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.

- ► 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 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.

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

A Beta(β) Afferent Fibers

- ► A Afferent Fibers (Neurons)

A Delta(δ) Afferent Fibers (Axons)

- ► A Afferent Fibers (Neurons)

A Delta(δ)-Mechanoheat Receptor

- ► Polymodal Nociceptors, Heat Transduction

A Delta(δ)-Mechanoreceptor

- ► Mechanonociceptors

AAV

- ► Adenoassociated Virus Vectors

Abacterial Meningitis

- ► Headache in Aseptic Meningitis

Abdominal Skin Reflex

Definition

Similar to the flexion withdrawal reflex, this reflex is a protective reflex of the trunk, and is intended to protect the abdominal organs from impact. In the adult, it is evoked by painful stimulation of the abdomen. However, in the infant, although more reliably elicited by noxious stimulation, it can also be elicited by innocuous stimuli such as calibrated monofilaments (von Frey hairs), its threshold in this age group being much lower than in the older child and adult. Nevertheless, above approximately one year of age, it is increasingly difficult to elicit the abdominal skin reflex using this type of stimulation.

- ► Infant Pain Mechanisms
- ► von Frey Hair

Abduction

Definition

Movement of a body part away from the midline of the body.

- ► 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, other psychiatric disorder, etc).

- ► 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.

- ► 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 secondary gain is believed to be important to the production of some or all of the patient’s symptoms. It is to be noted that for factitious disorders and malingering, secondary gain is thought to operate on a conscious level, but at an unconscious level for the other illness affirming states.

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

Abnormal Illness Behavior

Definition

It is the persistence of an inappropriate or maladaptive mode of perceiving, evaluating, or acting in relation to one’s own state of health, despite the fact that the doctor has offered an accurate and reasonably lucid explanation about the illness, with opportunities for discussion, negotiations & clarifications, based on an adequate assessment of all biological, psychological, social & cultural factors.

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

Abnormal Illness Behaviour of the Unconsciously Motivated, Somatically Focussed Type

- ► Hypochondriasis, Somatoform Disorders and Abnormal Illness Behaviour

Abnormal Temporal Summation

Definition

Abnormal Temporal Summation is an abnormal, intense pain resulting from repetitive stimulation of a painful skin area in patients with neuropathic pain.

- ► 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.

► 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.

► Dental Pain, Etiology, Pathogenesis and Management

Absolute Detection Threshold

Definition

On a stimulus continuum: a, What is the minimum value of a stimulus that is "just detectable" by a subject? This value is called the 'absolute threshold'.

► Pain Evaluation, Psychophysical Methods

Absorption

Definition

The absorption of a drug contains all events from the site of its administration to the site of the measurement. An essential requirement for absorption is that the drug is solved in a solvent.

► NSAIDs, Pharmacokinetics

ACC

► Anterior Cingulate Cortex

Accelerated Recovery Programs

► Postoperative Pain, Importance of Mobilisation

Acceleration-Deceleration Injury

► Whiplash

Accelerometer

Definition

An instrument for measuring acceleration or change of velocity with respect to time

► Assessment of Pain Behaviors

Accommodation (of a Nerve Fiber)

Definition

The use dependant changes of action potential conduction and initiation of a nerve fiber, manifesting as conduction velocity, slowing or increasing the activation threshold.

► Mechano-Insensitive C-Fibres, Biophysics

Acculturation

Acculturation is the ability to function with ease in another culture by learning the rules of that culture.

► Cancer Pain, Assessment of Cultural Issues

Accuracy and Reliability of Memory

Definition

The distinction between accuracy and reliability of memory is important for studies of pain memory. Reliability is determined by the correlation between the report of pain at the time of its occurrence, e.g. a score on a rating scale, and the estimate of that score at a later time (the remembered pain). In studies with a group of people, the correlation preserves the relative order of the magnitude of pain and its recall. Accuracy refers to the extent of agreement between records of the original event and the corresponding memory. Under certain conditions, it is possible to assess accuracy for an individual; which is not possible for reliability. Also, according to this distinction, memories may be reliable but not accurate.

► Pain Memory

ACE-Inhibitors, Beta(β)-Blockers

Definition

Drugs used to lower blood pressure and relieve heart failure.

► Postoperative Pain, Acute Pain Management, Principles

Acetaminophen

► Paracetamol
► 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.

► Cyclooxygenases in Biology and Disease

Acetylcholine

Synonyms

Ach; 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.

► 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, ACh

► Acetylcholine

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 non-adapting nociceptor excitation and contributes to hyperalgesia and allodynia in inflammation.

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

Acid-Sensing Ion Channels

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Synonyms

ASIC; ASIC1a; brain sodium channel 2 (BNC2, BNaC2); ASIC1b: ASICβ; ASIC2a: mammalian degenerin 1 (MDEG1), brain sodium channel 1 (BNC1, BNaC1); ASIC2b: mammalian degenerin 2 (MDEG2); ASIC3: dorsal-root acid-sensing ion channel (DRASIC)

Definition

Acid-Sensing Ion Channels (ASICs) are membrane protein complexes that form depolarizing ion channels present on peripheral and/or central neurons. These channels are opened by extracellular protons. Their activation induces action potential triggering on neurons after an extracellular pH decrease to acidic values. Such tissue ► acidosis occurs during ► inflammation or ► ischemia, and is a major source of pain.

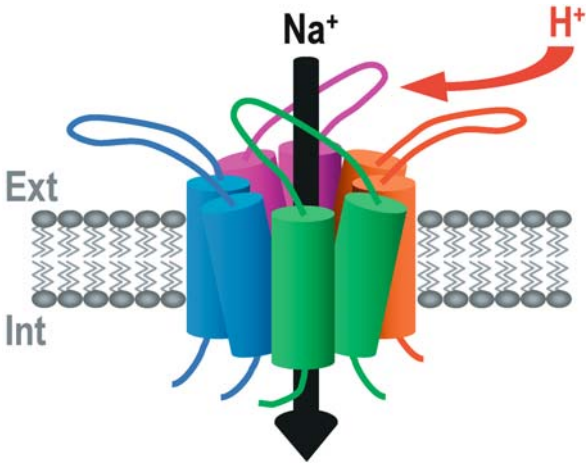
A

Characteristics

ASICs are membrane protein complexes formed by four subunits among the six characterized isoforms (Fig. 1). The isoforms are coded by four different genes, two of them spliