 steps over a week or two. Although head-to-head prospective studies comparing the relative efficacy of gabapentin and pregabalin are lacking, it is appropriate to consider a follow-on trial of the alternate drug if an attempt with the first does not yield a benefit.

Other anticonvulsants also have been studied as analgesics. Divalproex and phenytoin are older drugs and have a long history of use for neuropathic pain. Newer anticonvulsants generally have more favorable side effect and safety profiles, however, and are preferred. Although evidence of analgesic effects is very limited for all of these drugs, trials of oxcarbazepine, topiramate, and lamotrigine are usually considered before others.

Other Multipurpose Drugs Used for Neuropathic Pain

Alpha-2 Adrenergic Agonists. Clonidine and tizanidine are alpha-2 adrenergic agonists. Clonidine has been used in diverse types of chronic pain; intraspinal clonidine has been shown to reduce neuropathic pain in patients with severe cancer pain partly responding to opioids (Eisenach et al. 1995). Tizanidine has demonstrated analgesic efficacy in myofascial pain syndrome and chronic headache. The use of these drugs is limited by their side effects, which include dry mouth, somnolence, and orthostatic hypotension. A trial usually is considered only after other adjuvant analgesics have proved ineffective. Tizanidine has less hypotensive effects and may be preferred over clonidine for a trial in medically frail patients with opioid-refractory pain. It may be initiated at 1–2 mg at night, and the dose is then gradually escalated while monitoring analgesia and adverse effects.

Cannabinoids. Cannabinoids interact with an endogenous system that includes cannabinoid-like ligands, the endocannabinoids, and multiple receptors in both the periphery and central nervous system. There are several drugs commercially available and others under study. An oromucosal spray containing tetrahydrocannabinol (THC) plus cannabidiol (and smaller concentrations of other compounds), known as nabiximols, is undergoing worldwide development and has already been approved in several countries for spasticity due to multiple sclerosis and opioid-refractory pain due to cancer (Russo et al. 2007).

Topical Analgesics. Although topical analgesics have been used for neuropathic pain, they have the potential for broader application. Creams and patches containing local anesthetics, capsaicin preparations, nonsteroidal anti-inflammatory drugs, tricyclic compounds, or other drugs are available commercially or may be compounded, singly or in combination. The most widely used topical therapies for pain contain local anesthetics. A lidocaine 5 % patch now is approved for the treatment of postherpetic neuralgia and now is widely used in focal and regional pains of all types. Topical analgesics containing local anesthetics are also available in creams and gels.

The mechanism of capsaicin is to release and then deplete substance P from the terminals of afferent C-fibers. Treatment with low-concentration (e.g., 0.1 %), commercially available creams has been demonstrated to yield weak to moderate analgesic effects in controlled trials of various types of neuropathic and arthropathic pain (Knotkova et al. 2008). A high-concentration (8 %) capsaicin patch has become available in some countries for the treatment of postherpetic neuralgia; this patch is applied for 1–2 h and if effective, can yield analgesia that lasts months.

Other Drugs

Several other drug classes also are considered for refractory cancer-related neuropathic pain.

Sodium channel blockade has been recognized as an analgesic mechanism for decades. Oral agents, such as mexiletine, and brief infusion of parenteral lidocaine, may have utility for pain. These drugs are generally safe (Wymer et al. 2009), but require cautious administration in medically ill populations. A new drug, lacosamide, has a unique mechanism involving sodium channel modulation and also may be considered for a trial in refractory neuropathic pain(Ben-Ari et al. 2007).

The *N*-methyl-D-aspartate (NMDA) receptor is involved in both the sensitization of central neurons and the functioning of the opioid receptor. Evidence that NMDA receptor antagonists are analgesic in clinical pain is very limited. In populations with cancer-related neuropathic pain, particularly those with advanced illness, ketamine often is considered (Chizh and Headley 2005). This drug is a dissociative anesthetic and has a side effect profile that includes psychotomimetic effects and a hypersympathetic state. For refractory pain, it may be tried in subanesthetic doses as a brief infusion (repeated as necessary), a more prolonged infusion, or oral therapy. Treatment must be carefully monitored and coadministration of a sedative-hypnotic drug is commonly used to reduce the risk of psychotomimetic side effects.

Other NMDA receptor antagonists, such as memantine, amantadine, and dextromethorphan, also have been studied in diverse types of neuropathic pain, but results have been mixed (Hugel et al. 2003). They are rarely considered for trials in cancer-related neuropathic pain that has not responded to other agents.

GABA receptors may be involved in pain processing. Among the GABA receptor inhibitors are the benzodiazepines, which affect the $GABA_A$ receptor subtype, and baclofen, which affects the $GABA_B$ subtype. Evidence supporting the use of benzodiazepines as analgesics is very limited. Based on clinical experience, a trial of clonazepam often is considered for refractory neuropathic pain, especially if pain is accompanied by anxiety (Fromm et al. 1984). Baclofen is an antispasticity drug with established efficacy in trigeminal neuralgia (Fromm et al. 1984). It has also been used anecdotally for neuropathic pain of other types.

Summary

The development of adjuvant analgesics during recent decades has been rapid, and there now are numerous drugs in many classes. The clinical approach to the selection and administration of these drugs in populations with cancer pain remains largely empirical, based on data obtained in other populations and experience. Studies that compare the safety and effectiveness of these drugs in various indications are badly needed.

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Adjuvant Arthritis

▶ Arthritis Model, Adjuvant-Induced Arthritis

Adjuvant-induced Arthritis

▶ Arthritis Model, Adjuvant-Induced Arthritis

Adolescent

▶ Pain in Children

Adrenergic Agonist

Definition

An adrenergic agonist is a ligand that binds to adrenergic receptors and elicits a response in the cell or tissue in which the receptors are present.

Cross-References

▶ Adrenergic Antagonist
▶ Sympathetically Maintained Pain, Clinical Pharmacological Tests

Adrenergic Antagonist

Definition

An adrenergic antagonist is either a drug that prevents other ligands from binding to adrenergic receptors in the case of a competitive antagonist or, in the case of a noncompetitive antagonist, a ligand that when bound to the receptor prevents agonists from eliciting a response.

Cross-References

▶ Adrenergic Agonist
▶ Sympathetically Maintained Pain, Clinical Pharmacological Tests

Adrenergic Receptors

Definition

Adrenoceptors (adrenergic receptors) are G protein-coupled receptors activated by release of norepinephrine (noradrenaline), epinephrine (adrenaline), and various adrenergic agonists. They are expressed by neurons in the central, peripheral sensory, and sympathetic nervous systems as well as in end organs innervated by sympathetic fibers. Activation of α_1- or $\beta_{1\ or\ 4}$-adrenoceptors produces neuronal excitation or smooth muscle contraction, whereas activation of α_2-adrenoceptors inhibits neuronal firing or neurotransmitter release, resulting in sedation, analgesia, or hypotension. Noradrenergic sympathetic postganglionic neurons express α_2-adrenoceptors, the activation of which presynaptically inhibits norepinephrine release; nociceptive primary sensory neurons also express α_2-adrenoceptors, the activation of which inhibits release of nociceptive neurotransmitters in spinal cord dorsal horn. Activation of $\beta_{2\ or\ 3}$-adrenoceptors produces smooth muscle relaxation or cardioinhibition; β-adrenoceptors appear less involved in pain than α-adrenoceptors.

Cross-References

▶ Sympathetically Maintained Pain in CRPS I, Human Experimentation

Adult Respiratory Distress Syndrome

▶ ARDS

Adverse Effects

Definition

Unwanted side effects of drug treatment.

Cross-References

▶ NSAIDs, Adverse Effects

Adverse Neural Tension

Definition

Adverse neural tension is defined as abnormal physiological and mechanical responses created by the nervous system components, when their normal range of motion and stretch capabilities are tested.

Cross-References

▶ Chronic Pelvic Pain, Physical Therapy Approaches, and Myofascial Abnormalities

Adverse Selection

Definition

Adverse selection can defined as a situation when people who have worse than average risks are most likely to acquire insurance.

Aerobic Exercise

▶ Exercise

Affective

Definition

Category of experiences associated with emotions that range from pleasant to unpleasant.

Cross-References

► McGill Pain Questionnaire

Affective Analgesia

Definition

Affective analgesia is the preferential suppression of the emotional reaction of humans and animals to noxious stimulation.

Cross-References

► Thalamo-Amygdala Interactions and Pain

Affective Component (Aspect, Dimension) of Pain

Definition

Affective component of pain refers to that quality of the pain experience that causes pain to be unpleasant or aversive. It may be involved in the "suffering" component of persistent pain, and could also involve separate neural pathways in the brain than those involved in the sensory-discriminative component of pain (discrimination and localization of a nociceptive stimulus).

Cross-References

► Amygdala, Pain Processing and Behavior in Animals
► Hypnotic Analgesia
► Primary Somatosensory Cortex (S1), Effect on Pain-Related Behavior in Humans
► Primary Somatosensory Cortex (SI)
► Thalamo-Amygdala Interactions and Pain

Affective Pain Processing

► Thalamo-Amygdala Interactions and Pain

Affective Responses

Definition

Changes in mood or emotion-related behaviors elicited by noxious stimuli. Examples of these responses include aggressive behavior and freezing.

Cross-References

► Spinohypothalamic Tract, Anatomical Organization, and Response Properties
► Spinothalamic Neuron

Affective-Motivational

Definition

Relating to affect and forces that drive behavior.

Cross-References

► Secondary Somatosensory Cortex (S2) and Insula, Effect on Pain-Related Behavior in Animals and Humans

Affective-Motivational Dimension of Pain

Definition

A component of the pain experience that signals the unpleasant hedonic qualities and emotional reactions to noxious stimulation and generates the motivational drive to escape from or

terminate such stimulation. This corresponds to the subjective experience of the immediate unpleasantness of pain and the urge to respond behaviorally.

Cross-References

- ▶ Pain Processing in the Cingulate Cortex, Behavioral Studies in Humans
- ▶ Thalamo-Amygdala Interactions and Pain

Afferent Fiber/Afferent Neuron

Definition

Afferent fibers are any of the nerve fibers that bring information in form of action potentials (spikes) to a target neuron. The term is most often used in relation to the peripheral nervous system. In this case afferent fibers carry information toward the central nervous system. The cell bodies of afferent fibers in the peripheral nerves reside in dorsal root, trigeminal or nodose ganglia.

Afferent Projections

Definition

See ▶ afferent fibers.

Cross-References

- ▶ Afferent Fiber/Afferent Neuron

Afferent Signal

Definition

An afferent signal is a neuronal signal in the form of action potentials (spikes) that are carried toward target neurons. In peripheral nerves the afferent signal is carried toward the central nervous system.

Cross-References

- ▶ Afferent Fiber/Afferent Neuron

Afterdischarge(s)

Definition

Afterdischarge is the continued neuronal response after an inciting stimulus has terminated, indicating a prolonged reaction.

Cross-References

- ▶ Molecular Contributions to the Mechanism of Central Pain
- ▶ Spinal Cord Injury Pain Model, Contusion Injury Model
- ▶ Trigeminal Neuralgia: Diagnosis and Treatment

Afterhyperpolarization

Synonyms

AHP

Definition

The term refers to the membrane potential of an axon or whole neuron during recovery following an action potential. AHP indicates a more negative potential compared to the resting or prestimulus membrane potential. AHPs in different neurons may have different time constants and different molecular mechanisms. AHPs influence the conduction velocity and excitability of axons.

Cross-References

- ▶ Mechano-insensitive C-Fibers, Biophysics
- ▶ Molecular Contributions to the Mechanism of Central Pain

Afterpains

- ▶ Postpartum Pain

Age and Chronicity

- ▶ Pain in the Workplace, Risk Factors for Chronicity, and Demographics

Age Regression

Definition

This refers to the use of hypnotic suggestion to return to an earlier time of life in imagination. This technique is used in the context of psychotherapy utilizing hypnosis and may be an exploratory or therapeutic technique. Studies suggest that age regression is extremely unreliable in retrieving accurate information about the past, but that it can be considered part of the individual's life narrative.

Cross-References

- ▶ Therapy of Pain, Hypnosis

Age-Related Pain Diagnoses

Definition

Pain diagnoses that are more frequent in the elderly, like osteoarthritis, zoster, arteritis, polymyalgia rheumatica, or artherosclerotic peripheral vascular disease.

Cross-References

- ▶ Psychological Treatment of Pain in Older Populations

Aggression

- ▶ Anger and Pain

Agonist

Definition

An agonist is an endogenous or exogenous substance that can interact with and activate a receptor, initiating a physiological or a pharmacological response characteristic of that receptor.

Cross-References

- ▶ Postoperative Pain, Appropriate Management

Agreed Medical Examination

- ▶ Independent Medical Examinations

AHP

- ▶ Afterhyperpolarization

AIDS and Pain

- ▶ Pain in Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

Alcock's Canal

Definition

This is the space within the obturator internus fascia lining the lateral wall of the ischiorectal fossa that transmits the pudendal vessels and nerves.

Cross-References

► Clitoral Pain

Alcock's Canal Syndrome

► Pudendal Neuralgia in Women

Alcohol-induced Pancreatitis

► Visceral Pain Model, Pancreatic Pain

Alcoholism

► Metabolic and Nutritional Neuropathies

Alfentanil

Definition

This is a very potent short-acting opioid.

Cross-References

► CRPS-1 in Children

Algesia

► Hyperalgesia

Algesic Agent/Algesic Chemical

Definition

A chemical substance that elicits pain when administered (or released from pathologically altered tissue) in a concentration that excites nociceptors. Examples are serotonin (5-hydroxytryptamine) and bradykinin (a nonapeptide).

Cross-References

► Sensitization of Muscular and Articular Nociceptors
► Visceral Pain Model, Angina Pain

Algodystrophy

► Complex Regional Pain Syndromes, Clinical Aspects
► CRPS, Evidence-Based Treatment
► Neuropathic Pain Models, CRPS-I Neuropathy Model
► Postoperative Pain, Acute Presentation of Complex Regional Pain Syndrome
► Sympathetically Maintained Pain in CRPS I, Human Experimentation

Algogen

Definition

Chemical substance with the ability to induce pain and hyperalgesia.

Cross-References

► Polymodal Nociceptors, Heat Transduction
► UV-Induced Erythema

Algogenic Actions of Protons

Definition

Lowering muscle pH causes acute ischemia pain since protons produce non-adapting excitation of muscle nociceptors.

Cross-References

► Tourniquet Test

Algometer

Definition

An algometer is a calibrated device that can apply painful stimuli of graded intensities. A commonly used device is the pressure algometer, which is used to evaluate deep tissue pain threshold (i.e., muscle, tendon, periosteum).

Cross-References

► Threshold Determination Protocols

Algoneuron

Definition

Algoneurons are peripheral afferents that, when activated, evoke a sensation of pain.

Note: In contrast to "nociceptor," "algoneuron" focuses on the *sensory effect* of the afferent's signal and *not its receptive field properties*. Under normal circumstances, Aδ- and C-nociceptors are algoneurons of high threshold. Peripheral sensitization might cause these to become low-threshold algoneurons. In the presence of central sensitization, Aβ low-threshold mechanoreceptors (LTMs) can function as algoneurons.

Alice-in-Wonderland Syndrome

Definition

A disorder of perception where visual disturbances occur. It was given its name due to the fact that the syndrome's symptoms are remarkably similar to the distortions in body image and shape as experienced by the main character in Lewis Carrol's 1865 novel "Alice in Wonderland." Objects either appear to be much larger (macropsia) or smaller (micropsia) than normal, and there is also usually an impaired perception of time and place.

Cross-References

► Migraine, Childhood Syndromes

ALIF

Synonyms

Anterior lumbar interbody fusion

Definition

Anterior lumbar interbody fusions are grafts/cages placed between the vertebral bodies by anterior approach.

Cross-References

► Spinal Fusion for Chronic Back Pain

Allele Dosage Study

► Association Study

Alleles

Definition

Alternate forms of a gene or genetic locus; the basic unit of genetic variability. Organisms inherit two alleles (maternal and paternal) of every gene, which may or may not be identical. Different alleles may produce protein isozymes (i.e., proteins with different amino acid sequences), alter expression levels of proteins, or have no effect whatsoever.

Cross-References

► Cell Therapy in the Treatment of Central Pain
► Opioid Analgesia, Strain Differences

Allocortex

Definition

The allocortex is a three-layered cortex. In the hippocampus, the three layers are the stratum oriens, the stratum pyramidale, and the molecular zone consisting of the stratum radiatum and stratum lacunosum-moleculare.

Cross-References

► Nociceptive Processing in the Hippocampus and Entorhinal Cortex, Neurophysiology and Pharmacology

Allodynia

► Calcium Channels in the Spinal Processing of Nociceptive Input

Allodynia (Clinical, Experimental)

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Synonyms

Dynamic mechanical hyperalgesia; Obsolete: hyperesthesia; Touch-evoked pain;

Definition

The term "allodynia" was introduced to describe a puzzling clinical phenomenon; in some patients, gentle touch may induce a pronounced pain sensation ("touch-evoked pain"). In the current taxonomy of the International Association for the Study of Pain (IASP), allodynia is defined as pain induced by stimuli that are not normally painful.

If taken literally, this definition means that any reduction in pain threshold would be called "allodynia." According to the IASP taxonomy, increases in pain to suprathreshold stimuli are called "► hyperalgesia." Because the neural mechanisms of ► sensitization typically cause a leftward shift in the stimulus-response function that encompasses both reduced thresholds and increased suprathreshold responses, these definitions have been controversial ever since their introduction. Moreover, behavioral studies in animals often use withdrawal threshold measures without any suprathreshold tests, leading to an inflationary use of the term "allodynia" in studies that often bear no resemblance to the initial clinical phenomenon. An alternative definition

that captures the spirit of the original clinical observations (Merskey 1982; Treede et al. 2004) defines allodynia as pain due to a non-nociceptive stimulus.

This definition implies that allodynia is pain in the absence of the adequate stimulus for nociceptive afferents (touch is not a "nociceptive stimulus"). Operationally, the presence of mechanical allodynia can be tested with stimulators that do not activate nociceptive afferents (e.g., a soft brush). The situation is less clear for other stimulus modalities such as cooling stimuli. For those cases, where it is not clinically possible to determine whether or not the test stimuli activate nociceptive afferents, "hyperalgesia" is useful as an umbrella term for all types of increased pain sensitivity.

Characteristics

Some patients – particularly after peripheral nerve lesions – experience pain from gentle touch to their skin, a faint current of air, or mild cooling from evaporation of a drop of alcohol. Touch-evoked pain may adapt during constant skin contact but is readily apparent for all stimuli applied in a stroking movement across the skin (Fig. 1). Touch-evoked pain is also called dynamic mechanical allodynia (Ochoa and Yarnitsky 1993). Reaction times of touch-evoked pain are too short for C-fiber latencies, and it can be abolished by an A-fiber conduction block (Campbell et al. 1988). Moreover, both mechanical and electrical pain thresholds in those patients are often identical to the normal tactile detection thresholds (Gracely et al. 1992). These lines of evidence suggest that this strange pain sensation is mediated by Aβ-fiber low-threshold mechanoreceptors (touch receptors).

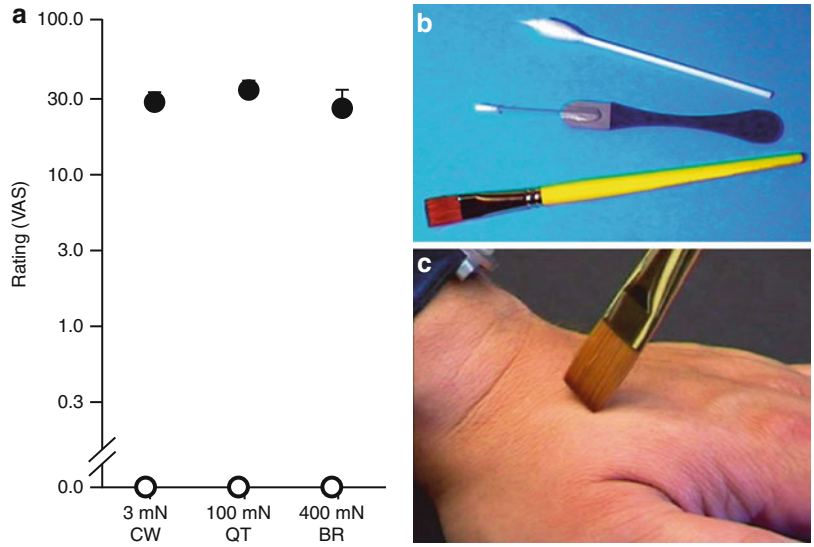
It was difficult to find the correct term to describe this clinical phenomenon. Because of the altered perceived quality of tactile stimuli, it was called "painful tactile dysesthesia." Due to the increased perception in response to a tactile stimulus, it was also called "hyperesthesia" defined as "a state in which a stimulus, which does not cause pain in normally innervated tissues, does cause pain in the affected region" (Noordenbos 1959; quoted from Loh and Nathan (1978), who added that this was typically a very slight stimulus). This definition, however, ignored the change in perceived quality (from tactile to painful). According to the perceived quality, this phenomenon should have been called "mechanical hyperalgesia."

At the time when most of the clinical characteristics of allodynia had been established, the only known neurobiological mechanism of hyperalgesia was peripheral sensitization of nociceptive afferents (Raja et al. 1999), leading to heat hyperalgesia at an injury site (primary hyperalgesia). Peripheral sensitization differs from the clinical phenomenon described above in many characteristics; it is spatially restricted to injured skin, and the enhanced sensitivity is for heat stimuli, not for mechanical stimuli. The concept of central sensitization was introduced much later than the concept of peripheral sensitization (Woolf 1983). Thus, hyperalgesia also appeared to be an inadequate term at that time. As a consequence, a new word was introduced, "allodynia," indicating "a different type of pain" (Merskey 1982).

Dynamic mechanical allodynia occurs in a variety of clinical situations: secondary hyperalgesia surrounding an injury site, postoperative pain, joint and bone pain, visceral pain and delayed onset muscle soreness, as well as many ▶ neuropathic pain states.

Mechanisms of Allodynia

The fact that both nociceptive and tactile primary afferents converge on one class of central nociceptive neurons (WDR, wide dynamic range) led to the proposal that central sensitization of WDR neurons to their normal synaptic input may be the mechanism behind dynamic mechanical allodynia. These mechanisms were elucidated in an experimental surrogate model (▶ secondary hyperalgesia surrounding a site of capsaicin injection). Parallel experiments in humans and monkeys showed that capsaicin injection induced dynamic mechanical allodynia (LaMotte et al. 1991) without any changes in the mechanical response properties of nociceptive afferents



Allodynia (Clinical, Experimental), Fig. 1 Assessment of dynamic mechanical allodynia. A 57-year-old male patient with a plexus lesion following abdominal surgery on the left side. (**a**) Gentle tactile stimuli that do not activate nociceptive afferents were moderately painful on the affected left leg (*filled circles*), whereas they elicited normal non-painful touch sensation on the unaffected right leg (*open circles*). Note that the intensity of allodynia was independent of the pressure exerted by the three stimulators that were stroked across the skin at the same speed. *CW* cotton wisp, *QT* cotton-tipped applicator, *BR* brush. Mean ± SEM across five measurements. (**b**) Photograph of the three stimulators used for the assessment of dynamic mechanical allodynia in the quantitative sensory testing (QST) protocol of the German Research Network on Neuropathic Pain (Rolke et al. 2006) and video of their mode of application

(Baumann et al. 1991). The responses of spinal cord WDR neurons to brushing, however, were increased following capsaicin injection; in addition, nociceptive-specific HT neurons became responsive to brushing stimuli (Simone et al. 1991). Thus, ▶ central sensitization consisted of enhanced responses of central nociceptive neurons to a normal peripheral input. This was confirmed in humans by electrical microstimulation of tactile Aβ-fibers that evoked a sensation of touch in normal skin but touch plus pain in hyperalgesic skin (Torebjörk et al. 1992). Central sensitization resembles long-term potentiation of excitatory synaptic transmission in other neural systems (Sandkühler 2000). High-frequency electrical stimulation patterns that induce long-term potentiation of synaptic transmission in the dorsal horn also induce mechanical allodynia in human subjects that may outlast the conditioning stimulus for several hours (Klein et al. 2004). Chronic maintenance of the central sensitization leading to allodynia, however, appears to depend on a continuous peripheral nociceptive input that can be dynamically modulated, e.g., by heating and cooling the skin (Gracely et al. 1992; Koltzenburg et al. 1994).

Conflicting Terminology and the Inflationary Use of "Allodynia"

After the introduction of the word "allodynia," there were two terms that could describe a state of increased pain sensitivity, hyperalgesia and allodynia. Researchers and clinicians alike started to wonder when to use which term. The 1994 edition of the IASP pain taxonomy addressed this issue by reserving the word "hyperalgesia" for an enhanced response to a stimulus that is normally painful. Pain induced by stimuli that are not normally painful was to be called "allodynia." Technically, this means that any reduction in pain threshold shall be called "allodynia" (Cervero and Laird 1996).

Allodynia (Clinical, Experimental), Table 1 Peripheral and central sensitization, allodynia, and hyperalgesia

Clinical phenomenon	Input	Peripheral sensitization	Central sensitization	IASP taxonomy 1994		Proposed taxonomy	
				Allodynia	Hyperalgesia	Allodynia	Hyperalgesia
Touch-evoked pain	Tactile Aβ-fibers		X	X		X	(X[a])
Reduced threshold to pinprick pain	Aδ-nociceptors		X	X			X
Increased response to pinprick pain	Aδ-nociceptors		X		X		X
Reduced threshold to heat pain	Aδ- and C-nociceptors	X		X			X
Increased response to heat pain	Aδ- and C-nociceptors	X			X		X

[a]Hyperalgesia is proposed to be used as an umbrella term for all types of enhanced pain sensitivity

Table 1 illustrates why this definition was controversial ever since its introduction. ▶ Peripheral sensitization leads to a leftward shift of the stimulus-response function for heat stimuli, consisting of both a reduction in threshold and an increase in response to suprathreshold stimuli (Raja et al. 1999). The psychophysical correlate, ▶ primary hyperalgesia to heat, now needs to be described with two different terms, simply depending on how it is being tested; if a researcher decides to determine heat pain threshold, its reduction is called "heat allodynia"; if the researcher decides to use suprathreshold stimuli, the increase in perceived pain is called "heat hyperalgesia." Thus, the 1994 IASP taxonomy led to the paradoxical situation that two different names are used to describe a unitary phenomenon, the psychophysical correlate of peripheral sensitization. Likewise, secondary hyperalgesia to pinprick stimuli as a psychophysical correlate of central sensitization to A-fiber nociceptor input is also characterized by reduced pain threshold plus increased suprathreshold pain (Treede et al. 2004).

The 1994 IASP taxonomy was only reluctantly accepted in the scientific community, since time-honored terms such as primary and secondary hyperalgesia (for review see Treede et al. 1992) were artificially fractionated. In the recent past, allodynia was used for an increasing number of phenomena, particularly in animal studies, simply because it is often less difficult to obtain a threshold measure than a suprathreshold measure. This excessive use of the term allodynia, however, has distracted from its original clinical implications. The mechanisms of reduced heat pain threshold have nothing in common with touch-evoked pain, yet both are being called allodynia. In fact, most of the animal studies that use the term "allodynia" are irrelevant for clinical allodynia, because they study reduced withdrawal thresholds for nociceptive stimuli (heat or pinprick).

Instead of artificially dividing two sub-phenomena that by mechanisms of sensitization are intimately linked (threshold and suprathreshold changes), the terms allodynia and hyperalgesia should provide guidance toward a mechanism-based classification of pain. Contrary to the intentions of the authors of the IASP taxonomy, the inflationary use of "allodynia" was also counterproductive for furthering the understanding of the clinical phenomenon that it was originally conceived for, touch-evoked pain.

Clinical Implications and a Unifying Proposal

Semantically, the term "allodynia" implies pain by a stimulus that is alien to the nociceptive system (αλλοσ, Greek for "other"). Thus, allodynia should only be used when the mode of testing allows inference to a pain mechanism that relies on activation of a non-nociceptive input (e.g., low-threshold mechanoreceptors). If pain is reported to stroking the skin with gentle tactile

stimuli, this mechanism is strongly implied, and such tests are easily employed in clinical trials as well as in daily practice. The distinction whether enhanced pain sensitivity is due to facilitation of nociceptive or non-nociceptive input is less clear for other stimuli. For example, pain due to gentle cooling, which is a frequent finding in some neuropathic pain states, is still enigmatic and so is the distinction of whether it should be called hyperalgesia or allodynia to cold. Peripheral sensitization of nociceptive afferents, central sensitization to non-nociceptive cold fiber input, or central disinhibition by selective loss of a sensory channel specific for non-noxious cold that exerts a tonic inhibition of nociceptive channels are valid alternatives (Wasner et al. 2004).

Thus, in many cases, the mechanism of enhanced pain sensitivity may be unknown, and it will not be evident whether or not a test stimulus activates nociceptive afferents. For these situations, it is useful to have an umbrella term that does not imply any specific mechanism. Hyperalgesia traditionally was such an umbrella term, corresponding to the leftward shift in the stimulus-response function relating magnitude of pain to stimulus intensity. Parallel to the definition of sensitization, hyperalgesia was characterized by a decrease in pain threshold, increased pain to suprathreshold stimuli, and spontaneous pain. We have therefore suggested the reinstitution of hyperalgesia as the umbrella term for increased pain sensitivity in general (as the antonym to ► hypoalgesia) and returning the term allodynia to its old definition, i.e., describing a state of altered somatosensory signal processing wherein activation of non-nociceptive afferents causes pain (Treede et al. 2004).

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Allodynia and Alloknesis

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Synonyms

Alloknesis and allodynia

Definition

Allodynia and alloknesis are abnormal sensory states wherein normally innocuous stimuli elicit unpleasant sensations or aversive responses.

▶ Allodynia is the nociceptive sensation or aversive response evoked by a stimulus that is normally non-nociceptive ("allo" – "other"; "dynia" – pain). For example, a light stroking of the skin produced by the lateral motion of clothing, or the heat produced by the body are stimuli that do not elicit nociceptive sensations or responses under normal circumstances. However, these stimuli may become nociceptive after a cutaneous injury produced, for example, by sunburn. In contrast, ▶ hyperalgesia is defined as the abnormal nociceptive state in which a normally painful stimulus such as the prick of a needle elicits a greater than normal duration and/or magnitude of pain.

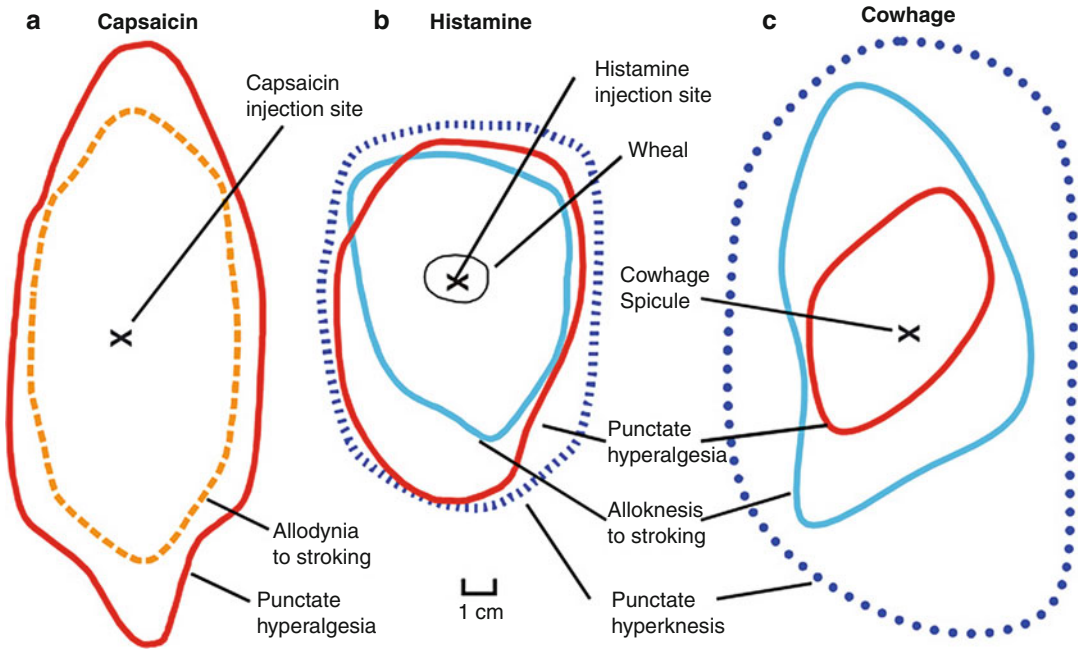
Alloknesis is the itch or ▶ pruriceptive sensation (from the Latin word *prurire*, to itch) or scratching behavior evoked by a stimulus that is normally non-pruriceptive ("allo", and "knesis", an ancient Greek word for itching). For example, a light stroking of the skin normally evokes the sensation of touch and perhaps tickle but not itch. However, when cutaneous alloknesis develops within the vicinity of a mosquito bite, or is present in an area of dermatitis, a light stroking of the skin can evoke an itch or exacerbate an ongoing itch. In contrast, ▶ hyperknesis is defined as the abnormal pruriceptive state in which a normally pruritic stimulus (such as a fine diameter hair which can elicit a prickle sensation followed by an itch) elicits a greater than normal duration and/or magnitude of itch. The cutaneous areas of enhanced itch (alloknesis and hyperknesis) are also referred to as "▶ itchy skin."

The abnormal sensory states of allodynia, alloknesis, hyperalgesia, and hyperknesis that are initiated by an inflammatory or irritating stimulus can exist both within the area directly exposed to the stimulus (in which case they are termed "primary") and can sometimes extend well beyond the area (in which case the sensory states outside the area are termed "secondary"). For example, when the skin receives a local, first-degree burn, primary allodynia and hyperalgesia may exist within the burned skin and secondary allodynia and hyperalgesia in the skin immediately surrounding the burn.

Characteristics

Allodynia is exhibited in a variety of forms such as the tenderness of the skin to combing the hair during a migraine headache, the discomfort of normal movements of the gut with irritable bowel syndrome, the soreness of muscles accompanying musculoskeletal inflammation or trauma, and the chronic tenderness to touch or to gentle warming of the skin associated with trauma or inflammatory diseases of the peripheral or central nervous system.

Allodynia can also be experimentally produced by the application of a noxious or irritant thermal, mechanical or chemical stimulus to the skin. For example, an intradermal injection into the forearm of capsaicin, the irritant agent in hot peppers, elicits not only a burning pain in the immediate vicinity of the injection site but allodynia and hyperalgesia to mechanical stimulation in the surrounding skin not in contact with the irritant (LaMotte et al. 1991) (Fig. 1a).



Allodynia and Alloknesis, Fig. 1 Abnormal sensory states produced by algesic or pruritic chemicals applied to the volar forearm in human. (**a**) The borders of punctate hyperalgesia and allodynia to stroking after an intradermal injection of capsaicin (100 μg). (**b**) The wheal and the borders of hyperalgesia and hyperknesis to punctate stimulation and alloknesis to stroking after an intradermal injection of histamine (20 μg). (**c**) The borders of hyperknesis, hyperalgesia, and alloknesis after the insertion a few cowhage spicules into the skin. Capsaicin and histamine evoked a flare (not shown), but cowhage did not. A different subject was used in each experiment

Alloknesis

Itchy skin and/or itch are characteristic of many cutaneous disorders such as atopic, allergic, and irritant contact dermatitis and can accompany such systemic diseases as renal insufficiency, cholestasis, Hodgkin's disease, polycythemia vera, tumors, and HIV infection.

Alloknesis can be experimentally produced in human volunteers by the iontophoresis (Magerl et al. 1990) or intradermal injection (Simone et al. 1991b) of histamine into the skin. The histamine evokes a sensation of itch accompanied by local cutaneous reactions consisting of a flare (redness of the skin mediated by a local axon reflex wherein vasodilatory neuropeptides are released by collaterals of activated nerve endings) and a wheal (local edema) (Simone et al. 1991b) (Fig. 1b). Within the wheal and within the surrounding skin that is not exposed to histamine, there develops alloknesis to lightly stroking the skin and hyperknesis and hyperalgesia to mechanical indentation of the skin with a fine prickly filament (Simone et al. 1991b; Atanassoff et al. 1999; LaMotte et al. 2009).

Itch and alloknesis can also be produced in the absence of a flare or wheal by single spicules of cowhage (*Mucuna pruriens*), a tropical legume (LaMotte et al. 2009) (Fig. 1c). Because the wheal and flare are elicited in response to histamine, the absence of these reactions in response to cowhage suggests that itch and itchy skin can be elicited by histamine-independent mechanisms, as is the case in most kinds of clinical pruritus.

Interactions Between Pain and Itch

Pain and hyperalgesia have an inhibitory effect on itch and itchy skin. The enhanced itch and itchy skin resulting from injecting histamine into an anesthetic bleb of skin (as opposed to a bleb of saline) have been explained on the basis of a reduced activation of histamine responsive nociceptive neurons (Atanassoff et al. 1999). In contrast,

histamine-induced itch and itchy skin are absent or attenuated in the hyperalgesic skin surrounding a capsaicin injection (Brull et al. 1999). Thus, even though alloknesis and hyperknesis co-exist with the area of mild hyperalgesia induced by histamine (Fig. 1b), they are suppressed or prevented from developing when the hyperalgesia becomes sufficiently intense, as is the case after the injection of capsaicin. Similarly, cowhage spicules produced neither itch nor alloknesis within an area of hyperalgesia produced by a heat injury of the skin (Graham et al. 1951). Observations such as these confirm the existence of functional interactions between pruriceptive and nociceptive neural systems and lend support to the hypothesis that the mechanisms of itch and itchy skin are inhibited centrally by mechanisms that underlie pain and hyperalgesia (Brull et al. 1999; Nilsson et al. 1997; Ward et al. 1996).

Neural Mechanisms of Allodynia and Alloknesis

Allodynia and hyperalgesia from an intradermal injection of capsaicin are believed to be initiated as a result of activity in a subpopulation of mechanically insensitive nociceptive afferent peripheral neurons (MIAs) (LaMotte 1992; Schmelz et al. 2003). A working model of the neural mechanisms of capsaicin-induced allodynia and hyperalgesia posits that capsaicin-responsive MIAs release neurochemicals that sensitize nociceptive neurons in the dorsal horn of the spinal cord. These neurons, in turn, receive convergent input from (a) low-threshold primary afferents with thickly myelinated axons mediating the sense of touch and (b) nociceptive afferents with thinly myelinated axons mediating the sense of mechanically evoked pricking pain. The sensitized neurons exhibit a de novo or greater than normal response to innocuous tactile stimuli, as well as an enhanced response to noxious punctate stimulation, thereby accounting for allodynia and hyperalgesia, respectively. In support of this is the reported sensitization of nociceptive spinothalamic tract (STT) neurons, recorded electrophysiologically in animals, to innocuous touch and to noxious punctate stimulation after an intradermal injection of capsaicin (Simone et al. 1991a) via a mechanism called ▶ central sensitization (see also Fig. 2 in ▶ Ectopia, Spontaneous regarding possible chronic central sensitization leading to allodynia and hyperalgesia after injury of peripheral sensory neurons).

Alloknesis and hyperknesis might be explained using a similar mechanistic model (LaMotte 1992). That is, there may exist pruriceptive STT neurons that can become sensitized to light mechanical touch and to punctate stimulation with a fine filament, after an application of histamine or cowhage to the skin, thereby accounting for alloknesis and hyperknesis respectively (Davidson et al. 2012).

A subpopulation of nociceptive peripheral MIAs, in humans, responds to histamine but not to cowhage (Schmelz et al. 2003; Namer et al. 2009). Also, subpopulations of mechanosensitive nociceptive neurons, some with unmyelinated axons and others with thinly myelinated axons, respond to histamine and/or to cowhage in humans, monkeys, and mice (Han et al. 2012; Johanek et al. 2008; Namer et al. 2009; Ringkamp et al. 2011). Other nociceptive peripheral neurons respond to thermal, mechanical, or chemical noxious stimuli but not to pruritic chemicals such as histamine or cowhage.

Some of these neurons in human and monkeys exhibited responses that were comparable in time course to the sensation of itch reported by humans in response to the same stimuli (LaMotte et al. 2009; Ringkamp et al. 2011).

In monkeys, a subpopulation of nociceptive STT neurons responded either to histamine or to cowhage but rarely to both (Davidson et al. 2012). But the majority of nociceptive STT neurons did not respond to either pruritic agent.

Scratching can reduce the ongoing histamine evoked activity in pruriceptive STT neurons (Davidson et al. 2009). Thus, chemically evoked itch may occur when there is a selective activation of pruriceptive neurons in the absence of sufficient activity in non-pruriceptive nociceptive neurons such as those normally activated by noxious mechanical stimuli. Similarly, alloknesis may be chemically evoked via activity in pruriceptive neurons but presumably in the absence of the sensitization of the non-pruriceptive central neurons that mediate allodynia.

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Allodynia in Fibromyalgia

Definition

A lowered pain threshold that characterizes clinical examination findings in fibromyalgia.

Cross-References

▶ Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)

Allodynia Test, Mechanical and Cold Allodynia

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Synonyms

Cold allodynia test; Mechanical allodynia test

Definition

Allodynia is defined as "pain due to a stimulus which does not normally provoke pain" by the International Association for the Study of Pain (Lindblom et al. 1986). It is important to recognize that allodynia involves a change in the quality of a sensation, since the original modality is normally non-painful but the response is painful. There is, thus, a loss of specificity of a sensory modality.

Characteristics

Because allodynia is an evoked pain, testing requires an external stimulation of non-painful quality. Mainly three different types of stimulation have been used to test allodynia in animal models of neuropathic pain: mechanical touch, cold, and air blow. All testing methods rely on withdrawal response of the affected body parts, such as the foot or face, to stimulus, based on the premise that the animal's avoidance of touching, cooling, or air blowing is an allodynic reaction.

Mechanical (Tactile) Allodynia Test: Foot Withdrawal Response to Von Frey Filament Stimulus

Since cutaneous tactile allodynia is a major complaint of neuropathic pain patients (Bonica 1990), testing for signs of mechanical (tactile) allodynia is an important aspect of behavioral tests for neuropathic pain. Mechanical allodynia is often tested by quantifying tactile sensitivity, using a set of von Frey filaments (also referred to as Semmes-Weinstein [S-W] monofilaments, a series of nylon monofilaments of increasing stiffness that exert defined levels of force as they are pressed to the point where they bend; Stoelting Co., Wood Dale, IL). Mechanical sensitivity is quantified either by determining mechanical threshold (Baik et al. 2003; Chaplan et al. 1994; Tal and Bennett 1994), or by measuring response frequency (Hashizume et al. 2000; Kim and Chung 1992).

Measurement of Mechanical Thresholds in Rodents

Although there are several ways of measuring mechanical thresholds, measurement of foot withdrawal thresholds to mechanical stimuli by using the up-down method has been utilized most extensively (Baik et al. 2003; Chaplan et al. 1994). The rats are placed under a transparent plastic dome (85 × 80 × 280 mm) on a metal wire mesh floor. A series of 8 von Frey (VF) filaments with approximately equal logarithmic incremental (0.22) VF values (3.65, 3.87, 4.10, 4.31, 4.52, 4.74, 4.92, and 5.16) are used to determine the threshold stiffness required for 50 % paw withdrawal. Because VF values are logarithmically related to gram (g) values [VF=log (1000×g)], the chosen VF numbers are equivalent to 0.45, 0.74, 1.26, 2.04, 3.31, 5.50, 8.32, and 14.45 in gram value, respectively. Starting with filament 4.31, VF filaments are applied perpendicular to the plantar surface of the hind paw and depressed until they bend for 2–3 s. Whenever a positive response to a stimulus occurs, the next smaller VF filament is applied. Whenever a negative response occurs, the next higher one is applied. The test is continued until the response of six stimuli, after the first change in response, has been obtained or until the test reaches either end of the spectrum of the VF set. The 50 % threshold value is calculated by using the formula of Dixon (Dixon 1980) : 50 % threshold=X+kd, where X is the value of the final VF filament used (in log units), k is the tabular value for the pattern of positive/negative responses, and d is the mean difference between stimuli in log units (0.22). In the case where continuous positive or negative responses are observed all the way out to the end of the stimulus spectrum, values of 3.54 or 5.27 are assigned, respectively, by assuming a value of ±0.5 for k. The outcome of behavioral data is expressed as VF values (maximum range, 3.545.27) and plotted in a linear scale. Because VF values are logarithmically related to gram values, plotting in gram values requires logarithmic plots. The mechanical threshold for foot withdrawal in a normal rat is usually a VF value of 5.27 (18.62 g) (Baik et al. 2003). After L5 spinal nerve ligation, mechanical thresholds

decline to around 3.54 (0.35 g) by the third day, and this level is maintained for weeks (Park et al. 2000). Since thresholds of most nociceptors are higher than 1.5 g (Leem et al. 1993), foot withdrawals elicited lower than this value can be assumed to be mechanical allodynia when the foot does not show a sign of inflammation and thus peripheral sensitization.

The same procedures can be applied to mice with a different set of VF filaments (VF values of 2.44, 2.63, 3.22, 3.61, 4.0, 4.35, and 4.74 that are equivalent to 0.03, 0.07, 0.2, 0.4, 1.0, 2.7, and 5.5 g force, respectively). In mice, the baseline mechanical sensitivity as well as the levels of developed hypersensitivity after nerve injury varied among different strains of mice (Mogil et al. 1999).

Another method has also been used to determine mechanical thresholds based on foot withdrawal reflex responses to VF filament stimulation. In this experimental paradigm, a series of VF filaments whose stiffness are within a non-painful stimulus range are selected, based on the testing locations. The VF filaments are applied perpendicular to the skin and depressed until they bend, flexor withdrawal reflexes are then observed. Starting from the weakest filament, the von Frey filaments are tested in order of increasing stiffness. The minimum force (determined as the stiffness of VF filament) required to elicit a flexor withdrawal reflex is recorded as the mechanical threshold. Depending on each specific experiment, the number of applications with each VF filament, times of intervals between stimuli, and the criteria of threshold determination were somewhat variable. For example, the first filament in the series that evoked at least one response from five applications was designated as the threshold by Tal and Bennett (1994), while Ma and Woolf (1996) determined that the minimum force required to elicit a reproducible flexor withdrawal reflex on each of three applications of the VF filaments would be recorded as the threshold.

Measurements of Paw Withdrawal Frequencies

The general method of stimulus application with VF filaments, and recording positive or negative withdrawal reflex responses, are the same as the method used for the threshold measurement. The differences are:

1. Sensitivity testing is done by repeated stimuli with each defined VF filament.
2. Frequency of positive response is measured and used as an indicator of mechanical sensitivity.

In one experiment, mechanical stimuli are applied to the plantar surface of the hind paw with six different von Frey filaments ranging from 0.86 to 19.0 g (0.86, 1.4, 2.5, 5.6, 10.2, 19.0 g). The 0.86 and 19.0 g filaments produce a faint sense of touch and a sense of pressure, respectively, when tested on our own palm. A single trial of stimuli consisted of 6–8 applications of a von Frey filament within a 2–3 s period; each trial is repeated five times at approximately 3-min. intervals on each hind paw. The occurrence of foot withdrawal in each of five trials was expressed as a percent response frequency [number of foot withdrawals/5 (number of trials) $\times$ 100 = % response frequency], and this percentage is used as an indication of mechanical sensitivity. For a given test day, the same procedure is repeated for the remaining five different von Frey filaments, in ascending order starting from the weakest. In the sham operated control rat, the strongest VF filament (19.0 g) produces a 10 % response, but none of the other filaments produced any response (0 %). Seven days after L5/6 spinal nerve ligation, response frequency increases to 40 % and 80 % by stimuli with 0.86 and 19.0 g filaments, respectively (Kim and Chung 1992).

Cold Allodynia Test: Foot Withdrawal Response to Acetone or Cold Plate

Two different methods have been used for cold allodynia testing in animal models of neuropathic pain: the acetone test and the cold plate test.

Acetone Test

The rat is placed under a transparent plastic dome on a metal mesh floor and acetone is applied to the plantar surface of the foot. Application of acetone is done by an acetone bubble formed at the tip of a piece of polyethylene

tubing (1/16 ID), which is connected to a syringe. The bubble is then gently touched to the heel. The acetone quickly spreads over the proximal region of the plantar surface of the foot and evaporates. On our own palm surface of the hand, this stimulus produces a strong but non-painful cooling sensation as the acetone evaporates. Normal rats either ignore the stimulus, or it produces a very brief withdrawal response. After L5/6 spinal nerve ligation, rats briskly withdraw the hind foot after some delay (about 0.2–0.3 s) and subsequently shake, tap, or lick the hind paw in response to acetone application to the affected paw. For quantification of cold allodynic behavior, acetone is applied five times (once every 5 min) to each paw. The frequency of foot withdrawal is expressed as a percent: (number of trials accompanied by brisk foot withdrawal) × 100/(number of total trials). As a control, warm water (30 °C) is applied in the same manner as acetone. A significant increase in the frequency of foot withdrawals in response to acetone application was interpreted as cold allodynia (Choi et al. 1994).

In another experiment, 0.15 ml of acetone was sprayed onto the plantar surface of the hind paw for assaying cold allodynia. As in the acetone bubble test, normal rats either ignore the stimulus or it produces a very brief and small withdrawal reflex. Rats with sciatic neuritis reacted with a large and prolonged withdrawal response. Approximately one-half of the neuritic rats displayed cold allodynia while almost all rats with chronic constriction injury to the sciatic nerve showed cold allodynia (Bennett 1999).

Cold Plate Test

In the cold plate test, rats are confined beneath an inverted, clear plastic cage (18 × 28 × 13 cm) placed upon a metal floor (e.g., aluminum plate), which is chilled to 4 °C by an underlying water bath. While exposed to the cold floor for 20 min, the animals' behavior is monitored, and the frequency of hind paw withdrawals and the duration the hind paw held above the floor (i.e., hind paw withdrawals related to stepping are not counted) are measured. The 4 °C floor does not produce any pain when our palm of the hand is immobilized on it for 20 min, and it does not evoke any pain-related responses from unoperated control rats. In neuropathic rats with sciatic chronic constriction injury, the average frequency and cumulative duration of hind paw withdrawals on the nerve-damaged side increases about fivefold and twofold, respectively, compared to that of normal rats. In addition, some rats also demonstrate vague, scratching-like movements and also lick the affected hind paw (Bennett and Xie 1988). This method is based on the premise that the animal's avoidance of touching the cold plate is an allodynic reaction. One notable fact, however, is that a complete denervation of the foot does not change this behavior (Choi et al. 1994), making it questionable that the foot lifting behavior is related to allodynia, since allodynia would require the presence of functioning sensory receptors.

Air-Puff Allodynia Test: Withdrawal Response to Air-Puff Stimuli

The air-puff testing has been used to quantify the mechanical allodynia of the orofacial region in the animal model of trigeminal neuralgia (Ahn et al. 2004, 2005). The testing is based on face withdrawal behavior in response to constant air puffs of graded pressures applied to the affected orofacial area. A custom-designed, pressure-regulated air-puff stimulator is used to provide air stimulation (Yeomans and Klukinov 2012). The withdrawal thresholds were estimated from 10 consecutive trials of constant-pressure air puffs, 4-s duration, a 10-s interstimulus interval (Ahn et al. 2005), are performed with a ramp of air-puff pressures. In normal naïve rats, the air-puff pressure that produces withdrawal behaviors is approximately 25 psi, but this pressure decreased to 5 psi 30 min after a subcutaneous injection of IL-1β into the vibrissa. This allodynia persisted at least 180 min (Ahn et al. 2004).

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Allodynia: General

Definition

The International Association for the Study of Pain (IASP) defines allodynia as: "Pain due to a stimulus that dose not normally provoke pain." This may occur in any somatosensory modality: mechanical, thermal, or chemical, and so tactile allodynia, heat allodynia, etc. Any reduction in pain threshold is "allodynia," whereas increased pain to suprathreshold stimuli is referred to as "hyperalgesia." Allodynia is a neologism derived from the Greek "allo" = "other" and "dynia" = pain.

Cross-References

▶ Allodynia and Alloknesis
▶ Anesthesia Dolorosa Model, Autotomy
▶ Calcium Channels in the Spinal Processing of Nociceptive Input
▶ Chronic Pelvic Pain, Musculoskeletal Syndromes
▶ Clitoral Pain
▶ Cognitive-Behavior Treatment of Pain
▶ Complex Regional Pain Syndromes, Clinical Aspects
▶ CRPS, Evidence-Based Treatment
▶ CRPS-1 in Children
▶ Deafferentation Pain
▶ Descending Circuits in the Forebrain, Imaging
▶ Diagnosis and Assessment of Clinical Characteristics of Central Pain
▶ Dietary Variables in Neuropathic Pain
▶ Drugs Targeting Voltage-Gated Sodium and Calcium Channels
▶ Drugs with Mixed Action and Combinations: Emphasis on Tramadol

- ▶ Freezing Model of Cutaneous Hyperalgesia
- ▶ Functional Changes in Sensory Neurons Following Spinal Cord Injury in Central Pain
- ▶ Human Thalamic Response to Experimental Pain (Neuroimaging)
- ▶ Hyperaesthesia, Assessment
- ▶ Hyperalgesia
- ▶ Hyperpathia
- ▶ Hyperpathia, Assessment
- ▶ Inflammatory Neuritis
- ▶ Metabotropic Glutamate Receptors in Spinal Nociceptive Processing
- ▶ Neuropathic Pain Model, Tail Nerve Transection Model
- ▶ Nociceptive Circuitry in the Spinal Cord
- ▶ Nociceptive Processing in the Amygdala: Neurophysiology and Neuropharmacology
- ▶ Opioid Receptor Trafficking in Pain States
- ▶ Pain-Modulatory Systems, History of Discovery
- ▶ PET and fMRI Imaging in Parietal Cortex (SI, SII, Inferior Parietal Cortex BA40)
- ▶ Postherpetic Neuralgia, Etiology, Pathogenesis, and Management
- ▶ Postherpetic Neuralgia, Pharmacological and Nonpharmacological Treatment Options
- ▶ Poststroke Pain Model, Thalamic Pain (Lesion)
- ▶ Psychiatric Aspects of Visceral Pain
- ▶ Purine Receptor Targets in the Treatment of Neuropathic Pain
- ▶ Satellite Glial Cells and Chronic Pain
- ▶ Spinal Cord Injury Pain Model, Contusion Injury Model
- ▶ Sympathetically Maintained Pain in CRPS II, Human Experimentation
- ▶ Thalamotomy, Pain Behavior in Animals
- ▶ Thalamus, Dynamics of Nociception
- ▶ Transition from Acute to Chronic Pain

Allodynia: Skin

Definition

See also "▶ Primary and Secondary Hyperalgesia."

Allodynia means pain due to a stimulus that does not normally provoke pain and is mostly used as a synonym for "Touch evoked hyperalgesia" (e.g., pain evoked by stroking the skin with a wisp of cotton wool). This kind of stimulation does not excite nociceptors – even in their sensitized state. It excites sensitive mechanoreceptor units belonging to "another sensory modality." It typically occurs in an inflamed area, but also in a surrounding secondary zone, and therefore has been attributed to altered central synaptic processes. However, it often depends on the ongoing barrage to projection neurons in the spinal cord by impulses of sensitized and spontaneously active nociceptors. For example, pricking capsaicin into the skin induces allodynia at the injection site and in a surrounding secondary zone. If the spontaneous activity of nociceptors is brought to subside by cooling the injection site, the allodynia vanishes.

Cross-References

- ▶ Spinothalamic Neuron
- ▶ Spinothalamic Tract Neurons, Role of Nitric Oxide

Alloknesis and Allodynia

- ▶ Allodynia and Alloknesis

Alpha(α) 2-Adrenoceptor Agonists

Definition

Drugs that activate α_2-adrenoceptors.

Cross-References

- ▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

Alpha(2)-Adrenergic Receptors

Definition

The sympathetic nervous system is an involuntary system that plays an important role in normal physiological functions, such as control of body temperature and regulation of blood flow to various tissues in the body. These nerves release a chemical called norepinephrine that activates specific receptors, called adrenergic receptors or adrenoceptors. There are two main subtypes of adrenoceptors – one of which is the alpha adrenoceptors.

Cross-References

► Sympathetically Maintained Pain in CRPS II, Human Experimentation

Alpha(α) 2-Adrenergic Agonists in Pain Treatment

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Synonyms

Alpha(α) 2-adrenergic receptor agonists; Alpha (α) 2-agonists; α_{2A} or α_{2C}-adrenoceptor agonists; α_2-adrenergic agonists; α_2-receptor agonists; α-agonists

Definition

Alpha$_2$-adrenergic agonists are drugs that mediate their analgesic (antinociceptive) effects by acting on α_2-adrenoceptors (α_{2A}, α_{2B}, α_{2C}) in the peripheral and central nervous system.

Characteristics

Indications and Patients

Alpha$_2$-adrenoceptor (α_2AR) agonists are used for treatment of acute (intra- and postoperative) as well as chronic (neuropathic) pain states. They are effective in patients of all age groups. α_2AR agonists have also been safely used in pregnancy, labor, and during cesarean sections. Furthermore, there is evidence that they provide hemodynamic stability in patients with coexisting cardiovascular diseases during phases of noxious stimulation (e.g., orotracheal intubation) by attenuating the sympathetic response.

Dose and Route of Administration

With ► clonidine being the prototypical α_2AR agonist, these drugs have been administered in different doses and by a wide variety of routes: systemic, peripheral, regional, neuraxial, and central (Table 1). They have been used as premedication, in combination with other drugs, or as sole analgesic during and after surgery, and in the treatment of chronic pain either by bolus or continuous infusions or as part of a ► patient-controlled analgesia (PCA) regimen.

Drug Interactions

Preclinical and clinical studies investigating the antinociceptive effect of α_2AR agonists and their interactions with other drug classes have demonstrated synergistic interaction with opioids as well as opioid-sparing effects. The rare observation of synergy between drugs of the same class has also been made with coadministration of clonidine and dexmedetomidine intrathecally in mice. Possible mechanisms are discussed below. It has also been demonstrated that α_2AR agonists have been demonstrated to reduce the ► minimal alveolar concentration (MAC) of volatile

Alpha(α) 2-Adrenergic Agonists in Pain Treatment,
Table 1 Alpha 2-adrenergic drug dosing: clonidine

Route		Dose	Duration
Premedication			
	Children	2–4 μg/kg	
	Elderly patients	1–2 μg/kg	
Perioperative analgesia			
Intrathecal		Max 1 μg/kg	
		Up to 75 μg	
Epidural	With opioid	1–4 μg/kg	Long; dose dependent
Caudal	With mepivacaine	0.75–3 μg/kg	Up to 24 h
Peripheral nerve block		0.1–0.5 μg/kg	
Bier block		1–2 μg/kg	
Postoperative analgesia			
Epidural	Clonidine alone	1–4 μg/kg	
		100–150 μg/h	
Analgesia for labor pain			
Intrathecal	With bupivacaine	50–200 μg	
		max 1 μg/kg	
Epidural	With bupivacaine + fentanyl	30–150 μg	
		75 μg	
Chronic pain			
Epidural	Infusion	100–900 μg	8 h
		30 μg/h	Up to 2 weeks

anesthetics and attenuate the pain from propofol injection. Numerous studies have shown that combining α_2AR agonists with local anesthetics both prolongs the sensory blockade and also improves the quality of the block. Subsequently, α_2AR agonists may be considered as an adjuvant therapy for both general and local anesthesia.

Other Effects

Compared to opioids, far less respiratory depression is seen with α_2AR agonists. Drugs of this class produce sedation by an action that originates in the brainstem and converges on the endogenous pathways responsible for non-REM sleep. Dose-dependent effects of α_2AR agonists are also noted in the cardiovascular system. At low doses, these drugs induce hypotension through actions on locus coeruleus and nucleus tractus solitarius, which results in a decrease in sympathetic outflow. At higher doses, α_2AR agonists induce vasoconstriction in the periphery and can result in a rise in systemic blood pressure. A combination of sympatholytic and vagomimetic actions of α_2AR agonists cause a decrease in heart rate. Additional features that are useful in the perioperative period include the ability of α_2AR agonistic drugs to produce xerostomia (dry mouth) and anxiolysis.

Analgesic (Antinociceptive) Sites of Action

The α_2ARs are G-protein-coupled receptors associated with $G_{i/o}$ heterotrimeric G proteins. They exist in three subtypes: A, B, and C (α_{2A}AR, α_{2B}AR, α_{2C}AR). They are present on peripheral nerves, in the spinal cord, and at supraspinal pain-modulating centers. They have therefore been applied to all parts of the nervous system in an effort to generate analgesia in patients or antinociception in animals (for review, see Fairbanks et al. 2009b).

Periphery

Although in preclinical models, peripheral injections or topical application of α_2AR agonists appeared promising for pain control (Li et al. 2007), the utility of local peripheral

administration has proven to be inconsistent in clinical studies. These inconsistencies may be due to the patient population examined, as topical clonidine has been shown to be antihyperalgesic in the subset of neuropathic pain patients with sympathetically maintained pain. Consistent with that inference, a very recent clinical trial demonstrated that patients suffering from diabetic neuropathy and retaining some nociceptive fibers in their feet received excellent therapeutic benefits from topical treatment with the α_2AR agonist clonidine (Campbell et al. 2012).

Peripheral α_2ARs are found on sympathetic and sensory nerves, where they have been proposed to act as autoreceptors to inhibit neuronal excitability and transmitter release. There is a growing body of evidence that an inflammatory response might be prerequisite for the peripheral site of action of α_2AR receptor agonists. This has been hypothesized because of the demonstration of α_2ARs on inflammatory cells, especially macrophages. Perineural application of the α_2AR agonist clonidine reduced nerve injury-induced release of the proinflammatory cytokine TNFα, and the time course of this action was paralleled by a clear antinociceptive effect in an animal model of ▶ neuropathic pain. Hence, it is now suggested that macrophages invade the site of traumatic nerve damage and contribute to an inflammation-maintained pathogenic mechanism through the release of proinflammatory cytokines and that α_2AR agonists attenuate this process by reducing the inflammatory response rather than by direct action on peripheral nerves (Lavand'homme and Eisenach 2003).

Spinal Cord

From recent data, the spinal cord dorsal horn has clearly emerged as a pivotal site of α_2AR analgesic action. Administration of α_2AR agonists result in antinociception and analgesia in animal models and human subjects by both pre- and postsynaptic actions. These spinal analgesic actions of α_2AR agonists are largely mediated by the α_{2A}AR subtype, and presynaptic α_{2A}ARs on primary afferent nociceptive Aδ- and C-fibers are positioned to directly modulate pain processing through attenuation of excitatory synaptic transmission (Stone et al. 1997, 1998; Riedl et al. 2009). This has been supported by results showing an inhibitory effect of α_2AR on spinal glutamate release in synaptosomal and electrophysiological experiments (Kawasaki et al. 2003; Li and Eisenach 2001). The mechanisms underlying the actions of the α_{2A}AR subtype have been investigated recognizing the known synergy of opioids and a_2AR agonists. Coexpression of the δ-opioid receptor (DOP) and the α_{2A}AR occurs on spinal primary afferent fibers and inhibition of calcitonin gene-related peptide (CRGP) release occurs on agonism of both. Using both the DOP agonist deltorphin II (DELT) and clonidine, possible mechanisms of signal transmission were evaluated in spinal slices (Overland et al. 2009). Coadministering inhibitors of phospholipase C (PLC), protein kinase A, and protein kinase C (PKC), the effects of individual agonist administration were found to be dependent only on PLC while synergy resulted from the activation of both PLC, and PKC together. PKA was found not to be involved in the action of either DELT or clonidine. Additionally, this CGRP release inhibition was maintained in the presence of tetrodotoxin, suggesting synergy occurs within a single subcellular compartment. This in vitro PKC-dependent system was further found to translate to synergistic antinoception in vivo when using a thermal antinociceptive test in mice. Worth noting simultaneously are the findings that antinociceptive synergy is seen preclinically when coadministering the two α_2AR agonists clonidine and dexmedetomidine intrathecally in mice (Fairbanks et al. 2009a). Both agonists have been thought to act via the α_{2A}AR subtype but observations made in knockout mice have shown that the α_{2C}AR subtype, likely on secondary dorsal horn neurons (Olave and Maxwell 2003), is simultaneously required for synergy to occur. Direct hyperpolarization of postsynaptic spinal neurons by α_2AR agonists may also play an important role in the spinal analgesic action of α_2AR agonists (Sonohata et al. 2004). Direct antinociceptive actions at the spinal cord level are mediated by α_{2A} and α_{2C} receptors. However, these actions are supported via descending noradrenergic pathways that may involve α_{2B} receptors as well.

There is also a growing body of evidence showing plasticity in the analgesic effects of α_2AR agonists, especially in hypersensitivity-maintained pain states. For example, α_2AR agonists have a greater efficacy under circumstances of neuropathic pain. This may be due to the upregulation of the α_{2C}AR subtype following nerve injury, resulting in an alteration of the α_2AR-agonist site of action, and the involvement of different pathways in the generation of α_2AR-induced antinociception (Duflo et al. 2002; Paqueron et al. 2003; Stone et al. 1999).

It has been suggested that the antihyperalgesic effect of α_2AR-agonists in hypersensitivity-maintained pain states (e.g., neuropathic pain) is mediated, at least in part, through non-α_{2A}ARs. Furthermore, under those conditions, antihyperalgesia against mechanical but not thermal stimuli seems to be dependent on cholinergic mechanisms. This is supported by most recent data indicating that α_2AR-agonists exert their action via cholinergic neurons, which have been modulated by the interaction of ▶ nerve growth factor (NGF) with its low-affinity p75 receptor. It has further been hypothesized that α_2-adrenergic agonists facilitate the release of acetylcholine (Ach). The released Ach has been shown to act mainly on muscarinergic and to a lesser extent on nicotinic ▶ acetylcholine receptors to induce the release of nitric oxide (NO) and thereby antinociception (Pan et al. 1999). The recent discovery that α_2AR agonists can suppress itch in mouse models implies alpha adrenoceptor involvement in the dysesthesia of itch and a subsequent effect of the descending noradrenergic system inhibition on signaling in the spinal cord (Gotoh et al. 2011).

Supraspinal Sites

The catecholaminergic cell groups A5, A6 (locus coeruleus, LC), and A7 in the dorsolateral pons of the brainstem have been identified as the most important supraspinal sites for α_2AR-mediated antinociception. These areas express α_2ARs and send and receive projections to and from other pain-modulating parts of the brain, for instance, the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM). Therefore, they act as important relay stations for pain-modulating pathways. They are also centers from which ▶ descending inhibitory noradrenergic (NA) pathways originate. These pathways terminate in parts of the spinal cord dorsal horn that modulate spinal pain processing.

Normally, tonic firing in LC neurons suppresses activity in A5/7 cell groups; consequently, the noradrenergic outflow through the descending NA pathways is inhibited (Bie et al. 2003; Nuseir and Proudfit 2000). Activation of α_2ARs in the LC can inhibit activity in certain cells resulting in behavioral changes, which are in accordance with antinociceptive actions of the injected drugs. These effects could be completely reversed by ▶ intrathecal application of an α_2AR antagonist, suggesting a mechanism of action involving increased spinal NA release in response to the supraspinal agonist injection (Dawson et al. 2004).

From these results, it has been suggested that α_2AR agonists, in decreasing the activity of LC neurons, disinhibit the A5/A7 cell groups and, therefore, indirectly activate the descending inhibitory noradrenergic pathways with the resultant increased spinal NA release. Evidence from recent studies suggests that the released NA acts on α_{2B}ARs in the spinal cord, which are not located on primary afferents; instead, these may be located on interneurons or ascending excitatory pathways to mediate antinociception (Dawson et al. 2004; Kingery et al. 2002). In addition to antinociception, the LC also mediates the sedative actions of α_2AR agonists by inhibition of cell firing in some LC neurons.

The possible importance of these noradrenergic pathways under circumstances of chronic pain has also recently been suggested. Data obtained from an animal model of neuropathic pain, for example, showed an increased expression of key enzymes of catecholamine synthesis, tyrosine hydroxylase and dopamine β-hydroxylase, in the LC and spinal cord. This increased expression has been interpreted as a reflection of an enhanced activity in the descending NA system, with an increased noradrenaline turnover in response to the ongoing activity in nociceptive pathways (Ma and Eisenach 2003).

Clinical Applications

The most commonly used α_2AR agonists clinically are clonidine and dexmedetomidine, and they have been deployed in all age groups in oral, intravenous, intramuscular, epidural, and intrathecal modalities. Due to increased cost and decreased availability, dexmedetomidine is the less frequently used. While the most common administrative uses are likely to be for analgesia and sedation, there is evidence that they are opioid sparing and can reduce perioperative myocardial ischemia, intraoperative blood loss, and postoperative nausea and vomiting (Wu et al. 2004). The clinical administration of α_2AR agonists will require balance of the required effect with their sedative properties. Where the desired effect is sedation, α_2AR agonists have found mixed response largely relating to their concurrent effects of hypotension and bradycardia. Usage varies in the intensive care setting; one study, including 240 German ICUs, documented two-thirds of local sedation regimens as including clonidine. The agonists are useful where sympathetic mediation results, for instance, in alcohol withdrawal, although the interactions of chronic alcohol use with α_{2A}ARs have resulted in prolonged sedation profiles (Berggren et al. 2002). Perioperative administration is another area of use. Oral clonidine has been associated with reduced perioperative blood loss in ENT and enhanced recovery programs, and these seem likely findings secondary to controlled hypotension and localized vasculature response (Mohseni and Ebneshahidi 2011). Postoperative analgesic regimes can include α_2AR agonists in bolus form or infusions under machine, nurse, or patient control. Evidence suggests that postoperative administration has no effect in enhancing the speed of onset or effectiveness of opioid analgesia, although the synergy of the two groups and opioid-sparing effects are well described. The recently described α_2AR agonist synergy between clonidine and dexmedetomidine is yet to be investigated in humans. The other major area of interest relates to the suggested findings of reduced myocardial ischemia following clonidine usage. This potentially significant finding is currently being investigated further by a randomized, international, double-blinded trial which could have global consequences (POISE-2 trial).

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Alpha(α) 2-Adrenergic Receptor Agonists

▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

Alpha(α) 2-Agonists

▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

Alpha(α) EEG Wave Intrusion

Definition

The intrusion of fast-frequency EEG alpha (7.5–11 Hz) activity into slow wave sleep (SWS). The SWS is dominated by large and slow EEG waves of delta type (0.5–4.0 Hz); it also characterizes sleep stages three and four.

Cross-References

▶ Orofacial Pain, Sleep Disturbance

Alpha(α)-D Galactose

Definition

Lectins are proteins that bind to the carbohydrate portion of glycoproteins and glycolipids.

The isolectin Griffonia simplicifolia I-B4 (IB4) binds specifically to terminal α-galactose, the terminal sugar on galactose-α1,3-galactose carbohydrates on glycoproteins and glycolipids. The IB4 lectin labels about one half of the small- and medium-diameter DRG neurons in rat and mouse. It is not yet clear which proteins or lipids in DRG neurons account for the majority of labeling by IB4 binding.

Cross-References

► Immunocytochemistry of Nociceptors

Alpha(α)-Delta(δ) Sleep

Definition

Simultaneous recordings of delta and alpha brainwaves during sleep.

Cross-References

► Fibromyalgia

Alpha(α)-I-Acid Glycoprotein

Definition

The most important serum binding protein for opioids and local anesthetics.

Cross-References

► Acute Pain in Children, Postoperative

AL-TENS (Acupuncture-like TENS)

► Transcutaneous Electrical Nerve Stimulation

Alternative Medicine

► Alternative Medicine in Neuropathic Pain

Alternative Medicine in Neuropathic Pain

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Synonyms

Alternative medicine; Alternative therapies; Complementary medicine; Complementary therapies; Holistic medicine; Nontraditional medicine; Unconventional medicine

Definition

In 1993, Eisenberg utilized a working definition of alternative medicine as interventions that are not taught widely in medical schools and that are not generally available in US hospitals (Eisenberg et al. 1993). However, there has been a rise in availability of complementary medical practices in Western-based medical institutions and more medical schools are incorporating unconventional therapies into their curricula. A broader definition of alternative and complementary medicine would be *those medical systems, practices, interventions, applications, theories or claims that are not part of the dominant or conventional medical system of that society* (National Institutes of Health on Alternative Medical systems and Practices in the United States). This definition is flexible in that it recognizes alternative and complementary medicine as culturally based. This definition also allows for changes in what constitutes alternative or complementary practices as a society evolves or changes.

The concept of *alternative medicine* implies practices used instead of conventional medical practice, whereas *complementary medicine* refers to practices that are integrated with conventional care. Neither of these terms accurately reflects the most common way in which unconventional practices are incorporated into treatment. Most of the time, physicians are unaware of their patients' use of alternative health practices that are applied simultaneously with conventional treatment. Thus, these practices are neither instead of, nor integrated with, conventional treatment. They are simply a separate, dual track of care.

Introduction

This chapter will provide a framework for understanding and organizing the wide array of alternative and complementary therapies, and will provide a perspective on those therapies that have been used to treat various neuropathic pain states. Wherever possible, evidence-based therapies will be highlighted and reviewed.

Characteristics

Medical conditions that have effective and well-tolerated treatments generally do not motivate a search for alternatives – especially when such alternatives may be based on theoretical constructs that are foreign to the patient and their physician. Complex pain problems, like chronic neuropathic pain, that have multiple mechanisms are hard to treat even with the availability of newer pharmacological modulators. Many of the conventional therapies for neuropathic pain have adverse effects that interfere substantially with quality of life. It is not surprising that patients suffering from neuropathic pain would look outside conventional medicine for more effective and better-tolerated treatments.

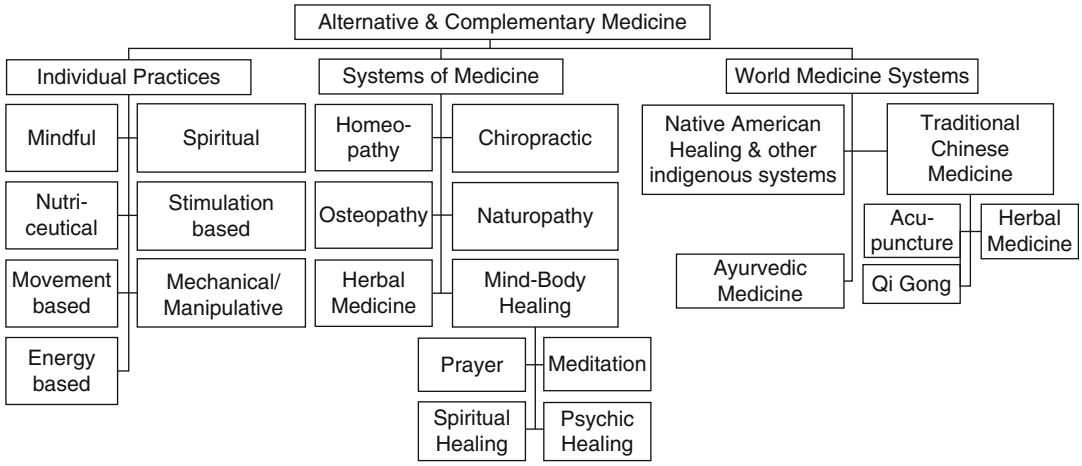
► Acupuncture, ► chiropractic, ► homeopathy, herbal medicine, traditional Chinese medicine, massage, ► biofeedback, the list of complementary and alternative therapies is seemingly limitless. Just as we categorize conventional medical practice into pharmacological, surgical, physical rehabilitative, and behavioral techniques, it is helpful to organize the broad array of alternative medicine practices into categories that allow practitioners to better understand the options available and how they differ from each other. It is convenient to separate all of CAM into three broad groups (Fig. 1):

1. World medicine systems
2. Other comprehensive systems of medicine that are not culturally based
3. Individual therapies

A system of medicine such as homeopathy or chiropractic consists of both a diagnostic and a therapeutic approach to a wide array of symptoms, illnesses, and diseases. It is based on a philosophy of health and disease that gives rise to the types of treatments that are utilized. A world medicine system like traditional Chinese medicine or Ayurvedic medicine is a system of medicine that is based on the traditions and philosophy of a world culture. Individual therapies are not linked to a culture or a complete medical system and are generally used to treat a certain subset of symptoms or problems. Examples include biofeedback, massage, and vitamin therapy. All therapies can be further subdivided into one or more of seven functional groups:

1. Meditative/mindful
2. Spiritual
3. Energy based
4. Stimulation based
5. Movement based
6. Mechanical or manipulative
7. ► Nutriceutical

Mindful or meditative therapies utilize the mind to produce changes in physical and emotional status. Meditation, hypnosis, and yoga can fall into this category. Spiritual therapies on the other hand, utilize a letting go of the mind and giving up control to a higher power as in prayer. Energy-based therapies rely on a construct of vital energy or an energy field that must be in proper balance to maintain health. Traditional acupuncture, healing touch, and yoga all use the concept of vital energy. Acupuncture can also be considered a stimulation-based therapy.



Alternative Medicine in Neuropathic Pain, Fig. 1 Organizational chart of alternative and complementary therapies (From Belgrade 2003)

Alternative Medicine in Neuropathic Pain, Table 1 Examples of complementary and alternative therapies organized into functional groups (From Belgrade 2003)

Mindful	Spiritual	Energy based	Stimulation based	Movement based	Mechanical/ manipulative	Nutriceutical
Hypnosis		Massage	TENS	Exercise		
Imagery	Prayer	Therapeutic touch	Acupuncture	Dance therapy	Chiropractic	Vitamins
Meditation	Spiritual healing	Homeopathy	Massage	Alexander technique	Osteopathy	Diet
Relaxation	Psychic healing	Acupuncture	Aromatherapy	Tai Chi	Massage	Herbal medicine
Biofeedback	Yoga	Qi Gong	Therapeutic touch	Qi Gong	Craniosacral therapy	Homeopathy
Yoga		Yoga	Music	Yoga	Rolfing	Aromatherapy

Thus, many practices fall into more than one functional category (Table 1).

Prevalence and Cost

Several large surveys in the United States, Europe, and Australia demonstrate extensive use of alternative and complementary therapies by the public. Prevalence estimates are confounded by what practices are included as unconventional. For example, are ice, heat, and prayer to be included when they are so commonly utilized? Aside from such universal practices, 42 % of the US population made use of alternative treatments as of 1997 (Eisenberg et al. 1998). Fifteen percent of Canadians visited an alternative health practitioner in the previous 12 months (Millar 1997). In Europe, prevalence of alternative health care use varies from 23 % in Denmark to 49 % in France (Fisher and Ward 1994). Alternative medicine use in Australia has also been estimated to be 49 % (MacLennon et al. 1996).

Brunelli and Gorson surveyed 180 consecutive patients with peripheral neuropathy about their use of complementary and alternative medicine (CAM) (Brunelli and Gorson 2004). Forty-three percent of patients reported using at least one type of CAM. Patients with burning neuropathic pain used CAM at a significantly higher rate than those without such pain. Diabetic

neuropathy patients were also significantly more likely to use CAM. Other predictors of CAM use were younger age and college educated. Types of treatments employed by patients were megavitamins (35 %), magnets (30 %), acupuncture (30 %), herbal remedies (22 %), and chiropractic (21 %). Lack of pain control was the most common reason for CAM use and nearly half of the patients did not discuss it with their physician.

The United States spends $27 billion each year on alternative medicine. That figure reflects out-of-pocket expenses alone and is nearly equal to the cost of physician services and triple the cost of hospitalizations (Eisenberg et al. 1998). Health benefit payers are facing the quandary of determining which alternative services are worthy of coverage and to what extent. The question of standards of care for the various alternative forms of therapy represents a quagmire that confronts everyone, patients, physicians, health benefit administrators, and the alternative practitioners themselves.

Acupuncture and Other Stimulation-Based Therapies

Acupuncture is one component of traditional Chinese medicine. As such, it has its theoretical roots in Taoist ideas about the universe, living systems, health, and disease. Modern scientific scrutiny has already yielded more information about acupuncture mechanisms than for any other alternative therapy. The discovery of opioid receptors and ▶ endorphins has led to a large number of investigations into the role these receptors and ▶ ligands play in producing acupuncture analgesia. Nearly all such studies support the conclusion that acupuncture analgesia is mediated in part by the opioid system. Acupuncture analgesia can be reversed with administration of ▶ naloxone (Meyer et al. 1977; Pomeranz and Cheng 1979; Tsunoda et al. 1980). Increased levels of endogenous opioid following acupuncture have been directly measured in humans (Clement-Jones et al. 1980; Pert et al. 1984). Antiserum to opioid receptors applied to the periaqueductal gray matter has been shown to block experimental acupuncture analgesia in primates.

Han and Terenius reviewed a number of studies that demonstrate the importance of biogenic amines in acupuncture analgesia (Han and Terenius 1982). Ablating the ▶ descending inhibitory pathway for pain at the dorsal and medial raphe nuclei blunted acupuncture analgesia. Blocking serotonin receptors in rabbits and rats also diminished acupuncture analgesia. Administering a serotonin precursor potentiates acupuncture analgesia. Serotonin and its by-products are increased in the lower brainstem during acupuncture analgesia. Other neurochemical mediators of experimental acupuncture analgesia have been implicated in preliminary investigations including ▶ substance P, ▶ CGRP, ▶ CCK, and ▶ C-fos (Belgrade 1994).

That stimulation of tissue, including neural tissue, produces analgesia has only recently gained acceptance in conventional medicine. Neurosurgeon Norman Shealy pioneered the use of transcutaneous electrical nerve stimulation (TENS) in the 1970s – less than a decade after Melzack and Wall published their gate theory of pain modulation that postulated a competitive inhibition of pain by non-noxious stimuli. Wallin and colleagues showed that spinal cord stimulation inhibits ▶ long-term potentiation of spinal ▶ wide dynamic range neurons (Wallin et al. 2003). Hanai (2000) demonstrated a similar response to peripheral nerve stimulation.

Clinical Studies

In one extensive multicenter randomized controlled trial of acupuncture, amitriptyline or placebo for HIV-related neuropathic pain, no differences were found between groups; but all groups showed significant reductions in pain (Shlay et al. 1998). Using an electro-acupuncture-like treatment, Hamza and colleagues showed a substantial reduction in pain scores and analgesic use and improvement in quality of life measures among patients with Type II diabetes and painful neuropathy in a sham-controlled crossover trial of 50 patients (Hamza et al. 2000). More recently, Schroeder et al. reported a pilot study of acupuncture compared with conventional treatment for chemotherapy-induced peripheral neuropathy. Those

patients receiving acupuncture tended to show more improvement in nerve conduction studies than the control group (Schroeder et al. 2011). Earlier, Schoreder had shown that acupuncture was effective for controlling pain and improving nerve conduction in idiopathic peripheral neuropathy (Schroder et al. 2007). In a randomized controlled trial of acupuncture for severe acute pain in Herpes Zoster, acupuncture was as effective as pharmacological treatment at controlling pain (Ursini et al. 2011).

In a multicenter randomized placebo-controlled study using static magnetic fields in the form of magnetized insoles for diabetic peripheral neuropathy, Weintraub et al. showed statistically significant reductions in burning, numbness, and tingling after 3–4 months (Weintraub et al. 2003). Cortical stimulation for neuropathic pain has also been reported. In a small case series, Rainov and Heidecke report a sustained >50 % reduction in trigeminal and glossopharyngeal neuralgia for 72 months with motor cortex stimulation using a quadripolar electrode contralateral to the side of pain (Rainov and Heidecke 2003).

Although clinical studies are lacking for specific neuropathic pain conditions, meditative and mindful therapies such as hypnosis have been utilized for pain management for more than a century. Rainville and colleagues used PET scanning in normal subjects to show that pain unpleasantness is mediated in the anterior cingulate, anterior insula, and posterior cerebellum (Rainville et al. 1997). He used hypnosis to reduce the unpleasantness of an experimental pain stimulus and to distinguish it from pain intensity, localizing the two components functionally in the brain. The growing understanding of unpleasantness as distinct from pain intensity leads one to conclude that many nonspecific therapies that "quiet" the nervous system's emotional, anticipatory component of pain can play just as important a role as analgesics. In this way, many alternative and complementary therapies can be beneficial. Obviously, much clinical research is needed to define the scope and value of these therapies as well as their mechanisms of action. In the meantime, the prevalence and popularity of CAM among patients with neuropathic pain requires that the physician be acquainted with these therapies and guide patients toward the better studied, safest, and most appropriate techniques for the neurological condition.

Manual Therapies

According to the 2007 National Health Interview Survey, manipulation ranked in the top ten CAM therapies among both adults and children. The survey found that 8.6 % of adults and 2.8 % of children had used manipulation (http://nccam.nih.gov/health/backgrounds/manipulative.htm 2007). Osteopathic manipulative treatment is a modality used by osteopathic physicians to complement conventional treatment. Osteopathic manipulative treatment is defined in the Glossary of Osteopathic Terminology as "the therapeutic application of manually guided forces by an osteopathic physician to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction" (Clinical Guideline Subcommittee on Low Back Pain: American Osteopathic Association 2010). Somatic dysfunction may be associated with pain generators that interfere with the body's innate ability to heal itself. OMT may be delivered to reduce or remove the identified somatic dysfunction and to modulate central and peripheral mechanisms involved in pain generation (Kuchera 2007).

Osteopathy is a comprehensive system of medicine that incorporates diagnostic and therapeutic strategies to address body unity issues, enhance homeostatic mechanisms, and maximize structure-function interrelationships (Seffinger et al. 2007). Although osteopathy is recognized by the National Institutes of Health (NIH) in the United States as mainstream medicine, OMT is classified by the NIH's National Center of Complementary and Alternative Medicine as one of several promising complementary manipulative/body-based practices in addition to chiropractic and massage therapy (http://nccam.nih.gov/health/backgrounds/manipulative.htm 2007).

Research regarding manual treatment for patients with neuropathic pain is lacking. The little evidence that does exist consists primarily

of small studies or case reports. In 1999, Raison-Peyron et al. demonstrated sustained improvements with paraspinal physiotherapy and manipulation in four of six patients with varying degrees of relief from 1 to 9 years. There has been one report of spinal manipulation being effective for patients with brachioradial pruritis (Richardson et al. 2009).

The Active Release Technique Soft Tissue Management System has proven to be clinically promising in treating conditions related to overuse. In a case study of posterior interosseous nerve syndrome using soft tissue manipulation therapy, overall improvement in symptoms was observed with restoration of motor deficits and decrease in pain. Positive results persisted 1 and 6 months following treatment (Saratsiotis and Myriokefalitakis 2010).

The technique of neural gliding attempts to take the nerve throughout the available range of motion to improve the actual excursion of the nerve, decrease adhesions, and reduce symptoms by allowing the nerve to move freely. The most current and best available evidence in regard to neural gliding exercises for treatment of carpal tunnel syndrome comes from a few uncontrolled, randomized clinical trials, incomplete systematic reviews and anecdotal clinical evidence. A systematic review of this evidence revealed a possible trend toward pain and symptom reduction, improved sensation, and improved function and strength (Medina McKeon and Yancosek 2008).

In a case report of a patient with notalgia paresthetica, a chronic sensory neuropathy affecting one of the cutaneous dorsal rami of the upper thoracic region, OMT techniques were applied to relieve pressure on the exiting dorsal rami thereby providing symptomatic relief (Richardson et al. 2009).

Although it has been suggested that manipulation is a safe and effective treatment of radicular symptoms, there is little evidence for its efficacy and it is considered to be contraindicated by some. In a prospective single-blind randomized controlled trial comparing OMT with chemonucleolysis for treatment of symptomatic lumbar disc herniation, outcomes of leg pain, back pain, and self-reported disability improved in both groups. There were no instances of major complications from either treatment (Burton et al. 2000). In a study of 40 patients randomized to either surgical microdiskectomy or standardized chiropractic spinal manipulation, significant improvement in both treatment groups compared to baseline was observed in all outcome measures. Sixty percent of patients with sciatica who had failed other medical management benefited from spinal manipulation to the same degree as if they underwent surgical intervention (McMorland et al. 2010). In a randomized double-blind trial comparing active and simulated manipulations to treat acute back pain and sciatica, manipulations appear more effective on the basis of percentage of pain-free cases and number of days with moderate or severe pain (Santilli et al. 2006).

Nutraceuticals Included in this section are those nutraceuticals that have shown promising results in clinical trials for treatment of neuropathic pain. While there are several others that have been studied, the evidence is not as convincing.

Alpha-Lipoic Acid (ALA) has been used as a treatment for peripheral neuropathy in Europe for decades. Three large-scale, double-blind, placebo-controlled trials – the Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) studies – have examined various routes, dosages, and neurological effects of ALA. The first ALADIN study found ALA 600 or 1,200 mg IV for 3 weeks was superior to placebo for reduction of neuropathic symptoms. The 600 mg dose yielded slightly better results with fewer side effects. A meta-analysis of four placebo-controlled trials ($n = 1{,}258$), all with the same protocol of ALA 600 mg IV for 3 weeks, found a continuous daily improvement in symptoms beginning on the eighth day of treatment. In an uncontrolled study of 26 patients with diabetic neuropathy, an oral dose of 600 mg ALA for 3 months resulted in reversal from symptomatic to asymptomatic neuropathy (Head 2006).

Acetyl-L-Carnitine (ALC) has been tested in clinical studies for treatment of peripheral

neuropathy. In two multicenter randomized controlled trials, ($n = 1{,}679$) patients with diabetic neuropathy were treated with ALC 1,500–3,000 mg orally for 1 year. Reductions in neuropathic pain were reported in both studies and nerve regeneration was documented in one study (Head 2006; Evans et al. 2008; Pitter and Ernst 2008). In a study of patients with chemotherapy-induced neuropathy, 26 patients with cisplatin- or paclitaxel-induced peripheral neuropathy were given ALC 1 g IV for 10–20 days. All cisplatin-treated patients experienced improvement in neuropathy symptoms, while 8 of 12 patients in the paclitaxel group and 8 of 10 in the combination group experienced improvement in symptoms (Head 2006). In a study of patients with HIV-associated antiretroviral toxic neuropathy, ALC 1,500 mg twice daily resulted in improvement of neuropathic pain in 15 of 21 patients (Hart et al. 2004).

Benfotiamine is the most extensively studied form of thiamine for treatment of peripheral neuropathy. In a double-blind, randomized placebo-controlled study, 40 patients with diabetic neuropathy were treated with benfotiamine 100 mg four times daily or placebo for 3 weeks. A statistically significant improvement in neuropathy was reported in the treatment group compared to placebo. A small study found benefit of benfotiamine for alcoholic neuropathy treated with 450 mg benfotiamine daily for 2 weeks, followed by 300 mg daily for an additional 4 weeks (Head 2006).

Vitamin B12 deficiency has been associated with peripheral neuropathy. In a double-blind, placebo-controlled trial, 21 patients with diabetic neuropathy were given oral methylcobalamin 500 mcg three times daily for 4 months, while 22 patients received placebo. Significant improvements in symptoms were reported in the treatment group compared to placebo (Head 2006).

The amino acid N-acetylcysteine (NAC) is a potent antioxidant. Fourteen colon cancer patients were randomly assigned to 1,200 mg oral NAC or placebo daily. After four cycles of chemotherapy, two of five in the NAC group and seven of nine in the placebo group experienced neuropathy; after eight cycles no one in the NAC group experienced neuropathy compared to five of nine in the placebo group. Only 1 in the NAC group, but 8 of 9 in the placebo group experienced neuropathy after 12 cycles (Head 2006).

Zinc is abundant in the central nervous system and regulates pain. In an animal study, zinc was found to alleviate pain through high-affinity binding to the *NMDA* receptor NR2A subunit (Nozaki et al. 2011). A clinical study examined the effect of zinc for diabetic neuropathy. Thirty patients with diabetic neuropathy were supplemented with 660 mg zinc sulfate daily or placebo for 6 weeks. Nerve conduction velocity significantly increased in the group supplemented with zinc (Head 2006).

Another cationic compound, agmatine (decarboxylated arginine), has recently been introduced as a nutraceutical and tested in about 60 patients with disc-associated radiculopathy using an open label dose escalation design followed by a placebo-controlled double-blind design (Keynan et al. 2010). In the first study, mild gastrointestinal side effects were noted in three patients at the highest doses, but these were reversed upon cessation of treatment. Continuous improvement of symptoms was evident in both groups of the latter study with no adverse events, but the agmatine group's symptoms improved more (70 % vs. 27 % relative to baseline).

Fatty acids are essential for nerve membrane structure. Patients with diabetes appear to have impaired conversion of linoleic acid to gamma-linolenic acid (GLA). In a double-blind study, 22 patients with diabetic neuropathy were assigned to 360 mg GLA or placebo for 6 months. Subjects treated with GLA exhibited significantly better neuropathy scores, nerve conduction velocity, and action potentials compared to placebo (Head 2006).

Geranium (*Pelargonium*) oil was tested for postherpetic neuropathy in a double-blind randomized controlled trial. It reported a dose-dependent reduction in pain compared with placebo.

Magnets It has been hypothesized that electromagnetic fields may benefit peripheral neuropathy by polarization of neurons that may be firing

ectopically. Pulsed magnetic field therapy was used to treat 24 subjects with peripheral neuropathy. Average pain scores decreased by 21 % at the end of nine treatments and by 49 % at a follow-up assessment. In a randomized controlled trial on 375 patients with diabetic neuropathy, subjects wore multipolar, static, 450 G magnetic insoles or placebo insoles in their shoes for 4 months. There was a significant reduction in neuropathic symptoms in the magnetic-insole group compared to placebo (Pitter and Ernst 2008).

Mindful, Meditative, and Psychological Therapies for Neuropathic Pain

Within the mindful and meditative therapies category of the complementary and alternative medicine (CAM) literature, various psychological techniques are often listed such as hypnosis, imagery, meditation, relaxation, and biofeedback. In actuality, there are many forms of psychological theories and techniques utilized in multidisciplinary chronic pain treatment centers by health psychologists and other therapists. While these theories and techniques have been labeled as CAM treatments by health professionals or the general public, pain specialists often consider them mainstream or under the label Integrative Medicine, depending on the definition. Regardless, there is strong empirical evidence to support the use of these techniques for chronic pain management. However, less research has been conducted demonstrating their efficacy for neuropathic pain.

As reviewed in Turk et al. (2010), since the initial publication of behavioral treatment for chronic pain by Fordyce et al. in 1968 (Fordyce 1976), a large number of clinical trials have been conducted demonstrating efficacy for psychological treatments for chronic pain. Cognitive-behavioral therapy (CBT) and operant conditioning have been the psychological approaches most commonly researched. Specific psychological techniques are also evaluated in the literature with cognitive therapy, supportive counseling, hypnosis, relaxation, biofeedback, and meditation being the most cited. It is also important to note that various psychological techniques can also be incorporated into CBT therapy. CBT also incorporates the behavioral principles of operant conditioning. Common psychological theories and techniques are listed in Table 2. While the article by Turk et al. focused on CBT, since theoretically based approaches

Alternative Medicine in Neuropathic Pain, Table 2 Examples of psychological approaches and techniques used with chronic pain patients

Psychological approaches and techniques	
Cognitive behavioral therapy	Using behavioral and cognitive techniques to achieve changes in behavior, thoughts, and emotions
Operant behavioral therapy	Using principles of behavioral psychology to reduce pain behaviors and increase appropriate ones
Mindfulness meditation	Intentional self-regulation of awareness, a systematic focus on inner and outer experiences
Acceptance and commitment therapy	Observing thoughts and feelings as they are, and acting in ways consistent with valued goals and life directions.
Motivational interviewing	General therapeutic approach and techniques to increase belief in and possibility to engage in adaptive behaviors
Eye movement desensitization and reprocessing (EMDR)	An information processing psychotherapy that uses an eight phase approach to address the experiential contributors to chronic pain
Supportive counseling	Empathetic listening, encouragement, and acknowledgement of distress
Cognitive therapy	Changing cognitive activity to change behavior, thoughts, and emotions
Hypnosis	An altered state of awareness designed to focus attention to change participants experience of pain
Relaxation	For example, progressive muscle relaxation (PMR), autogenic training
Biofeedback	Measuring psychophysiological data by noninvasive electrical devices, and providing real-time feedback to raise awareness and conscious control of the autonomic nervous system
Imagery	Using imagination to reduce stress, relieve pain, and stimulate healing responses in your body

have better quality research, our focus will be on all psychotherapeutic research with neuropathic pain patients.

Psychological interventions as a whole have been found to be effective for many pain diagnoses in improvements for measures of pain, mood/affect, cognitive coping and appraisal, health-related quality of life, and depression (Eccleston et al. 2009; Morley et al. 1999; Hoffman et al. 2007). However, further evidence is needed to clarify long-term efficacy and vocationally relevant outcomes (Eccleston et al. 2009; Hoffman et al. 2007). In a meta-analysis of psychological treatment for chronic low back pain, CBT and self-regulatory treatments (e.g., biofeedback, relaxation, or hypnosis) were found to be specifically effective for pain intensity (Hoffman et al. 2007). Hypnosis has been found to reduce pain relative to no treatment or standard medical interventions, and results have been similar to interventions such as progressive muscle relaxation (PMR) and autogenic training (Elkins et al. 2007; Jensen and Patteson 2006). Further research is needed to compare the effects of hypnosis for chronic pain to similar therapies.

Recent literature has also focused on newer psychological approaches to chronic pain including mindfulness-based stress reduction (MBSR) or mindfulness meditation and acceptance and commitment therapy (ACT) (McCracken and Thompson 2011). Research on mindfulness meditation for chronic pain has been promising and found to improve mental and physical aspect of chronic pain in several studies (Gardner-Nix 2009). Initial studies of ACT was found to be related to lower disability and distress, and overall functioning in patients (McCracken and Thompson 2011; McCracken and Zhao-O'Brien 2010; McCracken and Vellerman 2010).

Clinical Studies in Neuropathic Pain *Cognitive-Behavioral Therapy*: In a recent systematic review (Mehta et al. 2011), two randomized controlled trials, six prospective controlled trials, and one cohort study of CBT for patients with spinal cord injuries (SCI) were analyzed. CBT was found to be moderately effective for depression, coping, and adjustment in adults following SCI. Pain was not specifically addressed in this review. Two studies, a prospective interventional study and nonrandomized parallel cohort design, were used to assess a comprehensive CBT pain management program for SCI (Perry et al. 2010; Budh et al. 2006). These studies found that a CBT group demonstrated improvements in mood, life interference, anxiety, pain catastrophizing, and sleep.

Behavioral Therapy: Minimal research was found specifically for behavioral therapy or operant techniques and neuropathic pain, other than case studies on the behavioral treatment of reflex sympathetic dystrophy (RSD) (Alioto 1981). These studies suggested that behavioral therapy may decrease pain, medication use, and improve mood after increased engagement in the treatment program.

Hypnosis: Multiple case studies were conducted showing promising effects of hypnosis for reflex sympathetic dystrophy (Gainer 1992) and phantom limb pain (Oakley et al. 2002). In a review (Oakley et al. 2002), research for hypnotic imagery for phantom limb pain has fallen into two categories, ipsative/imagery-based and movement/imagery-based. The ipsative/imagery approach takes into account the way an individual represents their pain and attempts to modify it, while the movement/imagery approach focuses on "moving" or taking control over the amputation. Both approaches appear to have promise from limited case study data.

A case series design was conducted (Jensen et al. 2005) using hypnosis in 33 patients with chronic pain from the following conditions: SCI, multiple sclerosis, amputation, cerebral palsy, post-polio syndrome, and Charcot Marie Tooth Syndrome. There was a decrease in pain intensity that lasted for at least 3 months, but no effect on mood or pain interference variables was found.

EMDR: Several case studies and a case series design were found for the effect of EMDR for phantom limb pain (Schneider et al. 2008). Schneider reported that for five cases, phantom

pain was decreased using EMDR. This effect lasted from 14 months to 2 years.

Relaxation Training: A few case studies have indicated that autogenic training may be beneficial for RSD (Kawano et al. 1989; Fialka et al. 1996). One small randomized pilot study (Fialka 1996) compared an autogenic training group to controls. Both groups participated in home therapy. A significant decrease in pain was found for both groups. The only intragroup difference found was for skin temperature. Hough and Kleinginna (2002) evaluated a variety of relaxation techniques (e.g., meditation, visual imagery, PMR) that were used for six patients with SCI of varying injury levels. Relaxation techniques were found to be beneficial for pain and mood. The authors concluded that clinicians should consider level of spinal cord injury and individual differences when selecting relaxation techniques.

Biofeedback: Recent attention has been given to the use of thermal biofeedback in patients with diabetes. Thermal biofeedback has been suggested to be helpful in diabetic patients to improve circulation, pain, neuropathy, ulcer healing, ambulatory activity, and quality of life (Galper et al. 2003). Patients who underwent thermal biofeedback and relaxation training or self-hypnosis training were found to have increased peripheral temperature (Needham et al. 1993; Rice and Schindler 1992) and decreased levels of depression (Rice and Schindler 1992). In a randomized controlled study, Rice et al. found that thermal biofeedback combined with autogenic training, PMR, and breathing exercises increased foot ulcer healing, sensory nerve function, patient activity, and blood flow to the feet (Rice et al. 2001).

There was some preliminary evidence that thermal biofeedback combined with other relaxation techniques may decrease pain in patients with phantom limb pain (Sherman et al. 1979; Belleggia and Birbaumer 2001; Harden et al. 2005) and reflex sympathetic dystrophy (Blanchard 1979; Barowsky et al. 1987).

Comparative Studies: Three preliminary studies, two randomized controlled trials and one quasi-experimental study, compared psychological treatments in patients with neuropathic pain. Self-hypnosis and EMG biofeedback were found to decrease pain intensity in 37 patients with SCI (Jensen et al. 2009a). The self-hypnosis group maintained gains at 3 months follow-up. In the second study, self-hypnosis was found to decrease pain levels and increase physical functioning in patients with multiple sclerosis for up to 3 months compared to a PMR relaxation group (Jensen et al. 2009b). CBT and supportive psychotherapy demonstrated decreased pain, but the CBT group also showed decreased pain interference and distress in a group of patients with peripheral neuropathy due to HIV (Evans et al. 2003). There was one study that suggested that a combination of psychological treatments such as hypnosis, imagery, and cognitive therapy helped to decrease pain in 25 amputees for up to 6 months (Bamford 2006).

Psychological therapies do appear to have a beneficial impact on chronic pain and its related psychosocial issues. Most of the studies are limited to case series, uncontrolled trials, or quasi-experimental designs. Neuropathic pain is represented by a smaller number of these trials but shows similar benefit and the larger studies are often in heterogeneous populations of pain patients.

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Alternative Rat Models of Ureteric Nociceptive Stimulation In Vivo

Definition

Noxious stimulation of the ureter in previous studies has been achieved using stimulus modalities other than experimentally induced "stones." For example:

- Electrical stimulation of the ureter has been employed in the unanesthetized rat (Giamberardino et al. 1988). Although the stimulus was not natural, this model offered the advantage of a stimulus that could be readily controlled and modulated in frequency, intensity, and duration. Unfortunately, nocifensive behaviors and referred muscle hyperalgesia associated with stimulation were inconstant.
- In another study, distension of the renal pelvis after cannulation of the ureteric-pelvic junction was evaluated. This stimulus produced rather variable pseud-affective responses that were unrelated to stimulus intensity (Brasch and Zetler 1982).
- More recently, the ureter in an anesthetized rat was cannulated close to the bladder and responses (cardiovascular changes) to graded ureter distension were characterized (Roza and Laird 1995). Responses to stimuli less than 25 mmHg were never observed whereas suprathreshold pressures evoked responses proportional to stimulus intensity. The stimulus-response curve was dose-dependently attenuated by morphine in a naloxone reversible manner. The authors concluded that the characteristics of the responses observed correlated well with pain sensations in man, and with the properties of ureteric primary afferent neurons in animals. This model fulfils most of the criteria proposed as ideal for a noxious visceral stimulus: the experiments are reproducible, the results consistent, and the responses proportional to stimulus intensity. However, the procedure is invasive and can only be applied in an anesthetized rat; it is therefore not suitable for behavioral studies. On the other hand, it is ideal for electrophysiological studies, not only in normal animals but also in animals with calculosis, allowing the comparison of neural processing of acute visceral noxious stimulation in normal animals with that of animals with chronic visceral pain and referred hyperalgesia using the same stimulation technique.

Cross-References

▶ Visceral Pain Model, Kidney Stone Pain

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Alternative Therapies

▶ Alternative Medicine in Neuropathic Pain

Ambiguity

▶ Impairment Rating, Ambiguity
▶ Impairment Rating, Ambiguity, IAIABC System

Amelioration

Definition

The improvement or bettering of the meaning of a word through semantic change. The opposite of pejoration.

Cross-References

▶ Lower Back Pain, Physical Examination

Amenorrhea

Definition

Amenorrhea is the absence of menstruation, which is normal before puberty, during pregnancy, or after menopause. Congenital a bnormalities of the reproductive tract, metabolic disorders (such as diabetes or obesity), and endocrine disorders (including altered pituitary, thyroid, or ovarian function) are the most common causes of amenorrhea. Medications that alter hormonal status, including opioids, can also lead to amenorrhea. In some cases, emotional disorders can lead to a cessation of menses.

Cross-References

▶ Cancer Pain Management, Opioid Side Effects, Endocrine Changes, and Sexual Dysfunction

American Society of Anesthesiologists' Status Category

Definition

Each status category/class gives an overall impression of the complexity of the patient's medical condition. If the procedure is performed as an emergency, an "E" is added to the category/class:

Class 1 – a healthy patient

Class 2 – a patient with mild systemic disease

Class 3 – a patient with severe systemic disease that limits activity but is not incapacitating

Class 4 – a patient with incapacitating systemic disease that is a constant threat to life

Class 5 – a moribund patient not expected to survive 24 h with or without surgery

Cross-References

▶ Postoperative Pain, Preoperative Education

Amide Anesthetic

Definition

A member of one of the two major chemical classes of local anesthetics, differentiated by

the intermediate chain linking a lipophilic group and an ionizable group (usually a tertiary amine). The pharmacologic class of agents comprised of lidocaine, bupivacaine, ropivacaine, mepivacaine, prilocaine, and etidocaine.

The other major class is ester anesthetic.

Cross-References

- ▶ Acute Pain in Children, Postoperative
- ▶ Drugs with Mixed Action and Combinations: Emphasis on Tramadol
- ▶ Postoperative Pain, Methadone

Amidine

- ▶ Postoperative Pain, Methadone

Amidine Hydrochloride

- ▶ Postoperative Pain, Methadone

Aminobisphosphonate

Definition

A class of drugs that blocks bone-resorbing cells (osteoclasts) and prevents bone loss.

Cross-References

- ▶ Cancer Pain Management, Orthopedic Surgery

Aminomethyl-Cyclohexane-Acetic Acid

- ▶ Postoperative Pain, Gabapentin

Amitriptyline

Definition

A tricyclic antidepressant drug utilized for the treatment of chronic pain, particularly effective in the craniofacial region. Its antinociceptive effect is independent of its antidepressive activity in that they occur at doses tenfold lower (10–25 mg/day) than antidepressant doses, possibly involving a blockade of voltage-gated sodium channels. Amitriptyline's prophylactic efficacy in chronic daily headache and migraine is limited.

Cross-References

- ▶ Atypical Facial Pain: Etiology, Pathogenesis, and Management
- ▶ Fibromyalgia, Mechanisms, and Treatment
- ▶ Preventive Migraine Therapy

AMPA Glutamate Receptor (AMPA Receptor)

Definition

A type of ionotropic glutamate receptor that is activated by the specific agonist *alpha*-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA). AMPA receptors comprise several subunits (GluR1, GluR2, GluR3, GluR4) that form a heteromeric receptor-ion channel complex, the composition of which affects the kinetic properties of the receptor-ion channel. AMPA receptors mediate the majority of fast synaptic transmission in the central nervous system.

Cross-References

- ▶ Metabotropic Glutamate Receptors in the Thalamus
- ▶ Opiates During Development

Amphibian Peptides

Definition

Amphibian skin contains a wide variety of peptides that are often homologous or even identical to the gastrointestinal hormones and neurotransmitters of the Mammalia.

Striking examples are cerulein, the amphibian counterpart of mammalian cholecystokinin and gastrin; physalemin and kassinin, counterparts of the mammalian neuropeptides substance P and neurokinins; the amphibian bombesins and litorins, which heralded the discovery of the gastrin-releasing peptides (mammalian bombesin) and neuromedin B; and finally, sauvagine, whose structure elucidation preceded that of the analogous, hypothalamic corticotropin-releasing hormone. Other peptide families common to amphibian skin and mammalian tissues are bradykinins, angiotensins, somatostatins, and the thyrotropin-releasing hormone. Opioid peptides have so far only been in the skin of the hylid frog of the Phyllomedusine stock. During his long scientific life, the pharmacologist Vittorio Erspamer sought biologically active molecules in more than 500 amphibian species from all over the world and showed that the amphibian skin and its secretions offer an inexhaustible supply of biologically active peptides for pharmacological research.

Cross-References

- ▶ Opioid Peptides from the Amphibian Skin

Amphipathic

Definition

An amphipathic segment is a segment with opposing hydrophobic and hydrophilic faces, oriented spatially along the axis of the segment

Cross-References

- ▶ Capsaicin Receptor
- ▶ Thalamus, Clinical Pain, Human Imaging

Amygdala

Definition

A prominent group of neurons forming an almond-shaped structure at the level of the temporal cortex in primates, and form part of the limbic system. In the rat, the amygdala is ventrolateral, close to both the temporal and perirhinal cortices. It is divided schematically into four groups: cortical and basal (main olfactory), medial (accessory olfactory), central (autonomic), basolateral and lateral (frontotemporal and temporal cortices). The precise role of this region remains incompletely understood. It seems that one of its roles is to mark perceptions with an affective label that provides an appropriate significance in the environment of the species. In the framework of pain, it triggers an aversive reaction and fear that causes the organism to avoid dangerous stimuli. It also plays a role in the development of memories with an emotional component.

Cross-References

- ▶ Amygdala, Pain Processing and Behavior in Animals

- ▶ Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee)
- ▶ Parabrachial Hypothalamic and Amygdaloid Projections

Amygdala, Functional Imaging

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Synonyms

Functional magnetic resonance imaging (fMRI); Positron emission tomography (PET)

Definition

The amygdala is an essential key structure in the cerebral limbic network underlying emotion processing. As such, it is suggested to be part of the brain circuit involved in the processing of pain, which is known to include strong affective components. Neuroimaging studies pointing to amygdala involvement during pain processing are currently increasing. The amygdala is a small almond shape structure in the anterior temporal lobe with a variety of functions for emotion processing together with learning and memory. It is supposed to execute an evaluative associative function, combining external cues with internal responses, thereby assessing and defining the valence, relevance, and significance of stimuli. It is its extensive connectivity with various cortical and subcortical areas that enables fast automatic, but also more conscious deliberate, responses. Its role in pain processing is however less clear.

Characteristics

Negative affect is typically evoked by acute pain. Key structures of the ▶ limbic system have been identified that play an important role in regulating affective behavior; among the most important are the subcortical and cortical areas, the anterior cingulate, the insula, and the prefrontal cortex. Most notably, assessment of emotional valence of stimuli and the provocation of distinct emotional reactions are mediated by the amygdala. This central role in emotion processing can be executed due to a broad cortical and subcortical network in which the amygdala is located and which is able to provide it with raw information via the short thalamus route but also with highly processed polymodal input from sensory cortices. Finally, the amygdala is not a unitary structure, but consists of several nuclei exerting different functions. It is believed to have a major role in pain because of the strong association and interaction between pain and emotion but also because of the specific nociceptive inputs to the latero-capsular part of the central nucleus, the major output system within the amygdala, indicating that, within this accumulation of nuclei, this part may represent the "nociceptive amygdala" (Neugebauer et al. 2004). For ▶ fMRI, mapping of activation within this region is, however, critical posing technical and methodological problems, which often call into question the validity and reliability of imaging results reporting amygdala activation. This may possibly be one of the reasons, why early neuroimaging findings mostly failed to demonstrate clear amygdala activation during pain perception. FMRI of this deep subcortical region is confronted with a set of difficulties, such as movement, respiratory, inflow, and susceptibility artifacts (see ▶ Inflow Artifacts) and nonetheless the rapid habituation of amygdala responses to repeated stimulus presentations. This is of special relevance for experimental pain studies, which mostly rely on the application of ▶ block designs, which are especially prone to habituation. Recent methodological advances in neuroimaging may have partly overcome these inherent mapping difficulties, accounting for the increase in pain studies successfully demonstrating amygdala participation (Bingel et al. 2002; Bornhövd et al. 2002).

Amygdala, Functional Imaging, Table 1 Overview of pain studies reporting amygdala activation

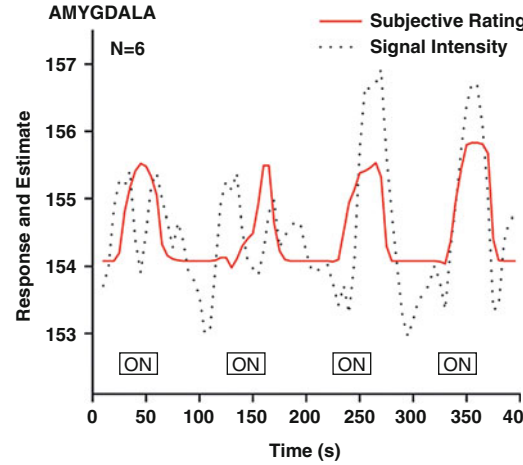
Author	Imaging method	Painful stimulation	Number of subjects	Amygdala activation/deactivation
Beccera et al. 1999	fMRI (1,5 T)	Thermal stimulation (Peltier-based thermode) 46 °C	2 groups of 6 healthy subjects	Deactivation of the amygdala
Becerra et al. 2001	fMRI (1,5 T)	Thermal stimulation (Peltier-based thermode) 46 °C compared to 41 °C	8 healthy subjects	Activation in the sublenticular extended amygdala in the early phase
Bingel et al. 2002	fMRI (1,5 T)	YAG infrared laser stimulation	14 healthy subjects	Bilateral activation to unilateral stimulation
Bornhövd et al. 2002	fMRI (1,5 T)	YAG infrared laser stimulation	9 healthy subjects	Activation increasing with stimulus intensity
Derbyshire et al. 1997	PET (H_2 ^{15}O)	CO_2 laser (mild/moderate pain vs. warm)	12 healthy subjects	Decreased rCBF
Evans et al. 2002	fMRI (1,5 T)	Mechanical ventilation at 12–14 breaths/min Air hunger vs. baseline	6 healthy subjects	Activation
Hsieh et al. 1995	PET (^{15}O Butanol)	Intracutaneous injection of a minute amount of ethanol vs. saline	4 healthy subjects	Nonsignificant activation
Lu et al. 2004	fMRI (3 T)	Fundus balloon distension (17.0 0.8 mmHg) vs. baseline	10 healthy subjects	Activation
Petrovic et al. 2004	PET (H_2 ^{15}O)	Cold pressure test (0–1 °C water with ice or glycol) vs. cold water (19 °C)	10 healthy subjects	Deactivation in response to context manipulations increasing anticipated pain duration
Schneider et al. 2001	fMRI (1,5 T)	Balloon dilatation of a dorsal foot vein	6 healthy subjects	Amygdala activation correlated with subjective online pain ratings
Wilder-Smith et al. 2004	fMRI (1,5 T)	Rectal balloon distention alone or with painful heterotopic stimulation of the foot with ice water	10 patients with irritable bowel syndrome, 10 healthy subjects	Amygdala activation in patients with irritable bowel syndrome (constipation) during heterotopic stimulation

Alternatively, it is also conceivable that the majority of pain stimulation techniques failed to evoke pain that provoked strong emotional responses, hence falling short of observing amygdala involvement. The frequent failure of these early studies to report changes in autonomic arousal during painful stimulation corroborates this assumption. In an attempt to model acute traumatic nociceptive pain, a ▶ PET study used intracutaneous injection of ethanol (Hsieh et al. 1995). Affective and heart rate changes were described in subjects, and cerebral activation was found in subcortical structures, specifically the hypothalamus and the periaqueductal gray. These regions are taken to constitute the brain defense system which functions as a modulator for aversive states. Although signal increases in the amygdala were detected by the authors, they failed to be significant.

Despite more recent neuroimaging findings reporting amygdala involvement in pain processing, a full characterization of its function during pain perception is still lacking and at first sight results seem to be equivocal, pointing to activations as well as deactivations of the amygdala in this context (Table 1).

One fMRI investigation applied painful stimulation with a strong affective component to measure pain related changes in cerebral activity (Schneider et al. 2001). By inflating an indwelling balloon catheter, a dorsal foot vein of healthy volunteers was stretched to a noxious distress physical level, which induced vascular pain associated with a particularly strong negative effect. Since the sensory innervation of veins exclusively subserves nociception, non-painful co-sensations were excluded. Additionally, brief

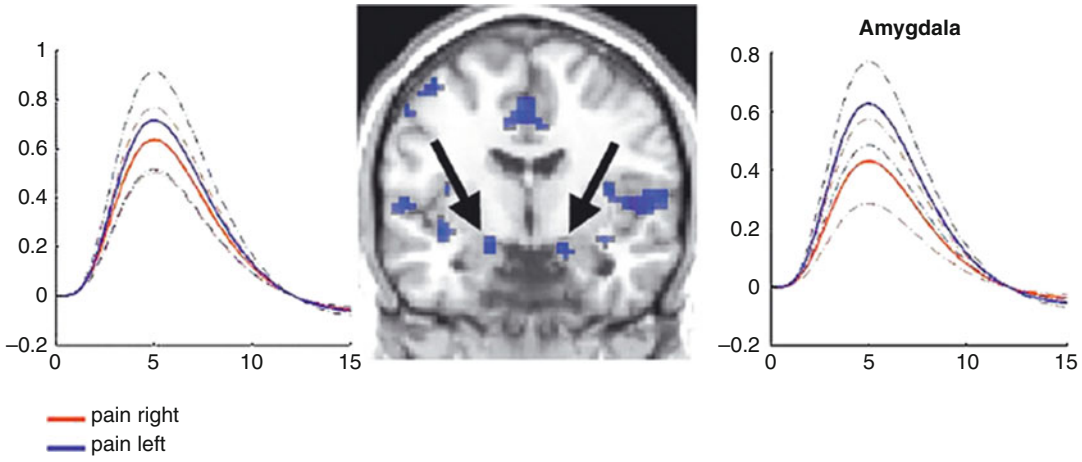
stimulations of only a few minutes produce vascular pain that escapes adaptation and is generally reported as particularly aching in character. During noxious stimulation, the subjects continuously rated perceived pain intensity on a pneumatically coupled visual analogue scale, which was used as permanent feedback to adjust balloon expansion so that the pain intensity could be kept at intended values at all times. The analysis strategy that focused primarily on correlations of signal changes with these subjective ratings, rather than the generally applied signal variations to a stimulation-based reference function (▶ Boxcar Design), facilitated producing evidence for amygdala activation (Fig. 1). Hence, these results indicated a relevant role of the amygdala in the subjective component of painful experiences and suggested that in the widespread cerebral network of pain perception, the limbic system and especially the amygdala may be instrumental in the affective aspects of pain. Supporting evidence for these conclusions come from neuroimaging findings during air hunger (Evans et al. 2002) or fundus balloon distension (Lu et al. 2004). Dyspnea was induced in healthy subjects by mechanical ventilation until a sensation of "urge to breathe" and "starved for air" was reached and compared to mild hypocapnia. This pain is also very afflicted with strong negative effect. Correspondingly, a network of limbic and paralimbic nodes was activated, including anterior insula, anterior cingulate, operculum, thalamus, cerebellum, basal ganglia, and also amygdala, that is, the majority of regions forming part of the limbic network also involved in emotion processing. Similarly, moderate gastric pain was induced in ten healthy subjects using fundus balloon distension (Lu et al. 2004) and resulted in a widespread activation pattern of subcortical as well as cortical regions, among them insula and amygdala. This may once again point especially to the strong affective component of visceral pain. Since visceral pain may be indicative of an urgent and marked system imbalance possibly endangering survival, strong affective responses with the objective of initiating adequate adaptations and reactions seem to have an evolutionary purpose and be necessary.



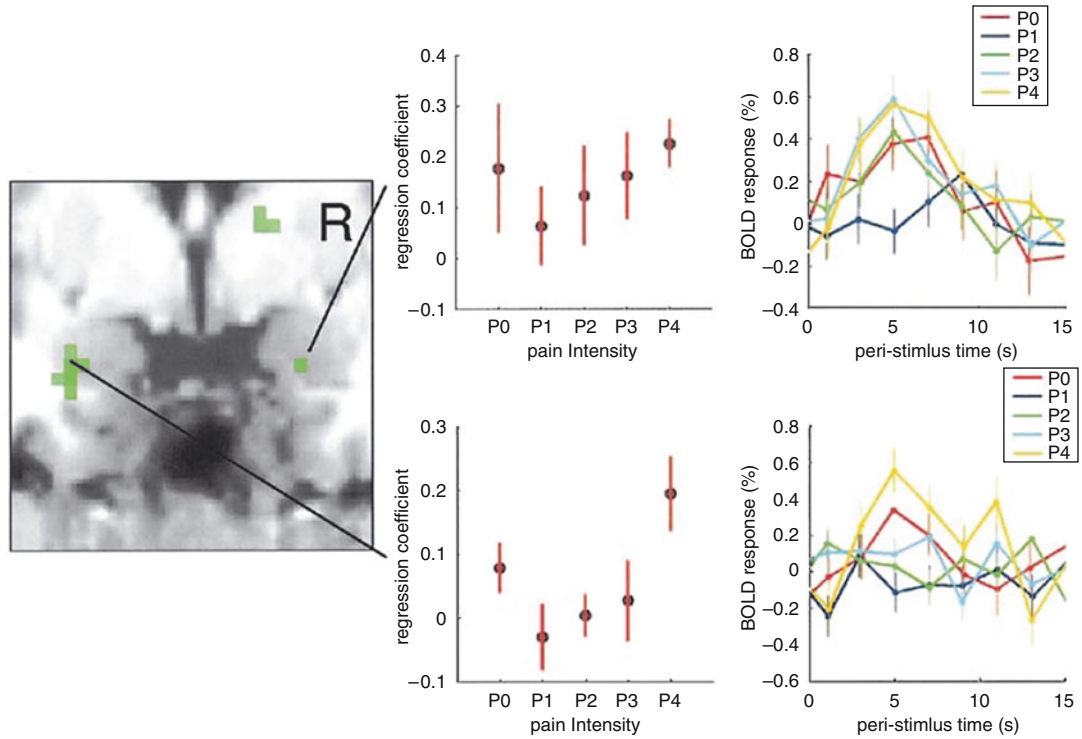
Amygdala, Functional Imaging, Fig. 1 Individual signal intensities in the amygdala following correlation with subjective ratings of the six individual participants (From Schneider et al. 2001)

Amygdala activation is however not restricted to visceral pain but also visible during other kinds of painful stimulation in animals as well as humans (Bingel et al. 2002). Unilateral laser that evoked painful stimuli of either side, which also avoided concomitant tactile stimulation and anticipation as well as habituation, successfully demonstrated bilateral amygdala activation, most probably representing the affective pain component (Fig. 2). In contrast, basal ganglia and cerebellum displayed corresponding unilateral activation and may probably be related to defensive and withdrawal behavior. RCBF (regional cerebral blood flow) changes were also found in limbic structures of rats during noxious formalin nociception (Morrow et al. 1998).

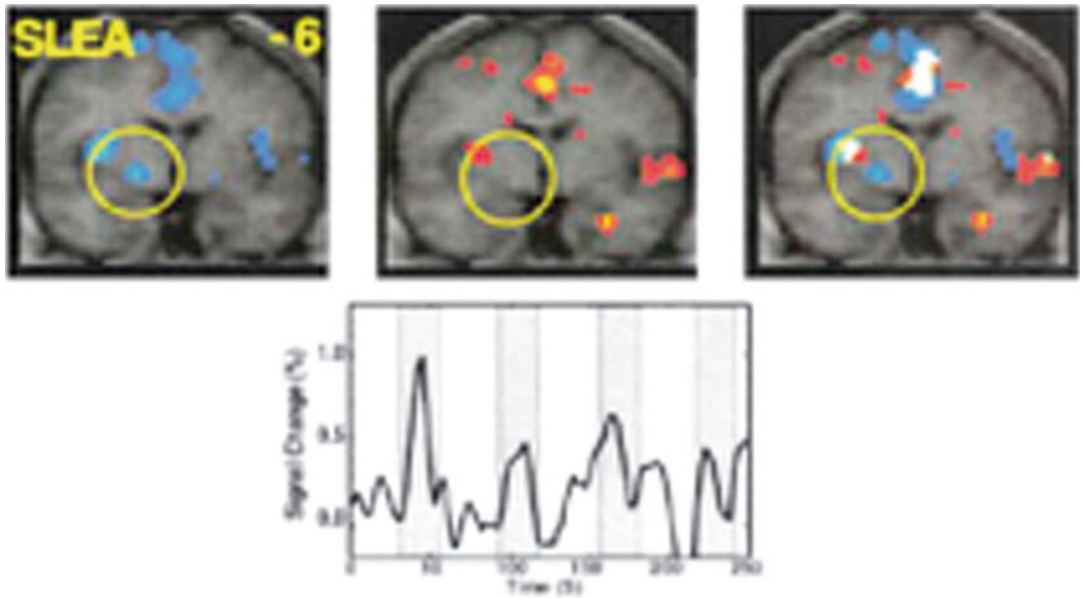
Hence, the role of the amygdala as a "sensory gateway to the emotions" (Aggleton and Mishkin 1986) with an evaluative function seems to extend to pain perception as well. An increasing number of studies supported the notion of a common evaluative system with a central role of the amygdala in the processing of painful but also non-painful or novel stimuli. The amygdala demonstrated not only coding of the pain amount by showing a linearly increasing response to augmenting painfulness (Fig. 3) but also significant responses during uncertain trials in which the stimulus was not perceived, and hence,



Amygdala, Functional Imaging, Fig. 2 Amygdala activation emerged bilaterally in response to painful unilateral laser stimulation. *Left*: Fitted responses applied to the *left* (*blue line*) or *right* (*red line*) hand for the left (*left graph*) and right (*right graph*) hemispheres. The *dotted lines* show the standard error of the mean (SEM) (From Bingel et al. 2002)



Amygdala, Functional Imaging, Fig. 3 Picture: Bilateral amygdala activation ($p = 0.001$) on a coronal slide. Graphs: *Left side* entails regression coefficients indicating amount of response for each trial (P0–P4). *Right side* depicts amount of signal change in the amygdala as a function of peristimulus time separately for all stimuli (P0–P4; from Bornhövd et al. 2002)



Amygdala, Functional Imaging, Fig. 4 Coronal slices showing sublenticular extended amygdala (SLEA) activation in the early (*left*) and late phases (*middle*) in response to a noxious thermal stimulation (46 °C). Overlap (*white*) of early (*yellow*/*red*) and late (*blue*) phases (*right*)

a judgment on the nature and valence is required (Bornhövd et al. 2002). Furthermore, the amygdala, here more specifically the sublenticular extended amygdala, seems to be characterized by early responses (to noxious thermal stimuli) in contrast to regions activated later and associated specifically to somatosensory processing, such as the thalamus, somatosensory cortex, and insula (Becerra et al. 2001) (Fig. 4). This is in accordance with the activation characteristic of the amygdala during ▶ classical conditioning (Büchel et al. 1998), in which a rapid adaptation to the conditioned stimulus has been observed, pointing to a major role of the amygdala during the early phase of learning, during the establishment of an association between the neutral stimulus and the (un)conditioned response. Hence, the early response during pain seems to reflect the association between the painful stimulus and an adequate internal response determining the negative valence of the stimulus.

However, sometimes deactivation as opposed to activation has been observed in the amygdala during painful stimulation, for example, with fMRI in response to thermal stimuli (45 °C) (Beccera et al. 1999). In this study only six subjects were investigated and changes were low level. Similar deactivations have also been reported using PET during mild or moderate pain due to CO_2 laser stimulation compared to non-painful warm sensations (Derbyshire et al. 1997). Hence, a possible moderating variable for activations and deactivations may be the specific thermal pain sensation, which was similar during both experiments. Alternatively, the deactivation may reflect another functional activation characteristic of the amygdala under certain circumstances. Hence, the deactivation may simply be the consequence of the nature of the experimental pain stimulus. An early activation in the amygdala for purposes of evaluation and affective judgment may be followed by a deactivation, possibly representing the attempt to regulate and cope with the affective aspects of the painful experience as well as the painful sensation itself that cannot be escaped in this special experimental setup. This interpretation is supported by recent PET findings. Petrovic et al. (2004) investigated the influence of context manipulations before the painful stimulation on the activation

pattern during noxious (cold pressure) stimulation. Subjects were informed prior to stimulation if it was going to be painful or not and if it would last for 1 or 2 min. Anticipating that the pain was going to last longer was accompanied by a decrease in amygdala activation and changes in autonomic parameters but also cognitive processes in the majority of subjects that consisted of strategies to cope with the stressful but unavoidable pain. This amygdala deactivation was paralleled by activation in the anterior cingulate, pointing to interactions within this limbic network constituting the brain's pain matrix responsible for the development and modulation as well as coverage and termination of the affective noxious events.

This study also highlights some methodological problems of pain imaging studies in general and those with a special focus on the amygdala. Anticipation may alter amygdala response characteristics and may lead to deactivations instead of activations. Furthermore, the individual variability in pain responses and several methodological factors, such as imaging method, data analysis, and control condition used for comparison with pain condition, influence results as well as their interpretation.

However, further indications that the amygdala serves coping functions during pain perception come from clinical trials. Here, visceral pain hypersensitivity is discussed as a possible relevant pathogenic factor in various chronic pain syndromes, such as ▶ irritable bowel syndrome (IBS). Reduced signals in the amygdala (as well as in further limbic network nodes such as insula and striatum) have also been observed in patients with irritable bowel syndrome during rectal pain stimulation (Bonaz et al. 2002) and are in accordance with the interpretation of deactivations found in healthy controls. It may be suggested that deactivations in patients may correspond to the effort to modulate and control the strong affective components of the painful experiences. Unfortunately this study failed to include healthy controls, and hence, a conclusion on the dysfunctional or compensatory aspects of these activations in patients remains elusive. Interestingly, a recent fMRI study (Wilder-Smith et al. 2004) investigating rectal pain alone or accompanied by painful foot stimulation (ice water, activating endogenous pain inhibitory mechanisms) in patients with irritable bowel syndrome as well as healthy controls found differential activations between groups in the amygdala (activation in constipated patients) as well as further affective-limbic regions (hippocampus, insula, anterior cingulate, prefrontal cortex, etc.) during heterotopic stimulation.

Hence, the amygdala is not only implicated in the affective aspects of pain processing, including both the appraisal of a painful stimulation and the initiation of adequate responses, and the experiential affective aspects, such as stress, fear, or anxiety, but also the modification, attenuation, and coping of these affective experiential aspects. This multiple functionality is supported by behavioral findings demonstrating amygdala activation during enhancement as well as inhibition of pain (Neugebauer et al. 2004). First, it may be a protective mechanism to detect a possible harmful stimulus, hence amplifying the painful experience; however, in case of unavoidable harm or pain, it may be the most suitable response to reduce the painfulness by inhibition (e.g., via the periaqueductal gray). Finally, the central role in pain and emotion makes it highly likely that it may also be involved in the dysfunctional aspects of chronic (visceral) pain. For example, the involvement of the amygdala during memory and learning may be relevant facets for the development of chronic pain.

However, the diversity of functions exerted by the amygdala as indicated by the different imaging studies on experimental and chronic pain, such as affective painful experience, but also modulation of this experience as an evolutionary sensible warning and evaluative survival system, including an effective adaptation mechanism in case of inescapable painful stimulation, suggests the involvement of other brain regions as well. Hence, the function of the amygdala cannot be determined alone but only within a greater cortical and subcortical network. Despite its relevance, it is only the continuous and intensive interconnections, interactions, and feedback mechanisms with other brain regions that account for the complex and intact function of this structure in pain and emotion.

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Amygdala, Nociceptive Processing

► Nociceptive Processing in the Amygdala: Neurophysiology and Neuropharmacology

Amygdala, Pain Processing and Behavior in Animals

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Synonyms

Amygdaloid complex; Nociceptive processing in the amygdala, behavioral and pharmacological studies

Definition

The ► amygdala is an almond-shaped structure in the ventromedial temporal lobe that constitutes part of the brain's limbic system. It comprises several neuroanatomically and functionally distinct nuclei with widespread connections to and from a variety of cortical and subcortical brain regions.

Characteristics

In a general sense, the amygdala plays a prominent role in the coordination of defense reactions to environmental threats (LeDoux 2003).

The hypothesized role of the amygdala in emotional information processing represents one component in this overall role. Clearly, environmental threats are diverse and include the animate (e.g., extraspecies predators, intraspecies rivals) and inanimate (e.g., thorns or spines on plants). Stimuli signaling the presence of threats can be "natural" elicitors of the psychological state of fear such as a sudden, novel sound or the presence of a larger animal. Or previously "neutral" stimuli (discrete sensory cues or distinct environmental contexts) can come to elicit defense reactions following occasions in which they coincided in time with an occurrence of injury or the presence of a natural threat (i.e., through ▶ classical conditioning processes). Such "conditioned" stimuli can elicit either acute fear or the qualitatively different state of ▶ anxiety, which is a more future-oriented psychological state that readies the animal for a potential environmental threat.

The amygdala is well connected to coordinate reactions to stimuli that signal potential danger. By way of incoming neuroanatomical connections to its central and basolateral subdivisions, the amygdala receives information from the organism's internal environment (▶ viscerosensation) and information from the external environment consisting of simple sensory inputs and complex ▶ multisensory perceptions. This information has already been highly processed by various subcortical and cortical brain structures (e.g., cortical sensory association areas), but the amygdala serves the purpose of attaching emotional significance to the input. By way of its outgoing neuroanatomical connections, the amygdala communicates with brain areas involved in motor preparation/action and autonomic responses. When sensory information arrives relating to environmental danger, the amygdala probably is involved both in the generation of emotional states (e.g., fear, anxiety) and the coordination of appropriate ▶ autonomic and behavioral changes that enhance the chance of survival (e.g., defensive fight or flight, subsequent avoidance behaviors, submissive postures, tonic immobilization, autonomic arousal, and hypoalgesia or ▶ hyperalgesia).

Since pain can signal injury or the potential for injury, it should not be surprising that the processing of nociceptive information by the amygdala can be one of the triggers of these events. Electrophysiological studies show that individual amygdala neurons, particularly in the central nucleus of the amygdala (CeA), respond to brief nociceptive thermal and mechanical stimulation of the skin and or nociceptive mechanical stimulation of deeper (knee joint) tissue (Bernard et al. 1996; Neugebauer et al. 2004). Many CeA neurons have large receptive fields, with some neurons being excited by and others inhibited by nociceptive stimulation. The lateral capsular and, to a lesser extent, the lateral division of the CeA have been termed the "nociceptive amygdala" and receive nociceptive input from lamina I of the spinal and trigeminal ▶ dorsal horns. This lamina I input arrives at the CeA via several different routes (Gauriau and Bernard 2002): (1) indirectly, from relays in the lateral and external medial areas of the brainstem parabrachial complex (lamina I → PB → CeA); (2) indirectly, from the posterior triangular nucleus of the thalamus (PoT) to the amygdalostriatal transition area (AStr), which overlaps partly with the CeA (lamina I → PoT →AStr/CeA); (3) indirectly, from the ▶ insular cortex by way of the PoT (lamina I → PoT → IC → CeA); and (4) to a much lesser extent, from direct, monosynaptic projections (lamina I → CeA). The basolateral complex of the amygdala also probably receives highly processed nociceptive information from unimodal and polymodal sensory areas of the cerebral cortex (Shi and Cassell 1998).

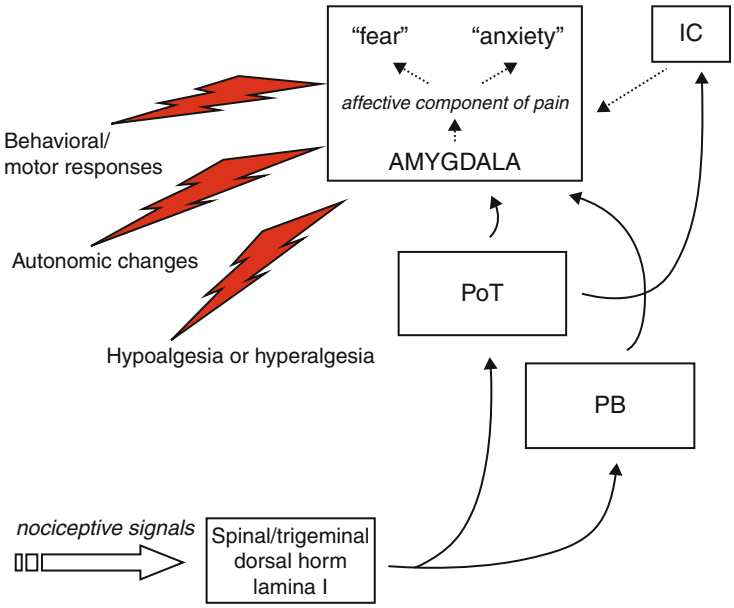
Human functional ▶ neuroimaging studies have supported a role for the amygdala in nociceptive processing by correlating changes in neural activity in the amygdala with the perception of brief painful stimuli. In a manner analogous to the different responses of individual CeA neurons described above, presentation of a painful thermal stimulus to skin of healthy human subjects can result in increases or decreases in neural activity in the amygdala as measured by ▶ positron emission tomography (PET) or functional ▶ magnetic resonance imaging (fMRI),

depending on the stimulation parameters employed. These changes appear to be linearly related to stimulus intensity (Bornhovd et al. 2002; Derbyshire et al. 1997).

In addition to brief pain, neuroplastic changes in amygdala neurons may contribute to the induction and maintenance of ▶ chronic pain states. Rodent studies utilizing indirect measures of neuronal activation in the forebrain (e.g., ▶ immediate early gene expression or changes in regional cerebral blood flow) have suggested increases in neural activity in the amygdala that correlate with behavioral indices of persistent pain. Several groups have analyzed patterns of Fos protein-like immunoreactivity (Fos-LI) in the rat forebrain after hind paw injection of formalin (i.e., the formalin test). The formalin test involves injecting a small volume of dilute formalin into a hind paw, resulting in an array of pain-related behaviors (paw lifting, licking, and flinching) that persists for 11/2–2 h. Behavioral indices of formalin-induced ▶ nociception correlate with appearance of Fos-LI in the basolateral amygdala (Nakagawa et al. 2003). Fos-LI also appears in the basolateral amygdala and CeA following stimulation of the trigeminal ▶ receptive field in conscious rats with ▶ capsaicin (Ter Horst et al. 2001) or after prolonged, nociceptive colonic distension (Monnikes et al. 2003). In a rat model of ▶ neuropathic pain (the chronic constriction injury, or CCI, model), a significant increase in regional cerebral blood flow (rCBF) is seen in the basolateral amygdala after 8 or 12 weeks, but not 2 weeks following CCI surgery (Paulson et al. 2002).

The response characteristics of individual CeA neurons have been studied in vivo in rats with or without experimental arthritis in a knee joint (Neugebauer et al. 2004). Prolonged nociception produced by injection of ▶ carrageenan and ▶ kaolin into the knee joint results in enhancement of both receptive field size and responsiveness to mechanical stimulation of a subset of CeA neurons. Infusion, by ▶ microdialysis, of a selective ▶ NMDA receptor antagonist (AP5) or an mGluR1 receptor antagonist (CPCCOEt) into the CeA inhibits the increased responses to nociceptive and normally innocuous mechanical stimuli more potently in the arthritic versus the control condition. By contrast, infusion of a non-NMDA (AMPA/kainate) receptor antagonist (NBQX) or an mGluR5 receptor antagonist (MPEP) inhibits background activity and evoked responses under both normal control and arthritic conditions. These data suggest a change in mGluR1 and NMDA receptor function and activation in the amygdala during pain-related sensitization, whereas mGluR5 and non-NMDA receptors probably are involved in brief as well as prolonged nociception.

In vitro brain slice ▶ electrophysiology has provided additional insights (Neugebauer et al. 2004). It is possible to study properties of synaptic transmission (using ▶ whole cell patch clamp recordings) in brain slices taken from control rats versus rats with persistent pain. In the nociceptive CeA of such rats, it is possible to study ▶ monosynaptic excitatory postsynaptic currents (EPSCs) evoked by electrical stimulation of afferents from the parabrachial complex or from the basolateral amygdala. In rats with experimental arthritis, enhanced synaptic transmission (larger amplitude of evoked monosynaptic EPSCs) is observed at both the nociceptive PB-CeA ▶ synapse and the polymodal (including nociceptive) BLA-CeA synapse as compared with control rats. CeA neurons from arthritic rats also develop an increase in excitability. Induction of experimental ▶ colitis (by intracolonic injection of ▶ zymosan) produces similar effects, except for the fact that enhanced synaptic transmission is observed only at the nociceptive PB-CeA synapse. In the arthritis model, synaptic plasticity in the amygdala is accompanied by an increase in ▶ presynaptic mGluR1 function. Both the selective mGluR1 antagonist CPCCOEt and the group III mGluR agonist LAP4 decrease the amplitude of EPSCs more potently in CeA neurons from arthritic rats than in control animals. The selective group III mGluR antagonist UBP1112 reverses the inhibitory effect of LAP4. During the application of LAP4, paired-pulse facilitation was increased, while no significant changes in slope conductance and action potential firing rate of CeA neurons were



Amygdala, Pain Processing and Behavior in Animals, Fig. 1 A simplified illustration of major nociceptive pathways to the amygdala and possible consequences of stimulation of these pathways. Abbreviations: *IC* insular cortex, *PB* parabrachial complex, *PoT* posterior triangular nucleus of the thalamus

observed. These data suggest that presynaptic mGluR1 receptors and group III mGluRs regulate synaptic plasticity in the amygdala in a rat model of arthritis.

Human neuroimaging studies have provided additional supporting evidence by correlating changes in neural activity in the amygdala with the perception of persistent pain. In patients suffering from ▶ irritable bowel syndrome (IBS), Wilder-Smith et al. (2005) demonstrated a bilateral decrease in neural activity in the amygdala during episodes of experimentally induced rectal pain.

Neuroimaging techniques, measurement of immediate early gene responses, and in vivo electrophysiological studies are useful for identifying brain regions with activity that covaries with the presence or absence of pain or nociception, but such studies are limited with respect to mechanistic insights and determining cause versus effect. On the contrary, rodent behavioral studies have been highly informative in this regard. Such studies provide evidence that the amygdala is involved in encoding the affective or aversive component of pain. Hebert et al. (1999) used an alley-shaped apparatus with an array of protruding, sharp pins situated in the middle of the alley to investigate this issue. During 10 min test sessions, the behavioral patterns of normal rats were characterized by voluntary contact with the pins followed by periods of avoidance and risk assessment (referred to by the investigators as "stretch attend" and "stretch approach" behaviors). Of the group of normal rats tested, few actually crossed the array of pins. In contrast, rats with bilateral lesions of the amygdala showed a significant increase in both the number of crossings of the pin array and the amount of time spent on the pins as compared with normal rats. The results suggest that the aversive quality of the painful mechanical stimulation imparted by the pin array is encoded at least partly by the amygdala.

The affective/aversive quality of pain in rodents also has been studied using a variation of the place-conditioning paradigm. In 2001, Johansen et al. introduced the formalin-induced condition place avoidance model (F-CPA). By pairing the experience of formalin-induced pain with a distinct environmental context/compartment within a place-conditioning apparatus, the investigators hoped to establish a behavioral endpoint that is directly related to the negative ▶ affective component of pain. After two pairings of formalin-induced pain (1 h) with the compartment, rats learned to avoid the

compartment and spend most of their time in the other two compartments of the apparatus. Lesions of the rostral anterior cingulate cortex (rACC) blocked the acquisition of F-CPA but did not affect the expression of acute formalin-induced pain behaviors (paw lifting, paw licking, etc.). The results suggested that the rACC lesions reduced the affective salience, but not the sensory-discriminative component of formalin-induced pain (Johansen et al. 2001). Using the F-CPA model, a similar pattern of results was obtained after bilateral lesions of either the CeA or basolateral amygdala (Tanimoto et al. 2003). The results provide strong causal data suggesting that the processing of nociceptive information in the amygdala and rACC relates to encoding of the affective component of pain. Furthermore, the results fit with the role in defense reactions ascribed to the amygdala at the beginning of this entry. By attaching emotional significance to a stimulus signaling danger (in this case the pain associated with formalin), the amygdala sets the stage for coordination of appropriate acute and delayed responses to the stimulus by way of its multitude of connections with other brain regions and neural circuitry (Fig. 1). These responses include acute protective behaviors and autonomic responses followed by avoidance of the environment in which the pain was experienced.

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Amygdaloid Complex

► Amygdala, Pain Processing and Behavior in Animals

Anaerobic Glycolysis

Definition

Glycolysis is a metabolic process that yields energy by converting glucose into lactic acid. It occurs in skeletal muscle when the blood supply is not sufficient for aerobic metabolism. The process is less effective than the aerobic metabolism (yields less ATP per mol. of glucose).

Cross-References

▶ Muscle Pain Model, Ischemia-Induced and Hypertonic Saline-Induced

Analgesia

Definition

A reduction or absence of pain. Also, a reduced response to a stimulation that would normally be painful. In humans, a decrease in the experience of pain (ongoing or spontaneous). It is sometimes described by increased thresholds to elicit sensation of pain following an evoked response. In the experimental (i.e., preclinical) setting, it can also be described as a situation in which the intensity of the stimulus required to evoke an escape or avoidance response is increased above normal, or the time required to respond to a noxious stimulus is increased above normal.

Cross-References

▶ Cancer Pain, Assessment in the Cognitively Impaired
▶ Cathepsin and Microglia
▶ Cytokine Modulation of Opioid Action
▶ Descending Circuitry, Opioids
▶ Lateral Thalamic Lesions, Pain Behavior in Animals
▶ Postsynaptic Dorsal Column Projection, Anatomical Organization

Analgesia During Labor and Delivery

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Characteristics

Analgesia for labor and delivery is now safer than ever. Anesthesia-related maternal mortality has decreased from 4.3 per million live births during the years 1979–1981 to 1.1 per million live births during the years 1995–2005. The increased use of regional anesthesia for the parturient is in part responsible for this decrease in mortality (Li et al. 2009). Safety is the primary goal of obstetrical anesthesia. For labor analgesia, a secondary goal is the minimization or elimination of maternal lower extremity muscle weakness associated with epidural and subarachnoid local anesthetics. While it has been widely accepted that no increase in the rate of cesarean sections can be attributed to epidural anesthesia (American College of Obstetricians and Gynecologists Committee on Obstetric Practice 2006), patients with less motor block are more satisfied with their anesthetic experience, and although controversial, motor blockade related to labor epidural analgesia has been implicated as a factor in an increase in forceps delivery. However, avoiding or limiting the motor block may attenuate or eliminate these effects (Chestnut 1997). In addition to epidural analgesia, anesthesiologists also provide spinal anesthesia and the combined spinal-epidural technique for labor analgesia. The purpose of this entry is to review analgesic techniques that are currently used to provide labor analgesia.

Epidural analgesia has been the most popular technique for the relief of labor pain. Its popularity is related to its efficacy and safety. Women can obtain almost complete relief from the pain of

labor. From the anesthesiologist's perspective, because a catheter is threaded into the epidural space allowing variable duration and intensity of analgesia, it is also a versatile technique. During the earlier stages of labor, dilute solutions of local anesthetic can be used to achieve analgesia. As labor progresses, a more concentrated solution of local anesthetic can be used, or an adjunct, such as an opioid, can be added. Additionally, the epidural catheter can be utilized to maintain a low dermatomal level of analgesia for labor (thoracic 10–lumbar 1), and, if needed, the dermatomal level can be raised to thoracic 4 for cesarean delivery.

The agent most commonly utilized for labor epidural analgesia is a local anesthetic. Opioids are commonly added to the local anesthetic to decrease the motor block. However, unless large doses of opioids are used, they do not on their own confer adequate analgesia for labor pain. Continuous infusions of epidural local anesthetic combined with an opioid are frequently employed during labor. Continuous infusions provide a more stable level of analgesia than that provided by intermittent bolus techniques. This effect translates into decreased work load for the anesthesiologist and better analgesia for the mother. Furthermore, without the frequent bolus injections, there may be less risk of maternal hypotension. Currently used continuous infusion solutions contain 0.04–0.125 % of a local anesthetic (bupivacaine or ropivacaine or levobupivacaine) with the addition of an opioid (fentanyl or sufentanil).

Some anesthesiologists use patient-controlled epidural analgesia (PCEA). This technique allows the patient to regulate the amount of anesthetic agent they receive, controlling their analgesic level. Despite the fact that there are many well-controlled studies regarding PCEA, the optimal dosing regimens have not been determined. Many current strategies have explored the use of mandatory scheduled boluses in conjunction with patient-controlled intermittent boluses; however, inadequate research has been conducted to confer an obvious advantage. Compared with continuous infusion or intermittent bolus techniques, PCEA is associated with fewer anesthetist interventions, lower total dose of local anesthetic used, and less motor block. Less anesthetic also decreases the frequency of maternal hypotension (Halpern and Carvalho 2009). A commonly used PCEA regimen is bupivacaine 0.0625 % with fentanyl 2 ug/cc at the following PCEA settings: 10 mL/h basal rate, 5 mL bolus dose, 10 min lockout, and a 30 mL/h maximum limit. This author is not aware of any reported complications to the parturient with PCEA use. But theoretical risks include those that have been seen in the general surgical patient including high dermatomal level or overdose from excessive self-administration, from a helpful family member, or secondary to a catheter that has migrated into the subarachnoid space.

The safety of epidural opioids has been well documented. Despite decreased neonatal neurobehavioral scores shortly after delivery, epidural fentanyl has not been linked to any long-term (4 years) developmental effects (Ounsted et al. 1978). The clinical relevance of lower neurobehavioral scores around the time of delivery is unknown. There is some data that epidural fentanyl at doses >150 ug may influence breastfeeding (Beilin et al. 2005), but these findings need to be confirmed. Respiratory depression in the neonate is also of little concern with epidural fentanyl. Respiratory parameters of neonates whose mothers received epidural fentanyl (up to 400 ug) are similar to neonates whose mothers did not receive any fentanyl.

There are a number of problems with labor epidural analgesia that have prompted some to seek alternative techniques. First, the time from epidural catheter placement until the patient is comfortable is variable but, depending on the local anesthetic used, can take up to 30 min. Other disadvantages of labor epidural analgesia include maternal hypotension, inadequate analgesia (15–20 % of cases), and, even with the very dilute local anesthetic solutions, motor blockade.

Subarachnoid opioids offer rapid, intense analgesia with minimal changes in blood pressure or motor function. The opioid is usually administered as part of a combined spinal-epidural (CSE) technique. After locating the

epidural space in the usual manner, a long small-gauge spinal needle with a pencil-point design is inserted through the epidural needle into the subarachnoid space. A subarachnoid opioid alone or in combination with local anesthetic is injected. The spinal needle is removed and an epidural catheter threaded for future use. Analgesia begins within 3–5 min and lasts 1–1.5 h. A continuous epidural infusion of dilute local anesthetic/opioid solution is immediately started after securing the epidural catheter. Starting the epidural infusion immediately, versus waiting for pain to recur, prolongs the spinal medication by approximately 60 min with minimal side effects (Beilin et al. 2002). It would be tempting to thread a catheter into the subarachnoid space to enable administration of repeated doses of opioid into this space; however, an increased risk of cauda equina syndrome has been associated with the placement of subarachnoid catheters, especially microcatheters. Therefore, this technique is infrequently used now with epidural catheters in rare instances such as morbid obesity, significant cardiac disease, the presence of a difficult airway, or previous extensive spine surgery (Palmer 2010).

Fentanyl or sufentanil are the most commonly utilized subarachnoid opioids with the CSE technique. Differences between the two drugs are subtle, and choice of one over the other is based on personal preference. However, the cost of sufentanil is greater than that of fentanyl. Most anesthesiologists use between 10 and 25 ug of fentanyl and between 2 and 5 ug of sufentanil. Adding 1 mL of bupivacaine 0.25 % to either fentanyl or sufentanil prolongs the duration by about 20 min for fentanyl and 30 min for sufentanil. Side effects of adding bupivacaine are minimal and may protect the patient from developing pruritus (Asokumar et al. 1998). Whether this added duration is worthwhile is based on personal preference. At Mount Sinai, we commonly use fentanyl 25 ug with 1 mL of bupivacaine 0.25 % for the subarachnoid dose.

There are several advantages to the CSE technique. The primary advantage is the rapid (3–5 min) onset of analgesia. Additionally, patients have less motor block and greater patient satisfaction with the CSE technique versus the "standard" epidural technique of bupivacaine 0.25 %. The greater satisfaction is related to the faster onset of action and less motor block (Simmons et al. 2007).

There are some concerns about the CSE technique, most of which are only theoretical. There is no increased risk of subarachnoid catheter migration of the epidural catheter, and metallic particles are not produced as a result of passing one needle through another. The incidence of post-dural puncture headache is not increased with the CSE technique. An increase in end-tidal carbon dioxide has been reported in women who received subarachnoid sufentanil, but the risk of clinically significant respiratory depression is extremely rare (Carvalho 2008). The risk of hypotension is also not greater with the CSE technique than with standard epidural regimens. The most common side effect of subarachnoid opioids is pruritus, with a reported incidence as great as 95 % that is easily treated with either an antihistamine or naloxone.

It is possible that the epidural catheter may not actually have been placed in the epidural space after the CSE technique is performed, and this may not be detected until the analgesia from the subarachnoid opioid has dissipated (1–2 h). If, during this time period, the woman requires an emergent cesarean delivery, the catheter may fail and the patient may require a general anesthetic. Lee et al. (2009) found that the risk of failed epidural catheters was lower in women who received CSE analgesia than those who received epidural analgesia, likely due to the confirmation of having reached the epidural space that is achieved with the recognition of free-flowing CSF in the spinal portion of the combined technique. However, it may be prudent not to use the CSE technique in a woman who is a poor risk for general analgesia, e.g., one with a bad airway or obesity, so that the epidural catheter can be immediately tested and effectiveness confirmed.

Many studies have reported fetal bradycardia associated with uterine hypertonus after subarachnoid opioid injection. One proposed theory

for increased uterine tone is related to the rapid decrease in maternal catecholamines associated with the onset of pain relief. With the decrease in circulating beta adrenergic agonists, there is a predominance of alpha activity that leads to uterine contractions. Most studies, prospective and retrospective, find neonatal outcome based on umbilical artery pH and base excess similar, if not improved, with neuraxial analgesia (CSE or standard epidural) versus other analgesic strategies. Further, a review of literature comparing cesarean rate between standard epidural technique and CSE has shown no difference in the rate if cesarean delivery (Van de Velde 2005). If hypertonus occurs, treatment should include subcutaneous terbutaline or intravenous nitroglycerin.

The term walking epidural has become popular in the lay community. The term walking epidural refers to any epidural or spinal technique that allows ambulation with analgesia. In most centers, few patients choose to ambulate. Most choose to rest or sleep once they have adequate labor analgesia. However, if patients do not want to ambulate, using a technique that produces minimal motor blockade will still improve maternal satisfaction. Both epidural analgesia using dilute local anesthetic/opioid solutions and a CSE technique can achieve this goal. Several precautions should be taken before allowing a parturient to walk during epidural or CSE analgesia. These women should be candidates for intermittent fetal heart rate monitoring. Maternal blood pressure and fetal heart rate should be monitored for 30–60 min after induction. Even small doses of subarachnoid and epidural local anesthetics can produce some motor deficits. Assess motor function by having the parturient perform a modified deep knee bend or stepping up and down on a stool. The patient must have an escort at all times. Fetal heart rate and maternal blood pressure should be reassessed at least every 30 min.

In summary, techniques and drugs available to the modern-day obstetric anesthesiologist approach the objectives of an ideal labor anesthetic. The future of obstetric anesthesia lies in further refining the pharmacologic agents utilized and our neuraxial techniques to make obstetric anesthesia safer and more efficacious as we work to better care for our patients.

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Analgesia for Labor and Delivery

Definition

Pain relief during labor and delivery can be administered intravenously or via the neuraxis as an epidural or spinal block. Intravenous medication is usually not adequate, as it only attenuates the pain but does not eliminate the pain. Epidural or spinal analgesia, generally administered by an anesthesiologist, virtually eliminates labor pain without a loss of consciousness.

Cross-References

► Analgesia During Labor and Delivery

Analgesic Effect of Oxycodone

Definition

The analgesic effect of oxycodone is mainly mediated by the parent compound.

Cross-References

► Postoperative Pain, Oxycodone

Analgesic Gap

Definition

The increase in pain sometimes associated with reduction in analgesic dosage or analgesic strategies.

Cross-References

► Postoperative Pain, Transition from Parenteral to Oral Drugs

Analgesic Guidelines for Infants and Children

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Synonyms

Drug guidelines; Pediatric dosing guidelines

Definition

The goal of administering analgesia is to relieve pain without intentionally producing a sedated state.

Characteristics

Oral Analgesics

Analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids. While acetaminophen and opioids remain the cornerstone for providing analgesia for our youngest patients, the scope and diversity of drugs expand as those patients grow older. ► Adjuvant analgesics include a variety of drugs with analgesic properties that were initially developed to treat other health problems. These adjuvant analgesics (such as anticonvulsants and antidepressants) have become a cornerstone of pain control for children with chronic pain, especially when pain has a neuropathic component.

Pain control should include regular pain assessments, appropriate analgesics and adjuvant analgesics administered at regular dosing intervals, adjunctive drug therapy for symptom and side effects control, and nondrug therapies to modify the situational factors that can exacerbate pain and suffering. The guiding principles of analgesic administration are "by the ladder," "by the clock," "by the child," and "by the mouth." "By the ladder" refers to a three-step approach for selecting drugs according to their

analgesic potency based on the child's pain level – acetaminophen to control mild pain, codeine to control moderate pain, and morphine for strong pain (World Health Organization 1990; Zernikow et al. 2006). The ladder approach was based on our scientific understanding of how analgesics affect pain of nociceptive origins (► nociceptive pain). If pain persists despite starting with the appropriate drug, recommended doses, and dosing schedule, move up the ladder and administer the next more potent analgesic. Even when children require opioid analgesics, they should continue to receive acetaminophen (and nonsteroidal anti-inflammatory drugs, if appropriate) as supplemental analgesics. The analgesic ladder approach is based on the premise that acetaminophen, codeine, and morphine should be available in all countries and that doctors and healthcare providers can relieve pain in the majority of children with a few drugs. Although there is a recommendation to delete codeine from the WHO list of essential medicines for children, at present the use of codeine remains an important element in the WHO pain ladder, and thus it is included in these opioid analgesic guidelines. It is well known that codeine is metabolized by CYP2D6 to morphine. If this enzyme is inhibited though, its analgesic efficacy will be diminished. A more recent and greater concern are the reported fatalities in patients who are ultrarapid metabolizers of codeine to morphine resulting in a greater production of morphine which could thus lead to respiratory depression (Kelly et al. 2012).

However, increasing attention is focusing on "thinking beyond the ladder" in accordance with our improved understanding of pain of neuropathic origins (Krane et al. 2003). Children should receive adjuvant analgesics to more specifically target neuropathic mechanisms. Regrettably, two of the main classes of adjuvant analgesics, antidepressants and anticonvulsants, have unfortunate names. Proper education of healthcare providers, parents, and children should lead to a wider acceptance and use of these medications for pain management. For example, amitriptyline may require 4–6 weeks to affect depression, but often requires only 1–2 weeks to affect pain. The newer classes of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), may be beneficial to treat depression in a child with pain, but have not been shown to be beneficial for pain management. Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) may be of greater benefit, but convincing clinical trials are not available. The other main class of adjuvant analgesics is the anticonvulsants. The two principal medications used for this purpose in pediatrics are carbamazepine and gabapentin. With gabapentin, the main dose limiting side effect is sedation, so that a slow titration to maximal dose is required. Because of its greater number of significant side effects, the use of carbamazepine has decreased and the use of gabapentin has increased. We still await published studies to support the wide use of gabapentin in children.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are similar in potency to aspirin. NSAIDs are used primarily to treat inflammatory disorders and to lessen mild to moderate acute pain. They should be used with caution in children with hepatic or renal impairment, compromised cardiac function, hypertension (since they may cause fluid retention and edema) and a history of GI bleeding or ulcers. NSAIDs may also inhibit platelet aggregation and thus must be monitored closely in patients with prolonged bleeding times. NSAIDs have been used for many years in pediatrics and with their minimal side effects and many advantages (no effect on ventilation, no physical dependence, morphine sparing effect, etc.), their use should be encouraged.

The specific drugs and doses are determined by the needs of each child. The drugs listed in this entry are based on guidelines from our institution (The Hospital for Sick Children 2011–2012), and do not necessarily reflect results of evidence-based reviews. Recommended starting doses for analgesic medications to control children's disease-related pain are listed in Tables 1 and 2; starting doses for adjuvant analgesic medications to control pain, drug-related side effects, and other symptoms are listed in Table 3. (For further

Analgesic Guidelines for Infants and Children, Table 1 Non-opioid drugs to control pain in children

Drug	Dosage	Comments
Acetaminophen	10–15 mg kg^{-1} PO, every 4–6 h	Lacks gastrointestinal and hematological side effects; lacks anti-inflammatory effects (may mask infection-associated fever)
		Dose limit of 65 mg kg^{-1} day^{-1} or 4 g day^{-1}, whichever is less
Ibuprofen	5–10 mg kg^{-1} PO, every 6–8 h	Anti-inflammatory activity
		Use with caution in patients with hepatic or renal impairment, compromised cardiac function or hypertension (may cause fluid retention, edema), history of GI bleeding or ulcers, may inhibit platelet aggregation
		Dose limit of 40 mg kg^{-1} day^{-1}; max dose of 2,400 mg day^{-1}
Naproxen	10–20 mg kg^{-1} day^{-1} PO, divided every 12 h	Anti-inflammatory activity. Use with caution and monitor closely in patients with impaired renal function. Avoid in patients with severe renal impairment
		Dose limit of 1 g day^{-1}
Diclofenac	1 mg kg^{-1} PO, every 8–12 h	Anti-inflammatory activity. Similar GI, renal, and hepatic precautions as noted above for ibuprofen and naproxen
		Dose limit of 50 mg/dose
Ketorolac	0.5 mg/kg/dose IV q6h PRN	Maximum duration of IV Ketorolac is 2 days. Do not use in tonsillectomy patients due to increase risk of bleeding, Do not use in patients with Impaired renal function.
		Dose limit <16yrs: 15 mg/dose >16yrs: 30mg/dose

Note: Increasing the dose of non-opioids beyond the recommended therapeutic level produces a "ceiling effect," in that there is no additional analgesia but there are major increases in toxicity and side effects. Abbreviations: *PO* by mouth, *GI* gastrointestinal (Modified from Brown and McGrath 2010)

review of analgesics and adjuvant analgesics in children, see Brown and McGrath (2010); Brown et al. (2010); Schechter et al. (2003)).

Oral Analgesic Dosing Schedules

Children should receive analgesics at regular times, "by the clock," to provide consistent pain relief and prevent breakthrough pain. The specific drug schedule (e.g., every 4 or 6 h) is based on the drug's duration of action and the child's pain severity. Although breakthrough pain episodes have been recognized as a problem in adult pain control, they may represent an even more serious problem for children. Unlike adults, who generally realize that they can demand more potent analgesic medications or demand more frequent dosing intervals, children have little control, little awareness of alternatives, and fear that their pain cannot be controlled. They may become progressively frightened, upset, and preoccupied with their symptoms. Thus, it is essential to establish and maintain a therapeutic window of pain relief for children.

Analgesic doses should be adjusted "by the child." There is no one dose that will be appropriate for all children with pain. The goal is to select a dose that prevents children from experiencing pain before they receive the next dose. It is essential to monitor the child's pain regularly and adjust analgesic doses as necessary to control the pain. The effective opioid dose to relieve pain varies widely among different children or in the same child at different times. Some children require large opioid doses at frequent intervals to control their pain. If such doses are necessary for effective pain control and the side effects can be managed by adjunctive medication (▶ adjunctive drugs) so that children are comfortable, then the doses are appropriate. Children receiving opioids may develop altered sleep patterns so that they are awake at night fearful and complaining about pain and sleep intermittently throughout the day. They should receive adequate analgesics at night with antidepressants or hypnotics as necessary to enable them to sleep throughout the night. To relieve ongoing pain, opioid doses should

Analgesic Guidelines for Infants and Children, Table 2 Opioid analgesics: usual starting doses for children

Drug	Equianalgesic dose (parenteral)	Starting dose IV	IV:PO ratio	Starting dose PO/ Transdermal	Duration of action
Morphine	10 mg	Bolus dose – 0.05–0.1 mg kg^{-1} every 2–4 h. Continuous infusion – 0.01–0.04 mg kg^{-1} h^{-1}	1:3	0.15–0.3 mg kg^{-1}/dose every 4 h	3–4 h
Hydromorphone	1.5 mg	0.015–0.02 mg kg^{-1} every 4 h	1:5	0.06 mg kg^{-1} every 3–4 h	2–4 h
Codeine	120 mg	Not recommended		1.0 mg kg^{-1} every 4 h (dose limit 1.5 mg kg^{-1}/ dose)	3–4 h
Oxycodone	5–10 mg	Not recommended		0.1–0.2 mg kg^{-1} every 3–4 h	3–4 h
Fentanyl[a]	100 μg	1–2 μg kg^{-1} h^{-1} as continuous infusion		12 μg patch for children, dependent on weight and previous opioid use	72 h (patch)
Methadone	10 mg	0.1 mg kg^{-1} every 4–8 h	1:2	0.2 mg kg^{-1} every 4–8 h	12–50 h
Tramadol	100 mg	2.0 mg kg^{-1} every 4–6 h		1.0 mg kg^{-1} every 4–6 h (dose limit 400 mg day^{-1})	4–6 h

Note: Doses are for opioid naïve patients. For infants under 6 months, start at one-quarter to one-third the suggested dose and titrate to effect

Principles of opioid administration:

1. If inadequate pain relief and no toxicity at peak onset of opioid action, increase dose in 50 % increments
2. Avoid IM administration
3. Whenever using continuous infusion, plan for hourly rescue doses with short onset opioids if needed. Rescue dose is usually 50–200 % of continuous hourly dose. If greater than six rescues are necessary in 24 h period, increase daily infusion total by the total amount of rescues for previous 24 h ÷ 24. An alternative is to increase infusion by 50 %
4. To change opioids – because of incomplete cross-tolerance, if changing between opioids with short duration of action, start new opioid at 50 % of equianalgesic dose. Titrate to effect. If changing between opioids from short to long duration of action (i.e., morphine to methadone), start at 25 % of equianalgesic dose and titrate to effect
5. To taper opioids – anyone on opioids over 1 week must be tapered to avoid withdrawal – taper by 50 % for 2 days and then decrease by 25 % every 2 days. When the dose is equianalgesic to an oral morphine dose of 0.6 mg kg^{-1} day^{-1}, it may be stopped. Some patients on opioids for prolonged periods may require much slower weaning

Abbreviations: *PO* by mouth, *IV* intravenous

[a]Potentially highly toxic. Not for use in acute pain control

Modified from Brown and McGrath (2010)

be increased steadily until comfort is achieved, unless the child experiences unacceptable side effects, such as somnolence or respiratory depression (Table 4).

"By the mouth" refers to the oral route of drug administration. Medication should be administered to children by the simplest and most effective route, usually by mouth. Since children are afraid of painful injections they may deny that they have pain or they may not request medication. When possible, children should receive medications through routes that do not cause additional pain. Although optimal analgesic administration for children requires flexibility in selecting routes according to children's needs, parenteral administration is often the most efficient route for providing direct and rapid pain relief. Since intravenous, intramuscular, and subcutaneous routes cause additional pain for children, serious efforts have been expended on developing more pain-free modes of administration that still provide relatively direct and rapid analgesia. Attention has focused on improving the effectiveness of oral routes.

Intravenous Analgesia

Many hospitals have restricted the use of intramuscular injections because they are painful and

Analgesic Guidelines for Infants and Children, Table 3 Adjuvant analgesics: doses for children

Drug category	Drug, dosage	Indications	Comments
Antidepressants	Amitriptyline, 0.2–0.5 mg kg^{-1} PO	Neuropathic pain (i.e., vincristine-induced, radiation plexopathy, tumor invasion, CRPS-1)	Usually improved sleep and pain relief within 3–5 days
	Titrate upward by 0.25 mg kg^{-1} every 2–3 days. Maintenance: 0.2–3.0 mg k^{-1}	Insomnia	
	Alternatives: nortriptyline, doxepin, imipramine		Anticholinergic side effects are dose limiting. Use with caution for children with increased risk for cardiac dysfunction
Anticonvulsants	Gabapentin, 5 mg kg^{-1} day^{-1} PO	Neuropathic pain, especially shooting, stabbing pain	Side effects: gastrointestinal upset, ataxia, dizziness, disorientation, and somnolence
	Titrate upward over 3–7 days Maintenance: up to 15–50 mg kg^{-1} day^{-1} PO divided TID		
	Carbamazepine, initial dosing: 10 mg kg^{-1} day^{-1} PO divided OD or BID. Maintenance: up to 20–30 mg kg^{-1} day^{-1} PO divided every 8 h. Increase dose gradually over 2–4 weeks		Monitor for hematological, hepatic, and allergic reactions with carbamazepine
	Alternatives: pregabalin, oxcarbazepine		
Sedatives, hypnotics, anxiolytics	Diazepam, 0.025–0.2 mg kg^{-1} PO every 6 h	Acute anxiety, muscle spasm	Sedative effect may limit opioid use. Other side effects include depression and dependence with prolonged use
	Lorazepam, 0.05 mg kg^{-1}/dose SL	Premedication for painful procedures	
	Midazolam, 0.5 mg kg^{-1}/dose PO administered 15–30 min prior to procedure; 0.05 mg kg^{-1}/dose IV for sedation		
Antihistamines	Hydroxyzine, 0.5 mg kg^{-1} PO every 6 h	Opioid-induced pruritus, anxiety, nausea	Sedative side effects may be helpful
	Diphenhydramine, 0.5–1.0 mg kg^{-1} PO/IV every 6 h		
Psychostimulants	Dextroamphetamine, Methylphenidate, 0.1–0.2 mg kg^{-1} BID	Opioid-induced somnolence	Side effects include agitation, sleep disturbance, and anorexia
	Escalate to 0.3–0.5 mg kg^{-1} as needed	Potentiation of opioid analgesia	Administer second dose in afternoon to avoid sleep disturbances
Corticosteroids	Prednisone, prednisolone, and dexamethasone dosage depends on clinical situation (i.e., dexamethasone initial dosing: 0.2 mg kg^{-1} I.V. Dose limit 10 mg. Subsequent dose 0.3 mg kg^{-1} day^{-1} I.V. divided every 6 h.)	Headache from increased intracranial pressure, spinal or nerve compression; widespread metastases	Side effects include edema, dyspeptic symptoms, and occasional gastrointestinal bleeding

Abbreviations: *CRPS-1* complex regional pain syndrome, Type 1, *PO* by mouth, *I.V.*, intravenous, *SL* sublingual
Modified from Brown and McGrath (2010)

Analgesic Guidelines for Infants and Children, Table 4 Opioid side effects

Side effect	Management
Respiratory depression	Reduction in opioid dose by 50 %, titrate to maintain pain relief without respiratory depression
Respiratory arrest	Naloxone, titrate to effect with 0.01 mg kg^{-1}/dose I.V./ETT increments or 0.1 mg kg^{-1}/dose I.V./ETT, repeat PRN. Small frequent doses of diluted naloxone or naloxone drip are preferable for patients on chronic opioid therapy to avoid severe, painful withdrawal syndrome. Repeated doses are often required until opioid side effect subsides
Drowsiness/sedation	Frequently subsides after a few days without dosage reduction; methylphenidate or dextroamphetamine (0.1 mg kg^{-1} administered twice daily, in the morning and midday so as not to interfere with nighttime sleep). The dose can be escalated in increments of 0.05–0.1 mg kg^{-1} to a maximum of 10 mg/dose for dextroamphetamine and 20 mg/dose for methylphenidate
Constipation	Increased fluids and bulk, prophylactic laxatives as indicated
Nausea/vomiting	Administer an antiemetic (e.g., ondansetron, 0.1 mg kg^{-1} I.V./PO every 8 h)
	Antihistamines (e.g., dimenhydrinate 0.5 mg kg^{-1}/dose every 4–6 h I.V./PO) may be used. Pre-chemotherapy, Nabilone 0.5–1.0 mg PO and then every 12 h may also be used
Confusion, nightmares, hallucinations	Reassurance only, if symptoms mild. A reduced dosage of opioid or a change to a different opioid or add neuroleptic (e.g., haloperidol 0.1 mg kg^{-1} PO/I.V. every 8 h to a maximum of 30 mg day^{-1})
Multifocal myoclonus; seizures	Generally occur only during extremely high dose therapy; reduction in opioid dose indicated if possible. Add a benzodiazepine (e.g., clonazepam 0.05 mg kg^{-1} day^{-1} divided BID or TID increasing by 0.05 mg kg^{-1} day^{-1} every 3 days PRN up to 0.2 mg kg^{-1} day^{-1}. Dose limit of 20 mg day^{-1})
Urinary retention	Rule out bladder outlet obstruction, neurogenic bladder, and other precipitating drug (e.g., tricyclic antidepressant). Particularly common with epidural opioids. Change of opioid, route of administration, and dose may relieve symptom. Bethanechol or catheter may be required

I.V. intravenous, *PO* by mouth, *ETT* endotracheal tube, *PRN* as needed
Reprinted from Brown and McGrath (2010)

drug absorption is not reliable; they advocate the use of intravenous lines into which drugs can be administered directly without causing further pain. Topical anesthetic creams should also be applied prior to the insertion of intravenous lines in children. The use of ▶ portacatheters has become the gold standard in pediatrics, particularly for children with cancer under the care of the physician, who require administration of multiple drugs at weekly intervals.

Continuous infusion has several advantages over intermittent subcutaneous, intramuscular, or intravenous routes. This method circumvents repetitive injections, prevents delays in analgesic drug administration, and provides continuous levels of pain control without children experiencing increased side effects at peak level and pain breakthroughs at trough level. Continuous infusion should be considered when children have pain for which oral and intermittent parenteral opioids do not provide satisfactory pain control, when intractable vomiting prevents the use of oral medications and when intravenous lines are not desirable. Children receiving a continuous infusion should continue to receive "rescue doses" to control breakthrough pain, as necessary. As outlined in Table 2, the rescue doses should be 50–200 % of the continuous infusion hourly dose. If children experience repeated breakthrough pain, the basal rate can be increased by 50 % or by the total amount of morphine administered through the rescue doses over a 24 h period (divided by 24 h).

Patient-Controlled Analgesia

▶ Patient-controlled analgesia (PCA) enables children to administer analgesic doses according to their pain level. PCA provides children with a continuum of analgesia that is prompt, economical, not nurse dependent and results in

a lower overall narcotic use (Rodgers et al. 1988; Schechter et al. 2003). It has a high degree of safety, allows for wide variability between patients and removes delay in analgesic administration (for a review, see Berde and Solodiuk 2003). It can now be regarded as a standard for the delivery of analgesia in children aged >5 years (McDonald and Cooper 2001). However, there are opposing views about the use of ▶ background infusions with PCA. Although they may improve efficacy, they may increase the occurrence of adverse effects such as nausea and respiratory depression. In a comparison of PCA with and without a background infusion for children having lower extremity surgery, the total morphine requirements were reduced in the PCA only group and the background infusion offered no advantage (McNeely and Trentadue 1997). In another study comparing background infusion and PCA, children between 9 and 15 achieved better pain relief with PCA, while children between 5 and 8 showed no difference (Bray et al. 1996). Our current standard is to add a background infusion to the PCA if the pain is not controlled adequately with PCA alone. The selection of opioid used in PCA is perhaps less critical than the appropriate selection of parameters such as bolus dose, lockout, and background infusion rate. The opioid choice may be based on adverse effect profile rather than efficacy. Clearly, patient-controlled analgesia offers special advantages to children who have little control and who are extremely frightened about uncontrolled pain. PCA is, as it states, patient-controlled analgesia. When special circumstances require that alternate people administer the medication, we do allow both nurse and parent-controlled analgesia. Under these circumstances, parents require our nurse educators to fully educate them on the use of PCA. In an alert by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), they advise that serious adverse events can result when family members, caregivers, or clinicians who are not authorized become involved in administering the analgesia for the patient "by proxy" (Sentinel Event Alert 2004).

Transdermal Fentanyl

Fentanyl is a potent synthetic opioid, which like morphine binds to mu receptors. However, fentanyl is 75–100 × more potent than morphine. The intravenous preparation of fentanyl has been used extensively in children. A transdermal preparation of fentanyl was introduced in 1991 for use with chronic pain. This route provides a noninvasive but continuously controlled delivery system. Although limited data is available on transdermal fentanyl (TF) in children, its use is increasing for children with pain. In a 2001 study, TF was well tolerated with effective pain relief in 11 of 13 children and provided an ideal approach for children where compliance with oral analgesics was problematic (Noyes and Irving 2001). In another study, when children were converted from oral morphine doses to TF, the investigators noted diminished side effects and improved convenience with TF (Hunt et al. 2001). The majority of parents and investigators considered TF to be better than previous treatment. No serious adverse events were attributed to fentanyl, suggesting that TF was both effective and acceptable for children and their families. Similarly, no adverse effects were noted in a study of TF for children with pain due to sickle cell crisis (Christensen et al. 1996). This study showed a significant relationship between TF dose and fentanyl concentration; pain control with the use of TF was improved in 7 of 10 patients in comparison to PCA alone. In a multicenter crossover study in adults, TF caused significantly less constipation and less daytime drowsiness in comparison to morphine, but greater sleep disturbance and shorter sleep duration (Ahmedzai and Brooks 1997). Of those patients able to express a preference, significantly more preferred fentanyl patches. As with all opioids, fatal adult complications have been noted with the use of multiple transdermal patches. In a review of TF use in the pediatric population (Zernikow et al. 2007), though there are no pediatric randomized or controlled cohort studies, pharmacokinetic studies in children show that the time to reach steady state serum drug concentrations seems to be longer, clearance higher, and elimination half-life shorter when

compared to adults. TF may be associated with less constipation compared to morphine use. Parents and medical professionals were satisfied with TF to a higher degree than with individual analgesic pretreatment regimens. An approximate conversion factor of 45 mg day/day oral morphine to 12 μg/h TF is used for initial therapy dose estimation for children receiving long-term morphine therapy. The 12 μg/h patch is the lowest dose patch available. I note that supplemental taping is often required to secure the patches in children and that I often recommend the changing of patches at 48 h instead of the manufacturers recommendation of 72 h. Evidence of the superiority of TF treatment over conventional opioid administration in children remains scarce and of low quality.

Summary

I have guided you through the basics of the administration of analgesics for the pediatric patient from the oral route through to intravenous and the PCA route and finally discussed an analgesic administered by the transdermal route. By the use of these drugs as examples and with the simple principles discussed to apply them, we can hopefully attain the goal of decreasing the intensity of pain in children – no matter what the setting.

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Analgesic Ladder

Definition

In 1986, WHO proposed a three step analgesic ladder. Although the specific elements are no longer viewed as a guideline, it remains important as an indication of an international consensus in favor of the use of opioid drugs as the mainstay in the treatment of moderate to severe cancer pain. The ladder suggests that non-opioids (step 1) be administered in case of mild pain. If this is not enough, or pain is moderate, so-called weak opioids (step 2) should be used, often in combination with a NSAID and an adjuvant drug if needed. If pain is severe, or step 2 drugs are not effective, treatment with a single-entity opioid should be used, the prototype of which is morphine. Again, co-treatment with a NSAID or adjuvant drug is used as appropriate.

Cross-References

- ▶ Cancer Pain

Analgesic Tolerance

- ▶ Opioids, Clinical Opioid Tolerance

Analgesic Treatment

Definition

A treatment used to reduce pain without causing loss of consciousness.

Cross-References

- ▶ Adjuvant Analgesics in Management of Cancer-Related Bone Pain
- ▶ Cancer Pain Management, Cancer-Related Breakthrough Pain, Therapy

Analgesics

Definition

Analgesics are drugs (pharmacological agents) that provide pain relief.

Cross-References

- ▶ History of Analgesics
- ▶ NSAIDs, COX-Independent Actions
- ▶ Opioids in Geriatric Application
- ▶ Opioids, Clinical Opioid Tolerance

Analysis of Pain Behavior

- ▶ Assessment of Pain Behaviors

Anaphylactic Reaction

Synonyms

Anaphylaxis

Definition

A severe allergic reaction that starts when the immune system mistakenly responds to a relatively harmless substance as if it were a serious threat.

Cross-References

- ▶ Diencephalic Mast Cells

Anaphylaxis

- ▶ Anaphylactic Reaction

Anesthesia

Definition

Loss of sensation and usually of consciousness without loss of vital functions, artificially produced by the administration of one or more agents that block the passage of pain impulses along nerve pathways to the brain

Cross-References

▶ Thalamic Nuclei Involved in Pain: Cat and Rat

Anesthesia Dolorosa

Definition

Literally "painful anesthesia," anesthesia dolorosa is spontaneous pain felt in a body part that has been denervated or deafferented. The limb itself is numb and unresponsive to applied stimuli but is nonetheless painful. This can occur as a result of a surgical lesion of peripheral nerves, sensory ganglia, or sensory roots, usually intended to relieve pain. Because of overlap of innervation territories, more than one adjacent nerve, ganglion, or root needs to be damaged. It also occurs following traumatic brachial plexus avulsion. Anesthesia dolorosa is similar to phantom limb pain (PLP) except that in PLP the painful limb is no longer present, due to amputation.

Cross-References

▶ Central Nervous System Stimulation for Pain
▶ Dorsal Root Ganglionectomy and Dorsal Rhizotomy
▶ Neuropathic Pain Model, Spared Nerve Injury
▶ Peripheral Neuropathic Pain

Anesthesia Dolorosa Due to Plexus Avulsion

▶ Plexus Injuries and Deafferentation Pain

Anesthesia Dolorosa Model, Autotomy

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Synonyms

Animal model for phantom limb pain; Animal model of spontaneous neuropathic pain; Autotomy model of neuropathic pain; Deafferentation model of neuropathic pain; Denervation model of neuropathic pain; Neuroma model of neuropathic pain

Definition

Anesthesia dolorosa (Latin for "painful numbness") is a seemingly paradoxical chronic pain state in which, despite the presence of ongoing pain, the painful body part is completely numb and insensate. Applied stimuli are not felt. To create this state in animals a limb is made insensate either (1) by cutting all peripheral nerves that serve it (▶ Denervation), or (2) by cutting the corresponding dorsal roots (▶ Deafferentation). Hence the animal model of anesthesia dolorosa is actually a family of models. The presence of ongoing pain is inferred from the observation of "autotomy" behavior or its consequences. ▶ Autotomy is a behavior pattern in which the animal licks, bites, and chews its denervated limb (self-mutilation). Quantification is usually based on the amount of tissue lost from the extremity as a function of time after the surgical denervation/deafferentation, or on the number of days required

to reach a criterion amount of tissue loss (Wall et al. 1979). This behavioral model is thought to emulate anesthesia dolorosa and phantom limb pain in humans. Anesthesia dolorosa (e.g., after brachial plexus avulsion) differs from phantom limb pain (e.g., after leg amputation) in that the body part in which the pain is felt is still present; it has not been amputated. Despite the continued presence of the limb the autotomy model is useful for studying both conditions, and spontaneous neuropathy in general. The key component is the nerve injury. It is unlikely that the presence of the insensate limb in the model, and in clinical anesthesia dolorosa, contributes materially to the spontaneous pain mechanism.

Characteristics

The presence of spontaneous ▶ dysesthesia and pain is probably the most common and troublesome symptom of painful neuropathies. It occurs in nearly all neuropathic pain patients either as an isolated symptom or in combination with exaggerated response to applied stimuli (▶ Allodynia and ▶ Hyperalgesia). In addition to being of great clinical significance, the presence of pain in an insensate limb is paradoxical and represents a challenge for theoretical understanding. Since its development, the denervation/deafferentation model has proved to be an important tool in identifying the biological mechanism(s) underlying neuropathic pain, and in evaluating the mode of action of therapeutic agents (Devor and Seltzer 1999; Devor 2006). It has also been an important platform for the discovery of genetic polymorphisms that affect susceptibility to developing neuropathic pain (Devor and Raber 1990; Nissenbaum et al. 2010). Although in recent years it has been largely superseded by partial denervation models which use as a behavioral endpoint the evaluation of allodynia and hyperalgesia (rather than autotomy), the model remains a useful behavioral probe of ongoing (spontaneous) painful dysesthesia in experimental animals.

Background and Ethical Considerations

Although it had been recognized previously that animals, rodents to primates, tend to lick, scratch, and bite an insensate body part, this autotomy behavior was not recognized as a potential indicator of ongoing pain until the mid-1970s (Basbaum 1974; Wall et al. 1979). Investigators rarely witness actual autotomy behavior. Rather, the accumulated amount of tissue loss is scored. Long-term observations and video monitoring indicate that autotomy may occur either in brief "attacks" or in quiet bouts of deliberate chewing, separated by hours or days in which no further tissue loss occurs. This suggests that autotomy may reflect transient, sometimes paroxysmal peaks of pain perhaps overlaid on a continuous ongoing pain. Across-strains genetic analysis in mice indicates that autotomy behavior is part of a pain "type" that includes thermal nociception (Mogil et al. 1999). Perhaps, in mice at least, the ongoing pain has a burning quality.

It is essential to understand that, since the limb is entirely numb, autotomy behavior per se is not painful, even when the self-inflicted tissue loss includes entire digits. Pain arises spontaneously in association with the underlying neural injury. The ongoing pain remains even when steps are taken to prevent autotomy behavior itself, such as with the use of a protective ruff placed around the animal's neck, or when a foul-tasting substance is painted on the limb (Devor and Seltzer 1999). If reports from human patients can serve as guidance, it is safe to assume that most animals that suffer allodynia and hyperalgesia in partially denervated limbs also have spontaneous pain. The only reason that autotomy does not occur along with allodynia and hyperalgesia in the partial nerve injury models is that the very act of licking and biting the limb provokes pain (Koplovitch et al. 2012). Autotomy is prevented by "nociceptive sensory cover." The absence of autotomy in a nerve-injured animal with residual sensation in the limb should, therefore, *not* be taken as evidence for the absence of ongoing pain. In the chronic constriction injury (CCI) model of neuropathic pain, for example, there may be patches of complete skin denervation and these are targets for autotomy behavior (Bennett and Xie 1988). Esthetic considerations aside, ethical constraints on the use of lesions

which trigger autotomy are no different in kind from those associated with the use of other neuropathic pain models.

Does Autotomy Behavior Reflect Pain?

Pain is a private experience (1st person) that cannot be felt by another, only inferred through context and the observation of nocifensive behavior (e.g., escape, distress vocalization, spoken language). Drawing inferences about ongoing pain from spontaneously emitted behavior, such as autotomy, is intrinsically more uncertain than concluding that pain is felt when an animal shows distress in response to an applied stimulus. Skeptics have questioned the proposition that autotomy reflects pain with two main arguments. First, anesthesia dolorosa does not typically trigger self-injurious behavior in human patients, and second, autotomy may reflect an animal's attempt to rid itself of a useless, insensate, but pain-free limb. The first critique is weak as socialization, and the anticipation of consequences are expected to prevent self-mutilation in humans with normal mental capacity, but not in animals. Moreover, compulsive autotomy-like behavior does occur in some people with ongoing dysesthesias (including itch) and pain (Mailis 1996; Symons 2011). As for the second critique, rendering a limb numb by sustained local anesthetic nerve block does not trigger autotomy (Blumenkopf and Lipman 1991). Likewise, when denervation is carried out in two stages, the latent time before autotomy behavior begins is linked to the moment of the initial nerve injury, even though it produces only partial denervation, and not the moment that the limb was finally rendered numb. The ability of a prior nerve lesion to accelerate the onset of autotomy when nociceptive sensory cover is ultimately removed is called the "priming effect" (Koplovitch et al. 2012).

There are many positive indicators that autotomy reflects spontaneous pain (Coderre et al. 1986; Levitt 1985; Seltzer 1995). These include the following:

- Limb denervation and deafferentation frequently cause ongoing neuropathic pain in humans. As in humans, palpating neuromas in rats evoke distress vocalization and struggling (Dorsi et al. 2008).
- Neural injuries that are followed by autotomy behavior trigger massive barrages of spontaneous discharge in injured afferents. There is a suggestive temporal correspondence between this discharge and autotomy, particularly for ectopia in nociceptive C-fibers (Devor and Seltzer 1999).
- Depletion of C-fibers with neonatal capsaicin treatment suppresses autotomy (Devor et al. 1982), and resecting neuromas in adults delays autotomy until a new spontaneously active neuroma forms (Seltzer 1995).
- Different forms of nerve section (cut, freeze, cautery, crush, etc.) produce identical anesthesia, but yield different degrees of autotomy, presumably because of differences in the resulting ectopia (Zeltser et al. 2000).
- Autotomy is suppressed in a dose-dependent manner by drugs that reduce ectopic firing and/or relieve neuropathic pain in humans (e.g., anticonvulsants, local anesthetics, tricyclics, NMDA receptor antagonists). Likewise, analgesics minimally effective against neuropathic pain, such as NSAIDs, do not suppress autotomy (Coderre et al. 1986; Seltzer 1995; Devor and Seltzer 1999).
- Spinal injection of excitants, such as strychnine, tetanus toxin, alumina cream, penicillin, and substance P, which almost certainly causes pain, induces scratching and biting of the corresponding limb, and sometimes frank autotomy (Coderre et al. 1986; Devor and Seltzer 1999).
- Blockade of descending antinociceptive control by appropriate brain stem or spinal tract lesions augments autotomy (Coderre et al. 1986; Saade et al. 1993), while midbrain or dorsal column stimulation and dorsal root entry zone (DREZ) lesions suppress it (Kauppila and Pertovaara 1991; Rossitch et al. 1993; Devor and Seltzer 1999; Guenot et al. 2002).
- Autotomy is accompanied by paw guarding, protective gait, sleep disturbances, sometimes weight loss, and stress-related increase in plasma corticosterone levels. It is augmented

by stressful conditions, such as isolation and cold stress, and reduced by taming and social contact (Coderre et al. 1986; Kauppila and Pertovaara 1991; Seltzer 1995; Devor and Seltzer 1999; Raber and Devor 2002).

- There is clear evidence that genes, as well as environmental factors, determine the level of autotomy behavior. For example, there are consistent differences in autotomy among strains of mice and rats, despite identical denervation and sensory loss. Likewise, genetic selection and interbreeding experiments indicate a high degree of heritability with at least one gene of major effect (Devor and Raber 1990; Mogil et al. 1999; Seltzer et al. 2001).
- An autotomy pain susceptibility gene located on mouse chromosome 15 has recently been identified as *Cacng2*. Polymorphisms in the human homolog of this gene, CACNG2, affect the likelihood that neuropathic pain will develop in women who have undergone partial or complete amputation of a breast (Nissenbaum et al. 2010).

Mechanisms of Ongoing Pain in the Denervation/Deafferentation Model

A limb may be rendered insensate by denervation or deafferentation and both situations may produce anesthesia dolorosa in humans and autotomy behavior in animals. The terms "denervation" and "deafferentation" are frequently confused and misused; they do not mean the same thing. ▶ Denervation in the present context refers to severing sensory axons that innervate the limb. Sensory endings rapidly degenerate in the process of anterograde (Wallerian) degeneration. However, sensory cell bodies in the DRG, their connectivity with the spinal cord, and the ability of (ectopically generated) afferent impulses to reach the CNS are largely preserved. ▶ Deafferentation refers to blocking the arrival of afferent impulses into the CNS by severing dorsal roots (▶ Dorsal Rhizotomy). The sensory neurons in the dorsal root ganglion (DRG) mostly survive, as do sensory endings in the skin. The limb is *not* denervated. It is very likely that pain due to denervation and deafferentation results from different mechanisms (Devor 2006).

Pain and autotomy after nerve injury is probably due to abnormal spontaneous afferent discharge generated ectopically at the nerve injury site, and in axotomized DRG neurons. There might also be a contribution by residual intact neurons that continue to innervate adjacent skin. The ectopic firing plays two roles. First, it constitutes a primary nociceptive afferent signal. Second, it probably triggers central sensitization in the spinal cord dorsal horn, and perhaps also in the brain. The sensitized CNS amplifies and augments pain sensation due to the spontaneous afferent discharge. It also renders light tactile input from residual neighboring afferents painful, yielding tactile allodynia in the skin bordering on the denervated zone (Defrin et al. 1996; Devor 2006).

Pain and autotomy after deafferentation must be due to another mechanism as dorsal rhizotomy does not trigger massive ectopia in axotomized afferents, and even if it did, the impulses would have no access to the CNS. Pain following rhizotomy is, therefore, presumed to be due to impulses that originate within the deafferented CNS itself. Deafferentation triggers many structural and neurochemical changes in the CNS, and abnormal bursting discharges have been recorded in deafferented spinal dorsal horn in animals and in humans (see ▶ Central Changes After Peripheral Nerve Injury). The possibility that deafferentation pain is indeed due to this activity is supported by the observation that surgical destruction of the abnormal dorsal horn tissue by ▶ DREZotomy often relieves this type of pain (Rossitch et al. 1993; Guenot et al. 2002).

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Anesthesiologic Interventions

► Cancer Pain Management, Anesthesiologic Interventions, Spinal Cord Stimulation, and Neuraxial Infusion

Anesthesiological Interventions

▶ Cancer Pain Management, Anesthesiologic Interventions, and Neural Blockade

Anesthesiologist

Definition

A medical doctor specializing in preventing and treating pain during surgery (general anesthesia (sleeping patient) or local or regional anesthesia (with part of the body made numb and feeling no pain)). Anesthesiologists also take care of critically ill patients in the intensive care units, in emergency, and pre-hospital settings.

Cross-References

▶ Postoperative Pain, Acute Pain Management Principles
▶ Postoperative Pain, Acute Pain Team

Anesthetic Block

▶ Cancer Pain Management, Anesthesiologic Interventions

Anesthetic Blockade

Definition

Injection of local anesthetics in a nerve branch or plexus

Cross-References

▶ Deafferentation Pain

Aneurysm

Definition

An aneurysm is a localized dilatation of a blood vessel, commonly an artery, which may cause symptoms by enlarging or bleeding.

Cross-References

▶ Primary Cough Headache

Anger and Pain

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Synonyms

Acting-out; Aggression; Anger-in; Frustration; Hostility

Definition

Anger is an emotional experience involving cognitive appraisal and action tendency (Smedslund 1992). There have been numerous anecdotal reports since the early days of pain medicine, suggesting that anger may be an associated or resultant emotional experience of pain. There are several terms that are used interchangeably. For the purpose of clarification, in this entry, the following definitions will be applied:

- Frustration: affective state that arises when one's effort has been blocked, thwarted
- Anger: strong feeling of displeasure associated with cognitive appraisal that injustice has occurred and action tendency to remedy the perceived injustice

- Hostility: unfriendly attitudinal disposition with tendency to become angry
- Aggression: behavioral actualization of the action tendency associated with anger

Characteristics

Anger is a common emotional experience associated with pain, particularly chronic pain. Pain, by virtue of its aversive phenomenological nature, frequently brings on the perception of injustice and frustration. Additionally, the sense of injustice may come with having to undergo multiple diagnostic tests without finding fruitful findings. This often raises a question of legitimacy of pain, leading to interpersonal hardship. Functional limitations associated with chronic pain may severely impair the patient's ability to be a productive member of a workforce, enjoy the recreations they used to engage in, and nurture their personal relationships with friends and families.

Parameters of Anger

Anger is a multidimensional construct. It involves the temporary parameters of the experience such as frequency, recurrence, duration, intensity of the experience, expression styles, and target of the anger. The earlier studies mostly focused on anger levels (state) or one's tendency to become angry (trait). Those earlier studies generally demonstrated the relationship between anger and pain severity in chronic pain patients (Wade et al. 1990). The directionality of the relationship has been a topic of much debate. Literature supports both, suggesting that the relationship is likely dynamic, reciprocal, and complex. For example, anger exacerbates pain severity in chronic pain patients (Gaskin et al. 1992). Pain also triggers angry reaction; the experimental studies show higher frustration and hostility as a result of noxious stimulation (Berkowitz and Thome 1987).

Another parameter of anger is how anger is experienced and expressed ("anger management style"). One of the two styles that have been most studied is "anger-in," in which people are aware of the presence of anger but the expression is suppressed. The concept of "trait" anger-in is thought to be confounded with a more general concept of negative affectivity (Burns et al. 2008), and the delineation of the true relationship between a tendency to inhibit anger and pain is difficult. Typically, trait anger-in and pain intensity in chronic pain patients are modest and positively related (Kerns et al. 1994; van Middendorp et al. 2010). Experimental manipulation of anger inhibition, on the other hand, consistently seems to heighten pain sensitivity in healthy people (Quartana and Burns 2007) as well as in chronic pain patients (Burns and Holly 2008). The other style is "anger-out," in which angry feelings are overtly expressed. The high degree of anger-out suggests undercontrolled, excessive demonstrations of anger. Anger-out seems to be implicated with higher pain sensitivity in various situations. It is correlated with greater sensitivity to acute pain in healthy people and pain patients (Bruehl et al. 2002) as well as greater pain in postsurgical patients (Bruehl et al. 2006). Clinical pain among chronic pain patients may also be related to their tendency to express anger (Bruehl et al. 2003).

Finally, a target parameter of anger may be important in understanding pain patients. Anger is generally a provoked feeling and requires a specific target, object, or person with whom one feels angry. The degree to which anger is related to pain may greatly differ, depending upon targets with which people experience anger. Self and healthcare providers appear to be common targets of anger among chronic pain patients. Interestingly, anger at self is related to depression, whereas anger at healthcare providers is related to the perceived level of functional disability (Okifuji et al. 1999). The results suggest that the assessment of specific targets with which patients experience anger may be important in understanding the overall clinical picture of their pain condition.

Mechanisms

Psychodynamic Model

The role of anger in medically unexplained pain complaints plays a central role in

a psychodynamic conceptualization. When a person experiences anger, the person's psyche classifies the emotion as unacceptable, and it channels the feeling into somatic symptoms. In the early days of research evaluating the etiology of chronic pain, the high prevalence of depressed mood in chronic pain patients led the psychodynamic paradigm to propose the notion of "masked depression," in which chronic pain was considered as a somatically expressed form of depression. Depression, in turn, was considered as "anger turned inward," with a person holding a self-depreciating view of self. However, empirical support for the psychodynamic model is limited to the correlational association between pain and negative moods.

Psychosocial-Behavioral Model

Behaviorally, anger, when it is poorly managed, may contribute to the suffering of a person living with pain. Functional limitations that often accompany their condition significantly compromise the quality of life, leading to frustration, and persistent irritability further compromises interpersonal relationships. Inhibition of anger expression has been found to be related to depression especially for chronic pain patients reporting severe pain (Estlander et al. 2008). Moreover, when expressed inappropriately, anger may interfere with how the person interacts with healthcare providers. Intense anger may jeopardize the cooperative relationship between the providers and the patient or decrease the patient's willingness to comply with the regimen; as a result, the patient may not receive the optimal benefit from the treatment.

Psychophysiological-Neurological Model

Anger may also contribute to pain via autonomic activation. Anger is associated with the general elevation in the sympathetic responses. The orchestrated arousal of the sympathetic tone is analogous to what we experience in response to a stressor. Such stress responses, particularly muscle tension, are known to be potentially problematic for pain patients. Pain patients exhibit a greater level of muscle tension in the pain-afflicted region than in other non-affected areas in response to a stressor (Flor and Turk 1989), suggesting that the elevation of muscle tension associated with anger may play a role in perpetuating the stress-tension-pain cycle. On the other hand, when patients who tend to suppress their anger reexperience/recall anger, they seem to show reduced paraspinal muscle reactivity (Burns 1997). More recently, it has been suggested that muscle tension may show marked elevation where there is a mismatch between a personal style of anger regulation and situational demand (e.g., high anger-out people trying to suppress anger) (Burns and Holly 2008).

Cardiovascular response to anger may also play a role in pain experience. Janssen et al. (2001) has shown that acutely induced anger might lead to elevation of blood pressure and increased pain thresholds, possibly indicating the presence of stress-induced analgesia. Similarly, a recent study (Quartana et al. 2010) showed that effort to suppress provoked anger attenuated blood pressure response to pain and was positively related to greater pain report, again suggestive of a possible role of autonomic stress response in how anger may modulate pain experience.

More recently, it has been suggested that the dysregulation in the endogenous opioid function may mediate the relationship between anger and pain. Expressed anger seems to compromise the endogenous opioid reactivity to experimentally induced pain (Bruehl et al. 2002; Bruehl et al. 2003). Reduced release of beta endorphin in response to pain has also been observed in those with high degree of anger-out (see Bruehl et al. (2009) for an excellent review on this topic).

Treatment Implications

Treatment of pain, particularly chronic pain, requires cooperation and active participation from patients. Anger, if not properly managed, is likely to interfere with treatment efficacy. It is reasonable to assume that angry patients may be reluctant to follow the regimen. Angry patients with suboptimal coping skills may also find it difficult to adaptively change their lifestyles to

accommodate rehabilitation. At this time, very little is known about how anger interacts with rehabilitative efforts for pain patients. Burns et al. (1998) reported that male patients showed the inverse relationship between the pretreatment level of anger suppression and improvement in mood and self-reported level of activity. The result from their subsequent study suggests (Burns et al. 1999) that patients with a high degree of anger-out may not develop a sense of rapport with their healthcare providers.

Anger is not necessarily maladaptive. Anger can be an adaptive emotional response to the injustice that patients perceive. However, the accumulation of research suggests that poorly managed anger exacerbates pain and disability and interferes with the treatment efforts. Effective self-management of anger may be essential for the successful rehabilitative effort of pain patients. Psychoeducational approaches help patients to better understand the concept and how poorly managed anger may contribute to their pain. Fernandez (2002) suggests several approaches to help patients acquire better anger coping skills via cognitive reappraisal, behavioral modification, and appropriate affective disclosure. There has been a proliferation of research demonstrating the salient effects of poorly managed anger on pain experience in the past decade. By contrast, however, very little has been done to test the efficacy of anger management in improving pain therapy outcomes. Future research is warranted to evaluate the enhancement effects of such approaches for pain rehabilitation.

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Anger-in

▶ Anger and Pain

Angiitis of the CNS

▶ Headache Due to Arteritis

Angina Pectoris

Definition

Severe chest discomfort usually caused by inadequate blood flow through the blood vessels of the heart as a result of cardiac disease resulting in myocardial ischemia (inadequate oxygen supply to the heart). It is often treated by medical means or by surgical or angioplastic revascularization. It is rarely treated by spinal cord stimulation. Angina is often accompanied by shortness of breath, sweating, nausea, and dizziness.

Cross-References

▶ Pain Treatment: Spinal Cord Stimulation
▶ Spinothalamic Tract Neurons, Visceral Input
▶ Thalamus
▶ Thalamus and Visceral Pain Processing (Human Imaging)
▶ Thalamus, Clinical Visceral Pain, Human Imaging
▶ Visceral Pain Model, Angina Pain

Angina Pectoris, Neurophysiology and Psychophysics

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Synonyms

Interoceptive sensation; Sympathetic afferents; Visceral sensation

Definition

The role of the somatic sensory ▶ thalamus in angina related to cardiac disease is demonstrated by stimulation of thalamus in patients with a history of angina and by the presence of cells projecting to monkey thalamus that respond to cardiac stimulation.

Characteristics

The sensory mechanisms of angina are poorly understood, although it is a common, clinically significant symptom. Recent evidence suggests that the perception of angina is correlated with central nervous system activity encoding cardiac injury. Noxious cardiac stimuli evoke activity in sympathetic afferent nerves (Foreman et al. 1986), in ascending spinal pathways (spinothalamic (STT) and ▶ dorsal column (DC) pathways) and in cells of the principal sensory nucleus of the ▶ thalamus (Horie and Yokota 1990).

STT cells in the upper thoracic spinal cord projecting to the region of VP respond to coronary artery occlusion (Blair et al. 1984) and intracardiac injection of bradykinin (Blair et al. 1982). Cells at the posteroinferior aspect of VP in

the cat respond to intracardiac injections of bradykinin (Horie and Yokota 1990) and to stimulation of cardiac sympathetic nerves (Taguchi et al. 1987). Neurons in the thalamic principal sensory nucleus also encode visceral inputs from gastrointestinal and genitourinary systems in monkeys (Bruggemann et al. 1998). Therefore, experimental studies suggest that cells in the region of VP encode noxious visceral and cardiac stimuli.

The spinothalamic tract sends a dense projection particularly to the posterior inferior lateral aspect of monkey VP (Apkarian and Hodge 1989). Projections from the spinothalamic tract are also found posterior and inferior to VP in the posterior nucleus and in the ventral posterior inferior nucleus. VP projects to primary somatosensory cortex while the region posterior and inferior to VP projects to secondary somatosensory cortex, insular cortex, and retroinsular cortex (Jones 1985).

Involvement of sympathetics in the perception of angina is based upon evidence that stimulation of the superior cervical ganglion produces pain and that lesions of the sympathetic ganglia and dorsal roots relieve angina (reviewed by Meller and Gebhart 1992). Involvement of thalamus in the sensation of angina is suggested by the case of a patient with angina successfully treated by balloon angioplasty (Lenz et al. 1994). During thalamic exploration for implantation of a stimulating electrode, microstimulation evoked a pain "almost identical" to her angina, except that it began and stopped instantaneously with stimulation. This time course of this sensation was typical of sensations evoked by thalamic microstimulation but not those evoked by cardiac disease (Lenz et al. 1993). Stimulation-associated angina was not accompanied by the cardiac indices of angina in the setting of myocardial infarction. A biochemical link between the experience of angina pectoris and activation of thalamic neurons may have been elucidated during experimentation with dipyridamole stress testing. Vagal release of adenosine to the A(1) receptors in thalamus and prefrontal cortex appears to play a role (Ito et al. 2002).

The description of her typical angina and stimulation-evoked angina included words with a strong affective dimension from a questionnaire. In a similar setting the atypical chest pain of panic disorder was "almost identical" to that produced by microstimulation in the same thalamic area as the present case (Lenz et al. 1995). Stimulation-evoked pain without an affective dimension was observed in a retrospective analysis of patients without experience of spontaneous chest pain with a strong affective dimension (Lenz et al. 1994, 1995). Therefore, stimulation-evoked chest pain included an affective dimension as a result of conditioning by the prior experience of angina of cardiac origin.

The affective dimension of stimulation-associated pain might be analogous to emotional phenomena evoked by stimulation of amygdala in patients with epilepsy who have prior experience of these phenomena during the aura of their seizures (Halgren et al. 1978). The region posterior to Vc is linked to nociceptive cortical areas that project to the amygdala. Vcpc projects to anterior insular cortex (Mehler 1962) whereas Vcpor projects to the inferior parietal lobule, including the parietal operculum and secondary somatosensory cortex (SII) (Locke et al. 1961) which project, directly or indirectly, to the amygdala. Noxious sensory input to these cortical areas is demonstrated by evoked potentials in response to tooth pulp stimulation (Chatrian et al. 1975). Lesions of SII interfere with discrimination of noxious stimuli (Greenspan and Winfield 1992) while lesions of insula impair emotional responses to painful stimuli (Berthier et al. 1988). Thus, there is good evidence that cortical areas receiving input from Vcpc and Vcpor are involved in pain processing.

SII and insular cortical areas involved in pain processing also satisfy criteria for areas involved in corticolimbic connections (see ▶ corticolimbic circuits). In monkeys, a nociceptive sub-modality selective area has been found within SII (Dong et al. 1989). SII cortex projects to insular areas that project to the amygdala (Friedman et al. 1986). SII and insular cortex have bilateral primary noxious sensory input (Chatrian et al. 1975), and cells in these areas responding to noxious stimuli have bilateral representation (Dong et al. 1989; Chatrian et al. 1975). Therefore,

cortical areas receiving input from Vcpc and Vcpor may be involved in memory for pain through corticolimbic connections (Mishkin 1979).

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Angiogenesis

Definition

Angiogenesis refers to the growth of new blood vessels, which is an important naturally occurring process in the organism, both in normal and tumor tissue. In the case of cancer, the new vessels provide oxygen and nutrition for the tumor cells and allow tumor cells to escape into the circulation and lodge into other organs (tumor metastases).

Cross-References

► NSAIDs and Cancer

Angiography

Definition

An angiography is necessary for the diagnosis of CNS vasculitides.

Cross-References

► Headache Due to Arteritis

Animal Model for Phantom Limb Pain

► Anesthesia Dolorosa Model, Autotomy

Animal Model of Spontaneous Neuropathic Pain

► Anesthesia Dolorosa Model, Autotomy

Animal Models

► Animal Models of Inflammatory Bowel Disease

Animal Models and Experimental Tests to Study Nociception and Pain

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Introduction

Animal models and experimental tests to study nociception and pain are important because they are the major tools that make studying nociception and pain possible. It would not be an exaggeration to say that progress on pain research has been made only to the degree that these essential research tools are available.

Among the oldest and the most commonly used nociceptive tests would be the ► tail flick test that was developed by D'Amour and Smith in 1941 (D'Amour and Smith 1941). This is a test for acute pain in normal rodents, and since then many other tests and models, focused primarily on chronic or persistent pain, have been developed. Availability of these tests and models enabled research on persistent pain to flourish during recent decades. The present section documents the majority of commonly used animal models and experimental tests.

Characteristics

Overview of Topics

Tests for Nociception and Pain

Nociceptive tests utilize observations of animal behavior after delivering noxious mechanical, heat, or chemical stimuli to a defined body part. In this section, we will address a variety of tests used to study nociception and pain. Two of these tests, the ► allodynia test, mechanical and cold allodynia, and the ► Randall-Selitto paw pressure test, use a mechanical stimulus to elicit responses. The tail flick test, the ► thermal nociception test, and the ► hot plate test (assay) use noxious heat as the stimulus. There are a number of ways to apply chemical stimuli to elicit pain behaviors. However, one of the most common methods is an injection of formalin into the paw of a rodent – the ► formalin test.

The thermal hyperalgesia test and the allodynia test, in particular, have been widely used in recent years. The thermal hyperalgesia test, which was developed by Hargreaves et al. (1988), uses the latency of escape behaviors of a rodent after application of a noxious heat stimulus to estimate changes in the heat pain threshold. This test has hence been frequently used to quantify the development of heat hyperalgesia in various painful conditions.

The allodynia test in a neuropathic pain model using von Frey filaments was first conducted by Seltzer et al. (1990) and quantifies changes in mechanical threshold for pain behavior. Kim and Chung (1991, 1992) subsequently used von Frey filaments extensively to quantify mechanical allodynia in their model of neuropathic pain. All these tests are for quantification of pain behavior in various pain models.

Animal Models

Numerous good animal models representing various pain syndromes have been developed in the past, particularly during the last couple of decades. These include various musculoskeletal pain models (▶ arthritis model, kaolin-carrageenan-induced arthritis (knee); ▶ arthritis model, adjuvant-induced arthritis; ▶ cancer pain model, bone cancer pain model; ▶ muscle pain model, ischemia-induced and hypertonic saline-induced; ▶ animal models of inflammatory muscle pain; ▶ sprained ankle pain model); and visceral pain models (pain originating from various parts of the gastrointestinal tract, heart, kidney, pancreas, urinary bladder, and female reproductive organs). In addition, there are a number of neuropathic pain models – produced by injuries to either the peripheral or the central nervous system. Many of these models are described in this section.

There has been an explosion in the development of peripheral neuropathic pain models in recent years, as well as in studies conducted using them. The field of neuropathic pain was revolutionized by the initial development of a model by Bennett and Xie (1988), which was followed by other models (Seltzer et al. 1990; Kim and Chung 1992; Na et al. 1994; Decosterd and Woolf 2000). All these models have in common: They produce a partial nerve injury so that an area of the skin is partially denervated but a part of the innervation is left intact. Direct comparison of multiple models in a single study is rare, but Kim et al. (1997) compared three neuropathic pain models, the chronic constriction injury (CCI) (▶ neuropathic pain model, chronic constriction injury), partial sciatic nerve ligation (PSL) (▶ neuropathic pain model, partial sciatic nerve ligation model), and spinal nerve ligation (SNL) (▶ neuropathic pain model, spinal nerve ligation model) models. They found that these three models displayed similar behavioral patterns with minor differences in specific features, presumably due to the difference in populations and numbers of afferent fibers that are denervated versus those left intact in each model. For example, the CCI model showed a relatively larger magnitude of behavioral signs representing ongoing pain whereas the spinal nerve ligation (SNL) model displayed more robust mechanical allodynia. As far as the nature of injury is concerned, the SNL model is highly artificial in that it produces an injury to one or two spinal nerves selectively, whereas the PSL model closely resembles the nerve injury produced by gunshot wounds, on which the description of classical causalgia was based (Mitchell 1872). On the other hand, if one wants to reduce the variability between animals, a stereotyped injury such as SNL would be beneficial. Therefore, having such a variety of models provides a good opportunity to select and use a model depending on the questions posed and the given circumstances.

Another area of animal modeling that has flourished in recent years is the area of central neuropathic pain, particularly spinal cord injury pain models. In the central nervous system, post-stroke pain models of the cerebral cortex as well as of the thalamus are available. In the spinal cord, we now have models for contusion, ischemic and focal injuries produced by mechanical as well as by chemical means. These are described in this section.

Visceral pain is a clinically important topic. There are animal models representing pain arising from various visceral organs, ranging from the heart to the kidney, pancreas, urinary bladder, and various parts of the gastrointestinal tract. All of these models attempt to imitate a clinical situation that causes pain, such as ischemia (e.g., angina), overdistension of the gastrointestinal tract, or chemical/mechanical irritation of ductal structures.

Discussion and Future Direction

Although this section describes a number of animal models and experimental tests used to study

nociception and pain, there are a large number of already developed tests and models that are not included here. We hope to be able to include them as their usage becomes more widespread. At the same time, there are a number of models and tests that need to be developed and these will be included in this section as they become available. Therefore, this section is expected to grow rapidly as we progress in pain research.

Ethical considerations in animal welfare are very important issues for all animal research, but this is especially important in pain studies because these require using painful stimuli; yet, the pain and stress of the animals must be minimized. Therefore, although the nature of the studies calls for inducing some levels of painful stimuli, pain and stress must be kept at the minimal level. Fortunately, animals in most models do not display signs of severe chronic pain and discomfort as evidenced by normal weight gain and grooming. However, should the animal show signs of unbearable discomfort, the experiment must be terminated by humanely euthanizing the animals. Maintaining pain and discomfort at the minimum level is important not only for the humane treatment of experimental animals but also for obtaining the most reliable scientific data without contamination by undesirable stress-induced factors.

How to define what a good animal model is can be debatable. However, a good animal model should at least: (1) replicate a human disease condition faithfully, (2) show little variability between investigators and between laboratories, and (3) be easy to produce. Most of the models presented in this section satisfy these criteria; however, some are better in one aspect and worse in others and some are the other way around. A good model should also replicate the most important aspect of a human pain condition and employ animal tests most relevant to these aspects. A model may employ a testing method that is designed to be convenient for experimenters but which does not necessarily test the most relevant aspect of pain in patients. This is a shortcoming which should be corrected.

It is sometimes difficult to relate the results of tests in animal models to human diseases. For example, in the case of a disease with motor deficits, a question may arise as to whether motor deficits seen in animals would be the same as those seen in human patients. This is particularly a problem in pain research because animals cannot verbally express sensory experience and we have to rely on their behaviors and our interpretation of them. Such an indirect approach leaves much room for a subjective interpretation. Therefore, we must pay particular attention to this problem when we deal with animal models and testing in animals.

As mentioned above, animals in all the models described in this section display pain behavior, but the intensity of the pain seems to be much less than the pain that is intended to be modeled. For example, although it is common for humans to lose their appetite and to lose weight while suffering from chronic pain, in most animal models of pain, the animals seldom show signs of severe suffering for an extended period. Another example would be that many neuropathic pain sufferers have excruciating sensitivity to tactile stimuli so that even gentle movement of hair will cause pain. However, rats in all neuropathic pain models can be handled and the affected areas touched without too much of a response. Furthermore, these rats usually bear some weight during locomotion although they invariably have some motor deficits. Why is there such a difference in the intensity of pain? It is possible that none of the developed models truly represent a severe human pain condition. It is also possible that animals react differently from humans to the same intensity of pain and that the models may still be valid. We can argue for one or the other with no definite answer, but this is something we need to consider when we deal with animal models.

Frequently, most of the animals used in a given animal model may consistently show signs of pain. Such consistency is a good thing in a pain model since there will be less variability between animals. On the other hand, this can be viewed as a bad feature in a model that represents a pain syndrome, since it is rare for all patients with a particular disease state to develop pain. For example, only 10–15 % of patients with a peripheral nerve injury develop neuropathic pain, yet virtually all rats in neuropathic pain models show pain behaviors. Why is this true? Are these still good models? These are difficult questions to answer.

One explanation commonly used is that a genetic factor may play a role so that some patients may have a genetic makeup prone to develop pain after peripheral nerve injury. In support of this contention, there are vast differences in pain behavioral responses to a peripheral nerve injury among different strains of rats or mice. However, there is no direct proof indicating that this is the true explanation. This is a factor we need to keep in mind as well when conducting studies of animal models.

Recently operant behavioral assays, which test "pain" in animals beyond simple motor reflex changes, have been developed. These tests are thought to give a different and possibly superior assay of clinical pain, especially tonic pain (Mogil 2009; King et al. 2009). This is an important emerging approach, and further development of operant assay methods is thus desirable.

Although animal models for many painful conditions are described in this section, more good animal models are needed for common painful conditions, such as lower back pain, headaches, and myofascial pain. The main reason for the lack of such models is that it is technically difficult to develop them. However, it is imperative to develop animal models for these clinically common painful conditions so that we can make scientific progress in understanding these important pain conditions.

Summary

Many good clinically relevant animal models for various painful conditions are available now and their availability provides powerful tools for scientific studies, as well as for the development of new analgesic drugs. Undoubtedly, we will need to refine existing models and to develop new models as well as test methods representing painful conditions faithfully.

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Animal Models of Inflammatory Bowel Disease

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Synonyms

Animal models; Colitis; Crohn's disease; Inflammatory bowel disease; Ulcerative colitis

Definition

Inflammatory bowel disease (IBD) manifests as a complex chronic inflammatory disorder thought to be caused by a combination of environmental and genetic factors. Clinically, IBD presents as either ulcerative colitis (UC) or Crohn's disease (CD), which predominantly affects the colon and/or the distal small intestine, respectively (Hendrickson et al. 2002).

Characteristics

Approximately 600,000 Americans suffer from IBD, with the majority of patients diagnosed with the disease during their third decade of life. The most common symptoms include diarrhea, abdominal pain, fever, weight loss, ▶ arthralgias, and arthritis (Hendrickson et al. 2002). While the exact causes of IBD remain unknown, certain environmental and genetic factors have been shown to play a role in the development of IBD. Environmental factors may include smoking, diet, physical activity, childhood infections, microbial agents, and stress (Fiocchi 1998). The familial incidence of both CD and UC is remarkably high. The frequency of IBD in first-degree relations has been reported to be as high as 40 %. Among populations, IBD is most common among whites of European descent, although it is present in all races and ethnic groups (Fiocchi 1998).

The onset of IBD is generally thought to arise from T lymphocytes infiltrating a weakened epithelial lining and thereby initiating a pathological immune response within the bowel (Bhan et al. 1999; Blumberg et al. 1999). For IBD, the focus of research has been on CD4 T cells, also known as T-helper cells. These cells are capable of secreting large amounts of ▶ cytokine or ▶ growth factors that affect other immune cells and interacting tissues. Mature CD4 cells can be divided into Th1 and Th2 cells based on the complement of cytokines they produce. Th1 cells secrete IL-2, IFNγ, and TNF, whereas Th2 cells secrete IL-4, IL-5, IL-13, and TGFβ cytokines (Fig. 1). A balance between these two cell types appears to be required for immunological homeostasis, as disruption of this balance can lead to pathological inflammation. Interestingly, Th1 and Th2 cell types predominate in CD and UC, respectively, and because of this, many animal models of IBD employ genetic deficiencies or antibodies against the cytokines associated with Th1 or Th2 CD4 cells (Bhan et al. 1999; Blumberg et al. 1999).

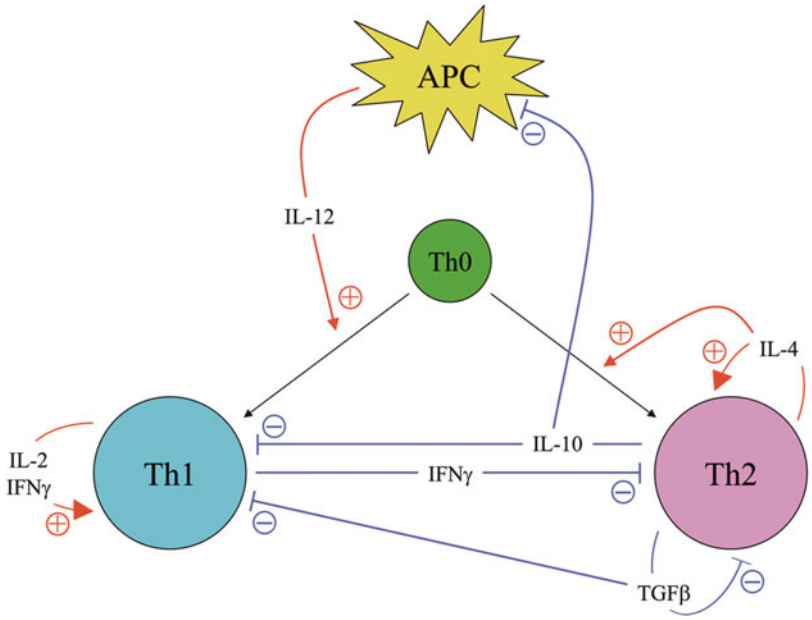
The important role played by these immune cells does not mean that environmental factors do not contribute significantly to the onset of IBD. Multiple studies have shown that animals housed in a pathogen-free environment do not develop IBD (Kim and Berstad 1992; Wirtz and Neurath 2000). This indicates that while alterations in the immune system are important for development of IBD, in most cases the development of pathology requires an environmental trigger that may include pathogens, stress, and nutrition.

Animal Models

Animal models of IBD can be separated into four main categories: spontaneous colitis, inducible colitis, adoptive transfer, and genetically engineered. Each model offers a novel approach to studying IBD; however none presents an exact model of the human condition.

Spontaneous Colitis

Symptoms of IBD occur naturally and are studied in C3H/HeJBir mice, SAMP1/Yit mice, cotton-top tamarins, and juvenile rhesus macaques. C3H/HeJBir mice can develop inflammation in the colon that peaks between 3 and 6 weeks of age and generally resolves by 10–12 weeks of age (Wirtz and Neurath 2000; Hendrickson et al. 2002). In contrast, SAMP1/Yit mice develop inflammation in the distal small intestine and cecum by 20 weeks of age with increasing lesion severity and incidence (Blumberg et al. 1999; Wirtz and Neurath 2000; Hendrickson et al. 2002). Cotton-top tamarins and juvenile rhesus monkeys are both primate models of UC, hallmarked by mucosal inflammation occurring only in the colon (Kim and Berstad 1992; Ribbons et al. 1997; Wirtz and Neurath 2000). Considering the high frequency of familial IBD,



Animal Models of Inflammatory Bowel Disease, Fig. 1 Imbalance between T-helper cells may contribute to CD and UC. T-helper cell type 1 (Th1) and T-helper cell type 2 (Th2) participate in cell-mediated immunity and antibody-mediated immunity, respectively. Antigen-presenting cells (APC) produce IL-12 in response to specific antigens, and this induces undifferentiated T-helper cells (Th0) to become Th1 cells. The cytokine(s) responsible for inducing Th0 cells to become Th2 cells have not been identified. Th1 and Th2 cells both secrete specific cytokines that act through positive and negative feedback loops. Th1 cytokines (IL-2, IFNγ) enhance Th1 cell proliferation while also inhibiting Th2 cell proliferation. IFNγ also functions to increase Th1 cell differentiation by upregulating IL-12 production. Th2 cytokines both increase (IL-4) and decrease (TGFβ) the proliferation of Th2 cells. TGFβ and IL-10 both suppress cytokine production by Th1 cells, and IL-10 also decreases the differentiation of Th1 cells by downregulating IL-12 production

spontaneous models of IBD are highly useful in the study of genetic susceptibility to IBD.

Inducible Colitis

Interruption of the mucosal barrier of the bowel can lead to transient or chronic inflammation. Various agents can induce IBD in this manner including formalin, acetic acid, carrageenan, dextran sulfate sodium (DSS), 2,4,6-trinitrobenzene sulfonic acid (TNBS), dinitrobenzene sulfonic acid (DNBS), indomethacin, oxazolone, or ethanol.

Intracolonic administration of dilute formalin or acetic acid induces a transient inflammation in the colon of rats or mice. Their effects occur very quickly and have been used extensively in the study of visceral pain (Kim and Berstad 1992). In contrast, chronic inflammation can be induced by oral ingestion of carrageenan or DSS, subcutaneous injection of indomethacin, or intracolonic administration of TNBS, DNBS, oxazolone, or ethanol. Carrageenan induces an early mucosal inflammation of the cecum with subsequent mucosal inflammation of the colon of rodents (Kim and Berstad 1992). Ingestion of DSS initially results in lesions and crypt formation within the mucosal lining of the colon of both rats and mice. This is followed by a secondary inflammation and infiltration of cytokines (Kim and Berstad 1992; Mahler et al. 1998). In mice, rats, and rabbits, intracolonic administration of TNBS or DNBS results in epithelial necrosis that leads to increased mucosal permeability and transmural inflammation (Kim and Berstad 1992; Elson et al. 1996). It is interesting to note that mouse strain differences exist regarding the susceptibility to either DDS or TNBS-induced IBD (Mahler et al. 1998). C3H/HeJ mice are highly susceptible to

both DSS and TNBS, whereas C57Bl/6 and DBA/2 mice are less vulnerable to DSS and resistant to TNBS, again emphasizing the importance of genetic factors in the occurrence of IBD (Elson et al. 1996; Mahler et al. 1998). In rats, subcutaneous injection of indomethacin produces both an acute and a chronic inflammation within the small bowel, as well as epithelial injury measurable by mucosal permeability (Yamada et al. 1993). Mice or rats given intrarectal oxazolone develop a severe mucosal inflammation of the distal colon (Wirtz and Neurath 2000). Similarly, intrarectal ethanol results in destruction of the surface epithelium and necrosis extending throughout the mucosal layer of both mice and rats (Kamp et al. 2003). Inducible models are important in the study of IBD in that they establish a mechanical or chemical disruption of the mucosal barrier within the bowel, thereby providing an adequate model to study the chain of events that occur during the initial activation of the mucosal immune system.

Adoptive Transfer

IBD can be generated by transferring activated immune cells from normal animals into immunocompromised host animals. The most common model involves transferring CD4-positive T cells with a high expression of CD45RB ($CD4^+CD45RB^{high}$) from wild-type animals into severe combined ▶ immunodeficient (SCID) or recombination activating gene (RAG) knockout mice (Wirtz and Neurath 2000; Hendrickson et al. 2002). $CD4^+CD45RB^{high}$ T cells produce high levels of Th1 cytokines, which have been shown to play a role in the induction and maintenance of IBD, in particular CD (Bhan et al. 1999; Blumberg et al. 1999). IBD can also be induced by introducing activated hsp60-specific $CD8^+$ T cells into immunodeficient or T cell receptor (TCR) β−/− mice (Wirtz and Neurath 2000). This results in degeneration of the mucosal epithelium in the small bowel with massive leukocytic infiltration within the ▶ lamina propria and epithelial layers. The adoptive transfer models have provided an excellent paradigm for gaining a better understanding for the role of T cells in the development and maintenance of IBD.

Genetically Engineered

The use of genetically altered mice has provided an excellent approach to studying the roles of specific immune cells and cytokines in IBD. As mentioned previously, an imbalance of Th1- and Th2-type cytokines has been shown to play a role in IBD (Bhan et al. 1999; Blumberg et al. 1999). Several transgenic and knockout mouse models have been generated to study the roles of Th1 and Th2 cytokines in IBD. Overexpression of HLA-B27 or STAT-4 both increases the production of Th1-type cytokines, including TNFα and IFNγ, most likely through the activation of IL-12 (Wirtz and Neurath 2000; Hendrickson et al. 2002). Similarly, mice with a deletion of IL-2, IL-2Rα, IL-10, CRF2-4, $G_{i\ \alpha}2$, STAT-3, or the AU-rich region of TNF overproduce Th1 cytokines and develop symptoms of IBD (Wirtz and Neurath 2000; Hendrickson et al. 2002). On the other hand, overexpression of IL-7 or a deletion of TCR-α results in a Th2-mediated IBD, mostly due to an increased production of Th1 cells (Wirtz and Neurath 2000).

Genetic models have also been generated to investigate aspects of IBD other than cytokine production. Disruption in the integrity of the intestinal epithelium has been implicated in IBD. This has been demonstrated in a mouse model that overexpresses a dominant negative form of N-cadherin using a small intestine-specific promoter (Wirtz and Neurath 2000). Similarly, deletion of the multiple drug-resistant gene (*mdr1a*) resulted in IBD, solely due to the lack of *mdr1 a* expression on intestinal epithelial cells (Wirtz and Neurath 2000). Intestinal trefoil factor (ITF) is luminally secreted after inflammation and is thought to aid in maintaining the barrier function of mucosal surfaces and facilitating healing processes after injury. Mice with a genetic deletion of ITF are significantly more susceptible to induction of IBD by DSS, indicated by increased colonic ulceration and morbidity (Mashimo et al. 1996; Wirtz and Neurath 2000). To investigate the role of enteric ganglia cells in IBD, a mouse model was developed that expresses herpes simplex virus (HSV) thymidine kinase (TK), driven by the glia-specific glial fibrillary acidic protein (GFAP) promoter.

When the antiviral agent ganciclovir (GCV) is injected subcutaneously, the HSV-TK metabolizes the GCV into toxic nucleotide analogs that induce cell death within their host cells, in this case enteric glial cells. Disruption of ileal and jejunal glial cells resulted in overt inflammation of the small bowel; however the colon remained unaffected (Bush et al. 1998). Genetic models have provided an excellent tool for investigating the possible roles of specific cytokines and structural proteins in IBD.

Implications for Pain Studies

As previously mentioned, patients with IBD often suffer from abdominal pain. Animal models, primarily models of inducible colitis, are often used to investigate changes in nociceptive processing that arise from IBD. The two most common methods for assessing visceral pain in animals are colorectal distension (CRD) and the acetic acid writhing test. CRD uses balloon distension of the distal colon to induce activation of both first- and second-order sensory afferents and contraction of abdominal muscles (visceromotor response), both of which can be quantifiably measured to determine visceral sensitivity (Kamp et al. 2003). In the writhing test, ► intraperitoneal injections of acetic acid induce abdominal contractions along the length of the torso with corresponding arching of the back (Martinez et al. 1999). The mechanisms underlying the acetic acid writhing test are relatively unknown; therefore CRD is a much more reliable and consequently more widely used test for visceral hypersensitivity.

Several studies have used CRD as a means to study the effects of acute and chronic colon inflammation in rodents. Intracolonic application of acetic acid or ethanol was shown to significantly increase the number of abdominal contractions as well as the visceromotor response, during CRD (Martinez et al. 1999; Kamp et al. 2003). Similar results were observed in a TNBS-induced model of IBD (Sengupta et al. 1999). Visceral hyperalgesia has largely gone unstudied in genetic models of IBD. This is unfortunate as these models present an excellent opportunity for investigating the possible roles that cytokines and other molecules may play in the genesis of visceral hyperalgesia associated with IBD.

Animal models of IBD provide researchers with the tools to investigate specific aspects of the disease in an in vivo setting. While none of the models wholly represents the disease as it appears in humans, they each provide a useful tool with which to study specific aspects of the disease, including the manifestation of visceral hyperalgesia.

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Animal Models of Inflammatory Muscle Pain

► Muscle Pain Model, Inflammatory Agents-Induced

Animal Models of Inflammatory Myalgia

► Muscle Pain Model, Inflammatory Agents-Induced

ANKTM1

► TRPA1 Channel

Ankylosing Spondylitis

Definition

Ankylosing spondylitis is an inflammatory joint disease that is characterized by enthesitis, an inflammation at points of attachment of tendons to bone. The vertebrae may become linked by bony bridging (bamboo spine).

Cross-References

► Chronic Low Back Pain: Definitions and Diagnosis
► NSAIDs and Their Indications
► Sacroiliac Joint Pain

Ankylosis

Definition

Bony ankylosis occurs when bone remodeling as a result of inflammation or damage occurs, resulting in a fusion of the joint. This causes joint immobility. Fibrous ankylosis occurs when inflammation of fibrous or connective tissues of the joint results in proliferation of tissue and in reduced mobility or stiffness of the joint.

Cross-References

► Arthritis Model, Adjuvant-Induced Arthritis

Annulus Fibrosus

Definition

Annulus fibrosus is an outer anatomical structure of the intervertebral disc composed of fibrocartilage and fibrous tissue, delimiting the nucleus pulposus. The annulus fibrosus has a nociceptive innervation.

Cross-References

► Lumbar Traction
► Whiplash

Anorexia

Definition

Loss of appetite.

Cross-References

► Clinical Migraine with Aura

Antecedents and Consequences of Behavior

Definition

The set of factors that occurred temporally before and after a behavioral event or experience. The antecedents may contribute to an individual's expectations for the future, and the behavioral responses that are received in close proximity to an event can serve to influence subsequent responses and experiences. Thus, antecedents and consequences play a role in determining the onset, maintenance, and exacerbation of inappropriate behaviors, or contribute to appropriate and adaptive responses to similar situations and sensations in the future.

Cross-References

► Psychological [Behavioral Health] Assessment of Pain

Anterior Cingulate Cortex

Synonyms

ACC

Definition

The anterior cingulate cortex (ACC), a component of the limbic system, is an area of the brain located just above the corpus callosum. The ACC is involved in many functions, including attention, emotion, and response selection, among others. Its descending connections to the medial thalamic nuclei and the periaqueductal gray, along with evidence from brain imaging studies, also support a role for the ACC in the descending modulation of pain.

Cross-References

► Cingulate Cortex, Nociceptive Processing, Behavioral Studies in Animals
► Descending Circuits in the Forebrain, Imaging

Anterior Lumbar Interbody Fusion

► ALIF

Anterior Primary Ramus

Definition

The anterior branch of a spinal nerve that provides the nerve supply to the extremities (e.g., brachial plexus) and the chest wall.

Cross-References

► Pain Treatment: Spinal Nerve Blocks

Anterior Pulvinar Nucleus

Definition

The anterior pulvinar nucleus extends from the medial pulvinar and posterior nuclei,

situated between the center median and ventral posterior nuclei.

Cross-References

► Thalamic Nuclei Involved in Pain, Human and Monkey

Anterior Spinothalamic Tract

► Paleospinothalamic Tract

Anterograde Axonal Tracer (Anterograde Labeling)

Definition

A substance (protein, enzyme) that is injected at the level of the neuronal soma. It is incorporated within the soma and then conveyed in an anterograde (orthodromic) direction in the axon up to the endings. The tracer is generally colored with a histochemical reaction, with or without an earlier immune amplification reaction.

Cross-References

► Parabrachial Hypothalamic and Amygdaloid Projections
► Spinal Dorsal Horn Pathways, Dorsal Column (Visceral)
► Spinohypothalamic Tract, Anatomical Organization, and Response Properties

Anterograde Transport

Definition

Anterograde transport is the movement of proteins away from the cell body.

Cross-References

► Opioid Receptor Trafficking in Pain States

Anterolateral Cordotomy

Definition

Ablation of the spinothalamic tract by open surgical section or through the application of a thermal coagulation probe.

Cross-References

► Cancer Pain Management, Neurosurgical Interventions
► Spinothalamic Neuron

Antiarrhythmics

► Drugs Targeting Voltage-Gated Sodium and Calcium Channels

Anticholinergics

Definition

A class of drugs also referred to as antimuscarinics that are used as smooth muscle antispasmodics and antisecretory drugs. Anticholinergic medications include the natural belladonna alkaloids (atropine and hyoscine) and synthetic and semisynthetic derivatives. The synthetic and semisynthetic derivatives are separated into tertiary amines (i.e., dicyclomine) and quaternary ammonium compounds (i.e., hyoscine butylbromide and glycopyrrolate). The quaternary ammonium compounds are less lipid soluble than the natural alkaloids and are, therefore, less likely to cross the blood-brain barrier and cause side effects such as agitation and hallucinations.

Cross-References

- ▶ Cancer Pain Management, Adjuvant Analgesics in Management of Pain Due to Bowel Obstruction

Anticipatory Anxiety

Definition

Anticipatory anxiety refers to fear experienced before encountering a threatening situation or experience. In relation to experimental pain, anticipatory anxiety relates to a child's perception of the extent to which the upcoming pain stimulus may lead to harm or damage to one's physical integrity.

Cross-References

- ▶ Experimental Pain in Children
- ▶ Respondent Conditioning of Chronic Pain

Anticoagulants

- ▶ NSAID-Induced Lesions of the Gastrointestinal Tract

Anticonvulsant (Agent)

Definition

Antiepileptics are agents that prevent or arrest seizures, and are primarily used in the management of epilepsy.

Cross-References

- ▶ Drugs Targeting Voltage-Gated Sodium and Calcium Channels
- ▶ Postoperative Pain, Anticonvulsant Medications
- ▶ Post-Seizure Headache
- ▶ Preventive Migraine Therapy

Anticonvulsant Medication

- ▶ Postoperative Pain, Anticonvulsant Medications

Anticonvulsants

- ▶ Drugs Targeting Voltage-Gated Sodium and Calcium Channels

Antidepressant Analgesics in Pain Management

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Synonyms

First-generation antidepressants; Heterocyclic antidepressants; Monoamine oxidase inhibitors; Norepinephrine-dopamine reuptake inhibitors; Norepinephrine-dopamine transporter inhibitors; Second-generation antidepressants; Serotonin antagonist reuptake inhibitors (SARIs); Serotonin selective reuptake inhibitors (SSRIs); Serotonin-norepinephrine reuptake inhibitors (SNRIs); Tricyclic antidepressants

Definition

Prevailing dogma holds that standard antidepressant drugs exert their primary therapeutic effects either through inhibition of one or more of the high-affinity neuronal plasma membrane

monoamine postsynaptic transporters, such as the norepinephrine transporter and the serotonin transporter, by blocking presynaptic receptors, or by inhibiting enzymes involved in monoamine metabolism. Whether by blocking reuptake into the presynaptic neuron, by increasing release, or inhibiting degradation, the end result is increased availability of key monoamines at the synapse.

Antidepressants can be characterized by structure (e.g., tricyclic or heterocyclic rings), function (e.g., transporter inhibition), or chronology. The advantage of definition by function is that it can assist with anticipation of adverse effects, and therefore with matching patients to a safer and more tolerable agent. Using this approach the tricyclic antidepressants (e.g., amitriptyline, imipramine) are nonselective serotonin-norepinephrine reuptake inhibitors because they block both presynaptic transport of these monoamines and they also have antimuscarinic-anticholinergic, a_1-adrenergic antagonist, and histamine (H_1) antihistaminic properties. The selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, sertraline) primarily bind to the serotonin transporter; selective dual serotonin-norepinephrine reuptake inhibitors block both serotonin and norepinephrine reuptake transporters (e.g., venlafaxine, duloxetine) but have limited effects on other receptors; and the norepinephrine agonist/dopamine reuptake inhibitors (e.g., bupropion) selectively block these respective receptors. Another major class is the alpha 2 adrenergic receptor antagonist/serotonin receptor blocker (e.g., mirtazapine) which increase serotonin and norepinephrine neurotransmission by novel blocking of adrenergic presynaptic receptors. The final major class is the monoamine oxidase (MAO) inhibitors (e.g., selegiline) which increase serotonin, norepinephrine, and dopamine neurotransmission by preventing enzymatic degradation of these key monoamines. In terms of classification by chronology, the tricyclics and monoamine oxidase inhibitors were the first antidepressants to be routinely prescribed in clinical care, and therefore are customarily referred to as "first-generation" agents. The newer more selective drugs are described as "second generation."

Characteristics

Historical

The historical context of antidepressant analgesia was thoroughly reviewed in the First Edition (2004) and is only briefly updated here. The MAO inhibitors, the first clinically effective antidepressants, were synthesized in the early 1950s after improvement in mood was observed in depressed patients treated for tuberculosis by iproniazid, an agent with some monoamine oxidase inhibitory effects. Throughout the1960s, they were employed in open-label trials for migraine headache based on a rationale that diminished serotonin neurotransmission was associated with cerebral vasodilation and subsequent migraine attacks. The open label nature of the trials made it difficult to evaluate efficacy, but it was argued that substantial and sustained improvement was achieved in patients who had a long record of prior treatment failures (e.g., Anthony and Lance 1969). Early agents (e.g., phenelzine) were nonselective inhibitors of MAO A and B, and the need for dietary restriction to avoid hypertensive crises, along with adverse drug-drug interactions with opioid analgesics, mitigated against their widespread use, and they were replaced in pain management by tricyclic antidepressants. Dietary restriction is not necessary with newer, selective MAO inhibitors (e.g., selegiline) but even these more tolerable agents have not been widely used or trialed for chronic pain.

The tricyclic antidepressants, so-named because their chemical structure contains three rings, were synthesized in the early 1950s and tested first as antipsychotics, based on the efficacy of other three-ringed molecules (i.e., chlorpromazine) in schizophrenia. Although they had no antipsychotic properties, an antidepressant effect was serendipitously noted, and these drugs came into psychiatric practice (e.g., imipramine, amitriptyline) by the early 1960s. Almost simultaneously case series in the French literature reported efficacy in chronic pain syndromes. Reports of efficacy in open-label and randomized trials began appearing in the mid-to late1960s for various syndromes,

including chronic "tension headache" (e.g., Lance and Curran 1964), postherpetic neuralgia (Woodforde et al. 1965), atypical facial pain (Lascelles 1966), migraine headache (e.g., Dalessio 1967), and "mixed arthritic disorders" (e.g., McDonald-Scott 1969). In the 1970s and early 1980s, initial trials reporting efficacy emerged for chronic low back pain (Jenkins 1976) and painful diabetic polyneuropathy (Turkington 1980). Several important developments characterize work from the late 1980s and throughout the 1990s to the present. First, scientific rigor of trials steadily improved. Second, it became clear that the antidepressant and analgesic effects of these agents were independent, and that treatment was efficacious for nondepressed individuals with certain chronic pain states. Third, studies were conducted to assess comparative efficacy of classical tricyclics with SSRIs (e.g., Max et al. 1992). Relatedly, clinical trials examined the effects of newly available SNRIs and NDRIs. There also was renewed interest in concentration-response effects of antidepressants, aimed at determining if higher doses or concentrations enhanced efficacy, or if instead there were therapeutic "windows" of efficacy. Fourth, the list of other potentially responsive conditions grew, to include functional bowel syndromes (e.g., see Drossman et al. 2009) and fibromyalgia (e.g., see Clauw 2008). Finally, in the last decade it has been possible to conduct systematic reviews and meta-analyses aimed at determining which chronic pain syndromes are responsive, to what drugs, and to what degree.

Pharmacodynamics

Antidepressants are agents with complex effects on neurotransmitter receptors or enzymes. A complete and adequate explanation of their mechanism of action is lacking. One theory is that antidepressants in part exert therapeutic effects by downregulating some postsynaptic receptors (e.g., β-adrenergic receptors, 5HT2a receptors), enhancing 5HT1a receptor transmission, and decreasing firing of auto-inhibitory monoamine neurons. Other evidence suggests antidepressants may have neuroprotective effects, and promote neurogenesis and synaptic connectivity. Some antidepressants have effects on cholinergic transmission, on acid-sensing sodium and calcium channels, on glutamate and *N*-methyl-D-aspartate (NMDA) receptors, on sigma 1 and 2 receptors, and on histone acetylation. With regard to both pain and mood, the clinical relevance of these many effects is uncertain. Site(s) of mechanistic action are also unclear and may involve inhibitory pain pathways descending from the dorsal raphe (serotonergic) or locus coeruleus (noradrenergic) to the dorsal horn of the spinal cord.

Because of their widespread effects on multiple neurotransmitter systems, the tricyclic antidepressants, compared to more selective agents, are much more likely to be associated with adverse effects. Within the tricyclic class, the parent drugs with a tertiary amine structure (e.g., amitriptyline, imipramine) are more likely than their metabolite, the secondary amines (e.g., nortryptyline, desipramine), to have adverse effects.

There is disagreement regarding the comparative efficacy among antidepressants with selective noradrenergic effects, serotonergic effects, or a balanced combination of both actions. Historically, most research up to the early 1990s employed tricyclic agents. The parent compounds (e.g., amitriptyline, imipramine) can be said to have relatively "balanced" effects, although their primary metabolites (e.g., nortriptyline, desipramine) are predominantly noradrenergic. An influential early meta-analyses (Onghena and Van Houdenhove 1992) concluded overall that agents with "balanced" serotonin and noradrenaline action are more efficacious than selective drugs. This conclusion still echoes in the literature, but in retrospect may be an oversimplification, since the analysis included few studies of serotonin selective agents.

There are two schools of thought with reference to differential efficacy across diagnostic categories antidepressant mechanisms. One argument is that chronic pain is a homogenous condition because all pain must have a common final pathway. It follows that efficacy demonstrated in one condition can be generalized to others. An alternative argument is that pain syndromes are

diagnostically distinct and that discussions of efficacy and of comparative efficacy must reference diagnostically homogeneous pain disorders. Differential responsiveness across pain disorders as determined by estimates of efficacy (e.g., number-needed-to-treat) provides evidence supporting this position. In this regard, studies of diabetic neuropathy often suggest superiority of both selective noradrenergic (desipramine) and balanced (amitriptyline, imipramine, clomipramine) agents over selective serotonergic drugs (e.g., fluoxetine, citalopram). Nevertheless, other research finds at least some analgesic action of serotonin selective agents for these same neuropathic pain diagnosis. Studies in chronic back pain suggest efficacy for more selective noradrenergic agents (nortriptyline, maprotiline) whereas an SSRI (paroxetine) is indistinguishable from placebo. Yet work in migraine headache argues for at least some efficacy of SSRIs, albeit inferior to agents with both noradrenergic and serotonergic actions. These data can make a case for the proposition that noradrenergic action is important if not essential to analgesic efficacy across various pain syndromes. But because of limitations in the field, as discussed below, it is difficult to appraise this hypothesis, or that dual action is fundamentally superior to action of either noradrenergic or serotonergic systems alone.

A related issue is whether there are dose-or concentration-response effects of antidepressant analgesia. Possibilities include (1) monotonic increases in analgesia as dose or concentration increases; (2) "thresholds" (i.e., a concentration which must be exceeded for analgesia); or (3) therapeutic "windows" of efficacy (i.e., boundaries of concentrations for efficacy, with diminished efficacy either above or below these boundaries). The question of dose-response is complicated by at least two considerations. One is that the pharmacodynamic properties of some antidepressants vary by dose: For example, venlafaxine usually is a very selective serotonin transport blocker at lower doses, but reliably also has noradrenergic effects commencing at higher doses (e.g., 225–375 mg); similarly, paroxetine is an SSRI at usual dosages, but also may have noradrenergic effects at doses of exceeding 40 mg daily. The other consideration involves pharmacokinetics: tricyclics and SSRIs, for example, are metabolized by the Cytochrome (CYP) P450 enzyme system. Because of genetic variability in rates of metabolism (slow, medium, fast), a given dose may result in tenfold differences in concentration across individuals.

Research does not consistently reveal dose- or concentration-related effects, a failure that has been attributed to study design, since most pain trials were not designed for clinical psychopharmacology (Max 1994). Fixed dose designs are limited by CYP 450 polymorphism. Individualized dosing to response is limited by the problem that patients achieving relief at low doses or concentrations would stay at that level, while patients with severe pain would be escalated to maximum tolerable dose, thus possibly masking a concentration-response correlation. Forced titration to maximal dosage or concentration is thought to be limited by the possibility that response may occur at lower concentrations, but may be attributed to the higher doses or concentrations. The most rigorous approach is concentration-controlled trials in which individuals are randomly allocated to preassigned low, medium, or high concentrations of the study drug, and therapeutic drug monitoring is used to confirm assignments. This design is complex and rarely implemented. It is not surprising then that the main question has not been answered. It is possible that concentration-response relationships may vary by pain disorder or pathophysiology. Considering the most rigorous studies, there is some evidence for a positive concentration-response relationship in diabetic neuropathy for imipramine and paroxetine, as well as evidence for a low concentration window for both postherpetic neuralgia with amitriptyline, and for desipramine in chronic back pain. Research on the newer "second-generation" antidepressants is scant. There is some evidence for a positive concentration-response relationship for venlafaxine in diabetic neuropathy, but studies of duloxetine show no correlations for diabetic neuropathy, back pain, or fibromyalgia.

The evidence base for efficacy of antidepressants in various chronic pain states is reviewed below. There are important gaps, however, in this literature (Kroenke et al. 2009). There are very few head-to-head trials – either within antidepressant classes or between antidepressants and other analgesics; thus, little is known of comparative efficacy. There is scant data to guide initial treatment, either in terms of which antidepressants or when and at what step in the analgesic "ladder" should antidepressants be employed. For example, we know far less than we should about the efficacy of the SSRIs in particular: There has been almost no follow-up after initial studies suggested potential efficacy for certain syndromes (e.g., diabetic neuropathy). Little research examines efficacy of combination treatment with antidepressants and other analgesics (e.g., opioids, nonsteroidals, anticonvulsants), or if combination treatment allows for dose reductions compared to monotherapy. Finally, almost all studies are very short term, rarely lasting over 3 months.

Evidence-Based Studies

The evidence base described here draws on systematic reviews and meta-analyses. When summarizing comparative efficacy between antidepressants, or between antidepressants and other drug classes (e.g., anticonvulsants), both indirect and direct meta-analyses are presented, where possible. Indirect evidence consists of trials that evaluate different drugs versus placebo. Direct evidence consists of studies of head-to-head trials of the competing agents. It is argued that direct and indirect comparisons usually agree, but may diverge if there are differences between trials in terms of methodological rigor, or target populations, measurement, or other factors (Chou and Huffman 2007).

Acute Pain Studies

Early studies of first-generation antidepressants for acute experimentally induced pain and postoperative dental extraction pain yielded negative or inconsistent results. One intriguing study in nondepressed patients with acute/subacute back pain (mean duration 60 days) suggested efficacy for high-dose amitriptyline (150 mg daily) compared to acetaminophen, but unfortunately this line of research has not been extended (Stein et al. 1996). The availability of effective analgesics for acute pain has perhaps limited interest in exploring possible acutely analgesic effects of newer antidepressants.

Cancer Pain

Cancer pain is of diverse and often complex etiology, often not diagnosable as a purely neuropathic, somatic, or visceral pain syndrome. Any one patient may experience pain both due to direct effects of tumor (e.g., invasion of viscera or nerve, metastasis to bone) or from consequences of surgery (e.g., deafferentation), radiotherapy, or chemotherapy. Most research in antidepressant analgesia in cancers focuses on neuropathic pain, but the body of research is exceedingly limited. Although there are a few small sample size studies suggesting efficacy of amitriptyline or venlafaxine for postmastectomy pain, these results are inconsistent, and there is other data suggesting no benefit for chemotherapy-induced (i.e., cisplatin) neuropathy and other neuropathic cancer pain. It is unfortunately the case that use of antidepressants for neuropathic cancer pain must be largely based on the unproven assumption that efficacy in noncancer pain (e.g., painful diabetic neuropathy or postherpetic neuralgia) is generalizable.

Chronic Nonmalignant, Nonneuropathic Pain

Chronic Low Back Pain

Chronic low back pain is one of the most prevalent and disabling conditions in clinics and the workplace. Its etiopathogenesis is uncertain, but it is thought to be a heterogeneous condition, with persistent pain attributed to both peripheral phenomenon like muscle inflammation and injury, or degenerative disease of the spine, as well as to central sensitization. Less than 5 % of chronic low back pain patients experience "sciatica" or lumbosacral radiculopathy, but this condition can markedly impair function and is treatment resistant.

Evidence for efficacy of first- and second-generation antidepressants in chronic low back

pain is mixed: Expert systematic reviews and meta-analyses, often even after examining virtually the same literature, may come to differing conclusions. Some suggest there is negligible benefit with these agents (White et al. 2011), some identify only minimal effects, and others find moderate efficacy with tricyclic antidepressants (e.g., Salerno et al. 2002; Chou and Huffman 2007; Kroenke et al. 2009) but little efficacy for SSRIs. One of the newer SNRIs, duloxetine, may be effective (Kroenke et al. 2009). Only a few studies specifically assess response rates in patients with sciatica or lumbar radiculopathy, and the results are not encouraging. This uncertainty in the literature regarding the overall efficacy in chronic back pain may in part be due to difficulties in sample specification – the unclear etiology of chronic back pain is compounded by the failure of many studies to attempt to rigorously diagnose or define the study sample. This likely diagnostic heterogeneity across samples may mean some relatively more – or less – responsive syndromes (e.g., sciatica) are combined and compared, with a weak treatment effect noted. A second problem is that some reviews and meta-analyses consider all antidepressants as a single class, thus obscuring possible differential response between agents. Another obvious problem is the very small sample size in most studies, meaning that results are unstable.

Fibromyalgia

Fibromyalgia is a complex disorder characterized by persistent widespread and decreased pain as well symptoms of fatigue, stiffness, insomnia, and mood and anxiety disorders. Two meta-analyses (e.g., see Arnold 2007) suggest efficacy of antidepressants in fibromyalgia pain and overall symptom burden, but careful drug selection may be important to outcome. One meta-analysis of antidepressants in the treatment of fibromyalgia (O'Malley et al. 2000) included 13 trials of antidepressants, including amitriptyline ($N = 8$), clomipramine, and maprotiline ($N = 1$); SSRIs (fluoxetine [$N = 2$]); citalopram [$N = 1$]; and a reversible inhibitor of the MAO-A enzyme, moclobemide [$N = 1$]. Outcomes included the number of tender points, and patient ratings of pain, sleep, fatigue, and overall well-being. The pooled results showed significant symptomatic benefit of antidepressants that was moderate for sleep, overall well-being, and pain severity, and mild for fatigue and number of tender points. Patients treated with antidepressants were more than four times as likely to improve as those on placebo. The overall positive impact of a broad spectrum of antidepressants as determined by these meta-analyses must be tempered by the problem that most studies did not exclude individuals with mood or anxiety disorders, which could confound outcomes. Nevertheless, the more careful studies which focus on patients with pain without psychiatric comorbidity still show positive effects.

The tricyclics (e.g., amitriptyline) are often described as more efficacious than second-generation agents in terms of NNT. But recent reviews suggest this apparent advantage may be an artifact of methodological deficits and a smaller number of participants enrolled in the earlier studies (Hauser et al. 2011). These reviews (Hauser et al. 2011) suggest SNRIs like duloxetine (60 or 120 mg) and milnacipran (100–200 mg) are comparable in efficacy to first-generation agents and are more tolerable. A trial of venlafaxine was negative, but the dose (<75 mg/day) was in the range where only serotonin transporter blockade would be expected. The role of SSRIs in general is unclear. One very methodologically sound trial of fluoxetine reported efficacy for nondepressed patients treated with a flexible dosing strategy (20–80 mg), but two trials of citalopram and one trial of paroxetine were negative. There is the suggestion that higher doses of SSRIs might be required. The role of MAOIs is still unclear. One randomized trial of moclobemide was negative, but a pilot trial of pirlindole suggested efficacy.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting disorder characterized by abdominal pain and change in bowel habit (diarrhea or constipation). The etiology is uncertain, and may involve visceral hypersensitivity to

distention, gut inflammatory or immune dysfunction, stress-induced hyperalgesia, or autonomic dysfunction (Ford et al. 2009).

The overall quality of clinical trials of antidepressants for IBS has been judged to be moderately good. One recent meta-analysis reporting on both first- and second-generation agents noted that in 9 studies comparing TCAs (amitriptyline, desipramine) to placebo, TCAs were beneficial with an overall NNT of 4. Doses were generally in the lower range used in other pain syndromes (e.g., amitriptyline or nortriptyline 10–50 mg, imipramine or desipramine 10–50 mg daily).

There were five studies of SSRIs (citalopram, fluoxetine, paroxetine) compared to placebo. SSRIs were efficacious, with an NNT of 3.5. Daily doses were generally in the range used to treat major depression (e.g., citalopram 20–40 mg, fluoxetine 20–40 mg, paroxetine 20–40 mg).

Depression and anxiety symptoms often accompany IBS, but improvement in pain symptoms was not correlated with scores on depression measures, suggesting that treatment exerted an analgesic effect independent of an antidepressant effect.

There are too few studies in children and adolescents to support the use of antidepressants for irritable bowel syndrome in this population.

Rheumatoid Arthritis, Ankylosing Spondylitis, and Osteoarthritis

Pain is a prominent symptom in inflammatory and degenerative arthritides like rheumatoid arthritis and hip and knee osteoarthritis. Despite the prevalence and impact of these illnesses, only a handful of studies have assessed the analgesic effects of antidepressants: This lack is thought to be attributable to the efficacy of standard, first-line anti-inflammatory regimens. Unfortunately, most research has combined patients with any of these syndromes into heterogeneous groups, and there has been work exclusively assessing effects on hip or knee osteoarthritis, despite their growing importance in an aging population. Results suggest that first-generation drugs (amitriptyline, dothiepin, trimipramine) in low doses may be efficacious. But most research includes patients with prominent depressive symptoms (e.g., fatigue, insomnia), making it unclear whether improvement is due to analgesic effects or antidepressive effects.

Neuropathic Pain (NP)

Neuropathic pain is an important, disabling condition affecting 5 % or more of the general population in industrialized countries. It arises from injury or disease of the peripheral or central nervous system, or a mixture of both. The most prevalent neuropathic pain syndrome is probably lumbosacral radiculopathy (its therapy has been addressed above, in Chronic Back Pain). Apart from this disorder, the most frequent conditions associated with neuropathic pain are diabetes mellitus, herpes zoster infection, HIV disease, physical trauma (e.g., spinal cord injury, amputation), multiple sclerosis, and direct or indirect (treatment-related) effects of neoplasm. Most research, and the strongest data on efficacy of selected antidepressants, addresses painful diabetic peripheral neuropathy and postherpetic neuralgia. There is much less research – and unfortunately only limited evidence of a benefit of antidepressants – for other neuropathic pain syndromes.

Painful Diabetic Peripheral Neuropathy and Postherpetic Neuralgia

As reviewed in the first edition of this encyclopedia, controlled studies conducted in the 1990s firmly established the efficacy of tricyclics as one of the "first-line" analgesics for postherpetic neuralgia and painful diabetic neuropathy (Dworkin et al. 2007). The number-needed-to-treat (NNT = 3) also established these syndromes as among the most treatment responsive of all chronic pain states. Subsequent work demonstrated that second-generation antidepressants with noradrenergic effects (e.g., SNRIs like duloxetine, higher dose venlafaxine) probably have almost comparable efficacy, and that bupropion may also be effective (Dworkin et al. 2007).

The efficacy of SSRIs is less certain. Some work in diabetic neuropathy suggests fluoxetine

is equivalent to placebo; other studies in this disorder having similarly small sample sizes report efficacy with paroxetine and citalopram. It is unfortunate that the role SSRIs have not been more definitively assessed, given their safety and tolerability.

Other Neuropathic Pain: HIV Neuropathy, Spinal Cord Injury, Phantom Limb Pain

TCAs have not differed significantly from placebo in RCTs of patients with HIV neuropathy, spinal cord injury-related neuropathic pain, and phantom limb pain. Despite the importance of each of these conditions, there are very few studies using first-generation drugs and none using second-generation antidepressants.

In summary, the most responsive neuropathic pain syndromes are all small fiber neuropathies (i.e., diabetic peripheral neuropathy, postherpetic neuralgia). Large fiber neuropathies (e.g., lumbosacral radiculopathy, cisplatin-induced neuropathy, and some HIV myeloneuropathy) appear to be treatment resistant.

Practical Guidelines

Patient-Specific Factors

Enhancing the likelihood of successful treatment requires consideration of patient-specific and drug-specific factors. Key patient factors include pain diagnosis, comorbid medical conditions, concurrent medications, and expectancy. Consideration of diagnosis and co-occurring medical conditions and treatment will assist in understanding the risk-benefit ratio of a treatment trial, such that antidepressants are prescribed only for pain syndromes most likely to be responsive, and potential adverse effects are understood. Evaluation of patient expectancy and therapeutic alliance is essential so that there is agreement on a course of action and a definition of "success." Some patients are biased against antidepressant pharmacotherapy because of stigma about "psychiatric" or "mind-altering" drugs, or concerns that such prescriptions means the physician believes pain is "imaginary." Other individuals have very high expectations for analgesia (e.g., complete pain relief). Education about possible analgesic mechanism of action of antidepressants, and their role as adjuncts to a comprehensive plan to reduce pain impact on life quality and function, may assist in promoting adherence and an alliance.

Drug-Specific Factors

The initial treatment decision is whether to select a first- or second-generation agent, taking into account efficacy, cost, and adverse effects. In terms of efficacy, the first-generation agents have a longer track record of success and lower cost, but a greater likelihood of adverse effects compared to second-generation agents. Among first-generation agents, tertiary amine tricyclics (e.g., amitriptyline, imipramine) are often recommended as standard therapy for responsive syndromes (e.g., painful diabetic neuropathy), but secondary amine tricyclics (e.g., nortriptyline, desipramine) have a lower risk of adverse effects and equivalent therapeutic effects. Individuals over age 50 or with history of cardiovascular disease should have a pretreatment electrocardiogram. TCAs are associated with repolarization abnormalities (QT interval prolongation), bundle branch block, hypotension, atrial and ventricular arrhythmias, and risk of myocardial infarction. Anticholinergic effects of these agents may cause urinary retention, especially in individuals who also use opioid analgesics.

Dosing for secondary tricyclic amines is usually low (e.g., nortriptyline or desipramine 25–75 mg daily), but may need to reach full antidepressant doses (e.g., nortriptyline or desipramine 100–150 mg daily).

In the medically ill or elderly, second-generation drugs like duloxetine or higher dose venlafaxine may be preferred alternatives. Duloxetine is contraindicated in hepatic insufficiency; doses of venlafaxine should be reduced by 25–50 % in renal or hepatic insufficiency. Both duloxetine and venlafaxine may increase blood pressure. There is much less data supporting the use of SSRIs in most chronic pain syndromes, but their favorable adverse effect profile make them worthy of consideration as second- or third-line treatment. An exception to this statement may be in IBS, where efficacy of SSRIs seems on par with TCAs. The SSRIs are

generally safe in renal or hepatic insufficiency; a main risk of SSRIs is rare induction of mania in individuals with bipolar disorder. Citalopram in dosages above 40 mg daily (20 mg in patients over age 60) is associated with cardiac conduction (OT_c interval) delay, suggesting other SSRIs may have this liability. When used in the third trimester of pregnancy, both SNRIs and SSRIs are associated with neonatal respiratory distress and other symptoms suggesting direct toxic or withdrawal syndromes.

Dosing for duloxetine is usually 60–120 mg daily, milnacipran 100–200 mg daily, and venlafaxine 150–325 mg daily.

Because of their ability to inhibit CYP 450 2D6, SNRIs and SSRIs may interfere with analgesic effects of codeine and may increase TCA concentrations. Migraine headache is prevalent and may be a co-occurring pain syndrome. Triptan antimigraine medications are serotonin 1 D receptor agonists and may interact with SSRIs or SNRIs to cause a serotonin syndrome of muscular rigidity, autonomic instability, and altered consciousness.

Elderly patients are at elevated risk for adverse effects due to antimuscarinic effects (e.g., delirium) or alpha-1 antagonism (e.g., hypotension) and cardiac conduction delays, as well as SSRI-induced hyponatremia.

There is insufficient evidence to support use of MAO inhibitors in chronic pain.

Management of Adverse Effects

Adverse effects may be time dependent (start immediately but often diminish over 1–2 weeks) or dose dependent (increase as dose increases). Most authorities agree there is no reason to preemptively treat anticipated adverse effects. The preferred strategy is to start antidepressants with low doses, increase slowly after 2–4 weeks, and wait for resolution of side effects. If adverse effects persist, the choice is whether to switch to a potentially more tolerable drug, or lastly, to treat the adverse effect. Effects due to alpha-1 antagonism (orthostatic hypotension) may be addressed with 9-alpha-fluorohydrocortison 0.025–0.050 mg qd; some due to alpha-2 presynaptic agonism (erectile dysfunction) may be managed with sildenafil 50–100 mg or similar agents, while others (delayed ejaculation, anorgasmia, diminished libido) may require bupropion 50–100 mg qd; histamine (H_1) antagonism (sedation) requires bedtime dosing, switching, or dose reduction; muscarinic antagonism (dry mouth) may be reduced by sugar free candies or gum; others (constipation) may respond to stool softeners (docusate sodium 100–200 mg qd), and some (urinary retention) may require bethanechol 10–50 mg qd to qid. Although most adverse effects diminish with time, hypotension and sexual adverse effects usually do not.

Drug Switching, Combination Treatments

Chronic pain by definition is treatment resistant. Depending upon the pain diagnosis, perhaps only 50 % of patients prescribed an antidepressant will achieve satisfactory analgesia (usually defined as a 30–50 % reduction in pain intensity) on the first treatment trial. Discontinuation of an ineffective regimen of a TCA, SNRI, or SSRI is best done by tapering by 25–50 % every 5 days to reduce likelihood of anticholinergic (TCA) rebound or serotonin withdrawal syndrome. One exception is that fluoxetine can be abruptly discontinued because of its very long half-life.

There is almost no data-based guidance on whether failure of one category of antidepressants (e.g., TCA or SNRI) implies likely failure of antidepressants as a class. Most authorities would advocate switching to another class of drugs altogether if there is a clearly suitable alternative (e.g., from an antidepressant to an anticonvulsant in neuropathic pain).

Likewise there is almost no data on efficacy of combination therapy (e.g., antidepressants with anticonvulsants or with opioids). In practice polypharmacy is the norm, and the usual rationale is to build upon incremental gains achieved using one class by adding another class of drugs concurrently. There is no rationale for combining within the antidepressant class (e.g., TCA + SNRI or SSRI), and such combinations may be associated with drug interactions and marked elevations of TCA concentrations due to CYP 450 2 D6 inhibition.

Treatment resistance (i.e., failure on two or more classes of agents) may indicate nonadherence, failure to diagnose comorbid psychiatric or substance use disorder, or misdiagnosis of the target pain syndrome.

Conclusions

Selected antidepressants with noradrenergic transporter blockade are effective in selected chronic pain syndromes, and most of these antidepressants also exhibit at least some serotonin transporter blockade. Interestingly the SSRIs seem to be less often efficacious, but this category of antidepressant also has a role in certain disorders, and the field would greatly benefit by additional investigations focusing on their role. More research also is needed assess the possible role of therapeutic drug monitoring, and to identify the most effective sequences of antidepressant treatment and the efficacy of combination therapies.

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Antidepressant Drugs

Definition

Antidepressant drugs are primarily used in the management of depressive disorders.

Cross-References

▶ Diabetic Neuropathy, Treatment
▶ Postoperative Pain, Antidepressants
▶ Preventive Migraine Therapy

Antidepressants in Neuropathic Pain

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Definition

Neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system. In peripheral neuropathic pain, the lesion is located in the peripheral nervous system, and painful polyneuropathies (diabetic and non-diabetic), post-herpetic neuralgia and chronic pain after surgery (e.g., post-mastectomy pain syndrome) are prominent examples of this category of neuropathic pain. Post-stroke pain, pain after spinal cord injury, and pain in multiple sclerosis represent examples of central neuropathic pain conditions.

Antidepressants are drugs primarily developed to treat depression. The antidepressants that have been found to relieve neuropathic pain are ▶ tricyclic antidepressants (TCAs), serotonin noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and a dopamine noradrenaline reuptake inhibitor (DNRI). Within the pain field, the important drugs in these categories are TCAs: amitriptyline, imipramine, clomipramine, nortriptyline, desipramine and maprotyline; SNRIs: venlafaxine and duloxetine; SSRIs: paroxetine, fluoxetine, citalopram and escitalopram (see Table 1).

Characteristics

TCAs were among the first ▶ evidence-based treatments for neuropathic pain and this drug class is still, together with anticonvulsants, the mainstay of treatment for this type of pain. TCAs have been tested in various peripheral and central neuropathic pain conditions and there are also data on SNRIs, SSRIs and a DNRI for some of the conditions (Sindrup et al. 2005; Finnerup et al. 2010).

Pharmacology of Antidepressants

TCAs have a genuine analgesic effect, since (1) they have analgesic efficacy in experimental pain in humans and animals; (2) relieve neuropathic pain in patients both with and without concomitant depression; and (3) have a more prompt effect at lower doses in pain than in depression (Sindrup et al. 2005). The pharmacological actions of TCAs are numerous (Table 1): inhibition of ▶ presynaptic reuptake of serotonin and noradrenaline, postsynaptic blockade of α-adrenergic and NMDA receptors, and blockade of sodium and possibly also calcium channels (Sindrup et al. 2005). All of these actions have a potential for relief of neuropathic pain, due to the specific mechanisms of this type of pain (Woolf and Mannion 1999) (Fig. 1). However, it is thought that the pain-relieving effect is mainly

Antidepressants in Neuropathic Pain, Table 1 Pharmacological profile of antidepressant drugs tried in neuropathic pain

		TCA		SNRI	DNRI	SSRI
						Fluoxetine
		Amitriptyline	Nortriptyline			
				Venlafaxine		Paroxetine
		Imipramine	Desipramine		Bupropion	
				Duloxetine		Citalopram
		Clomipramine	Maprotiline			
						escitalopram
Reuptake inhibition	Serotonin	+	−/(+)	+	−	+
	Noradrenaline	+	+	+	+	−
	Dopamine	−	−	−	+	−
Receptor Blockade	α-adrenergic	+	+	−	−	−
	H^1-histaminergic	+	+	−	−	−
	Musc. cholinergic	+	+	−	−	−
	NMDA	+	+	−	?	−
Ion channel blockade	Sodium	+	+	−/(+)	?	−/(+)/?
	Calcium	+	+	?	?	?

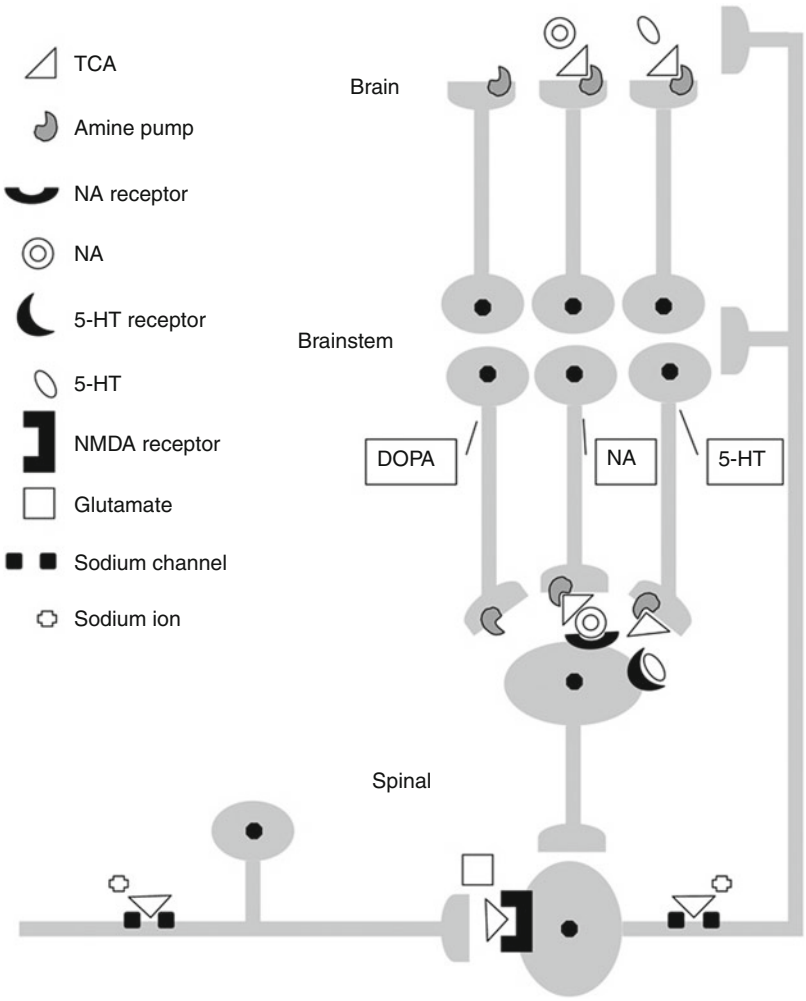
attributed to the TCA action on monoamines and sodium channels. The more selective antidepressants, SNRIs, SSRIs and one DNRI (bupropion), have an effect on the reuptake of amines, apparently without other actions. Therefore, the latter drug classes may only interfere with parts of the neuropathic pain mechanisms (Table 1).

Evidence

Numerous ▶ randomised, ▶ double-blind, placebo-controlled clinical trials have shown that TCAs relieve painful polyneuropathies and post-herpetic neuralgia, and a few trials have indicated that TCAs also have the potential to relieve central post-stroke pain and post-mastectomy pain syndrome (Finnerup et al. 2010). Lack of effect of the TCA amitriptyline in spinal cord injury pain in a single trial may have been caused by insufficient dosing, and a negative outcome in a study on amitriptyline in post-amputation pain could be related to inclusion of a number of patients with minimal pain. Thus, TCAs appear to be effective in central and peripheral neuropathic pain. The SNRIs venlafaxine and duloxetine relieve painful diabetic polyneuropathy, and SSRIs also apparently have a weak effect in this condition (Finnerup et al. 2010). In a study including a mixture of different types of peripheral neuropathic pain, bupropion provided astonishing pain relief (Semenchuk et al. 2001).

Efficacy of Antidepressants in Neuropathic Pain

▶ Numbers needed to treat (NNT) to obtain one patient with more than 50 % pain relief, calculated from pooled data from randomised placebo-controlled trials, is used to give a rough estimate of the efficacy of different antidepressants in peripheral and central neuropathic pain and some of their subcategories (Table 2) (Sindrup et al. 2005; Finnerup et al. 2010). For TCAs, the NNT is 4.0 (CI 2.6–8.5) in central pain and 2.3 (2.1–2.7) in peripheral neuropathic pain, and there are only minor differences between the efficacy of TCAs in different peripheral neuropathic pain conditions. The SNRIs venlafaxine and duloxetine seem to have slightly lower efficacy than TCA in painful polyneuropathy. The SSRIs have been tested in painful diabetic polyneuropathy and appear to have rather low efficacy, with an NNT value of 6.8.



Antidepressants in Neuropathic Pain, Fig. 1 Mechanisms and sites of action of tricyclic antidepressants (*TCA*) in neuropathic pain on peripheral nerves, in the dorsal horn of the spinal cord and at supraspinal levels. *NA* noradrenaline; 5-HT serotonin; *DOPA* dopamine; *NMDA* *N*-methyl-D-aspartate

Antidepressants in Neuropathic Pain, Table 2 Efficacy of antidepressants in neuropathic pain as estimated by Numbers Needed to Treat (NNT) for one patient with more than 50 % pain relief

	NNT	95 % CI	N
Peripheral neuropathic pain			
TCAs	2.3	2.1–2.7	397
Serotonergic and noradrenergic TCAs (Amitriptyline, imipramine, clomipramine)	2.2	1.9–2.6	232
Noradrenergic TCAs (desipramine, nortriptyline, maprotiline)	2.5	2.1–3.3	165
DNRI (bupropion)	1.6	1.3–2.1	41
SNRI (venlafaxine, duloxetine)	5.0	3.9–6.8	435
SSRI (fluoxetine, paroxetine, citalopram, escitalopram)	6.8	3.9–27	122
Central neuropathic pain			
TCAs	4.0	2.6–8.5	59

TCA tricyclic antidepressants, *DNRI* dopamine and noradrenaline reuptake inhibitor, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *N* number of patients exposed to active treatment in the underlying trials

A surprisingly low NNT of 1.6 was calculated for the DNRI bupropion in a group of patients with a range of different etiologies to their neuropathic pain. In general, the efficacy ranking in peripheral neuropathic pain is in line with the supposed mechanism of action of the different antidepressants, i.e., multiple mechanisms for TCAs versus more selective effects of the other antidepressants.

Data on the effects of antidepressants on specific neuropathic pain symptoms are sparse. The TCA imipramine and the SNRI venlafaxine apparently relieve some ▶ spontaneous pain symptoms (constant deep aching pain and lancinating pain), and at least one type of ▶ stimulus-evoked pain (pain on pressure) in painful polyneuropathy (Sindrup et al. 2003). A general effect of TCAs on different pain symptoms has also been reported for amitriptyline and desipramine in postherpetic neuralgia (Kishore-Kumar et al. 1990; Max et al. 1988) and painful diabetic polyneuropathy (Max et al. 1987, 1991).

Dosing of Antidepressants in Neuropathic Pain

TCAs exhibit a large interindividual variability in pharmacokinetics, and concentration-response relations have been found for some of these drugs, e.g., imipramine and amitriptyline (Rasmussen 2004; Sindrup 2005). Thus, standard dosing may cause toxicity in some patients due to the relatively low therapeutic index of TCAs, and leave others at subtherapeutic drug levels. Dosing according to effect and side-effect is not expected to be successful, since side-effects are often present even at subtherapeutic concentrations, and not all patients will obtain a pain-relieving effect at all. Dosing guided by measurements of serum drug concentrations (▶ therapeutic drug monitoring) is suggested to improve therapeutic outcome, i.e., a start dose of 25–50 mg/day and dose adjustment according to a drug level measured after 2–3 weeks on the start dose.

The pharmacokinetics of SNRIs, DNRI and SSRIs show less interindividual variability and the therapeutic index is probably higher. Dosing according to effect and side-effects is therefore feasible. The studies on venlafaxine showed that a dose of 75 mg/day was ineffective, whereas 225 mg/day relieved pain (Rowbotham et al. 2004), and low serum drug levels were associated with non-response (Sindrup et al. 2003). This result fits with the experimental data showing that noradrenaline reuptake inhibition is first present at higher drug concentration, and the noradrenergic effect is expected to be important for the analgesic effect. The data on duloxetine indicate that 60–120 mg/day provides pain relief, whereas 20 mg/day is ineffective (Goldstein et al. 2005).

Side-Effects of Antidepressants in Neuropathic Pain

TCAs cannot be used in patients with cardiac conduction disturbances, cardiac incompensation and epilepsy. Side-effects including dry mouth, sweating, dizziness, orthostatic hypotension, fatigue, constipation and problems with micturition are often bothersome and will lead to discontinuation of TCAs in a number of patients. The SSRIs and SNRI are better tolerated, but drugs from these groups also cause side-effects. The SSRIs may induce nausea, vomiting and dyspepsia, and the same types of side-effects are seen with the SNRIs. Bupropion may cause gastric upset like the SNRIs and like the TCAs dry mouth. The SNRIs may also lead to rising blood pressure.

Drop-outs due to side-effects during clinical trials with antidepressants in neuropathic pain can be used to calculate ▶ Number Needed to Harm (NNH), as the reciprocal value of the difference in drop-out rates on active and placebo treatment, and this provides a rough estimate of tolerability of the drugs. The overall NNHs are 13.6 (9.8–22.5) for TCAs, 19 (8.1–∞) for SSRIs and 13.1 (9.6–21) for SNRIs. The somewhat better tolerability of SSRIs and SNRIs than of TCAs is reflected in these figures. Treatment discontinuation may be more frequent in daily clinical practice than in the setting of a clinical trial.

Discussion and Conclusion

To summarize, TCAs and SNRIs are evidence-based treatments of peripheral neuropathic pain and TCAs appear to be more efficacious than SNRIs. SSRIs relieve peripheral neuropathic

pain with low efficacy, whereas a limited amount of data indicates that the DNRI bupropion could be very effective for this type of pain. TCAs may work for central pain, whereas none of the other antidepressants have been tried for this category of neuropathic pain. Thus, antidepressants are, together with anticonvulsants, first line treatments for peripheral (TCAs and SNRIs) and central (TCAs) neuropathic pain. Our present knowledge does not allow us to predict which patients with neuropathic pain will respond to treatment with antidepressants.

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Antidromic Activation/Invasion

Definition

Eliciting action potentials in the axon of a neuron, which propagate toward the cell body to invade the soma and the dendrites, in an opposite direction to that observed when the neurons are naturally excited (orthodromic direction). The stimulation of an axonal ending triggers a potential that is conveyed in the antidromic direction. The recognition of an antidromic potential on three criteria (latency stability, ability to follow high-frequency stimulation, and observation of collision between orthodromic and antidromic potential) permitted the identification of one projection of a recorded neuron.

Cross-References

- ▶ Corticothalamic and Thalamocortical Interactions
- ▶ Nociceptor, Fatigue
- ▶ Nociceptors in the Orofacial Region (Temporomandibular Joint and Masseter Muscle)
- ▶ Parabrachial Hypothalamic and Amygdaloid Projections
- ▶ Spinohypothalamic Tract, Anatomical Organization, and Response Properties
- ▶ Spinothalamic Neuron

Antidromic Microstimulation Mapping

Definition

Antidromic microstimulation is a technique that can be used to map the locations of the cell bodies of origin of a nervous system pathway. An electrical stimulus is applied through a microelectrode that is inserted into a nervous system region of interest. The stimulus intensity

is kept minimal to prevent stimulus spread. A series of microelectrode tracks are made transversely across a region suspected to contain the cells of origin of the pathway terminating near the stimulating electrode. Recordings are made through this electrode so that antidromically activated neurons can be identified. The stimulating and recording sites are reconstructed after the experiment, often with the assistance of electrolytic lesions or other types of marks made by passing current through the electrodes.

Cross-References

- ▶ Spinothalamic Input: Cells of Origin (Monkey)

Antiepileptic

- ▶ Postoperative Pain, Gabapentin

Antiepileptic Agents

- ▶ Postoperative Pain, Anticonvulsant Medications

Antiepileptic Drugs (Agents)

Definition

Antiepileptic drugs are primarily used in the management of epilepsy.

Cross-References

- ▶ Diabetic Neuropathy, Treatment
- ▶ Postoperative Pain, Anticonvulsant Medications
- ▶ Postoperative Pain, Gabapentin

Antihyperalgesic Effect

Definition

An effect leading to the attenuation of hyperalgesia, usually produced by surgical or pharmacological methods.

Cross-References

- ▶ Muscle Pain Model, Inflammatory Agents-Induced
- ▶ NSAIDs, Mode of Action
- ▶ Opioid Modulation of Nociceptive Afferents in Vivo

Anti-Inflammatories

- ▶ NSAIDs, Survey

Anti-inflammatory Cytokines

Definition

Cytokines involved in negatively regulating the inflammatory response.

Cross-References

- ▶ Cytokines, Regulation in Inflammation

Antinociception

Definition

Attenuation of nociceptive processing in the nervous system, due either to an attenuation of synaptic nociceptive transmission or an increased inhibition of nociceptive transmission.

Cross-References

- ▶ Cell Therapy in the Treatment of Central Pain
- ▶ Cytokines, Effects on Nociceptors
- ▶ Dietary Variables in Neuropathic Pain
- ▶ GABA Mechanisms and Descending Inhibitory Mechanisms
- ▶ Nitrous Oxide Antinociception and Opioid Receptors
- ▶ Opioids in the Spinal Cord and Modulation of Ascending Pathways (N. gracilis)
- ▶ Secondary Somatosensory Cortex (S2) and Insula, Effect on Pain-Related Behavior in Animals and Humans
- ▶ Stimulation-Produced Analgesia
- ▶ Vagal Input and Descending Modulation

Antinociceptive Effects of General Anesthetics

Definition

Nociceptors are inhibited to varying degrees when under anesthesia.

Cross-References

- ▶ Thalamic Nuclei Involved in Pain: Cat and Rat

Antinociceptive Models

Definition

More properly named "experimental pain models." A model might consist of tests performed in animals or in healthy human volunteers. It is useful for testing antinociception when the test-results are indicative of antinociceptive actions, e.g., by drugs. Animal models of experimental pain include the tail flick test, ▶ Hot Plate Test (Assay), hot water tail withdrawal, paw pressure, and others. In all cases, a measured nociceptive stimulus of a thermal, chemical, or pressure nature is applied and the response of the animal or human subject is monitored. The comparison of behavioral reactions under medication and placebo serves as measure of antinociception.

Cross-References

- ▶ Nitrous Oxide Antinociception and Opioid Receptors

Antiphospholipid Syndrome

Definition

Diagnosis with the detection of lupus anticoagulant and IgG-anticardiolipin antibodies; primary or secondary in collagen vascular disease (SLE).

Cross-References

- ▶ Headache Due to Arteritis

Antipyretic Analgesics

- ▶ NSAIDs and Their Indications

Antisense Oligonucleotide

Synonyms

ASO

Definition

A DNA sequence, typically 15–25 nucleotides in length, designed to bind to a complementary sequence on a target RNA molecule. As a result, the protein product coded by that

particular RNA is not synthesized. ASO can be delivered in vitro or in vivo to reversibly inhibit the synthesis of a protein of interest.

Cross-References

- Purine Receptor Targets in the Treatment of Neuropathic Pain

Anxiety

Definition

Anxiety is the subjective feeling of apprehension, dread, or foreboding accompanied by a variety of autonomic signs and symptoms, with or without a stressful situation. The focus of anticipated danger may be internal or external. The state of anxiety places defensive physiological mechanisms in a heightened state, facilitating the fight-flight response in case the threatening event occurs. Anxiety is often distinguished from fear of a concrete danger. Anxiety is more reflective of a threat that is not immediately apparent.

Cross-References

- Amygdala, Pain Processing and Behavior in Animals
- Fear and Pain
- Pain in the Workplace, Risk Factors for Chronicity, and Psychosocial Factors

Anxiety Sensitivity

Definition

Anxiety sensitivity refers to the fear of anxiety symptoms arising from the belief that anxiety has harmful somatic, psychological, and social consequences.

Cross-References

- Fear and Pain

Anxiolysis

- Minimal Sedation

Apamin

Definition

Bee venom blocking the SK type of Ca^{2+}-activated K^+ channels.

Cross-References

- Mechano-insensitive C-Fibers, Biophysics

Apophyseal Joint

- Zygapophyseal Joint

Apoptosis

Synonyms

Programmed cell death

Definition

Apoptosis is a type of cell death in which the cell uses a specialized cellular machinery to kill itself; it is also called programmed cell death. It is a physiological process of the organism to eliminate 'damaged or overaged cells.

Cross-References

- ▶ NSAIDs and Cancer
- ▶ NSAIDs, COX-Independent Actions

Apoptotic Degeneration

Definition

Programmed cell death, which involves a tightly controlled death pathway. It helps avoid tissue inflammation, which usually accompanies cell death through cell damage.

Cross-References

- ▶ GABA and Glycine in Spinal Nociceptive Processing

Application Route

- ▶ Opioid Therapy in Cancer Pain Management, Route of Administration

Appraisal

Definition

The mental act of evaluating the significance of a particular symptom, situation, or outcome, or the assessment of the threat value of a particular symptom or stimulus.

Cross-References

- ▶ Catastrophizing
- ▶ Psychology of Pain, Assessment of Cognitive Variables
- ▶ Stress and Pain

APS

- ▶ Acute Pain Service

APT

- ▶ Acute Pain Team

Arachidonic Acid

Definition

Arachidonic acid is a C_{20} carboxylic acid with four isolated double bonds at positions 5, 8, 11, and 14. This esterified fatty acid is released from phospholipids in cell membranes by the action of phospholipase A_2, activated by pro-inflammatory cytokines. Further enzymatic processing of arachidonic acid results in the production of a range of prostanoids (prostaglandins and thromboxanes). This includes PGE_2 (this has a role in limiting inflammation by inhibiting production of some cytokines such as interleukin-1) and TXA_2 (involved in platelet aggregation and hemostasis). Metabolites are named "eicosanoids" referring to the common structural feature of 20 carbon atoms.

Cross-References

- ▶ Coxibs and Novel Compounds, Chemistry
- ▶ Cyclooxygenases in Biology and Disease
- ▶ NSAIDs, Chemical Structure and Molecular Mode of Action
- ▶ Postoperative Pain, COX-2 Inhibitors

Arachnoid Membrane

Definition

The arachnoid membrane is a delicate, nonvascular membrane that is closely attached to the outermost layer, the dura mater. The epidural space surrounds the dura mater sac.

Cross-References

► Postoperative Pain, Intrathecal Drug Administration

Archispinothalamic Tract

Definition

Part of the paleospinothalamic tract, it is an intersegmental nerve fiber tract that travels for 2–4 segments.

Cross-References

► Parafascicular Nucleus, Pain Modulation

ARDS

Synonyms

Adult respiratory distress syndrome

Definition

ARDS is a severe form of acute lung failure requiring mechanical ventilation.

Cross-References

► Pain Control in Children with Burns

Area Postrema

Definition

One of the circumventricular organs interfacing between the brain and cerebral spinal fluid. Receives nerve fibers from the solitary nucleus, spinal cord, and adjacent areas of the medulla.

Cross-References

► Brainstem Subnucleus Reticularis Dorsalis Neuron

Arousal

Definition

Arousal is both a behavioral and an electroencephalographic response to a variety of strong stimuli, including painful ones. During arousal, there is a heightened level of conscious awareness.

Cross-References

► Spinothalamic Tract Neurons, Descending Control by Brain Stem Neurons

Arterial Spasm

Definition

Arterial constriction, vasospasm.

Cross-References

► Primary Exertional Headache

Arthralgias

Definition

Neuralgic pain in a joint or joints.

Cross-References

- ▶ Animal Models of Inflammatory Bowel Disease

Arthritis

Definition

Arthritis is defined as inflammation of a joint, usually a synovial joint. Arthritis can be acute or chronic. Examples are gout and rheumatoid arthritis. Symptoms of arthritis are swelling, warmth, pain, and loss of function, in particular in arthritis with destructive components. Gout and rheumatoid arthritis are primarily inflammatory diseases which are characterized by synovitis. Gout is usually observed in a single joint, whereas rheumatoid arthritis is a polyarthritis that involves peripheral and proximal joints with a symmetric distribution. An inflammatory component is also typical for many cases of osteoarthritis. The hallmark of osteoarthritis is the progressive destruction and loss of cartilage, but more recently strong inflammatory components are described in osteoarthritis. However, while rheumatoid arthritis is a systematic inflammation, osteoarthritis is usually localized to single joints. Histologically, arthritic joints show an inflammatory cell infiltrate, and the types of infiltrating cells depend on the stage and the type of inflammation. At acute stages the infiltrate consists usually of granulocytes but at the chronic stage monocytes may prevail. Depending on the type of arthritis the bone shows considerable changes. While osteoarthritis is characterized by new bone formation, rheumatoid arthritis is characterized by bone loss near the joint.

Cross-References

- ▶ Arthritis Model, Adjuvant-Induced Arthritis
- ▶ Arthritis Model, Osteoarthritis
- ▶ Nocifensive Behaviors, Muscle and Joint
- ▶ TRPV1, Regulation by Protons

Arthritis Model, Adjuvant-Induced Arthritis

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Synonyms

Adjuvant arthritis; Adjuvant-induced arthritis

Definition

Adjuvant-induced ▶ arthritis is a model of chronic immune-mediated joint inflammation that is induced by injection, usually sub- or intradermally, of a suspension of heat killed *Mycobacterium tuberculosis* (▶ Mycobacterium Species) in oil (▶ Freund's Complete Adjuvant or FCA).

Characteristics

The classical model of adjuvant-induced polyarthritis is induced in rats, using an intradermal injection of mycobacterium tuberculosis suspension in paraffin oil at the tail base. The reaction to adjuvant injection is generally one of systemic illness, with inflammation affecting tarsal, carpal, phalangeal, and spinal joints after 11–16 days (Pearson and Wood 1959). Arthritis is accompanied by lesions of the eyes, ears, nose, skin, and genitals, in addition to anorexia and profound weight loss. The disease follows a relapsing-remitting course after the initial 2 weeks and may persist for several months (Pearson and Wood 1959).

The appearance of the arthritis is very similar to that of rheumatoid arthritis in humans, and for this reason this model has been used as an animal model of rheumatoid arthritis, in studies of both disease mechanisms and in the development of

potential analgesic drugs (Rainsford 1982). Gross lesions in animals with adjuvant arthritis are seen as edematous swellings of multiple joints, particularly the tibiotarsal joints of the hindpaws. As the disease progresses, periarticular swellings develop in the hind limbs and tail. Persistent disease over several months may ultimately result in chronic joint deformation. Microscopic features of adjuvant arthritis are apparent before the gross lesions. As the disease progresses there are signs of joint destruction, with joints showing new bone formation, synovitis, inflammation of the bone marrow, and fibrous and bony ► ankylosis. Joint destruction is thought to be a result of the production of autoantibodies, possibly as a result of cross-reactivity of antibodies against mycobacterial proteins with host proteoglycans (van Eden et al. 1985) in response to the FCA injection.

Behaviorally rats show weight loss, reduced mobility, increased vocalization, and irritability (Pearson and Wood 1959; De Castro Costa et al. 1981). Animals also exhibit signs of chronic pain, such as altered ► nociceptive thresholds and increased self-administration of analgesic drugs (Colpaert et al. 1982). Adjuvant arthritis has also been used as a model of chronic stress as animals show increased corticosterone secretion, loss of diurnal rhythm of secretion, and other parameters of increased physiological stress, such as increased adrenal and splenic weight, and decreased thymic weight (Sarlis et al. 1992).

Although classical adjuvant polyarthritis has been considered to be a good model of rheumatoid arthritis, the original model has been modified by several groups to reduce the severity of the disease and hence the potential suffering of the animals, in line with ethical recommendations on the reduction in the severity of animal models of human disease.

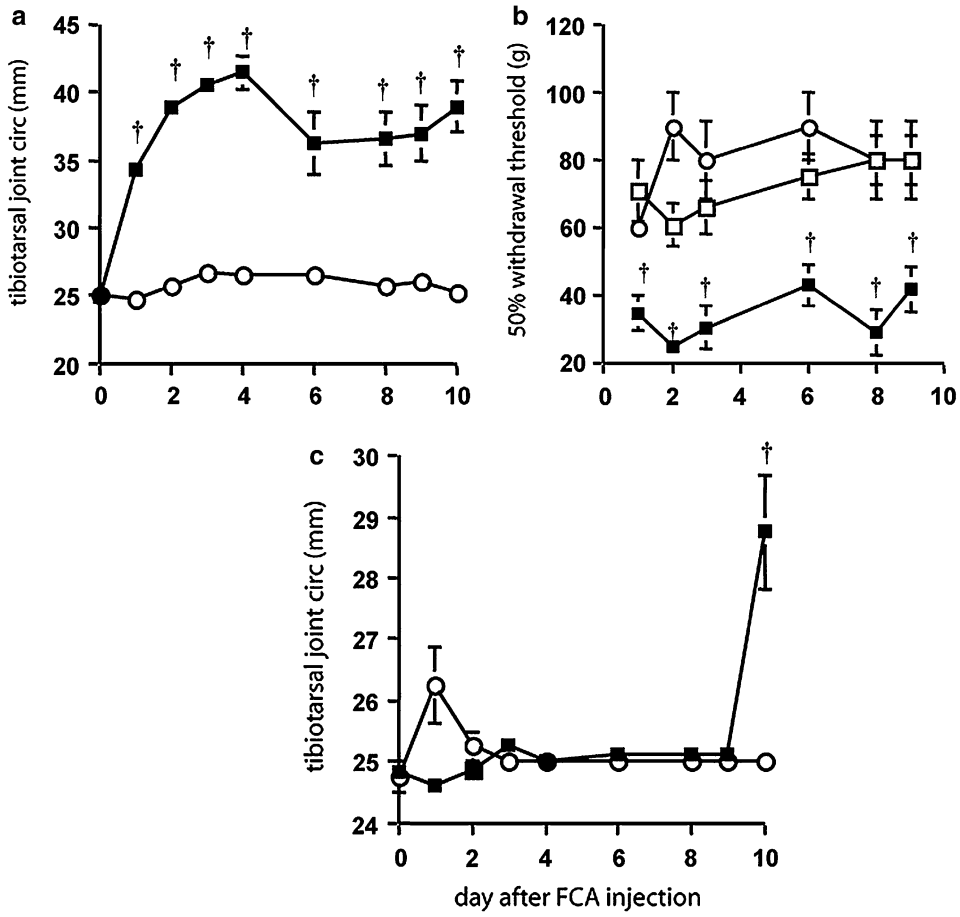
Adjuvant arthritis has been modified by (a) reduction of the amount of mycobacterium injected and (b) the route of injection of the adjuvant. Injection of adjuvant into one footpad has been used to induce a localized arthritis, but this model can result in more widespread inflammation if not carefully controlled. Refinement of classical adjuvant arthritis has led to definition of models of unilateral arthritis that affects only one joint, rather than the polyarthritis seen in the original model. This type of model has several advantages, in that principally it enables study of a limited arthritis without the complications of systemic disease seen in polyarthritis. The advantage of an internal uninflamed control joint contralateral to the arthritic joint was thought to be an added advantage of this model, until the limitations of this approach were identified (see below).

Modified Adjuvant-Induced Arthritis Models

One of the most commonly used refined models of adjuvant arthritis is that in which FCA is injected locally around a joint in which arthritis is to be induced (Donaldson et al. 1993). Intra-articular injection of FCA is also possible and also results in a stable and reliable monoarthritis (Butler et al. 1992), however, when the tibiotarsal joint is used, such intra-articular injection is complicated, as the joint space is small. Intra-articular injection of FCA in larger joints, such as the knee joint, also gives a reliable arthritis.

Injection of FCA into the skin around the tibiotarsal joint results in a reproducible arthritis after 14 days, which is maintained as a unilateral arthritis for at least 60 days postinjection (Donaldson et al. 1993). Gross features of this monoarthritis include tibiotarsal joint swelling, often resulting in a near doubling in the circumference of the joint (Fig. 1a), with cutaneous erythema and occasional breakdown of the skin over the joint. Mobility of the animals and use of the inflamed paw is only slightly altered, and most animals continue to show normal exploratory behaviors, although there is significant mechanical allodynia in the inflamed paw (Fig. 1b). Weight gain of the animals is also normal.

Histologically, the affected joint shows most of the features seen in classical adjuvant arthritis, except for the more severe aspects such as ankylosis. Inflammatory infiltrate into bone marrow, joint space, and synovium is seen, as is synovial hyperplasia and pannus (Fig. 2). There are no obvious changes in the contralateral tibiotarsal

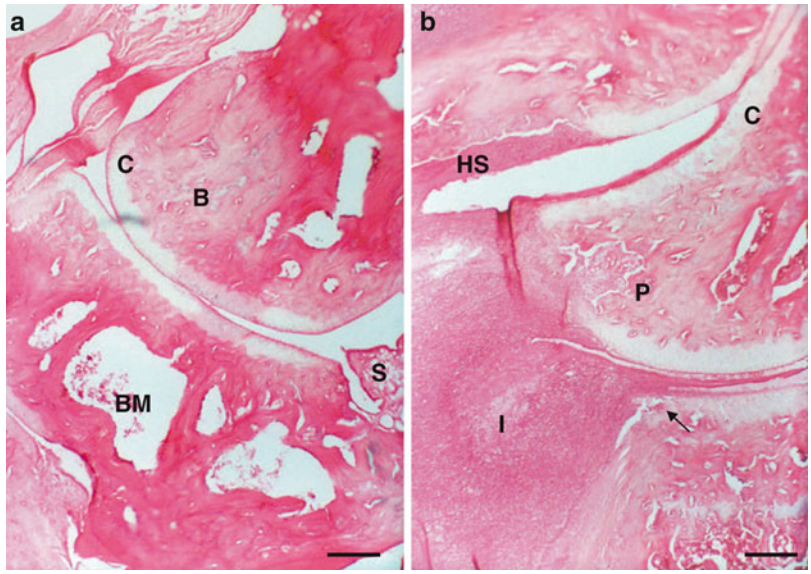


Arthritis Model, Adjuvant-Induced Arthritis, Fig. 1 (**a**) Joint circumferences of rats injected with FCA around one tibiotarsal joint (■ν) or control animals injected with vehicle (○μ). FCA results in a significant increase in joint circumference ($^{\dagger}p < 0.001$) over the 10 days of study. (**b**) Change in 50 % mechanical withdrawal threshold in FCA-induced monoarthritis. Graphs show the withdrawal thresholds in the FCA-injected joint (ν■), the contralateral uninflamed paw (θ□), and in control, uninjected rats (μ○). There is a significant decrease in withdrawal threshold seen in FCA-induced arthritis ($^{\dagger}p < 0.001$). (**c**) Contralateral joint circumferences in rats with FCA-induced monoarthritis. The contralateral joint remains unaffected by arthritis until day 10, when there is a significant increase in joint swelling in FCA-injected (■ν) but not vehicle-injected rats (○μ). Note that the degree of swelling is not as great as in the FCA-injected limb ($^{\dagger}p < 0.001$)

joint, either at the gross or histological level (but see also below).

This modified adjuvant monoarthritis also results in decreased mechanical nociceptive thresholds in the inflamed limb (Fig. 1b), but not in the contralateral limb, and thus this model has been used in studies of chronic pain. Not surprisingly, in an animal in chronic discomfort, rats do exhibit some signs of stress, but these are extremely mild and only include a loss of diurnal variation in corticosterone secretion with no effect on other parameters associated with chronic hypothalamic-pituitary-adrenal axis activation (Donaldson et al. 1994).

Thus, a modified adjuvant monoarthritis is a commonly used alternative to the classical adjuvant polyarthritis. Monoarthritis has similar features to polyarthritis and models rheumatoid arthritis well, but with fewer confounding features.



Arthritis Model, Adjuvant-Induced Arthritis, Fig. 2 Histological appearance of FCA-induced monoarthritis and control joint. (**a**) Photomicrograph of the right (uninjected) tibiotarsal joint showing normal cartilage (*C*), subchondral bone (*B*), and synovium (*S*). Bone marrow spaces (*BM*) can also be seen. (**b**) Photomicrograph of the left injected tibiotarsal joint showing hyperplastic synovium (*HS*) and inflammatory infiltrate in the joint (*I*). There is early cartilage and subchondral bone destruction evident (*arrow*) with more advanced pannus seen invading subchondral bone (*P*). Scale bars = 100 μm

Neurogenic Inflammation in Adjuvant Arthritis

The injection of FCA into the tail base of rats results in arthritis that affects multiple joints. The spread of arthritis is not due to a spread of mycobacterium from the site of injection to the joints, but rather to an activation of the immune system resulting in a systemic delayed hypersensitivity reaction. Whole body irradiation and ablation of active T lymphocytes delays the onset of adjuvant polyarthritis (Wakesman et al. 1960), but does not abolish it completely.

However, it has been hypothesized that immune activation alone cannot explain the precise symmetry often seen in both clinical and experimental arthritis. Damage to the peripheral nervous system in adjuvant polyarthritis can result in the sparing of specific joints, implying that the development of arthritis in this model is dependent on an interaction between an intact nervous system and the immune system (Donaldson et al. 1995). This suggests that the involvement of multiple joints in the tail base model is not purely an immune-mediated effect, but that ▶ neurogenic inflammation is involved in arthritis. The precise nervous pathway through which signals are transmitted, which results in the spread of arthritis from one joint to another, is not yet known. It is, however, known that in addition to the peripheral nerves being integral to this effect (Donaldson et al. 1995), spinal mechanisms are also important as damage to the appropriate spinal cord segment will also stop contralateral joint damage (Decaris et al. 1999).

In modified models of adjuvant arthritis, local injection of FCA around the joint can also result in neurogenic spread of arthritis to the contralateral tibiotarsal joint after 10–14 days (Fig. 1c). This effect is dependent on the amount of adjuvant injected, that is, greater amounts of adjuvant result in a more distant spread of disease (Donaldson et al. 1993). For this reason, the use of the contralateral limb/joint as an internal control is often inappropriate in monoarthritic models, as there may be covert arthritis in the

contralateral joint that may affect behavioral (pain behaviors) or physiological parameters (neuronal activity).

Adjuvant Arthritis in Other Experimental Animals

FCA is used as an immunological adjuvant in other species to enhance autoimmune reactions to co-injected antigens, such as in ovalbumin-induced arthritis in rabbits (Pettipher and Henderson 1988), where cell-mediated immunity is required for full development of the disease. Adjuvant polyarthritis or monoarthritis has been very difficult to induce in species other than the rat using FCA alone, rather than as an adjuvant for immunization. Guinea pigs form granulomas at the site of adjuvant injection and do not develop polyarthritis, but do develop a monoarthritis when FCA is injected into the hindpaw (Hood et al. 2001).

The mouse is a species in which it has been notoriously difficult to induce adjuvant arthritis. There are very few reports of adjuvant arthritis in mice, and those that have attempted to induce arthritis in this species have had limited success. Tail base injection of FCA does not induce widespread arthritis in mice (Larson et al. 1986), and local FCA injection in mice does not reliably induce arthritis in all animals (Ratkay et al. 1994). In addition, altered nociception in adjuvant inflammation in mice is also inconsistent (Larson et al. 1986). Recent work has, however, defined an adjuvant arthritis model in mice that is reliable both in terms of the consistent induction of arthritis in all animals and in which all animals exhibit thermal hyperalgesia and mechanical allodynia similar to that seen in rats (Chillingworth and Donaldson 2003; Gauldie et al. 2004). In adjuvant arthritis in mice, thermal hyperalgesia and mechanical allodynia develop very rapidly (within 24 h) and are maintained for at least 15 days (Chillingworth and Donaldson 2003; Gauldie et al. 2004). This model requires the use of very much higher concentrations of FCA than those usually used to induce monoarthritis in rats (25 $mgkg^{-1}$ in mice vs. 0.6 $mgkg^{-1}$ in rats). Probably as a result of the relative resistance of mice to immune stimulation by FCA, arthritis remains unilateral in mice for at least 20 days, despite the much higher concentration of FCA used, with no apparent signs of contralateral inflammation. The reasons for this apparent resistance in mice and other species to the arthritic effects of FCA are unknown, but it is probably attributable to differences in the immune reactions to the mycobacterium antigens (Audibert and Chedid 1976).

Thus, a reliable model of adjuvant arthritis now also exists in mice that can be used for similar purposes as that in rats, but can also be used to extend studies on disease progression and modification to include the use of genetically modified mice.

Adjuvant polyarthritis is still used as a model of rheumatoid arthritis, but has confounding features such as poor animal health. Modifications of adjuvant polyarthritis to limit the disease to a single joint have improved this model, from both the animal welfare perspective and in the ease of data interpretation. This model is now established in both rats and mice, allowing study of arthritis and inflammatory nociception in the two most commonly used experimental species.

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Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee)

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Synonyms

Acute experimental monoarthritis; Acute experimental synovitis; Acute knee joint inflammation; Kaolin-Carrageenan-induced arthritis; K/C arthritis

Definition

Aseptic inflammatory monoarthritis induced by injections of kaolin and carrageenan into the synovial cavity of one knee joint results in damage to the cartilage, inflammation of the synovia and synovial fluid exudates, as well as pain behavior and neuroplastic changes in the peripheral and central nervous system.

Characteristics

The K/C arthritis is a well-established model of an acute onset monoarthritis resembling osteoarthritis, which is characterized by degeneration of hyaline articular cartilage and subsequent inflammation and pain. The K/C arthritis model has been used in cats (Coggeshall et al. 1983; Schaible and Grubb 1993), monkeys (Dougherty et al. 1992), rats (Neugebauer et al. 1993;

Sluka and Westlund 1993), mice (Zhang et al. 2001; Gatta et al. 2012), and guinea pigs (Gomis et al. 2007) to study pain mechanisms in the peripheral and central nervous systems. The K/C arthritis model produces inflammation, behavioral changes, and ▶ neuroplasticity with a distinct time-course of acute onset (1–3 h) and plateau phase (after 5–6 h) that persists for at least 1 week (Neugebauer et al. 2007).

Induction of Arthritis

This experimental arthritis is induced in one knee by intra-articular injections of kaolin and carrageenan into the knee joint. The inorganic kaolin (bolus alba, "China clay"), which is hydrated aluminum silicate ($H_2Al_2Si_2O_8.H_2O$) (Merck 13, 5300), is used to inflict mechanical damage to the cartilage as in osteoarthritis and, as an adjuvant, to increase the effectiveness of the active inflammatory compound carrageenan. Lambda carrageenan type IV (name derived from the Irish coastal town of Carragheen) is a mixture of sulfated polysaccharides extracted from the red seaweed *Gigartina* (Merck 13, 1878). Although subcutaneous, intramuscular, and intra-articular injections of each compound alone can produce inflammation, the combination of kaolin and carrageenan results in a more robust and longer lasting inflammation with a more constant and highly reproducible time-course. Several experimental protocols exist for the induction of the K/C arthritis in different species.

Monkey

0.5 ml of a solution containing 5 % carrageenan plus 5 % kaolin is injected into the knee joint cavity through the lateral aspect of the leg. The knee joint is then repeatedly flexed and extended for 15 min (Dougherty et al. 1992).

Cat

0.4–0.5 ml of a 4 % kaolin suspension is injected into the synovial cavity through the lateral aspect of the knee joint. After alternating flexions and extensions of the knee for 15 min, 0.3 ml of a 2 % carrageenan solution is injected intra-articularly, and the knee is flexed and extended for 5 min. The movements facilitate the damage to the cartilage and the development of inflammation (Coggeshall et al. 1983; Schaible and Grubb 1993).

Rat

Kaolin and carrageenan are injected either sequentially or together according to the following protocols: (1) 80–100 µl of a 4 % kaolin suspension is injected into the joint cavity through the patellar ligament. After repetitive flexions and extensions of the knee for 15 min, a carrageenan solution (2 %, 80–100 µl) is injected into the knee joint cavity and the leg is flexed and extended for another 5 min (Neugebauer et al. 1993). (2) 100 µl of a solution of 3 % kaolin and 3 % carrageenan is injected into the knee joint cavity, and the knee joint is flexed and extended for 1 min (14) or 5–10 min (Sluka and Westlund 1993), 50 µl of a mixture of 3 % kaolin and 3 % carrageenan is injected into one knee joint.

Mouse

As in the rat, two protocols are used: (1) 40 µl of a 4 % kaolin suspension is injected into the articular cavity through the patellar ligament. After flexing and extending the joint for 15 min, 40 µl of a carrageenan solution (2 %) is injected and the leg is moved for another 5 min (Gatta et al. 2012). (2) A mixture of kaolin (3 %) and carrageenan (3 %) in 50 µl of saline is injected into the knee through the patellar ligament (Zhang et al. 2001).

Histopathology

Intra-articular injections of kaolin and carrageenan cause a unilateral aseptic inflammation with the following characteristics: swelling of the knee joint (measured as increased circumference of the knee), increased intra-articular pressure, hyperthermia of the knee, and edema with marked cellular infiltration (polymorphonuclear leucocytes) (Schaible and Grubb 1993; Schaible et al. 2002; Sluka and Westlund 1993).

Pain Behavior

The K/C arthritis model is accompanied by spontaneous pain behavior in awake freely moving animals, including limping, guarding of the leg with the arthritic knee, avoidance of joint movements, decreased weight bearing on the leg with the arthritic knee, and reduced exploratory behavior

(Neugebauer et al. 2003; Schaible and Grubb 1993; Sluka and Westlund 1993). Awake arthritic animals also show increased evoked pain behavior (Neugebauer et al. 2003; Schaible et al. 2002; Sluka 1996; Sluka and Westlund 1993; Urban et al. 1999; Yang et al. 1996; Yu et al. 2002; Zhang et al. 2001): primary mechanical ► allodynia (reduced vocalization threshold to mechanical stimulation of the arthritic knee); secondary allodynia and ► hyperalgesia (reduced paw withdrawal threshold and latency, respectively) for mechanical and thermal stimuli applied to the hindpaw. Frequency and total duration of vocalizations in the audible and ultrasonic ranges are increased (Neugebauer et al. 2007). Arthritic animals also show increased anxiety-like behavior in the elevated plus maze test (Neugebauer et al. 2007).

Neurochemical Changes

Inflammatory mediators, neuropeptides, and excitatory amino acids accumulate in the inflamed tissue of the knee and the synovial fluid (Lawand et al. 2000; Schaible and Grubb 1993; Schaible et al. 2002). Sources include immune cells, inflammatory cells, serum (plasma extravasation), and articular nerve fibers (neurogenic component). These substances play an important role in the "► peripheral sensitization" of articular afferent nerve fibers (see below and Fig. 1), which results in the enhanced production and release of various neurotransmitters (amino acids) and neuromodulators (peptides) into the spinal cord. Changes and mechanisms in the K/C arthritis pain model are listed below:

Inflammation

- Edema (increased knee joint circumference ipsilateral but not contralateral)
- Increased intra-articular pressure
- Increased temperature of arthritic (but not contralateral) knee
- Cellular infiltration (neutrophils)

Pain Behavior

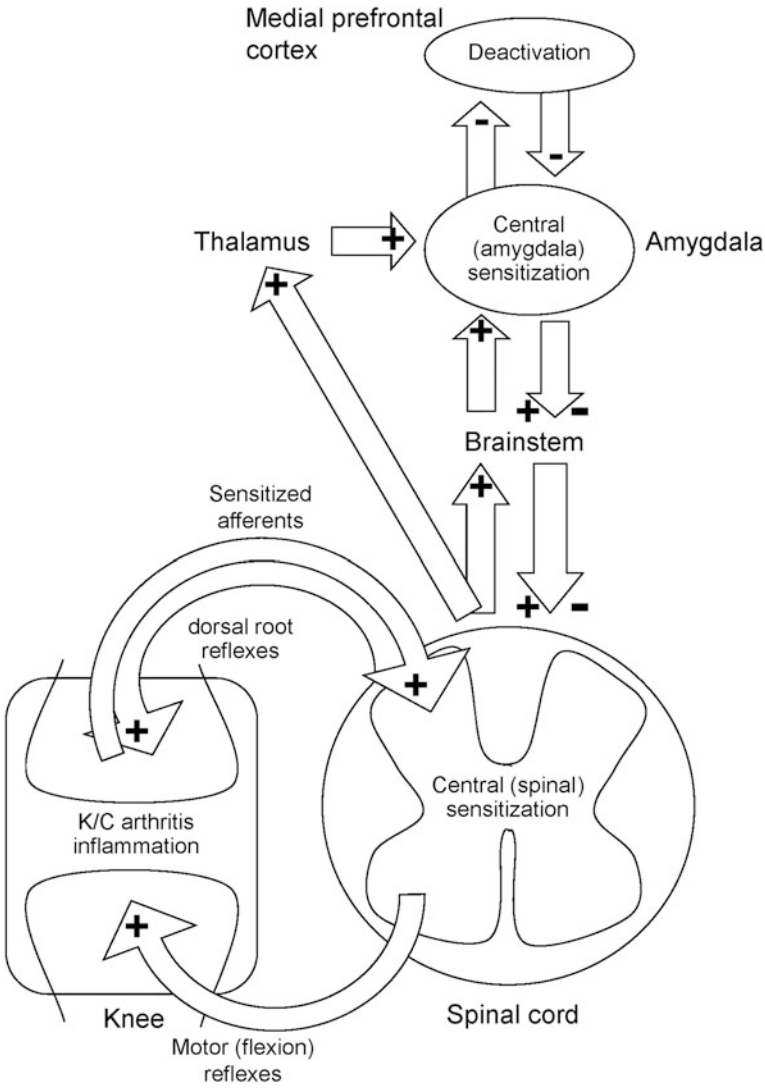
- Spontaneous pain behavior
- Primary allodynia (mechanical)
- Secondary hyperalgesia (mechanical and thermal)
- Secondary allodynia (mechanical and thermal)

Neurochemistry

- Periphery
  - Prostaglandins (PGE2, PGI2)
  - Bradykinin
  - Leukotrienes
  - Histamine
  - Serotonin
  - Excitatory amino acids (EAA; glutamate but not aspartate)
  - Nitric oxide (NO) metabolites (arginine, citrulline)
  - Substance P
  - Calcitonin gene–related peptide (CGRP)
  - Galanin
  - NPY
  - Somatostatin (SST)
- Spinal Cord
  - EAA (Glutamate, glutamine, aspartate)
  - NO metabolites (citrulline)
  - Substance P
  - NKA
  - Calcitonin gene–related peptide (CGRP)
  - Prostaglandins (PGE2)
  - Endocannabinoid COX-2 metabolites (prostamide $F_{2\alpha}$ $PMF_{2\alpha}$)

Electrophysiology

- Periphery
  - Sensitization of groups II, III, and IV (Aβ, Aδ, and C) articular afferent nerve fibers, including silent nociceptors
  - Dorsal root reflexes in groups II, III, and IV (Aβ, Aδ, and C) articular afferent fibers
- Spinal Cord
  - Sensitization of spinal neurons in the superficial and deep dorsal horn and in the ventral horn (nociceptive-specific, wide-dynamic-range, inhibited, nonresponsive types)
- Brainstem/Brain
  - Increased descending inhibition and facilitation
  - Sensitization of neurons in the amygdala (multireceptive neurons in the basolateral and central nuclei but not nociceptive-specific neurons in the central nucleus)
  - Decreased responsiveness of neurons in the infra- and pre-limbic regions of the medial prefrontal cortex (mPFC)



Arthritis Model, Kaolin-Carrageenan-Induced Arthritis (Knee),

Fig. 1 Peripheral and central pain mechanisms in the K/C arthritis model. Knee joint inflammation causes sensitization of articular afferent nerve fibers, which results in enhanced input to the spinal cord, dorsal root reflexes back to the arthritic knee, increased flexion reflexes, and central sensitization of spinal neurons. Sensitized spinal neurons send their enhanced signals through pain pathways to the brainstem and brain to cause central sensitization of amygdala neurons and deactivation of medial prefrontal cortical pyramidal cells (plasticity in other brain areas remains to be determined in the K/C model). The amygdala can modulate pain behavior by activating or inhibiting descending facilitation or descending inhibition

Pharmacology

- Periphery
  Excitatory: NMDA receptor, Non-NMDA receptor, Neurokinin 1 (NK1) receptor, Neurokinin 2 (NK2) receptor, NO/NOS
  Inhibitory: Galanin receptor, Opioid receptors (mu, kappa, ORL1), Somatostatin receptor
- Spinal Cord
  Excitatory: NMDA receptor, Non-NMDA receptor, Metabotropic glutamate receptor (mGluR) group I, Neurokinin 1 (NK1) receptor, Neurokinin 2 (NK2) receptor, Calcitonin gene–related peptide (CGRP1) receptor, Calcium channels (L-, N-, P-type), Prostaglandins (PGE_2), Prostamide $F_{2\alpha}$ ($PMF_{2\alpha}$), Nicotinic cholinergic receptor
  Inhibitory: $GABA_A$ (but not $GABA_B$) receptor, Cannabinoid CB-1 receptor
- Amygdala
  Excitatory: NMDA receptor, non-NMDA receptor, Metabotropic glutamate receptor (mGluR) group I, Corticotropin-releasing factor (CRF), Calcitonin gene–related peptide (CGRP)
  Inhibitory: Metabotropic glutamate receptor (mGluR) groups II and III

Peripheral Sensitization

Physical (increased intra-articular pressure; increased temperature) and chemical (low pH, inflammatory mediators, peptides, and amino acids) factors lead to the enhanced excitability and responsiveness (i.e., sensitization) of articular afferent nerve fibers to mechanical and chemical stimuli. Some low-threshold non-nociceptive articular afferents (groups II and III or Aβ and Aδ fibers, respectively) show enhanced responses to mechanical compression and movements of the knee joint. Numerous high-threshold nociceptive groups III and IV (Aδ and C fibers, respectively) become activated by a normally Innocuous Input/Stimulus – compression – and movements of the knee joint. Importantly, initially mechano-insensitive articular afferent fibers (► Silent Nociceptors) become responsive to mechanical stimulation of the knee joint (Schaible and Grubb 1993; Schaible et al. 2002). A variety of pharmacological receptor blockers or agonists can prevent or reduce the sensitization (see above list), which is believed to contribute to primary allodynia/hyperalgesia. The enhanced afferent inflow into the spinal cord, as a consequence of the peripheral sensitization, causes enhanced activation of spinal dorsal horn circuitry (Dougherty et al. 1992; Neugebauer et al. 2003) and excess primary afferent depolarization in the dorsal horn, leading to ► dorsal root reflexes in articular afferents. As a positive feedback loop, signals would travel back out to the periphery; release substances in the knee joint, and contribute to the inflammation (Sluka et al. 1995). Importantly, the sympathetic nervous system does not seem to contribute to the inflammatory, behavioral, and peripheral electrophysiological changes in the K/C arthritis pain model (Schaible and Grubb 1993; Schaible et al. 2002; Sluka 1996).

Central Sensitization

Enhanced incoming signals in articular afferents from the arthritic knee result in the intraspinal release of various substances (transmitters, modulators), and trigger the development of neuroplastic changes of spinal neurons (Dougherty et al. 1992; Neugebauer et al. 1993). The responses of ► wide-dynamic-range neurons to innocuous and noxious compression (see ► noxious stimulus) of the arthritic joint increase gradually. The threshold of ► nociceptive-specific neurons is lowered, such that they are activated by normally innocuous stimuli. Typically, the receptive fields of these neurons expand, and their responses to stimulation of non-inflamed tissue remote from the arthritic knee also increase; both are considered evidence of central sensitization (i.e., spinal pain mechanisms that are not simply a reflection of the peripheral sensitization; Schaible and Grubb 1993; Schaible et al. 2002; Sluka 1996). Central sensitization is generated and maintained through a variety of neurotransmitters, modulators, and their receptors (see above list) at pre- and post-synaptic sites in the spinal cord, but the signal transduction pathways involved are largely unknown in the K/C arthritis model. The excitability of spinal neurons is not only regulated by peripheral mechanisms but also through tonic descending inhibitory and excitatory supraspinal controls, which exert enhanced effects on spinal neurons in the K/C arthritis model (Schaible and Grubb 1993; Urban et al. 1999). Among the spinal neurons that become sensitized in the arthritis state are those that send their axons to various brain areas including the thalamus (spinothalamic tract cells) (Dougherty et al. 1992). K/C arthritis pain-related changes in the brain have only been studied in the ► amygdala, a temporal lobe structure, which as part of the ► limbic system plays a key role in emotionality and negative affective states, and is believed to be a neural substrate of the reciprocal relationship between emotion and pain. Two major subpopulations of neurons in the latero-capsular part of the central nucleus of the amygdala ("nociceptive amygdala") develop nociceptive plasticity in the K/C arthritis pain model: multireceptive neurons (comparable to spinal wide-dynamic-range neurons) and nonresponsive neurons without a receptive field, but not nociceptive-specific neurons (Neugebauer and Li 2003). Synaptic transmission and neuronal excitability are enhanced in amygdala neurons in brain slices from rats with K/C arthritis, suggesting that plasticity in the

amygdala can be maintained independently of afferent input from the arthritic knee (Neugebauer et al. 2003). Both purely nociceptive inputs from the spino-parabrachio-amygdaloid pain pathway, and highly integrated polymodal inputs from the fear/anxiety-circuitry in the lateral and basolateral amygdala are required to produce these plastic changes, which is consistent with a role of the amygdala as the interface between pain and affect (Neugebauer and Li 2003; Neugebauer et al. 2003). Multireceptive neurons in the basolateral amygdala also show central sensitization and synaptic plasticity (Ji et al. 2010). Enhanced nociceptive processing and increased neuronal excitability in the amygdala in the K/C arthritis model critically depend on the upregulation of presynaptic G-protein-coupled metabotropic glutamate receptors of the mGluR1 subtype, activation of postsynaptic corticotropin-releasing factor CRF1 receptors, and enhanced function of postsynaptic N-methyl-D-aspartate (NMDA) receptors through protein kinase A (PKA)-dependent phosphorylation. The amygdala is closely interconnected with other forebrain structures and brainstem centers known to be part of the endogenous pain control system. In contrast to amygdala hyperactivity, pyramidal neurons in the infra- and pre-limbic regions of the medial prefrontal cortex (mPFC) show decreased background and evoked activity in the K/C model, which may contribute to cognitive decision-making deficits (Ji et al. 2010). Pain-related plasticity in other brain areas remains to be determined in the K/C arthritis model.

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Arthritis Model, Osteoarthritis

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Synonyms

Arthritis; Degenerative joint disease; Osteoarthritis; Osteoarthritis model

Definition

Osteoarthritis is a condition in which physical or biological damage to the cartilage of ▶ synovial joints leads to destruction of the ▶ cartilage and remodeling of the bone underneath the affected cartilage.

Introduction

Osteoarthritis (OA) is a progressive disease of the joints characterized by the loss of articular cartilage, damage to subchondral bone, and joint space narrowing. According to the Centers for Disease Control, the prevalence of OA in the United States is estimated to be almost 14 % in adults age 25 and older and greater than 33 % in adults over the age of 65. However, it has also been estimated that 80–90 % of adults 65 and older have evidence of OA. Age is the greatest risk factor for the development of OA, and as the population over the age of 65 is rising dramatically, the prevalence of the disease is likewise expected to increase (Elders 2000; Hinton et al. 2002).

OA is frequently associated with severe pain, but the source of this pain is not fully understood. A clue to understanding the source of OA-related pain may well be found in the pathology associated with the condition. This pathology is characterized by damage to the cartilage in synovial joints, alterations in the physiology of chondrocytes, and profound changes in the subchondral bone including sclerosis, cyst formation, and the development of osteophytes or bony spurs beneath the affected cartilage (Bendele and Hulman 1988). Over time, these changes lead to radiologic evidence for the presence of OA, and in fact, this is the primary method for diagnosis of OA in humans. OA tends to be most common in specific joints, namely, the knees, hips, small joints of the hands, and the cervical and lumbar spine (Cushnaghan et al. 1990).

Current treatment for OA-related pain can be divided into three categories: physical/occupational therapy, pharmacological treatment, and surgical intervention. Physical therapy can maintain muscle strength around the joint and provide a benefit by increasing joint stability (Altma et al. 2000). Therapeutic intervention is most commonly achieved by using nonsteroidal anti-inflammatory drugs (NSAIDs). Although these drugs have been shown clinically to provide pain relief in OA patients, this pain relief is often incomplete, and their use is often accompanied by unwanted side effects including the induction of ulcers (Altma et al. 2000; Scheiman 2003; Marnett 2009). The use of cyclooxygenase-2 selective inhibitors such as celecoxib has mitigated the frequency of GI-related adverse events, but these therapies have been under scrutiny for concerns related to cardiovascular events. Other pharmacological therapies include injections of steroids or high molecular weight hyaluronate into the affected joints. Finally, the incidence of surgical intervention has grown rapidly over the past 30 years but is typically considered when the pain associated with the OA has become intractable. As such, the need for safer and more effective analgesics for the treatment of OA-related pain represents an area of significant research need.

The necessity to discover new therapeutics for the treatment of OA-related pain logically requires the development of animal models of OA that are more refined in terms of the pathology and/or the etiology of the disease as seen in the clinical population. To this end, three main approaches have been pursued: genetic models, surgical models, and chemical models (Moskowitz et al. 1979; Sandy et al. 1984; Ameye and Young 2006).

Spontaneous models of OA include the Dunkin Hartley guinea pig model of OA, in which animals show mild degeneration of articular cartilage beginning at approximately 3 months of age that continues to progress as the animals age (McDougall et al. 2009). Strains of mice have also been reported to show evidence of OA with age (Rostand et al. 1986). Surgical models of OA typically involve damage to the meniscus, often via a partial meniscectomy, and may also involve transection of the anterior cruciate ligament (van der Kraan et al. 1989; Fernihough et al. 2004). Chemical models of OA involve intra-articular injection of substances such as papain or monosodium iodoacetate (MIA) that are known to disrupt chondrocyte metabolism and hence promote joint degeneration (Guingamp et al. 1997; Guzman et al. 2003).

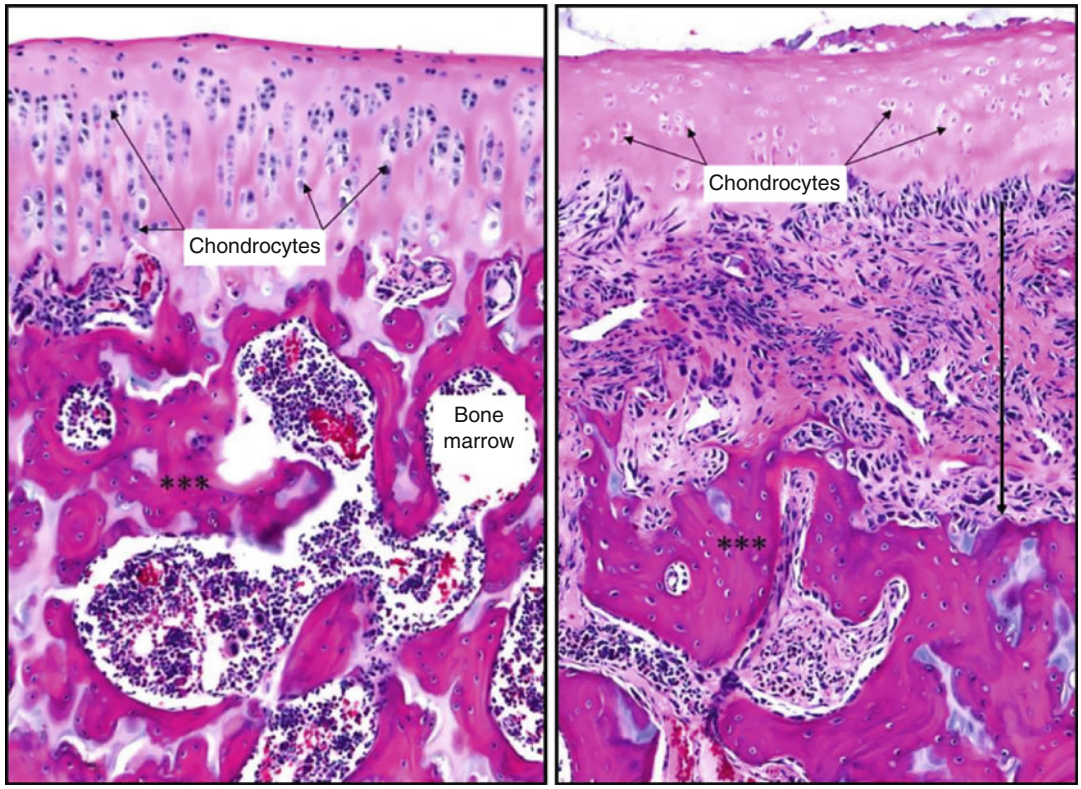
The vast majority of the initial studies using any of these models primarily investigated the pathological characteristics of the models, but little or no attention was given to investigating the pain behavior associated with the models. That changed when Guingamp and colleagues (1997) used biotelemetry to examine the effects of intra-articular injection of MIA on spontaneous mobility. In that study, they found a strong, positive correlation of the amount of MIA injected, the resultant pathological changes in the affected knee joints, and decreased mobility. Although these data indicated that MIA-induced OA produces pain-related behaviors in rodents, it had not been demonstrated whether these behavioral changes could be reversed with administration of analgesics. Furthermore, the use of biotelemetry limited the number of laboratories that were capable of performing this assay. The next significant advance in the establishment of the MIA model came from studies involving the use of hind limb weight bearing both as a measure of the pain due to MIA injection as well as the effect of various analgesic compounds on these altered.

These advances in the ability to assess pain-related behaviors in the various animal models of OA led to significant effort related to discerning which model would be the model of choice for the study of novel analgesics. Early comparative studies between chemical and surgical models of OA as well as the various chemical models of OA indicated that the MIA model of OA was preferable as it showed appropriate, chronic pathology and was both highly reproducible and feasible across laboratories (Fernihough et al. 2004; Pomonis et al. 2005). This remainder of this chapter will focus on the MIA model of OA in rats. It is important to note that it is best to consider this model as a model for OA-related pain, as it is well suited for the study of potential therapies for the treatment of this pain. However, its suitability for assessing potential disease modifying therapies may be lessened due to the nature and onset of the pathology.

Characteristics

Induction of OA using MIA is a relatively simple process involving a single injection of MIA solution into the articular space of one knee joint (Marker and Pomonis 2012). The amount of MIA injected may vary, but most frequently ranges from 1 mg to 3 mg in a 25–50 μL volume. The injection is most often unilateral, but bilateral injections have also been used. MIA is a metabolic inhibitor that blocks the activity of glyceraldehyde-3-phosphate dehydrogenase, preventing glycolysis. As such, this inhibition ultimately leads to the death of the cells that are exposed to the MIA. When injected into a joint space, MIA preferentially acts on chondrocytes, causing damage to the cartilage of the joint.

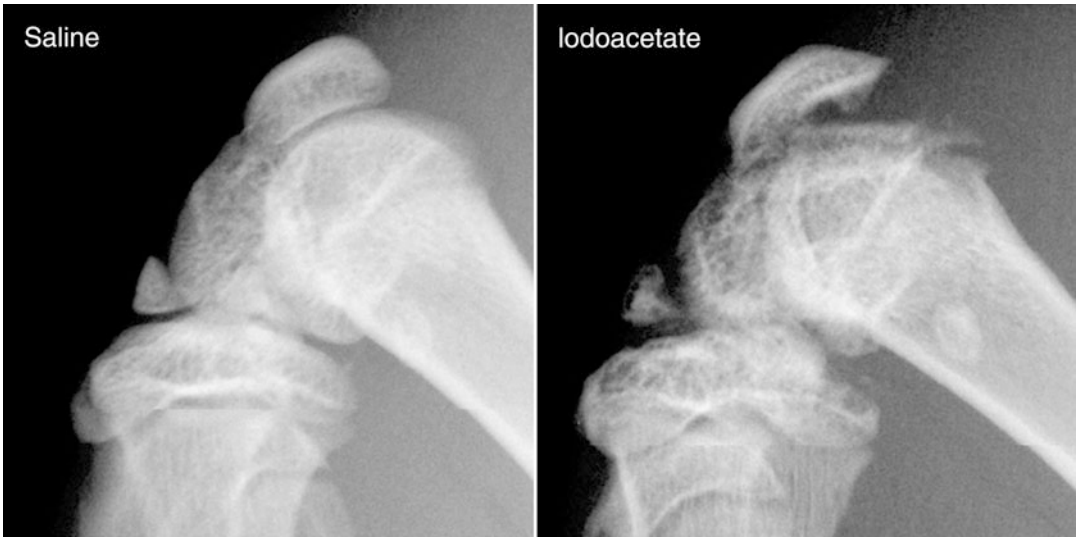
Following the MIA injection, there is a time-dependent, biphasic response that is observed both in terms of the cellular effects



Arthritis Model, Osteoarthritis, Fig. 1 Hematoxylin and eosin stained sections of normal and osteoarthritic knee joint of the rat. Shown are the articular surface and subchondral bone regions of femoral condyles after saline injection (*left*) or MIA injection (*right*). Necrotic chondrocytes are shrunken in their lacunae and a dense fibrous matrix fills the area where bone spicules have degenerated and lost their continuity with the articular surface (*double headed arrow*). The bone marrow is severely damaged in this region

and the resultant behaviors displayed by the animals. Initially, there is an acute inflammatory response that peaks approximately 3 days after MIA injection and resolves within 7 days of the injection. While pain-related behaviors are present during this early phase, they are unlikely to represent pain associated with OA per se, as there is little or no pathology observed indicating that the behaviors observed during the first 7 days are a result of any OA-like condition. While there is noticeable edema and infiltration of various inflammatory cells, the articular cartilage is still relatively intact and the subchondral bone does not begin to show effects of the MIA injection until day 7 post-injection or later (Guzman et al. 2003).

However, by 14 days after MIA injection, certain key pathologies are observed that are consistent with the presence of OA in these animals including changes to the subchondral bone, often manifest as replacement of bone marrow with spindle cells, particularly beneath damaged cartilage (Fig. 1). It is at this time that radiographic evidence of OA becomes visible before becoming extremely pronounced in the following weeks (Fig. 2). The changes to the subchondral bone progress with time and extensive bone remodeling can be observed. These changes in the subchondral bone may play a very significant role in the development and maintenance of OA-related pain, as subchondral bone and bone marrow represent a likely source for the mechanistic drivers of this pain. Cartilage, the tissue that is most profoundly affected in OA, is not innervated. However, cortical and subchondral bone are innervated by sensory as

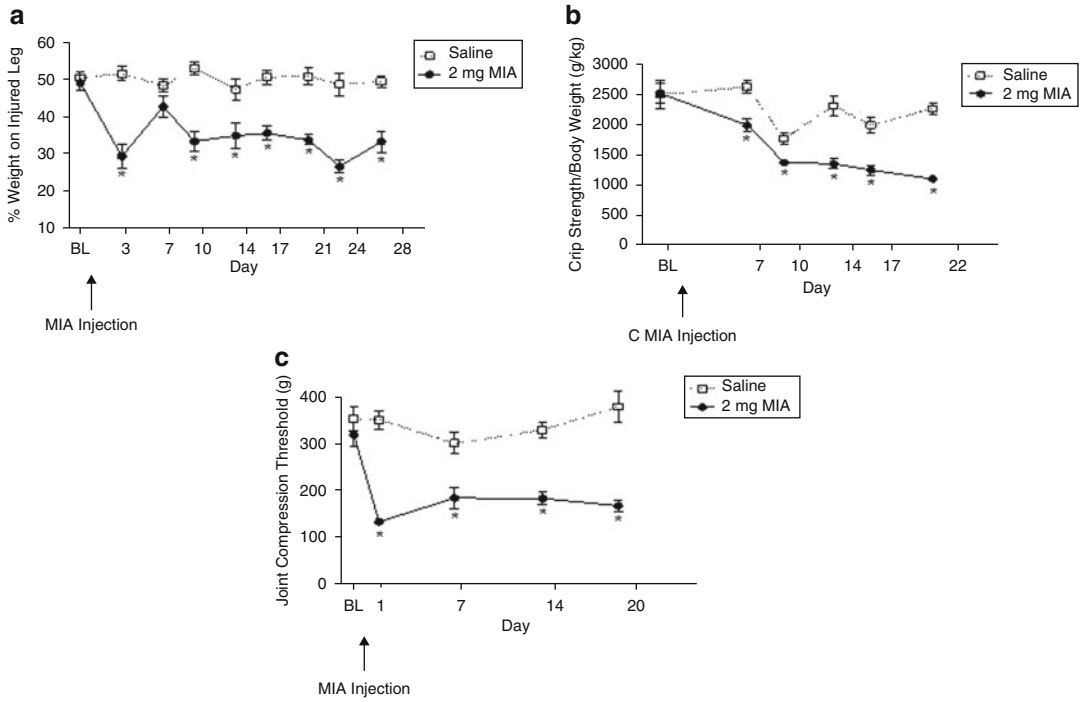


Arthritis Model, Osteoarthritis, Fig. 2 Radiograph showing the effect of iodoacetate on the bones of the rat knee joint. Injection of 3 mg iodoacetate (*right panel*) leads to profound deformation of the bones relative to saline-injected control of the knee joint (*left panel*). These changes are present as rough edges of the bone, apparent loss of bone density, and displacement of the patella (kneecap), indicating joint swelling

well as sympathetic fibers (Mach et al. 2002). Although this innervation does not establish the link between subchondral bone and the mechanisms of OA-related pain, MRI imaging showed a significant, positive correlation between the presence of bone marrow lesions and pain in patients with radiographically confirmed OA of the knee (Felson et al. 2001). Further evidence for the involvement of subchondral bone is supported by the observation that administration of bisphosphonates – a class of compounds that inhibit osteoclast-mediated bone resorption – can prevent and even reverse pain-related behaviors in the MIA model (Strassle et al. 2010).

The efficacy of NSAIDs for the management of OA-related pain indicates that inflammation plays a role in the generation and maintenance of this pain. However, there is also evidence that neuropathy may also play a prominent role. Expression of ATF-3 (a marker of neuronal injury) in DRG neurons that innervate the knee increases after injection of MIA (Ivanavicius et al. 2007; Orita et al. 2011; Ferreira Gomes et al. 2012), astrocytes and microglia in the spinal cord become activated as the disease progresses (Sagar et al., 2011), and deep dorsal horn neurons show increased sensitivity to mechanical stimulation in their receptive field, an effect which is reversed by administration of pregabalin (Harvey and Dickenson 2009; Thakur et al. 2012). While it is unclear whether a similar neuropathic pathology is present in human OA, it is worth noting that duloxetine is approved for the treatment of chronic musculoskeletal pain due to osteoarthritis, suggesting a neuropathic component to human OA pain.

Behavioral assessment of pain associated with models of OA significantly lagged behind the pathological and mechanistic studies that were being performed in the various models. To further complicate the picture, the OA models were different from many of the other models of inflammatory and neuropathic pain that are characterized by primary or secondary hyperalgesia or allodynia in a hind paw. The OA models involved pain at the tibiofemoral joint, an anatomical site for which no standardized testing approaches had yet been established. However, as the assessment of pain behaviors in rodents became more refined, researchers were able to apply new techniques to the models of OA to determine if the pathology seen in these



Arthritis Model, Osteoarthritis, Fig. 3 Time course of the development of OA-related pain behaviors in the MIA model of OA in the rat. Intra-articular injection of 2 mg MIA produces significant and prolonged behavioral changes indicative of OA-related pain including alterations in hind limb weight bearing (**a**), decreased hind limb grip strength (**b**), and primary mechanical hyperalgesia at the affected knee (**c**)

models correlated in any way with alterations in behavior. In general, these approaches led to the assessment of movement-evoked or use-related pain as opposed to mechanical or thermal sensitivity. This in and of itself was desirable to researchers as it was believed that these assessments would more closely mimic spontaneous pain and therefore would have more predictive validity to human clinical trials.

The assessment of hind limb weight bearing was one of the first behavioral assays to be widely used to study OA-related pain and is very likely the most widely used assay for this purpose to date (Bove et al. 2003; Kobayashi et al. 2003). The assay is performed by using an incapacitance meter to measure the amount of weight borne by each hind limb individually when the animal is in a semi-rearing position. Following injection of MIA, there is a significant reduction in the weight borne on the affected hind limb that peaks approximately 3 days after MIA injection and at least partially resolves by 7–10 days post-injection. Beginning around day 10 post-injection, the deficits in weight bearing begin to become apparent again and progress over the subsequent weeks (Fernihough et al. 2004; Pomonis et al. 2005). These MIA-induced alterations in weight bearing are not only time-dependent but also vary with the amount of MIA injected. Injection of 0.3 mg MIA does not produce significant changes in hind limb weight bearing, but injections of 1, 2, or 3 mg MIA produce graded changes in behavior (Fig. 3a).

At present, there is no consensus on what aspect of pain-related behavior the weight bearing assay is measuring – it may assess use-related pain, ongoing pain, mechanical hyperalgesia, or a learned behavior to avoid use of the affected limb. However, it is clear that the alterations in weight bearing induced by MIA injection can be normalized by administration of a range of analgesic compounds including

opiates, NSAIDs, TRPV1 antagonists, and monoamine reuptake inhibitors.

MIA-induced OA is also characterized by deficits in hind limb grip strength, another potential assay for use-related pain (Chandran et al. 2009). As seen with measurements of hind limb weight bearing following MIA injection, assessment of hind limb grip strength shows progressive nature over time (Fig. 3b), and the deficits in grip strength can be restored with a range of analgesics including NSAIDs, antiepileptic drugs such as lamotrigine and gabapentin, and the monoamine reuptake inhibitor duloxetine. A unique feature of using the hind limb grip strength assay to assess the efficacy of therapeutics is the impact of motor impairing side effects. Unlike most stimulus-response assays in which sedative or motor impairing side effects lead to false-positives, any such effects in the grip strength assay will lead to an apparent lack of efficacy.

Along with the use- and movement-related pain behaviors seen in rats after MIA injection, mechanical sensitivity is also present, manifest as primary mechanical hyperalgesia at the arthritic knee and secondary mechanical allodynia at the hind paw ipsilateral to the injected knee (Marker and Pomonis 2012). As with the other behaviors seen following MIA injection, both of these traits are dose- and time-dependent (Fig. 3c). Although secondary mechanical allodynia is not a commonly reported symptom of OA patients, primary mechanical sensitivity has been reported in patients with painful OA. These behaviors also are sensitive to pharmacological reversal with clinically relevant compounds such NSAIDs and duloxetine, indicating that this behavioral readout may be relevant for the assessment of novel therapeutics.

As the study of the MIA model has continued, new insights have been gained regarding additional behavioral measures of the pain associated with joint damage. One important consequence of OA in humans is the effect the condition has on functional status. Indeed, OA is the most common cause for disability claims in the United States. As such, if the MIA model is to be considered to have significant face validity, it should result in the suppression of certain spontaneous behaviors. This effect has been confirmed using two separate approaches. MIA injection suppresses spontaneous home cage activity and also inhibits wheel running (Stevenson et al. 2011) in the subgroup of rats that showed a relatively high level of baseline wheel running. Further evidence for spontaneous pain in the MIA model comes from studies using the conditioned place preference test (Liu et al. 2011; Okun et al. 2012).

Summary

The MIA model of OA-related pain has several features and characteristics that have made it the model of choice for many groups investigating the efficacy of novel therapeutics for the treatment of OA pain. The model is technically simple in terms of induction, is highly reproducible in terms of the onset and magnitude of pain-related behaviors, and offers several behavioral assessments that can be used to test potential therapeutics. The pathology present in the model shows many similarities with the pathology of advanced OA in humans, and while the model may not be appropriate for the assessment of disease modifying therapies, it does represent a logical, practical tool especially for drug discovery.

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Arthritis Urethritica

► Reiter's Syndrome

Arthritogenic Pain

► Muscle Pain in Systemic Inflammation (Polymyalgia Rheumatica, Giant Cell Arteritis, Rheumatoid Arthritis)

Articular

Definition

Pertaining to the joints.

Cross-References

► Sacroiliac Joint Pain

Articular Afferents, Morphology

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Synonyms

Articular sensory receptors; Sensory endings in joint tissues

Definition

Afferent nerve fibers innervating articular tissues, in a narrow sense the sensory endings of afferent fibers in joint tissues, particularly in joint capsules and articular ligaments. Thick myelinated afferents form corpuscular nerve endings, and thin myelinated and unmyelinated afferents are without a corpuscular end structure (non-corpuscular endings, free nerve endings).

Characteristics

Remarks on the Classification of Sensory Endings

Sensory receptors are classified either according to their morphological appearance, which is thought to be correlated with functional properties, or according to the electrophysiological properties of their sensory axons within peripheral nerves. The velocity of action potentials running along the afferent fiber is used for a basic classification, dividing the afferents into slowly conducting (Aδ or group III, and C or group IV) and fast conducting groups (Aβ or group II). Whereas the Aβ fibers possess corpuscular nerve endings, the thinly myelinated Aδ and the unmyelinated C fibers terminate as so-called free nerve endings in peripheral tissues. This term has been used since the late nineteenth century, when new staining techniques enabled anatomists to visualize fine nerve endings that were obviously not enclosed or accompanied by specific cellular

end structures (Hinsey 1927). In the middle of the twentieth century, researchers combined psychophysiological and histological methods, and found that spot-like areas in human skin and deep tissues, the noxious stimulation of which was painful, contained nothing more than "free nerve endings" (Weddell and Harpman 1940). This led to the general conclusion that "free nerve endings" are the sensory end structures of nociceptors. Subsequent studies have shown, however, that sensory receptors signaling (innocuous) warm and cold, as well as many low-threshold mechanoreceptors, are also slowly conducting. New trials to correlate electrophysiological and histological data on slowly conducting afferents have not been much more conclusive with respect to morpho-functional characteristics (see below), whereas many additional structural details have been acquired by selective marking and high-resolution techniques, such as confocal and electron microscopy. We now know that those (previously described) unmyelinated peripheral nerve fibers and "free nerve endings," which are visible with the light microscope, are usually Remak bundles composed of several unmyelinated sensory axons and Schwann cells.

Composition of Articular Nerves

The distribution of different types of nerve fibers has been studied in detail in the medial and posterior articular nerves (MAN and PAN) innervating the knee joint in cat, rat, and mouse, using electron microscopy (Langford and Schmidt 1983; Hildebrandt et al. 1991; Salo and Theriault 1997; Ebinger et al. 2001). The composition of these nerves is similar, with a proportion of about 80 % being unmyelinated fibers, although the total number of nerve fibers differs between the three species (e.g., in the PAN: cat about 1,200, rat 400–600, mouse about 200). Comparisons between normal and sympathectomized animals have revealed that up to 50 % of unmyelinated fibers are afferent (Langford and Schmidt 1983; Salo and Theriault 1997). The diameters of myelinated sensory axons range from 1 to 8 μm in the rat (Hildebrandt et al. 1991), and from 1 to 18 μm in the cat. The majority of myelinated fibers in the MAN have diameters below 6 μm (belonging to group III), whereas in the PAN, thicker nerve fibers (group II) predominate (Heppelmann et al. 1988).

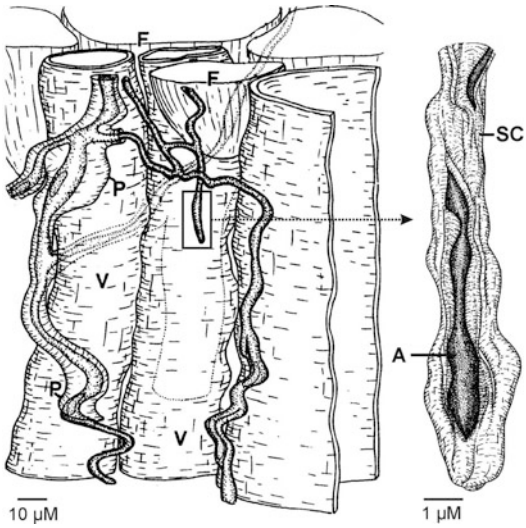
Neuropeptide Content of Articular Afferents

The proportion of neuropeptide-containing ▶ dorsal root ganglion (DRG) cells innervating the cat knee joint has been determined with retrograde labeling techniques and immunohistochemistry. ▶ Calcitonin gene-related peptide (CGRP) immunoreactivity was found in 35 % and ▶ substance P (SP) immunoreactivity in 17 % of labeled afferents from the MAN (Hanesch et al. 1991). In the PAN, the proportions are similar. Whereas all SP immunoreactive DRG neurons were found to be small or medium-sized cells, CGRP immunoreactivity was also detected in some large neurons with a diameter of more than 50 μm (Hanesch et al. 1991). ▶ Somatostatin (Som) seems to be colocalized with SP in nearly all MAN afferents (Hanesch et al. 1995). An acute experimental knee joint arthritis caused significant upregulation of the number of CGRP – but not SP-positive neurons (Hanesch et al. 1997), whereas in the human, arthritic painful hip joint upregulation of both neuropeptides has been observed (Saxler et al. 2007). In the rat knee joint, the proportion of CGRP and SP immunoreactive afferents was 33 % and 10 %, respectively (Salo and Theriault 1997). In the dog, the respective proportions were 29 % for CGRP and 17 % for SP; in 10 % of afferents these two neuropeptides seemed to be colocalized (Tamura et al. 1998). A major proportion of peptidergic mouse (knee and ankle) joint afferents have been found to express the vanilloid TRPV1 receptor, an important nociceptive transduction channel (Cho and Valtschanoff 2008).

Ultrastructure of Fine Sensory Endings in Articular Tissues

The fine sensory innervation of the cat knee joint has been studied by electron microscopy followed by quantitative analysis of structures

and 3D-reconstruction (Heppelmann et al. 1990, 1995) and reviewed with respect to their presumptive functional role (Messlinger 1996). In this paragraph, general ultrastructural features are discussed that probably apply to all non-corpuscular sensory endings in deep tissues. As fine sensory endings lack a corpuscular structure, the only morphological landmark that may indicate the end of the conductive part of the nerve fibers, and the beginning of the sensory endings, is the termination of the perineurial sheath surrounding the peripheral nerve (Fig. 1). In group III fibers, an additional transition zone exists in which the nerve fibers have lost their myelin sheath but are still enclosed by the perineurium. Distal to the perineurial sheath, the sensory axons maintain their accompanying ► Schwann cells. Individual group III fibers are usually encased by their own Schwann cell, whereas several group IV axons are frequently bound together sharing a common Schwann cell, as is the case within the peripheral nerve (Remak bundles). These bundles of group IV, as well as the individual group III fibers, ramify several times to form tree-like sensory endings (Fig. 1). Apart from the larger mean diameter of group III compared to group IV fibers, the sensory endings of group III fibers can be identified by a characteristic "neurofilament core," a bundle of centrally arranged neurofilaments that run along the whole length of the sensory axon up to their terminal branches. There is morphological evidence that the afferents are receptive along their entire tree-like sensory endings, which can measure up to several hundred µm in length. Each sensory axon forms periodically arranged varicose segments that are characterized by bare areas, where there are gaps in the cover formed by the Schwann cell so that the axon membrane is partly exposed to the surrounding tissue. Membrane channels may be concentrated here and exposed to the extracellular space. Accumulated mitochondria, glycogen particles, and some vesicles are regularly found in the varicosities. The axoplasm beneath the bare areas has an electron dense substructure, which has been described as a "receptor matrix" in various types of sensory nerve endings (Andres and von Düring 1973). These specialized areas, presumably receptive in nature, stretch along the whole sensory branches of non-corpuscular endings.



Articular Afferents, Morphology, Fig. 1 Three-dimensional reconstruction, based on serial electron microscopic images, of the sensory endings of a group III fiber in the cat knee joint (*left*) with a terminal branch at higher magnification (*right*). The branched endings arise from a peripheral nerve ensheathed by perineurium (*P*) and extend between venous vessels (*V*) and fat cells (*F*). They are wrapped up to their terminals by Schwann cells (*SC*) that form gaps in which the sensory axon (*A*) is exposed to the surrounding (*right*)

Topography of Fine Sensory Endings in the Knee Joint

Sensory endings of group III and group IV fibers are found in nearly all tissues of the knee joint, in particular the articular capsule, the superficial layers of the ligaments, and the tendons and muscles that insert at the joint. Most of the fine sensory endings are located within vascularized layers of the articular capsule running along venous vessels, while others extend into dense connective tissue or between fat cells. In search of a functional consequence of this differential topography, trials have been made to combine electrophysiological and morphological techniques (Messlinger et al. 1995). In these experiments, the sensory endings of functionally

characterized group III units were marked with fine needles within their receptive fields, the positioning of which was guided by impulse responses to the needles. The results of this study were fairly conclusive with respect to the mechanical and chemical sensitivity of units. The sensory endings of high-threshold afferents that can be regarded as mechano-nociceptors were most frequently located in structures of dense connective tissue (ligaments, tendons, collagenous layers of the articular capsule), whereas the endings of low-threshold afferents were usually found innervating vascularized and soft connective tissues. Secondly, nociceptors that terminated in dense connective tissues were clearly less chemosensitive to the close arterial application of bradykinin or prostaglandins compared to the low mechanical threshold afferents that innervated vascularized tissues. It is not yet clear if these functional differences are determined by intracellular modifications, differences in the receptor equipment of the sensory endings, or whether they are simply dependent on the surrounding tissues.

Corpuscular Nerve Endings in Articular Tissues

Corpuscular sensory endings in the joint are Ruffini- and Pacini-like corpuscles that have been classified as type I and type II endings in early morphological studies (Freeman and Wyke 1967). Ruffini-like corpuscles are found in the fibrous joint capsule and within ligaments in different joints, while Golgi tendon organs (type III) can be found in muscles inserting at the joint (review by Zimny 1988). Morphologically these two types are very similar. Ruffini-like corpuscles have a globular or ovoid shape, are enclosed by a capsule of several cell layers, and are supplied by a myelinated nerve fiber of 5–8 μm in diameter. One nerve fiber can innervate up to six corpuscles. Within the capsule, the sensory axon ramifies forming several unmyelinated branches that wind around bundles of collagen fibers. The intracorpuscular collagen fibers may be connected with the extracorpuscular network of collagen to conduct mechanical distension to the corpuscle (Andres and von Düring 1973). According to ultrastructural data from different species including man, there is a broad variety of corpuscular form and size, and there are also transient corpuscle types, for which the corpuscle may be incomplete or absent (Halata et al. 1985). Functionally, Ruffini-like corpuscular receptors are low-threshold, slowly adapting mechanoreceptors that respond to distension of articular structures. Pacini-like corpuscles (type II endings) are localized in the joint capsule and in periarticular fatty tissue (Freeman and Wyke 1967). They have an oval or longish form, a capsule composed of many cell layers (derived from fibroblasts and perineurial cells), and they are supplied by a thick myelinated nerve fiber, which is not ramified but runs through the long axis of the corpuscle as a central cylinder. Detailed electron microscopic studies were made on Pacini-like corpuscles in the knee joint of different species including man (Halata et al. 1985). Functionally, Pacini-like corpuscles are rapidly adapting mechanoreceptors with a very low threshold for movement and vibratory stimuli. Corpuscular sensory endings play only a minor, if any, role in articular nociception and pain. It is likely, however, that they regulate reflexes and posture programs that are modulated by nociceptive inputs.

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Articular Nociceptors

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Synonyms

Joint nociceptors

Definition

▶ Articular nociceptors are primary afferent neurons in joint nerves (or primary afferent neurons supplying joints) that signal and encode the impact of noxious stimuli to joints. In the normal joint, articular nociceptors are mainly or exclusively activated by noxious mechanical stimuli applied to the joint. Articular nociceptors are sensitized for mechanical stimulation in the process of joint inflammation.

Such processes are involved in inflammatory joint diseases such as rheumatid arthritis as well as in osteoarthritis.

Characteristics

Pain in Joints

Pain in a normal joint is commonly elicited by twisting or hitting the joint. In conscious humans pain in the normal joint can be elicited when

noxious mechanical or chemical stimuli are applied to the fibrous structures, such as ligaments and fibrous capsule. No pain is elicited by stimulation of cartilage. Stimulation of normal synovial tissue rarely evokes pain. Stimulation of fibrous structures with innocuous mechanical stimulation can evoke pressure sensations.

Joint inflammation such as rheumatoid arthritis or gout is characterized by hyperalgesia and persistent pain at rest. Noxious stimuli cause stronger pain than normal, and pain is even evoked by mechanical stimuli whose intensity does not normally elicit pain, i.e., movements in the working range and gentle pressure, e.g., during palpation. Discharge properties of joint nociceptors correspond to these characteristic phenomena of joint pain (Schaible and Grubb 1993; Schaible 2006).

The most frequent cause of joint pain is osteoarthritis (OA) (Felson 2005). In the initial stages, pain in the osteoarthritic joints is elicited by movements and loading of the joint but at later stages resting pain may occur (Scott 2006). It is conceivable that pain during OA has a strong inflammatory component because severe inflammatory processes such as infiltration of osteoarthritic joints with inflammatory cells may occur, and the profile of elevated cytokine production may be similar to that of inflammatory diseases (Schaible 2012).

Anatomy of Joint Innervation

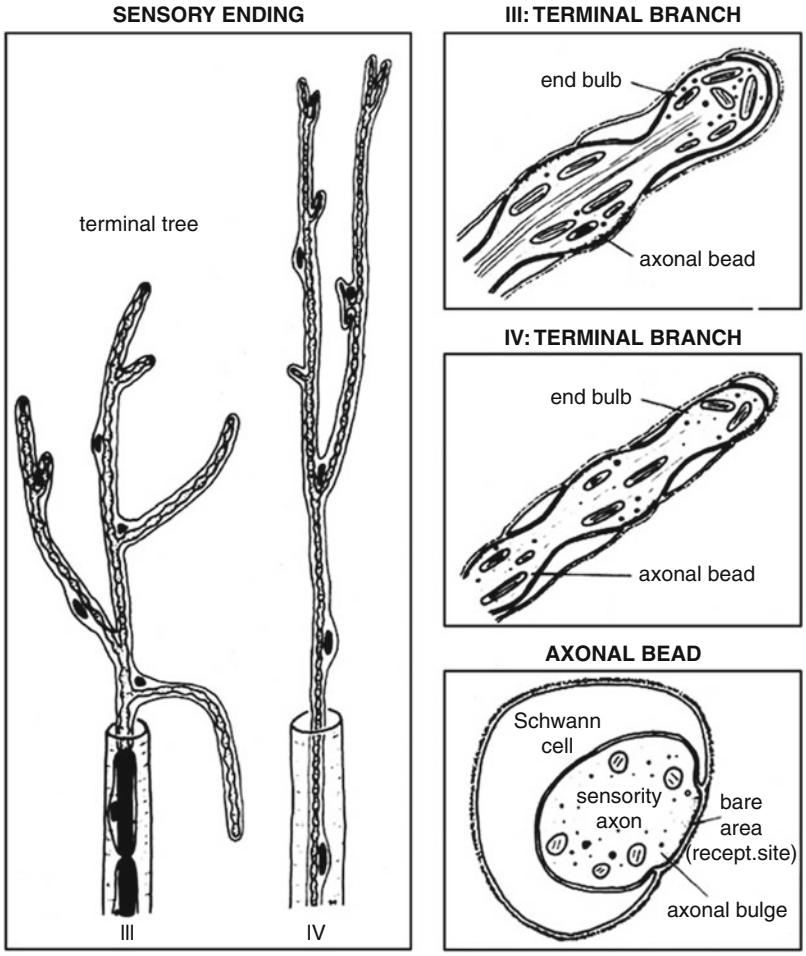
Joints are innervated by branches descending from main nerve trunks or their muscular, cutaneous, and periosteal branches. A typical joint nerve contains thick myelinated Aβ (group II), thinly myelinated Aδ (group III), and a high proportion (∼80 %) of unmyelinated C (group IV) fibers. The latter are either sensory afferents or sympathetic efferents (each ∼50 %). While Aβ fibers with corpuscular endings of the Ruffini, Golgi, and Pacini type in fibrous capsule, articular ligaments, menisci, and adjacent periosteum are not nociceptive, numerous articular Aδ and C fibers are nociceptive. Aδ and C fibers terminate as unencapsulated free nerve endings in the fibrous capsule, adipose tissue, ligaments, menisci, and the periosteum. Using staining for nerve fibers and neuropeptides, endings were also identified in the synovial layer. The major neuropeptides in joint nerves are ▶ substance P, ▶ CGRP, and ▶ somatostatin. Neurokinin A, ▶ galanin, enkephalins, and neuropeptide Y have also been localized in joint afferents. The cartilage is not innervated (Schaible 2006, 2013).

Figure 1 shows the reconstruction of peripheral nerve endings of joint afferents of cat's knee joint. Typical free nerve endings of joint afferents are ensheathed by ▶ Schwann cells, and only some sites are not covered. These exposed areas appear as a string of beads. It is assumed that these exposed areas are receptive sites along the fibers (Heppelmann et al. 1990).

Mechanosensitivity of Joint Afferents

Joint afferents have been mainly recorded in articular nerves supplying cat knee and rat knee and ankle joints. They were characterized after their responses to innocuous and noxious mechanical stimuli. Light to moderate pressure applied to the joint and movements within the working range of the joint are innocuous stimuli which are not normally painful. Noxious stimuli are strong pressure at intensities that are felt as pain and movements exceeding the working range of the joint, such as twisting against the resistance of the tissue.

Figure 2 shows four typical joint afferents of cat's knee joint with different sensitivities to movements. Figure 2a displays a low-threshold Aδ fiber. This fiber had two receptive fields in the fibrous capsule (dots). It responded phasically to extension (ext) of the knee, and it was strongly activated by inward rotation (IR) within the working range of the knee joint. This fiber was thus activated by innocuous movements, i.e., the threshold was in the innocuous range. However, strongest responses were elicited by noxious movements such as noxious inward rotation (n.IR). Typically, these neurons are also activated by light pressure applied to the receptive field. Such a response pattern is also seen in many low-threshold Aβ fibers in the fibrous capsule and in ligaments including the anterior cruciate ligament. Although these units have their

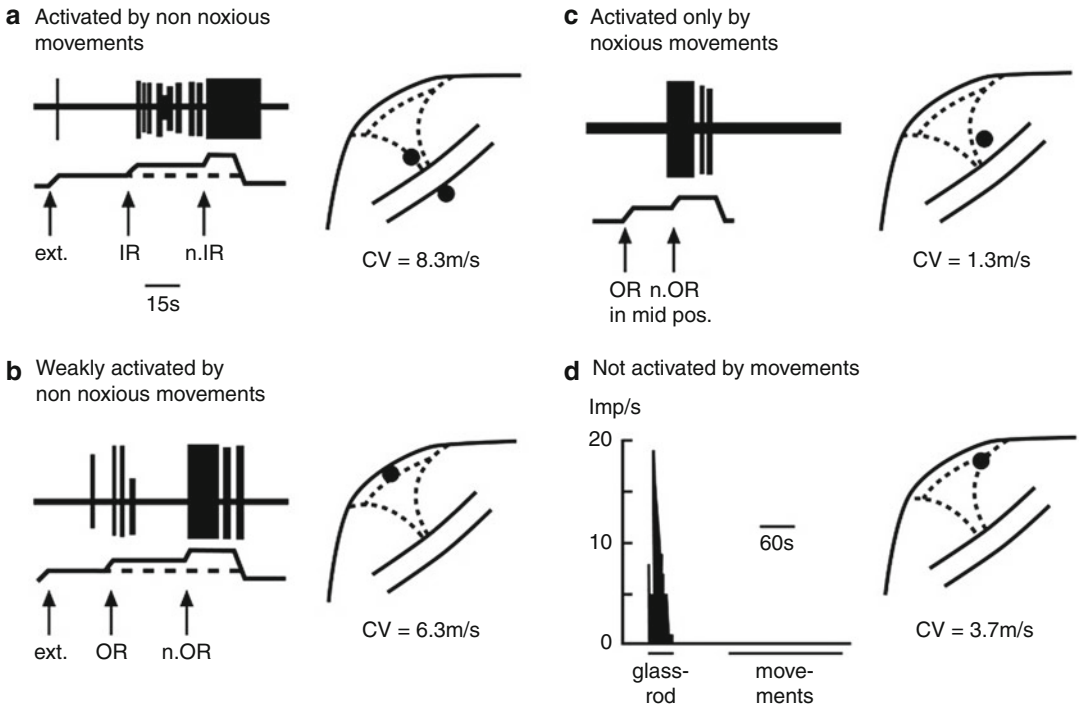


Articular Nociceptors, Fig. 1 Schematic drawings of a group III (Aδ) and group IV (C) fiber sensory ending in the knee joint capsule of the cat. A terminal tree is formed by several long and short branches. The sensory axons consist of periodically arranged thick and thin segments forming spindle-shaped beads. The axolemma is not completely unsheathed by its accompanying Schwann cells; the bare areas are presumably receptive sites (From Heppelmann et al. (1990))

strongest response in the noxious range they are not considered nociceptive neurons. The discharge rate seems to encode the strength of a stimulus from the innocuous to the noxious range, but it does not encode the presence of a noxious stimulus *per se*. In fact, the most adequate innocuous mechanical stimulus can evoke a stronger response than a noxious mechanical stimulus, e.g., a noxious movement in another direction.

The other fiber types shown in Fig. 2 respond mainly or exclusively to noxious mechanical stimuli. Figure 2b shows an Aδ fiber with a receptive field in the patellar ligament (dot). This unit responded weakly, with a few spikes only, during outward rotation in the working range (OR), but it had a strong response to noxious outward rotation (n.OR). The C fiber in Fig. 2c, with a receptive field in the fibrous capsule, was exclusively activated by noxious movements. It did not respond to any innocuous movement, but showed pronounced responses when the joint was twisted (noxious outward rotation, n.OR). These neurons require also high pressure intensity to elicit a response by probing the receptive field. Figure 2d displays an Aδ fiber with a receptive field in the anterior capsule that did not respond to any innocuous or noxious movement, but responded to noxious pressure onto the receptive field.

Not shown in Fig. 2 are sensory neurons which are mechanoinsensitive under normal conditions. These neurons can be identified by electrical stimulation of the joint nerve, but under normal



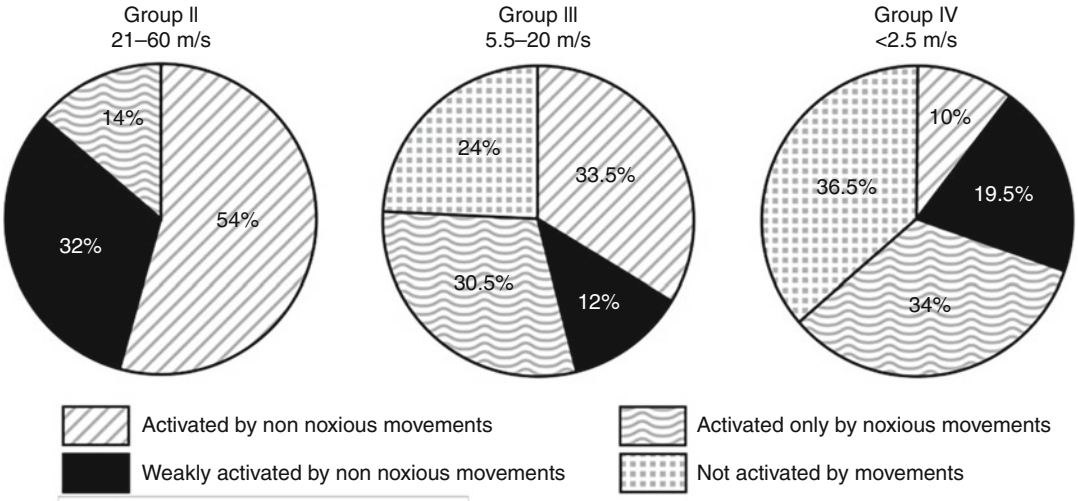
Articular Nociceptors, Fig. 2 Four different articular afferents of cats knee joint exemplifying classes of afferents according to their responses to passive movements. *Dots* in the insets: receptive fields identified by probing the joint. *Ext* extension, *IR* inward rotation (pronation), *OR* outward rotation (supination), *n.IR* and *n.OR* noxious IR and OR; mid pos, mid (resting) position (From Schaible and Grubb (1993))

conditions, no receptive field is found, and no response is elicited by any innocuous and noxious movement. They respond to injection of KCl into the joint artery, and some seem to respond to inflammatory mediators. However, a proportion of these neurons is rendered mechanosensitive during inflammation in the joint (see below), and therefore these units were called silent nociceptors. An estimation is that about one-third of the sensory C fibers and a small proportion of Aδ fibers in the joint nerve are mechanoinsensitive. The proportion of silent nociceptors can be different in different joint nerves. For example, the posterior articular nerve of cat's knee seems to contain many more silent nociceptors than the medial articular nerve.

Figure 3 shows for the medial articular nerve of cat's knee joint the proportions of Aβ, Aδ, and C fibers in the categories defined in Fig. 2. Only those neurons that had a detectable receptive field and that were activated by innocuous and/or noxious mechanical stimuli applied to the normal joint are included (initially mechanoinsensitive sensory neurons are not included). It is shown that most Aβ fibers were either strongly or weakly activated by innocuous stimuli. More than 50 % of the Aδ fibers and about 70 % of the sensory C fibers were classified as high-threshold units (Schaible and Grubb 1993; Schaible 2006).

Changes of Mechanosensitivity of Joint Afferents During Inflammation

It has been pointed out above that an inflamed joint hurts during movements in the working range and during palpation, and that pain may occur under resting conditions. It is a characteristic feature of joint nociceptors that their mechanosensitivity is increased during inflammation. Many low-threshold Aδ and C fibers show increased responses to movements in the working range. Most strikingly, a large proportion of high-threshold afferents (see Fig. 2c, d)



Articular Nociceptors, Fig. 3 Mechanosensitivity of primary afferent neurons supplying normal cat's knee joint. The graph shows the proportions of Aβ, Aδ, and C fibers in the different sensitivity classes (From Schaible and Grubb (1993))

are sensitized such that they respond to movements in the working range of the joint.

Furthermore, initially mechanoinsensitive afferents (silent nociceptors) are sensitized and become mechanosensitive (Schaible and Grubb 1993). Thus, silent nociceptors are recruited for the encoding of noxious events during an inflammatory process. Increased mechanosensitivity has also been noted during chronic forms of arthritis, suggesting that mechanical sensitization is an important neuronal basis for chronic persistent hyperalgesia of the inflamed joint (Guilbaud et al. 1985).

Chemosensitivity of Joint Afferents

The vast majority of sensory Aδ and C fibers in the joint nerve are chemosensitive for endogenous compounds that are produced and released during pathophysiological conditions and that contribute to the inflammatory process itself. Such mediators are able to excite and/or sensitize primary afferent neurons for mechanical stimuli and for chemical stimuli. The following general aspects should be noted. First, these mediators only affect Aδ and C fibers of the joint nerve, not Aβ fibers. Second, an effect is typically elicited only in subpopulations of the articular units (i.e., not all units express the full range of chemosensitivity). Third, high-threshold (nociceptive) as well as low-threshold Aδ and C articular afferents (not nociceptive specific) are affected or not affected by a certain mediator. Thus, the chemosensitivity of a unit is not strictly correlated to its mechanosensitivity (Schaible and Grubb 1993; Schaible 2006).

Mediators such as bradykinin, prostaglandins E_2 and I_2, and serotonin can induce firing of neurons and/or increase their responses to movements. After bolus injections of the compounds into the joint artery, differences in the pattern of effects were noted. Bradykinin excited joint afferents less than 1 min, but sensitized them for mechanical stimuli for several minutes even if bradykinin did not excite the neuron. Both PGE_2 and PGI_2 cause ongoing discharges and/or sensitization to mechanical stimulation of the joint. The effect of PGE_2 has a slow onset and duration of minutes, the action of PGI_2 begins quickly and has a short duration. In the rat ankle joint PGI_2 excites and sensitizes a much larger proportion of units than PGE_2. In addition, these PGs sensitize joint afferents to the effects of bradykinin, whether or not they have an excitatory effect by themselves. PGE_2 and bradykinin together can cause a stronger sensitization to mechanical stimulation than bradykinin or PGE_2 alone.

Bradykinin receptors are also involved in mechanical sensitization evoked by the

proteinase-activated receptor-4 (Russell et al. 2010). Aδ- and C-fibers of the joint are also sensitized to mechanical stimuli by serotonin (Schaible and Grubb 1993; Schaible 2006), substance P, and VIP (Herbert and Schmidt 2001). Acid-sensing ion channel 3 may be involved in the increase of mechanosensitivity because ASIC3 gene knockout mice showed less arthritis-induced mechanical hyperalgesia (Yuan et al. 2010). Mainly excitatory effects were elicited by capsaicin, ATP, and adenosin (Dowd et al. 1998a, b). The peptides galanin (Heppelmann et al. 2000), neuropeptide Y (Just and Heppelmann 2001), and nociceptin (McDougall et al. 2000) sensitized some neurons and reduced responses in other neurons. However, some mediators are just inhibitory (see below).

Recordings from joint nociceptors of rat knee joint showed that a single intraarticular injection of proinflammatory cytokines causes a slow increase in mechanosensitivity (Schaible et al. 2010). The cytokines tumor necrosis factor-α (TNF-α), interleukin-1ß (IL-1ß), and interleukin-6 (IL-6) play a major role in the pathogenesis of immune-mediated arthritis, and they are involved in human RA and OA models (Schaible 2013). Administration of TNF- or IL-6 into the normal knee joint sensitized Aδ- (TNF-α) and C-fibers (TNF-α and IL-6) to innocuous and noxious rotation of the knee joint. The mechanical sensitization by IL-6 was enhanced by coadministration of the soluble receptor sIL-6R. Increases in the mechanosensitivity of C-fibers were also generated by interleukin-1ß (IL-1ß) and interleukin-17A (IL-17A) (Ebbinghaus et al. 2012; Richter et al. 2012). The so-induced mechanical sensitization persisted for hours which contrasts to the short-lasting mechanosensitivity increases after intraartertial injection of "classical mediators" (see above). However, IL-1ß significantly reduced the mechanosensitivity of Aδ-fibers (Ebbinghaus et al. 2012).

A number of compounds reduce the (enhanced) mechanosensitivity of Aδ- and C-fibers of the joint. Intraarticular opioids reduce the discharges of joint afferents (Russell et al. 1987) and peripheral opioids produce profound analgesia (Stein et al. 2009). A reduction of mechanosensitivity of joint afferents is also produced by somatostatin (Heppelmann and Pawlak 1997; Pawlak and Schmidt 2004). The activation of somatostatin receptors may be an interesting option for future pain therapy (Helyes et al. 2004; Imhof et al. 2011; Yao et al. 2008). Cannabinoid receptor agonists reduce mechanosensitivity which may be of therapeutical relevance (Schuelert and McDougall 2008). However, the CB1 receptor agonist anandamide may also activate TRPV1 receptors (Schuelert and McDougall 2008), and a cannabinoid 2 receptor agonist may even cause excitation of joint afferents of the osteoarthritic joint (Schuelert et al. 2010).

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Articular Sensory Receptors

▶ Articular Afferents, Morphology

As Needed Dosage Regimen

Definition

A method of dose titration where the dose of drug is fixed and the interval between

administered doses is determined by the response of the patient.

In analgesic therapy using "as needed" regimen, the dose of an opioid is not repeated until the patient reports the return of some intensity of pain.

Cross-References

► Opioid Rotation

Ascending Nociceptive Pathways

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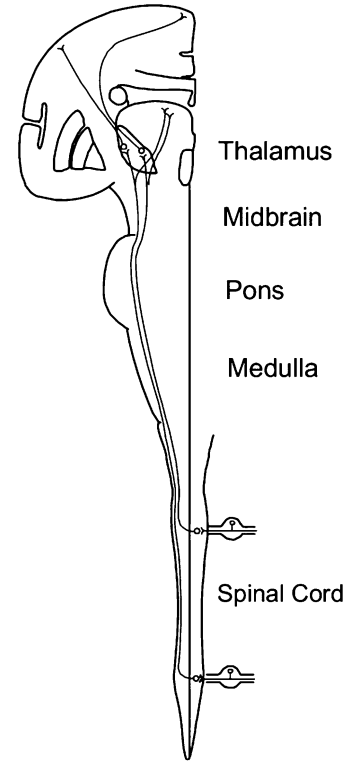
Introduction

Nociceptive neurons in the spinal cord and trigeminal nuclei send their axons to terminate within a large number of regions in the upper cervical spinal cord, brain stem, and diencephalon. The precise roles of each of these pathways in nociception have not yet been established with certainty, and it is likely that their roles vary among species. This entry presents a summary of prominent findings on several of the most thoroughly examined ascending nociceptive projections. Many specific topics are dealt with in more detail by individual contributors to the Encyclopedic Reference of Pain. These are referred to throughout this entry.

Characteristics

Spinothalamic Tract

The most widely studied ascending nociceptive pathway originating in the spinal cord is the spinothalamic tract (STT). Nearly 100 years ago, anatomical studies indicated that lesions of the spinal cord caused the degeneration of axons within the thalamus. These early studies were performed in a variety of species including primates. The first description of spinothalamic tract axons has been attributed to Edinger (Willis and Coggeshall 2004). In the early 1970s, antidromic activation techniques were first used to identify and functionally characterize spinothalamic tract neurons. These methods have been used in a large number of studies in the intervening years to examine many facets of the function and organization of this pathway. Both anterograde and retrograde tracing techniques have also been used extensively to determine the locations and numbers of the cells of origin of the spinothalamic tract in several species as well as the areas of termination of spinothalamic tract axons. Several of the prominent features of the spinothalamic tract are schematically illustrated in Fig. 1. The cells of origin of this pathway are found within the spinal gray matter at all levels of the cord. STT neurons comprise a small percentage of spinal cord



Ascending Nociceptive Pathways, Fig. 1 Schematic representation of spinothalamic tract and thalamic projection to primary somatic sensory cortex from the ventral posterior lateral nucleus of thalamus

neurons. It has been estimated, based on retrograde tracing studies, that there are between 10,000 and 20,000 STT neurons in the spinal cord of primates (Apkarian and Hodge 1989; Willis and Coggeshall 2004). Particularly high concentrations have been described in upper cervical segments. Within the gray matter, STT neurons are concentrated in the marginal zone (see ▶ Spinothalamic Tract Neurons, Morphology) and within the deep dorsal horn (lamina V; see ▶ Spinothalamic Tract Neurons, in Deep Dorsal Horn). A sizeable number of STT neurons are also located within the intermediate gray zone and the ventral horn (Willis et al. 1979; Giesler et al. 1981). STT cell bodies and dendrites receive glutamatergic inputs (see ▶ Spinothalamic Tract Neurons, Glutamatergic input) and several types of peptidergic inputs including substance P and CGRP (see ▶ Spinothalamic Tract Neurons, Peptidergic input). Nitric oxide appears to play an important role in modulating the activity of STT neurons (see ▶ Spinothalamic Tract Neurons, Descending Control by Brain Stem Neurons). Axons of STT neurons decussate at a level near the cell body, and the majority turns and ascends within the ventral half of the lateral funiculus. Several groups of investigators have shown that STT axons originating in marginal zone neurons ascend in a position that is dorsal to STT axons originating in neurons within the deep dorsal horn. Within thoracic levels, STT axons of marginal zone neurons are generally located dorsal to the denticulate ligament in the dorsal lateral funiculus, whereas the axons of lamina V neurons are found within the ventral part of the lateral funiculus (Apkarian and Hodge 1989; Zhang et al. 2000). There is also a somatotopic organization of STT axons. Axons from lumbosacral levels ascend on the periphery of the lateral funiculus, whereas STT axons from rostral levels are located closer to the gray matter (Applebaum et al. 1975).

STT axons ascend through the lateral and ventral brain stem. Collateral branches are frequently given off by these axons supplying nociceptive sensory information to a number of nuclei, particularly within the reticular formation, throughout the length of the brain stem.

Several early clinical cases in which injury to the spinal cord had blocked the sense of pain in patients indicated that the axons carrying nociceptive information crossed within the spinal cord and ascended within the ventral or anterior half (see ▶ Cordotomy Effects on Humans and Animal Models; Willis and Coggeshall 2004). These observations led to the first surgical attempts to relieve chronic pain by cutting the anterolateral quadrant of the spinal cord, the area that carries the overwhelming majority of spinothalamic tract axons. This procedure, cordotomy, can very effectively produce pain relief for patients, but the positive effects are short lived and pain frequently returns within a few months or a year. It is not known which tracts begin to carry the nociceptive information following a cordotomy. More studies are needed on this important phenomenon.

Although cordotomies are infrequently used now in the United States to relieve pain (they have generally been replaced with the use of opiates), they continue to be used by neurosurgeons in many countries. In the early years, laminectomies were performed to allow the lesions to be made. Cordotomies are now frequently done percutaneously under local anesthesia.

STT axons terminate in three principal regions of the thalamus including the ventral posterior lateral (VPL), central lateral and adjacent parts of the medial dorsal nucleus, and posterior thalamic nuclei (Mehler 1969; Cliffer et al. 1989; Craig 2004; Craig et al. 1994; Graziano and Jones 2004). STT terminations within VPL are somatotopically organized. Axons ascending from lumbosacral levels terminate within the lateral part of VPL; those from cervical levels end within the medial part of the nucleus. Within VPL of primates, STT terminals are concentrated within small areas that are surrounded by large regions that are dominated by the endings of medial lemniscal axons. In carnivores, STT axons are concentrated within the periphery of VPL. It has been shown that a high percentage of nociceptive neurons within the primate VPL can be antidromically activated from SI parietal cortex, indicating that nociceptive input to VPL

neurons via STT axons is transmitted to the cortex.

A second area of termination of the STT is the central lateral nucleus and the adjacent lateral region of the medial dorsal nucleus. There does not appear to be a somatotopic organization to this termination. Many of the nociceptive neurons within this area of the thalamus have large, bilateral, even whole-body receptive fields. Thus, it is unlikely that this region is involved in localization of nociceptive stimuli. It appears more likely that STT inputs and thalamic neurons within this region are involved in the production of affective/emotional and motor responses to nociceptive stimulation via their widespread cortical projections. It has been shown that STT neurons that project to this region are frequently located within the intermediate zone and ventral horn of the spinal cord. Many of these STT neurons have whole-body receptive fields including the face.

Responses of STT neurons to a variety of somatic and visceral stimuli have been examined (Willis and Coggeshall 2004). In primates, the vast majority of STT neurons have been classified as nociceptive, responding either preferentially (wide dynamic range, WDR) or specifically (high threshold, HT) to noxious stimuli. In most (but not all) studies, higher percentages of HT-STT neurons have been found in the marginal zone and more WDR neurons within the deep dorsal horn. Receptive fields of neurons in the marginal zone tend to be smaller sometimes being restricted to a single toe. The receptive fields of deeper neurons often cover much of the ipsilateral leg. Many STT cells are powerfully activated by noxious thermal stimulation of their receptive fields. Response thresholds to noxious heat stimuli are often between 45 °C and 55 °C (Kenshalo et al. 1979). Repeated applications of noxious heat stimuli leads to sensitization including reduced responses thresholds, increased responses to identical noxious heat stimuli, and the production of ongoing activity (see ▶ Spinothalamic Tract Neurons, Central Sensitization). STT neurons also receive nociceptive input from muscles and joints (Foreman et al. 1979), and they are activated by stimulation using noxious chemicals (▶ Spinothalamic Tract Neurons, Responses to Chemical Stimulation). Nociceptive information originating from receptors on the face in the oral and nasal cavities is carried to the ventral posterior medial nucleus of thalamus by trigeminothalamic tract projections (see ▶ Trigeminothalamic Tract Projections).

In a large number of studies, STT neurons at a number of levels of the spinal cord have been examined for possible input from visceral structures. It has been shown that STT neurons can be activated by noxious stimulation of the heart, esophagus, urinary bladder, testicles, vagina, colon, rectum, gall bladder, and bile duct (see ▶ Spinothalamic Tract Neurons, Visceral Input). In almost all cases, STT neurons that respond to stimulation of a visceral organ have somatic receptive fields as well. Frequently, the somatic receptive fields were found to be located in areas to which noxious stimulation of the examined organ produced referred pain in human studies. These findings indicate that STT axons are capable of carrying nociceptive visceral information and that the convergence of somatic and visceral nociceptive input probably contributes to the production of referred pain.

Spinohypothalamic Tract (SHT)

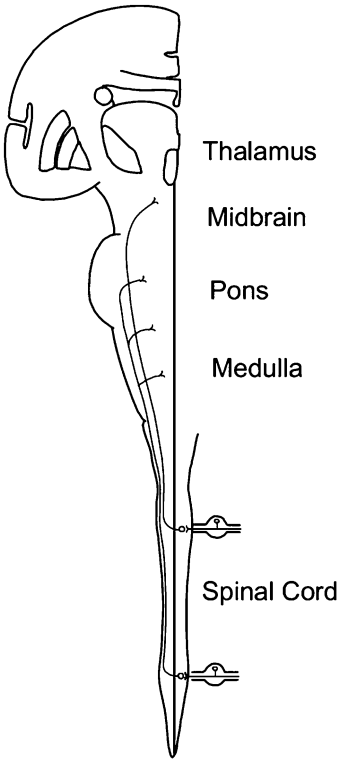
In the late 1980s, Burstein et al. (1987) noted that spinal cord neurons could be antidromically activated using small amplitude current pulses delivered through electrodes located within the hypothalamus of rats. In addition, injections of anterograde tracers into the spinal cord labeled axons within several areas of the hypothalamus including the lateral, posterior, and ventromedial hypothalamus. Injections of retrograde tracers that were restricted to the hypothalamus labeled thousands of neurons within the spinal cords of rats. SHT cell bodies are located in the marginal zone and the deep dorsal horn. SHT axons have been shown to ascend to the posterior thalamus, then turn ventrally and laterally entering the supraoptic decussation. These axons continue to ascend in a position just dorsal to the optic tract and enter the hypothalamus. Many SHT axons ascend to the level of the optic chiasm where they decussate, turn posteriorly, and descend

within the supraoptic decussation on the side ipsilateral to the cell body. SHT axons have been shown to end in the ipsilateral hypothalamus, posterior thalamus, and brain stem. Some have even been shown to descend as far as the level of the medulla (Zhang et al. 1995). SHT neurons are frequently nociceptive. Some also receive an apparent input from innocuous thermoreceptors. It has been suggested that through their complex, bilateral projections and frequent branches, SHT axons could provide nociceptive input to a variety of areas of the brain stem and forebrain that are involved in nociceptive processing (see ▶ Spinohypothalamic Tract, Anatomical Organization, and Response Properties). SHT neurons have also been identified and characterized in monkeys. Large numbers of neurons within all divisions of the trigeminal complex and upper cervical segments also send axonal projections to the hypothalamus (see ▶ Trigeminohypothalamic Tract).

Spinoreticular Tract (SRT)

The SRT is a direct projection from spinal cord neurons to the reticular formation of medulla, pons, and midbrain (Fig. 2; see ▶ Spinomesencephalic Tract). Regions that receive these direct spinal afferent fibers include the nucleus gigantocellularis and nucleus dorsalis both within the medulla and the cuneiform nucleus of the midbrain. Since several of these regions in the reticular formation in turn send ascending nociceptive projections to the forebrain, it is believed that the SRT is part of a multisynaptic projection system to the thalamus and probably is involved in providing nociceptive information that is used in producing cortical arousal.

It is difficult to identify the cells of origin of this projection with certainty since it is known that at least some axons ascending to higher levels of the brain stem or diencephalon pass through or near the reticular formation without giving off collaterals within it. Such axons would not be considered as part of the SRT since they do not provide information to neurons within the reticular formation. Injections of retrograde tracers into the reticular formation could be taken up by such axons as well as by SRT axons. In addition, such axons may

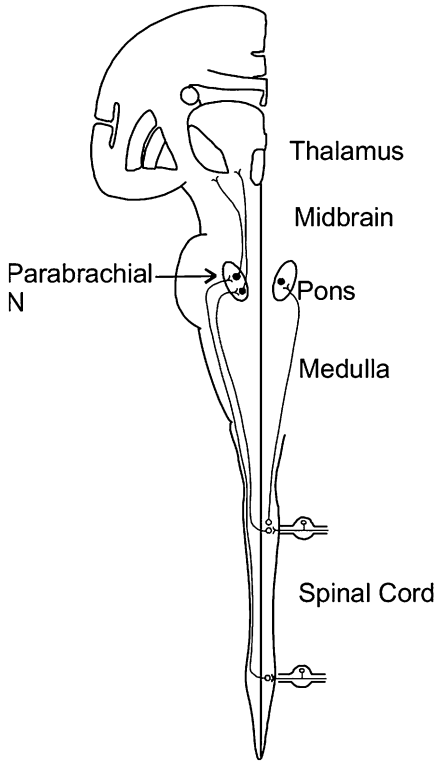


Ascending Nociceptive Pathways, Fig. 2 Schematic illustration of spinoreticular tract

be activated in studies in which antidromic activation techniques are used to examine SRT neurons. Measures have been taken such as stimulating with high amplitude current pulses at higher levels of the neuraxis to insure that examined axons do not ascend beyond the area of interest. Studies in which antidromic methods have been used have shown that many SRT neurons are nociceptive (Fields et al. 1975; Haber et al. 1982; Yezierski and Schwartz 1986). These neurons have been frequently recorded deep within the spinal gray matter and have large complex receptive fields frequently including the face. Retrograde tracing studies indicate that SRT neurons are found within the marginal zone and deep dorsal horn, but a large percentage are located within the intermediate zone and ventral horn (Menetrey et al. 1983).

Spinoparabrachial Tract

Somatic sensory and nociceptive information ascends directly from the spinal cord to several



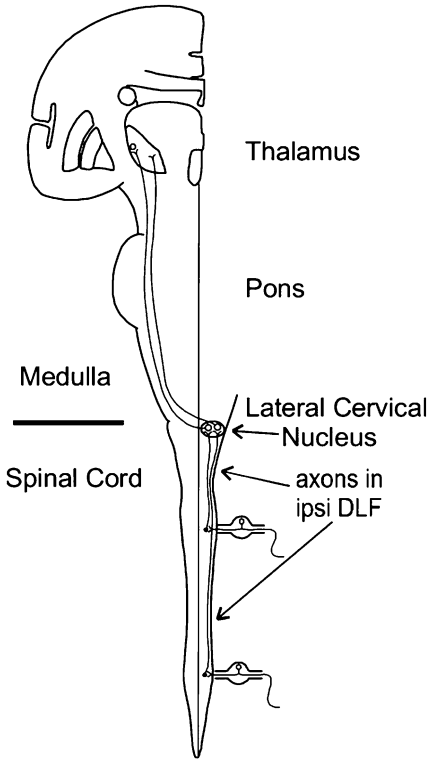
Ascending Nociceptive Pathways, Fig. 3 Schematic representation of spinoparabrachial tract projection

sub-nuclei of the parabrachial nucleus, which is located lateral to the superior cerebellar peduncle within the rostral pons and caudal midbrain (Fig. 3; see ▶ Spinoparabrachial Tract and ▶ Parabrachial Hypothalamic and Amygdaloid Projections). The locations of the cells of origin of the spinoparabrachial tract have been established using electrophysiological and anatomical techniques. Injections of retrograde tracers that are restricted to the parabrachial nucleus label a large number of spinal neurons at all levels of the spinal cord of rats and cats. Although spinoparabrachial tract neurons are found throughout much of the gray matter, the fact that they are highly concentrated within the marginal zone has attracted a great deal of interest in this projection. Anterograde tracing studies indicate that neurons in the marginal zone send a large projection via the dorsal part of the lateral funiculus to the parabrachial nuclei on both sides (Bernard et al. 1989, 1995). Studies in which antidromic activation has been used to identify spinoparabrachial tract neurons in cats indicate that the overwhelming majority is activated by noxious stimuli (Hylden et al. 1986; Light et al. 1993). The parabrachial nuclei are known to have large projections to several areas of the forebrain that are involved in nociception including the hypothalamus and the amygdala (Bernard et al. 1989; see ▶ Parabrachial Hypothalamic and Amygdaloid Projections). Therefore, this projection appears well suited for providing nociceptive information that is used for producing cognitive, emotional, or affective responses to pain.

Spinocervicothalamic Tract (SCT)

The spinocervicothalamic projection is schematically depicted in Fig. 4. Spinocervical tract neurons are located throughout the length of the spinal cord (Craig 1978). These neurons send their ascending axons into the dorsal part of the ipsilateral lateral funiculus. SCT axons ascend to upper cervical segments where they terminate within the lateral cervical nucleus, an island of neurons located with the dorsal lateral funiculus. The lateral cervical nucleus (LCN) extends from segment C3 through C1. The number of neurons that form the LCN varies greatly among species. The LCN is a large prominent nucleus in carnivores (Truex et al. 1970) and can contain as many as 10,000 neurons. In cats, lesions of the dorsal lateral funiculus have been reported to reduce nociceptive responses. A. G. Brown and colleagues (1981) performed an elegant and thorough series of studies of SCT neurons in cats. SCT neurons are located in the deep dorsal horn (laminae III-V). Many receive a powerful afferent input from innocuous mechanoreceptors. Evidence from a number of studies indicates that as many as half of SCT neurons also receive a nociceptive input (Cervero et al. 1977; Brown 1981; Kniffki et al. 1977). These SCT neurons respond to noxious mechanical and thermal stimuli.

In rodents, the LCN has been shown to be at least an order of magnitude smaller. The LCN is also comparatively small in monkeys although precise cell counts are not available. The LCN



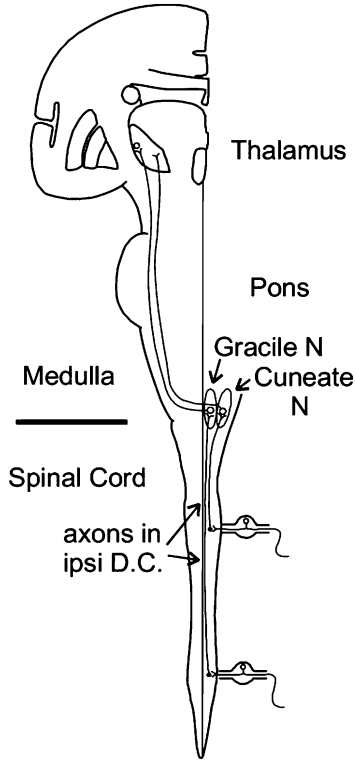
Ascending Nociceptive Pathways, Fig. 4 Schematic representation of the spinocervicothalamic tract

has been examined in humans, and it has been reported to be highly variable. Truex et al. (1970) reported that some individuals appear to have a prominent LCN on one side and few if any LCN neurons on the other. No evidence in Nissl-stained material could be found for an LCN in several other individuals. Other individuals appeared to have a clear LCN on both sides. These findings suggest a lesser, variable role for the spinocervicothalamic tract in nociception in individual humans.

Physiological studies have indicated that roughly half of LCN neurons in carnivores are nociceptive (Kajander and Giesler 1987). LCN neurons have been shown to respond specifically or preferentially to noxious mechanical stimuli. Many of these neurons can also be activated by noxious heat stimuli. LCN neurons that receive mechanoreceptive or nociceptive input are somatotopically organized; neurons in the lateral LCN receive input from lumbosacral segments, whereas neurons in the medial LCN receive input from cervical levels. Craig and Tapper (1978) reported that a small number of neurons in the medial LCN have nociceptive whole-body receptive fields. Axons of LCN decussate in upper cervical spinal cord and ascend to terminate in the contralateral VPL (Boivie 1970). As many as half of ascending axons of LCN neurons give off branches that terminate within the midbrain.

Postsynaptic Dorsal Column Projection (PSDC)

Early evidence for the existence of the PSDC projection was discovered in electrophysiological experiments by Uddenberg (1968). He noted that some axons that were recorded in the dorsal columns responded to stimulation of ipsilateral peripheral nerves with multiple spike discharges, an indication that at least one synapse intervened between the stimulated and recorded axons. A schematic drawing illustrating the basic organization of this projection is illustrated in Fig. 5. Injections of retrograde tracers into the dorsal column nuclei of cats, rats, and monkeys label large numbers of neurons throughout the length of the spinal cord (Bennett et al. 1983; Giesler et al. 1984). Many of these are located in nucleus proprius or laminae III and IV. A smaller number are found near the central canal (see ▶ Postsynaptic Dorsal Column Projection, Functional Characteristics). Anterograde tracing studies indicate that most axons of this type ascend within the ipsilateral dorsal columns but some appear to ascend within the dorsal lateral funiculus (Cliffer and Giesler 1989). Such studies also show that the terminals of this projection were somewhat separated from the endings of primary afferent axons within the dorsal column nuclei. In cats, PSDC axons frequently terminate in the periphery of the nuclei and primary afferent fibers often terminate in the cores of the two nuclei. In rats, the terminations of these projections appear to overlap more substantially. It is difficult to determine the frequencies with which PSDC axons terminate on neurons within the dorsal column nuclei that project to the contralateral VPL. In cats, several electrophysiological studies have shown that roughly half of PSDC



Ascending Nociceptive Pathways, Fig. 5 The postsynaptic dorsal column pathway

neurons can be driven exclusively by innocuous mechanical stimulation and the remainder can be classified as WDR neurons (Uddenberg 1968; Angaut-Petit 1975), indicating that this projection in cats is capable of conveying nociceptive information. These cells have been shown to be powerfully activated by noxious mechanical and heat stimuli. PSDC neurons have not been systematically examined in monkeys, but the presence of nociceptive neurons within the dorsal column nuclei in monkeys is consistent with the idea that PSDC neurons are nociceptive primates. Accurate functional classification in rats is less clear. In one early study, it was concluded that few, if any, PSDC neurons were conclusively nociceptive in rats. On the other hand, several lines of evidence indicate that nociceptive visceral information is carried by this projection in rats, monkeys, and possibly humans. Willis, Al-Chaer, and colleagues (Al-Chaer et al. 1996, 1998; see ▶ Postsynaptic Dorsal Column Neurons, Responses to Visceral Input) have performed an elegant series of studies showing that PSDC neurons convey nociceptive visceral information that reaches the thalamus. They have also pointed out that surgical section of the medial area of the dorsal columns can relieve chronic visceral pain in patients. This result would appear to indicate that axons carrying nociceptive visceral information within the lateral funiculus (e.g., spinothalamic, spinoreticular, spinohypothalamic tract axons) are not sufficient to maintain visceral nociception since these axons are spared when the dorsal columns are sectioned. This seems surprising since many spinothalamic tract axons carry nociceptive visceral information and anterolateral cordotomies have been used for nearly 100 years to relieve chronic visceral pain. More studies are needed to resolve the precise roles of these pathways in carrying nociceptive information from the viscera, particularly in primates including humans.

Spinosolitary Tract

Several types of information indicate that a number of spinal cord neurons send a direct projection to the solitary nucleus in the medulla. Injections of anterograde tracers into the spinal cord gray matter label small numbers of axons within the solitary nucleus (Cliffer et al. 1989). Injections of retrograde tracers restricted to the solitary nucleus label neurons at all segmental levels in rats (Menetrey and Basbaum 1987; Esteves et al. 1993). Spinosolitary neurons were found in the marginal zone, lamina V, and the area around the central canal, the primary areas of the spinal gray matter in which nociceptive processing occurs. At this time, the neurons in the spinal cord that project to the solitary nuclei have not been physiologically identified and characterized. Therefore, it has not been established beyond doubt that they carry nociceptive information. Thus, the role of this projection is not certain. Many neurons within the solitary nuclei have ascending projections, suggesting that this polysynaptic projection could contribute to nociceptive processing.

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Aseptic Meningitis

► Headache in Aseptic Meningitis

ASIC

► Acid-Sensing Ion Channels

ASIC1a

► Acid-Sensing Ion Channels

ASIC1b: ASICβ, BNaC2β

► Acid-Sensing Ion Channels

ASIC2a: Mammalian Degenerin 1 (MDEG1), Brain Sodium Channel 1 (BNC1a, BNaC1a)

► Acid-Sensing Ion Channels

ASIC2b: Mammalian Degenerin 2 (MDEG2), Brain Sodium Channel 1 (BNaC1b)

► Acid-Sensing Ion Channels

ASIC3: Dorsal-Root Acid-Sensing Ion Channel (DRASIC)

► Acid-Sensing Ion Channels

ASICa, Brain Sodium Channel 2 (BNC2, BNaC2a)

► Acid-Sensing Ion Channels

ASICs

Synonyms

Acid-sensing ion channels

Definition

A family of proteins combined to form *a*cid-*s*ensing *i*on *c*hannels (ASIC) of the degenerin family. The channels are gated by acidity (threshold pH 6.8) and are often found in nociceptive afferents. There are several subtypes of ASICs including ASIC1, ASIC2, ASIC3, and ASIC4. ASICs are expressed throughout the central and peripheral nervous system. ASIC channels are related to epithelial sodium channels in the kidney (ENaC) and to degenerins in the model organism *Caenorhabditis elegans*. ASIC channels may play a role in mediating cardiac ischemic pain by sensing extracellular acidification. Mice and *C. elegans* worms, deficient in ASIC subunits, show deficits in mechanosensation.

Cross-References

- ▶ Acid-Sensing Ion Channels
- ▶ Nociceptors in the Orofacial Region (Skin/Mucosa)
- ▶ TRPV1, Regulation by Protons
- ▶ Visceral Pain Model; Esophageal Pain

ASO

- ▶ Antisense Oligonucleotide

Aspartate

Definition

Aspartate is an excitatory amino-acid neurotransmitter.

Cross-References

- ▶ Somatic Pain

A

Aspirin-like Drugs

- ▶ Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- ▶ NSAIDs and Their Indications
- ▶ NSAIDs, Mode of Action

Assessment

Definition

An assessment is a comprehensive description of a patient's condition designed to constitute a basis for treating or otherwise managing that condition. One systematic approach to assessment requires identifying the patient's physical, psychological, social, and vocational complaints, problems, or disabilities. Having been identified, these may be targeted individually and separately, or collectively, for treatment.

An assessment may be formulated in the absence of a diagnosis, and is thereby a substitute for a diagnosis; but it can also complement a diagnosis. In some instances, although a diagnosis may be available, it may not be possible to cure or to rectify the condition responsible for a patient's pain. In that event, formulating an assessment allows treatment to target the pain and its consequences instead of the actual cause.

Some practitioners might prefer to restrict the term "assessment" to apply to the act or process of obtaining information about a patient, and use the term "formulation" to apply to the actual description that results from this process.

Cross-References

- ▶ Psychological [Behavioral Health] Assessment of Pain

Assessment of Discomfort in Dementia Protocol

Synonyms

ADD protocol

Definition

Assessment of Discomfort in Dementia Protocol is an algorithm approach involving exclusion of common physical causes for discomfort in adults with dementia.

Cross-References

► Cancer Pain, Assessment in the Cognitively Impaired

Assessment of Hypoalgesia

► Hypoalgesia, Assessment

Assessment of Pain Behaviors

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Synonyms

Analysis of Pain Behavior; Observation of Pain Behavior; Recording of Pain Behavior

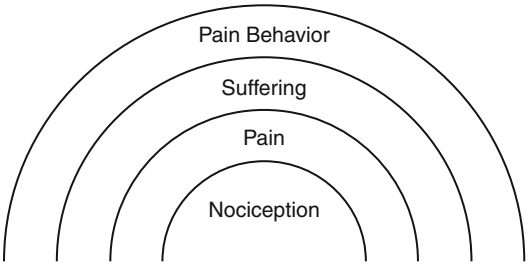
Definition

Patients who have pain exhibit a variety of behaviors that serve to communicate the fact that pain is being experienced. These behaviors have been termed "pain behaviors" (Fordyce 1976). Pain behaviors can be verbal (e.g., verbal descriptions of the intensity, location, and quality of pain; vocalizations of distress; moaning, or complaining) or nonverbal (e.g., withdrawing from activities, taking pain medication, pain-related body postures or facial expressions). Fordyce (1976) was one of the first to address the importance of pain behaviors. According to Fordyce's operant behavioral model, pain behaviors that initially occur in response to acute injury are sometimes maintained over much longer periods of time because they lead to reinforcing consequences. For example, a brief period of bed rest can be adaptive in response to ► acute pain, but when pain persists, excessive bed rest can promote deconditioning and decrease a person's tolerance for pain. In addition, attention from a concerned spouse may initially be helpful for someone coping with pain, but if that spouse becomes overly ► solicitous, such behavior may actually increase physical and psychological disability in the person experiencing pain (Fordyce 1976; Keefe and Lefebvre 1994). Pain behavior assessment allows one to identify problem pain behaviors and analyze the variables controlling those behaviors.

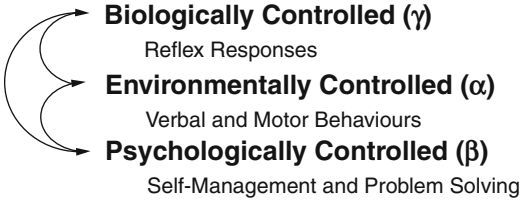
In the operant behavioral model (depicted in Fig. 1, adapted from Fordyce 1979), pain behaviors reflect the influence of three important factors:

1. Nociception: nervous system responses that produce aversive input
2. Pain: the conscious perception of nociception
3. Suffering: the negative emotional responses to nociception and pain

This model has several important implications. First, the model maintains that pain and pain behavior may be related and influence each other but are not necessarily synonymous. Thus, careful assessments of persons with pain should focus not only on underlying biological factors (e.g., nociception) but also on overt behaviors (e.g., verbalizations of pain, time spent in bed, pain-related body postures). Second, the model serves to guide treatment efforts designed to improve adjustment to persistent pain by



Assessment of Pain Behaviors, Fig. 1 Fordyce's (1979) behavioral model of pain



Assessment of Pain Behaviors, Fig. 2 Keefe and Lefebvre's (1994) systems model of pain behavior

modifying pain behavior. Behavioral treatments based on this model include graded activation programs in which:

- Patients learn to gradually increase their activity level
- Pain medications are switched from a ▶ pro re nata (prn) basis to time-contingent basis

Behavioral treatment protocols based on these methods have been found to be effective in randomized clinical trials (see Turner 1996 for a review of this literature).

Recently, behavioral theorists (e.g., Keefe and Lefebvre 1999) have developed more comprehensive models of pain behavior based on ▶ systems theory. As illustrated by Fig. 2, these models maintain that pain behavior can influence and be influenced by an array of environmental, psychological, and behavioral factors. For example, social reinforcement for engaging in exercise (an environmental factor) could increase ▶ self-efficacy (a psychological factor), which, in turn, could decrease emotional arousal (a biological factor) related to engaging in painful activities. Consistent with this model, researchers have identified a number of psychological and social variables related to pain behaviors. Patients who are depressed, for example, have been shown to exhibit higher levels of pain behavior (Keefe et al. 1986), while those who report a high degree of self-efficacy, or confidence in their ability to control pain, exhibit lower levels of pain behavior (Buckelew et al. 1994).

Characteristics

There are three basic methods of pain behavior assessment: self-monitoring, automated recording, and direct observation.

Self-monitoring

In self-monitoring, patients directly record their own behavior, including key, pain-related behaviors. This is often done using a daily diary, similar to that initially used by Fordyce (1976), which asked the individuals to record on an hourly basis the amount of time they spent sitting, standing or walking, and reclining, along with their pain medication intake. Diary data can often be examined and analyzed in treatment sessions using simple graphs. Patients, for example, who show a very low level of uptime (time spent up and out of the reclining position) may benefit from behavioral and physical therapy interventions designed to increase their level and range of activity. One concern about using self-monitoring is the degree to which these records are reliable and valid. However, recent research indicates that high-quality data can be obtained from daily diary recording methods if patients receive systematic training (Keefe et al. 1997).

The major strengths of self-monitoring are that it is simple and inexpensive, can be used over long time periods, provides a better real-time measure of behavior than retrospective reports or questionnaires, and can increase a patient's awareness of his or her own behavior.

Automated Recording

Several electromechanical devices have been developed to automatically record important behaviors, such as time spent up and out of bed or activity level. Recently, actigraphy has been

used to monitor activity level (Sugimoto et al. 1997). A commercially available device, the Actigraph, monitors activity level by using an advanced ▶ accelerometer to detect motion and a microprocessor to control how data on such motion is collected and stored. The device can be worn by patients in their natural environment to provide continuous, objective information concerning their overall activity level (Sugimoto et al. 1997).

Direct Observation

In direct observation, observers who are trained in the coding of pain behavior carefully watch patients as they engage in daily activities and record the pain behaviors that are observed. Two approaches to direct observation have been used: standard behavior sampling and naturalistic observation.

Standard Behavior Sampling

Clinical observations suggest that the level of pain behavior varies depending on what activities a patient is engaged in. To standardize the conditions under which pain behavior is sampled, researchers have asked patients to engage in a series of standard activities, and then observed the pain behaviors that occur. A good example of this strategy is the observation method developed by Keefe and Block (1982) for recording pain behavior in chronic low back pain patients. Patients participated in a 10-min session in which they were asked to sit, stand, walk, and recline for 1–2 min, each in randomized order. The sessions were videotaped and then scored by trained observers using an interval recording strategy, in which the observer watches for 20 s and records for 10 s. The observers coded five pain behaviors:

1. Guarding: abnormally slow, stiff, interrupted, or rigid movement
2. Bracing: stiff pain avoidant static position
3. Rubbing: touching or holding of pain area
4. Grimacing: obvious pain-related facial expression
5. Sighing

Standard behavioral sampling can yield data that is both highly reliable and highly valid. Keefe and Block (1982) tested and found high interobserver ▶ reliability (independent observers showed a high percentage of agreement on the behaviors observed), construct ▶ validity (behavior observed correlated significantly with pain ratings of naïve observers), and discriminate validity (the measures discriminated between the low back pain patients and pain-free controls). The procedure used by Keefe and Block has been modified to record the pain behaviors of arthritis patients and has been shown to be similarly reliable and valid (McDaniel et al. 1986).

Standard behavior sampling is a useful method of pain behavior assessment. Pain behaviors have been shown to be more frequently observed when a patient is moving, than when in a static position (Keefe and Block 1982). One can thus structure a standardized situation to elicit more pain behaviors than might otherwise be observed. Clinicians can use standard behavior sampling to evaluate treatment effects, by comparing the pain behaviors observed before and after treatment is received. By standardizing the situation under which pain behavior is observed, it is possible to analyze the social and psychological variables that contribute to those behaviors. For example, patients who report higher levels of pain when in the room with their spouse, as opposed to a neutral observer, may have an overly solicitous spouse who contributes to their display of pain behaviors. Romano et al. (1992) videotaped 50 chronic pain patients and their spouses as they jointly preformed specified tasks. It was found that spouse solicitous behaviors were significantly more likely than chance to both precede and follow nonverbal pain behaviors.

Naturalistic Observation

It is often desirable to observe and record pain behavior in naturalistic clinical settings, such as an inpatient unit or physical examination. Keefe et al. (1987) developed an observation method for recording the pain behaviors and activity level of patients in inpatient pain management units. Their method was designed to be performed by the nursing staff as part of their normal duties.

Daily graphs of activity level and pain behavior generated from these observations were used to identify problem behaviors, make treatment decisions, and evaluate patient progress. Pain behavior assessment can also be conducted during a physical examination. For example, Keefe et al. (1984) recorded the pain behavior exhibited by low back pain patients during a physical examination. A higher level of pain behavior was significantly correlated with a greater number of mechanical and neurological findings.

It is possible to combine elements of naturalistic and standard behavior sampling. For example, Richards et al. (1982) designed a standardized observation method, the University of Alabama at Birmingham (UAB) Pain Behavior Scale, which is intended to be used in a naturalistic setting. During morning rounds, the patient is briefly observed walking, standing, and moving from sitting to standing and from standing to sitting. Behaviors are recorded and rated as to their frequency and severity on a three-point scale. Reliability between observers is generally quite high, and the method requires minimal training.

In sum, over the past 25 years, clinical researchers have developed and refined a number of methods for pain behavior assessment. These methods have been shown to be reliable and valid, and are now being widely used in the assessment of patients suffering from ▶ chronic pain and persistent, disease-related pain. In clinical settings, pain behavior assessment is an important component of any comprehensive assessment of patients suffering from chronic pain.

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Assimilation

Definition

Giving up the values, beliefs, material culture, and practices of their native group and adopting those of the host culture

Cross-References

▶ Cancer Pain, Assessment of Cultural Aspects

Association Study

Synonyms

Allele dosage study

Definition

Also known as an allele dosage study, this involves comparing the frequencies of alleles of genes or DNA markers between different phenotypic groups (e.g., those with a disease versus those without). If allele frequencies differ between the groups, the gene examined (or one very nearby) is implicated in the trait in question.

Cross-References

▶ Alleles
▶ Opioid Analgesia, Strain Differences

Astrocytes

Synonyms

Astroglia

Definition

Astrocytes are star-shaped glial cells integrally involved in synaptic communication by providing nutrients, support, and insulation for neurons of the central nervous system. As immunocompetent cells, astrocytes can be activated by bacteria and viruses to release classical immune products. Current studies suggest that astrocytes maintain exaggerated pain in pathological pain models.

Cross-References

▶ Cord Glial Activation
▶ Diencephalic Mast Cells
▶ Glial Cells in Orofacial Pathological Pain Mechanisms

Astroglia

▶ Astrocytes

Asymmetric Junctions

Definition

Gray (1962) divided the central synapse into two types, based on the differences in synaptic density between the pre- and postsynaptic membranes, asymmetric (type I) and symmetric (type II).

Cross-References

▶ Trigeminal Brainstem Nuclear Complex, Anatomy

Ataxia

Definition

Imbalance and poor control of various parts of the body; may reflect damage to the large sensory neurons that subserve joint position sense and coordination.

Cross-References

► Diabetic Neuropathies

Atenolol

Definition

Beta-blocker

Cross-References

► Preventive Migraine Therapy

At-Level Neuropathic Pain

Definition

Neuropathic pain located in the segments adjacent to the level of the spinal cord lesion. Also referred to as border-reaction, end-zone, segmental, or radicular pain.

Cross-References

► Spinal Cord Injury Pain Model, Contusion Injury Model

At-Level Phenomena

Definition

Alterations in sensations or spontaneous sensations that are referred to the body region, which is represented by the region of the spinal cord that is damaged by spinal injury

Cross-References

► Spinal Cord Injury Pain Model, Cordotomy Model

ATP

► Adenosine 5′ Triphosphate

ATP-Dependent Na+/K+ Pump

Definition

The principal primary active transport system in neurons, Na/K-ATPase, utilizes energy to maintain cation cellular concentrations by extruding Na and accumulating K ions, thus creating an electrical potential across the neuronal cell membrane. It is estimated that 25–40 % of brain energy utilization may be related to Na/K-ATPase activity. Abnormalities in the pump may lead to neuronal dysfunction, although the exact relationship to familial hemiplegic migraine is not known.

Cross-References

► Migraine, Childhood Syndromes

ATrPw

► Attachment Trigger Point

Attachment Trigger Point

Synonyms

ATrPw

Definition

An attachment trigger point is pathogenetically distinct from, and secondary to, a central myofascial trigger point. It is a region of inflammatory-type reaction (an enthesopathy) at the musculotendinous junction, or at the bony attachment of the muscle where the taut band fibers attach and produce increased sustained tension.

Cross-References

► Myofascial Trigger Points

Attentional Bias

Definition

The tendency to selectively attend to threatening information in comparison to neutral information

Cross-References

► Hypervigilance and Attention to Pain

Attentional Mechanisms

Definition

Attentional mechanisms are cognitive processes that focus sensory processing on particular inputs and de-emphasize other inputs.

Cross-References

► Spinothalamic Tract Neurons, Descending Control by Brain Stem Neurons

Attitude

► Chronic Gynecological Pain, Doctor-Patient Interaction

Attributable Effect

► Effect Size

Attributable Effect and Number Needed to Treat

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Synonyms

Effectiveness; Efficacy; NTT; Number needed to treat

Definition

The ► attributable effect of a treatment is the extent to which it achieves its outcomes, beyond that achieved by nonspecific effects of the intervention. It is the extent to which outcomes can be attributed to the specific components of a treatment by which it is purported to work.

The ► number needed to treat (NNT) is a measure of how effective a treatment is. Specifically, it is the number of patients who must achieve a particular outcome before one of those patients, on average, can be claimed to have responded because of the specific effects of the treatment (as opposed to having responded to the nonspecific effects of treatment). As a measure of

the power of a treatment, NNT effectively discounts the apparent power by the extent to which outcomes are achieved by nonspecific effects. The larger the number, the more the treatment works by nonspecific effects. The smaller the number, the more the treatment has a specific effect.

Attributable Effect and Number Needed to Treat, Table 1 The categorical results of a clinical trial of an index treatment

Treatment	Result	
	Success	Failure
Index	a	b
Control	c	d

Characteristics

The attributable effect is derived from categorical data. It requires data on whether the treatment has worked or not, in comparison with a control treatment, in the form shown in Table 1. Ideally, the control treatment should be one with no specific effects, i.e., a ▶ placebo.

For the purposes of the initial explanation, it does not matter what the definitions are of success or failure; that comes later. All that is important is that (somehow) a decision is made as to whether the treatment has been successful or not.

The proportion of patients who succeeded with the index treatment is a/(a + b). Let this proportion be P_{index}, which is expressed as a decimal.

The proportion of patients who succeeded with the control treatment is c/(c + d). Let this proportion be $P_{control}$, which is expressed as a decimal.

The attributable effect (AE) of the index treatment is the extent to which its success rate exceeds that achieved by the control treatment. The argument is that the control treatment provides nonspecific effects, but these are also a component of the index treatment. The attributable effect of the index treatment is what remains when the success rate of the index treatment is discounted for these nonspecific effects.

Mathematically,

$$AE = P_{index} - P_{control}$$

Since P_{index} and $P_{control}$ are both proportions, AE is also a proportion. It stipulates the proportion of patients treated, whose successful outcome can be legitimately attributed to the effects of the index treatment, above and beyond any nonspecific effects.

Thus, if N patients are subjected to the index treatment, one would expect that $(N \times P_{index})$ patients would have a successful outcome. However, $(N \times P_{control})$ of these patients would, on average, have responded because of nonspecific effects of the treatment.

Therefore, only $N(P_{index} - P_{control})$ would have responded because of the specific effects of the treatment, i.e., $(N \times AE)$. In other words, when N patients are treated, only $(N \times AE)$ patients respond to the attributable effect of the treatment.

Any group of patients who achieve a successful outcome will consist of those who responded to the attributable effect of the treatment and those who responded to nonspecific effects of treatment. There is no way of determining which particular patient or patients responded to the attributable effect or to nonspecific effects, but outcome data from large samples of patients can be used to show how many, on average, would have responded to the attributable effect. The number needed to treat (NNT) is used to indicate this proportion.

Let N_S be the number of patients who achieve a successful outcome. This number consists of two types of patients: those whose outcome was due to the attributable effect (N_{AE}) and those who had nonspecific responses (N_{NS}), i.e.,

$$N_S = N_{AE} + N_{NS}$$

But

$$N_{AE} = N_S \times AE$$

And

$$N_{NS} = N_S \times (1 - AE)$$

Wherefore,

$$N_S = [N_S \times AE] + [N_S \times (1 - AE)]$$

In large studies, N_S will be large, and both $[N_S \times AE]$ and $[N_S \times (1 - AE)]$ will be large. In small studies, N_S will be small, and both $[N_S \times AE]$ and $[N_S \times (1 - AE)]$ will be correspondingly small. Nevertheless, the proportion between $[N_S \times AE]$ and N_S will be the same.

Clearly, that proportion is mathematically simply the attributable effect, i.e.,

$$[N_S \times AE]/N_S = AE$$

However, this is an abstract number, with no immediate, apparent relationship to clinical practice.

A way of expressing the proportion more meaningfully is to express it in terms of whole patients.

Since $[N_S \times AE]$ will always be smaller than N_S, the smallest sample size in which the proportion can be expressed in terms of whole patients is one in which $[N_S \times AE]$ equals 1:

$$[N_S \times AE] = 1.$$

In which case,

$$N_S = 1/AE$$

Under these conditions, N_S becomes the number needed to treat (Cook and Sackett 1995, Laupacis et al. 1988), i.e.,

$$NNT = 1/AE$$

Under these conditions, for every NNT patient with a successful outcome, 1 will have responded to the attributable effect, and the remainder will have responded to nonspecific effects. All that is required to determine the ratio between attributable and nonspecific effects is a knowledge of the attributable effect.

For example, if an index treatment has a success rate of 78 %, and a control treatment has a success rate of 45 %,

$$P_{index} = 0.78$$

$$P_{control} = 0.45$$

$$P_{index} - P_{control} = 0.33$$

$$AE = 0.33$$

$$1/AE = 3$$

$$NNT = 3$$

Thus, for every three patients with a successful outcome, 1 can be attributed to the specific effects of the treatment, while the other 2 outcomes were due to nonspecific effects. If 30 patients were to have a successful outcome, 10 would be due to the attributable effect and 20 due to nonspecific effects.

Consider another example, in which the success rate of a treatment is 56 % and that of the control treatment is 36 %:

$$P_{index} = 0.56$$

$$P_{control} = 0.36$$

$$P_{index} - P_{control} = 0.20$$

$$AE = 0.20$$

$$1/AE = 5$$

$$NNT = 5$$

For every five patients with a successful outcome, 1 is due to the specific effects of treatment, and 4 are due to nonspecific effects.

Clearly, the larger the NNT, the weaker the treatment is, for a greater proportion of patients who appear to respond do so because of nonspecific effects. Conversely, the smaller the NNT, the more powerful the treatment is. As a benchmark, an NNT of 3 or less is considered to be good.

However, NNT is not a measure of how effective a treatment is overall. It is a measure of how much a particular outcome is due to specific effects of the treatment, compared with nonspecific effects. In these terms, a powerful treatment is one in which much, or most, of the outcome is due to specific effects, i.e., the attributable effect, as opposed to nonspecific effects. Less powerful treatments may nevertheless be effective, but their outcomes are due less to the attributable effect and more to nonspecific effects. NNT reveals the proportion between these two types of effect.

The implication of a large NNT is that most of the outcome observed is due to nonspecific effects and could be achieved without using the index treatment at all. Accordingly, NNT is an index of the utility of a treatment.

If a treatment is costly, or carries a high risk of complications, and has a large NNT, its use can be called into question. The large NNT indicates that because most of the effect is nonspecific, the cost and risk of the index treatment may not be justified, because the same, or similar, outcome might be achieved by other means.

If the NNT is high, it means that doctors will need to treat large numbers of patients before they get an attributable effect. This consumes time and effort. The doctors might consider if this large effort is worthwhile and whether their efforts might not be better spent using another treatment.

A large NNT also means that funds are being expended on large numbers of patients in order to get gains in a minority. Doctors might reflect as to whether these funds might be better spent differently or if as good a result might be achieved, on average, by using less expensive treatments.

For example, the NNT for epidural steroids is about 11 (McQuay and Moore 1996). Effectively, this means that for every 11 patients who get a successful outcome, only one can be claimed to have responded to the specific effects of the injections. The cost of that one success is not just the time and expense required for that one case but also the costs incurred for the other 10 patients.

Subscripts

The NNT is not a single measure of all of the effects of a treatment. It measures the power of a treatment only with respect to the outcomes specified in the original table of data from which the NNT was derived. Therefore, the pedantic but accurate use of NNT requires that the outcome be specified. This might be done as a subscript but is usually omitted in practice because of the typographic impositions incurred. Nevertheless, the concept is conveyed by this notation.

If the success in question is "ability to walk 1 km in 10 min," the NNT for that outcome would be recorded as

$$\mathrm{NNT}_{\text{ability to walk1 km in 10 min}}$$

If the success in question is "achieving a reduction of at least 50 % in VAS score," the NNT for that outcome would be

$$\mathrm{NNT}_{\text{reduction inVAS by 50\%}}$$

No one uses this notation, but it is taken as understood. Readers should understand that authors leave this implicit. They expect readers to have noticed what outcome they are addressing. Therefore, readers should consult the methods and results sections of any study to find out what the subscript would have been had the authors used this complete notation.

This is not an example of academic pedantry or an idiosyncrasy. It is an important realization lest NNT be abused. As a number, an NNT might look good and might be used to extol a treatment as successful and useful. However, the treatment might not be as good as it sounds if the reader realizes that the NNT pertains to an unconvincing or uncompelling outcome.

For example, the NNT for many drug therapies in pain medicine is about 3, which is considered a good score. Readers might, however, care to ask: Exactly what was the outcome measure? The risk is of readers being lulled into believing that with an NNT of 3, they could expect that for every three patients that they treat, one will be totally cured. This is not the case, for the NNT in question actually refers to "patients lowering

their VAS by 50 %." It says nothing about patients being completely relieved. In actual fact, in this instance, an NNT of 3 means that for every three patients who obtained greater than 50 % relief of their pain, only one achieved this because of the effects of the drug used.

For NNT to be meaningful, the subscript must be specified. For a complete picture of how powerful a treatment is, authors should indicate the NNT for each outcome, e.g., $NNT_{complete\ relief}$, $NNT_{50\ \%\ relief}$, and $NNT_{return\ to\ work}$.

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Atypical Facial Neuralgia

► Atypical Facial Pain: Etiology, Pathogenesis, and Management

Atypical Odontalgia

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Definition

The IASP (International Association for the Study of Pain) has defined atypical odontalgia as a severe throbbing pain without major pathology, or it may be defined as pain of dental origin without a definitive organic cause (Woda and Pionchon 1999).

Characteristics

Pain is localized to a tooth, or sometimes more than one tooth, which shows no dental pathology. Pain may be spontaneous or evoked by hot or cold foods and is usually strong and may throb (Czerninsky et al. 1999).

Etiology

Marbach (1978) postulated that pain is the result of previous trauma, such as tooth extraction or tooth pulp extirpation, which interferes with the central nervous system pain modulatory mechanisms and coined the name "phantom tooth pain." This idea is supported by the observation that experimental tooth extraction produces brainstem lesions in the trigeminal nucleus caudalis and that more extensive tooth pulp injury is associated with heightened excitability changes of trigeminal brainstem neurons (Hu et al. 1990). Although far from proven, a ► deafferentation associated with peripheral nerve injury may be responsible for some types of atypical facial pain. Vascular changes are other possible underlying mechanisms for atypical facial pain. ► Neurovascular orofacial pain (NVOP) may be especially relevant to the diagnosis of atypical intraoral pain (atypical odontalgia). NVOP, possibly a new diagnostic entity (Sharav and Benoliel 2008), shares many of the signs and symptoms common to other ► neurovascular-type craniofacial pain. It was found to be associated with atypical toothache (Benoliel et al. 1997) and to mimic ► pulpitis (Czerninsky et al. 1999). The onset of VOP is around 40–50 years of age, and it affects females at a rate of 2.5 times more than males.

It is possible that cases with neurovascular or other undiagnosed orofacial pain metamorphose into and coexist with trigeminal neuropathy as a result of nerve injury from repeated dental interventions aimed at pain relief. This theory is supported by findings that chronic orofacial pain patients undergo extensive but often misguided surgical interventions (Sharav and Benoliel 2008).

While pulp extirpation may eliminate the pain for a short time, pain tends to recur in another

tooth (Czerninsky et al. 1999). The prophylactic use of beta-blockers or tricyclic antidepressants is usually beneficial (Benoliel et al. 1997; Czerninsky et al. 1999; Sharav and Benoliel 2008, and see Chap. 9).

Cross-References

► Atypical Facial Pain: Etiology, Pathogenesis, and Management

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Atypical Facial Pain: Etiology, Pathogenesis, and Management

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Synonyms

Atypical facial neuralgia; Atypical odontalgia; Burning mouth syndrome; Complex regional pain syndrome; Idiopathic orofacial pain; Phantom tooth pain; Stomatodynia

Definition

The original term, atypical facial pain, is a historical counterpart to the "typical" presentation of trigeminal neuralgia. This ill-defined chronic facial pain condition is employed as a "wastebasket" definition, applied by elimination, of facial pain "not fulfilling other criteria." Recently, attempts have been made to define atypical facial pain in a more positive way and not merely by elimination (Woda and Pionchon 1999; Sharav and Benoliel 2008). Atypical facial pain can be described as chronic facial pain of constant intensity, which usually has a burning quality and occasionally intensifies to produce a throbbing sensation. Pain does not wake the patient from sleep and is not triggered by remote stimuli, but may be intensified by stimulation of the painful area itself. No local signs are present that can be related to the pain. No etiological factors are identifiable in the orofacial region.

Characteristics

This chronic intraoral or facial pain may start in one quadrant of the mouth and often spreads across the midline. Changes in pain location are frequent and may result in extensive dental work, alcohol nerve blocks, and surgery that do not usually alleviate the pain. Pain location is often ill-defined. Pain is usually constant and of moderate intensity and has a burning quality that occasionally intensifies to produce a throbbing sensation. However, pain does not wake the patient from sleep. The pain is not triggered by remote stimuli, but may be intensified by stimulation of the painful area itself. Accompanying ► autonomic phenomena are not observed. Typically, there is a lack of objective signs in most of these patients. The age range at examination is wide (20–82 years); the mean age of patients with ► atypical odontalgia is around 45–50 years (Marbach 1978; Vickers et al. 1998) and of patients with ► burning mouth syndrome is around 55 years (Grushka et al. 1987). All reports of atypical oral and facial pain indicate that an overwhelming majority are females (82–100 %).

Atypical facial pain should be differentiated from pains associated with a causative lesion. The symptoms of chronic atypical facial pain may be observed secondary to a slow-growing cerebellopontine angle tumor. The most common intraoral presentations of atypical facial pain are ▶ atypical odontalgia and ▶ burning mouth syndrome, and these are therefore discussed separately below.

Etiology

There is no identifiable uniform etiology of atypical oral and facial pain (Loeser 1989). Several underlying mechanisms have been proposed. A number of reports have suggested that atypical facial pain is a psychiatric disorder (Feinmann et al. 1984). Depression is considered the most likely diagnosis and is explained based on the catecholamine hypothesis of affective disorders. However, Sharav et al. (1987) showed that only 2 of their 28 patients with chronic facial pain were cortisol non-suppressors on the dexamethasone suppression test and that half the patients were not depressed at all. Grushka et al. (1987) conclude that the personality characteristics of patients with burning mouth syndrome are similar to those seen in other chronic pain patients and that these personality disturbances tend to increase with increased pain. The major logical fallacy for the purely psychological model of orofacial pain is that it assumes that failure to find a biological marker for a particular orofacial pain condition implies that psychological factors must be primary. However, pain researchers increasingly recognize that the association between observable tissue damage or other identifiable pathological process and the presence or extent of pain is weak at best (Sharav and Benoliel 2008). Vickers et al. (1998) suggested a possible neuropathic pain mechanism, but pointed out that it cannot explain all cases, and suggested that some may fit the diagnosis of ▶ complex regional pain syndrome.

Treatment

While various treatment modalities are used for atypical oral and facial pain, the predominant trends are clear. All authors firmly recommend avoiding surgical or dental interventions for the relief of pain (Loeser 1989) since such interventions usually exacerbate the condition. Reassurance, psychological counseling, and the use of antidepressants, particularly from the tricyclic group, have been found to be a promising mode of therapy. Two double-blind controlled studies demonstrated that tricyclic antidepressant drugs were superior to placebo in reducing chronic facial pain (Feinmann et al. 1984; Sharav et al. 1987). Furthermore, Sharav et al. (1987) showed that ▶ amitriptyline was effective, for most chronic facial pain states, in a daily dose of 30 mg or less, and that the relief of pain was independent of the antidepressant activity. As with other chronic pain conditions, particularly those with unclear etiologies, it has been associated with underlying psychological distress, and these patients may particularly benefit from cognitive behavioral therapy (CBT) (Sharav and Benoliel 2008).

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Audit

▶ Postoperative Pain, Data Gathering and Auditing

Audit Report

Definition

An audit report refers to conclusions made by grouping data according to criteria, so that inferences can be made from them.

Cross-References

▶ Postoperative Pain, Data Gathering and Auditing

Aura

Definition

In the context of migraine, a recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 min and last for less than 60 min. The most common aura is visual consisting of a bright zig-zag pattern of visual disturbance moving slowly across the filed and leaving after it an area of visual loss.

Cross-References

▶ Hemicrania Continua
▶ Migraine, Pathophysiology
▶ New Daily Persistent Headache

Autacoids

▶ Prostaglandins, Spinal Effects

Autobiographical Memory

Definition

Autobiographical memory is memory of one's life. It is central to the establishment and maintenance of the self-concept and one's personal and social identity, i.e., the sense of who you are. Autobiographical memory is considered to comprise of two types of memories: memories about specific experiences at specific times and knowledge of facts relevant to the self, e.g., one's date of birth, information about family relationships, schooling, and historical events that have occurred in one's lifetime.

Cross-References

▶ Pain Memory

Autogenic Feedback

Definition

A combination of autogenic training and thermal biofeedback, used for the purpose of promoting hand warming and generalized relaxation.

Cross-References

▶ Biofeedback in the Treatment of Pain

Autogenic Training

Definition

A form of relaxation training where verbal cues (e.g., "my hands are heavy and warm") are paired with physiological aspects of the relaxation process.

Cross-References

▶ Relaxation in the Treatment of Pain
▶ Relaxation Training
▶ Therapy of Pain, Hypnosis

Autologous Graft

Definition

Transplant tissue or cell source that is taken from the same or genetically identical individual

Cross-References

► Cell Therapy in the Treatment of Central Pain

Autonomic

Definition

Pertaining to the part of the vertebrate nervous system that regulates involuntary action, as of the intestines, heart, and glands. This is divided into the sympathetic nervous system, the parasympathetic and the enteric (Furness 2006; Jänig 2006) nervous system (Furness 2006; Jänig 2006).

Cross-References

► Psychiatric Aspects of Visceral Pain

References

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Autonomic Dysreflexia

Definition

Autonomic dysreflexia is a syndrome in persons with spinal cord injury (mostly complete) above the midthoracic segmental level. This syndrome is characterized by hypertension (increase of diastolic and systolic arterial blood pressure), increased sweating, piloerection, decrease of blood flow through skin, nasal congestion, bradycardia, and headache. It is generated by reflex activation of sympathetic systems to stimulation of spinal afferent neurons innervating viscera (e.g., during distension or contraction of urinary bladder or rectum) or deep somatic structures (joints, skeletal muscle). Bradycardia is secondary to stimulation of arterial baroreceptors via reflex activation of parasympathetic cardiomotor neurons (Jänig 2006; Mathias and Bannister 2012).

Cross-References

► Spinal Cord Injury Pain

References

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Autonomic Features

Definition

Symptoms referable to activation or inhibition of the peripheral pathways of the autonomic nervous system. These symptoms may include increase or decrease of blood flow, blood pressure, and sweating, changes in functioning of visceral organs, ptosis, miosis, lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. For example, the latter autonomic symptoms classically accompany attacks of cluster headache but may also occur during painful exacerbations of hemicrania continua.

Cross-References

▶ Hemicrania Continua

Autonomic Functions

Definition

Nervous regulation of the homeostasis of blood pressure, cardiac rhythm, blood circulation, blood fluid balance, respiration, pupil diameter, visceral motility, exocrine and neuroendocrine secretions, energy metabolism, and internal temperature. This is achieved by a constant interaction between the central and peripheral nervous systems.

Cross-References

▶ Hypothalamus and Nociceptive Pathways
▶ Pain Processing in the Cingulate Cortex, Behavioral Studies in Humans

Autonomic Nervous System

Definition

The autonomic nervous system is that part of the nervous system that controls body functions not under our direct voluntary control, such as the cardiovascular system, gastrointestinal tract, pelvic organs, body temperature, and some other functions. It includes in the periphery the sympathetic, parasympathetic, and enteric nervous system (Jänig 2006).

Cross-References

▶ Amygdala, Pain Processing and Behavior in Animals
▶ Diabetic Neuropathies
▶ Hereditary Neuropathies

References

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Autonomic Phenomena

Definition

Signs and symptoms pertaining to the functioning of the autonomic nervous system. For example, local autonomic signs in vascular-type craniofacial pain include tearing, redness of eye, nasal congestion, rhinorrhea, and cheek swelling.

Autonomic Reactions/Symptoms

Definition

Changes of blood pressure, heart rate, blood flow, sweating, pupil diameter, visceral motility, visceral secretion, etc., mediated by autonomic systems (mostly sympathetic when triggered by a noxious stimulus).

Cross-References

▶ Autonomic Functions
▶ Hypnic Headache
▶ Parabrachial Hypothalamic and Amygdaloid Projections

Autoregulation of the Cerebral Vessels

Definition

Autoregulation of the cerebral vessels refers to the capability of the cerebral vascular system to hold the cerebral perfusion stable during a wide range of systemic blood pressure.

Cross-References

► Primary Exertional Headache

Autotomy

Definition

Self-injurious behavior in which a body part that has been denervated or deafferented is compulsively licked, bitten, and chewed (self-mutilation). This is commonly observed in animals following neurectomy or dorsal rhizotomy, and is widely (although not universally) presumed to reflect the animal's response to dysesthesias or pain in the affected limb (anesthesia dolorosa). In the animal model of peripheral neurectomy, animals typically begin biting off nails and digits on the denervated paw within a few days following nerve injury.

Cross-References

► Anesthesia Dolorosa Model, Autotomy
► Dietary Variables in Neuropathic Pain

Autotomy Model of Neuropathic Pain

► Anesthesia Dolorosa Model, Autotomy

Autotraction

► Traction

Avocado-Soybean Unsaponifiables

► Nutraceuticals

Avoidance Behavior

Definition

Behavior aimed at avoiding or postponing undesirable situations or experiences. In chronic low back pain patients, avoidance behavior often consists of avoiding those activities that are believed to promote pain and/or (re)injury.

Cross-References

► Disability, Fear of Movement
► Hypervigilance and Attention to Pain
► Muscle Pain, Fear-Avoidance Model

Avulsion

Definition

Avulsion refers to the traumatic disconnection of nerve root from the spinal cord.

Cross-References

► Plexus Injuries and Deafferentation Pain

Avulsion Fracture

Definition

A fracture caused by a muscle pulling off a piece of bone from the area of the muscle's attachment.

Cross-References

► Cancer Pain Management, Orthopedic Surgery

Awakening

Definition

An increase in EEG and heart rate frequency with a rise in muscle tone that lasts more than 10 s. Subjects remain in sleep and are not usually aware of external influences. They could complain of non-refreshing sleep on the following day.

Cross-References

► Orofacial Pain, Sleep Disturbance

Awareness

► Consciousness and Pain

Axillary Block

Definition

Injection of local anesthetic into the axillary brachial plexus sheath resulting in sensory blockade of the hand. The forearm and inner aspect of the arm may be incompletely blocked due to inadequate blockade of the musculocutaneous and median nerves.

Cross-References

► Acute Pain in Children, Postoperative

Axolemma

Definition

Membrane around the nerve cell; the membranous sheath that encloses the long thin extension of a nerve cell (axon)

Cross-References

► Perireceptor Elements

Axon

Definition

An appendix of a neuron which carries action potentials either from the cell body away or, in case of afferent neurons in the peripheral nervous system, from the peripheral axon terminals toward the central nervous system. Axons can be very long, in case of peripheral nerves more than a meter, and might be branched. Branches are called axon collaterals. In contrast, dendrites, the other type of appendices of neurons, carry information toward the cell body of the neuron (in some rare cases also as action potentials).

By some authors axons have been simply defined as neuronal appendices carrying information from the cell body away. This excludes, however, the peripheral afferent nerves from this definition. Otherwise, they have much in common with other axons.

Cross-References

► Nociceptors, Action Potentials, and Post-Firing Excitability Changes
► Spinothalamic Tract Neurons, Morphology
► Toxic Neuropathies
► Wallerian Degeneration

Axon Reflex

Definition

The activation of a nociceptive C-fiber results not only in the transmission of action potentials toward the CNS but also along its branching fibers back toward the skin. This leads to the release of the vasoactive substances CGRP

(calcitonin-gene-related peptide) and substance P. CGRP induces vasodilatation by binding to receptors at precapillary arterioles (flare reaction), Substance P induces plasma extravasation from venoles. These reactions are confined to the extension of the arborization of the excited C-unit(s) and have been called "neurogenic inflammation."

Cross-References

- ▶ Nociceptor, Axonal Branching
- ▶ Nociceptors in the Dental Pulp

Axonal Action Potentials

- ▶ Nociceptors, Action Potentials, and Post-Firing Excitability Changes

Axonal Arborization

Definition

All branches of an axon can be seen as an axonal arborization. Branches may depart from a stem axon often, but not always, in the periphery, close to the terminals.

Cross-References

- ▶ Spinothalamic Tract Neurons, Morphology

Axonal Degeneration

Definition

The pathologic term to describe disintegration of nerve fibers (axons). If an axon is cut, the distal part separated from the neuronal cell body will always degenerate. Degeneration may also occur in some forms of neuropathies, usually starting from the peripheral terminals which are the first to lose their receptive and conductile properties (dying back neuropathy).

Cross-References

- ▶ Toxic Neuropathies

Axonal Sprouting

- ▶ Sympathetic and Sensory Neurons After Nerve Lesions, Structural Basis for Interactions

Axonal/Axoplasmic Transport

Definition

Anterograde axonal (or axoplasmic) transport is the energy-dependent mechanism by which materials synthesized in the cell body are moved to distal regions of neuronal processes. It is broadly divided into fast axonal transport, which involves the movement of materials within vesicles such as neurotransmitters, and slow axonal transport, incorporating movement of cytoskeletal proteins and cytoplasmic constituents. Retrograde axonal transport is the movement of materials such as proteins destined for degradation or molecules acquired from the external environment back to the cell body. Impaired axonal transport has been implicated in many neuropathies, including diabetic neuropathy, as it would be likely to starve peripheral parts of the axons of critical materials and also disrupt the delivery of factors from the environment back to the cell body.

Cross-References

- ▶ Dietary Variables in Neuropathic Pain
- ▶ Neuropathic Pain Model, Diabetic Neuropathy Model
- ▶ Opioids and Inflammatory Pain
- ▶ Toxic Neuropathies

Axotomy

Definition

Separation of an axon from its cell body (perikaryon). Axotomy of a nerve or a dorsal root is frequently used as an animal model for nerve injury and neuropathic pain, particularly in rats or mice. When the axon of a neurone is separated from the cell body, the neurone is said to be axotomized. While the distal part of the lesion degenerates, the proximal stump often becomes swollen with accumulated organelles originally destined for the nerve terminals. The soma responds within ~6 h, by changing the synthesis of proteins from transmitter synthesizing enzymes, to those associated with regeneration of axonal membrane and other structural components. If regeneration is prevented, e.g., by scar formation, a neuroma forms.

Cross-References

- ▶ Immunocytochemistry of Nociceptors
- ▶ Peptides in Neuropathic Pain States
- ▶ Retrograde Cellular Changes After Nerve Injury
- ▶ Sympathetic and Sensory Neurons after Nerve Lesions, Structural Basis for Interactions

Azathioprine

Definition

Azathioprine is an immunosuppressive agent, purine derivate, steroid-sparing agent in cranial arteritis, and treatment of choice in Behçet's disease.

Cross-References

- ▶ Headache Due to Arteritis
- ▶ Vascular Neuropathies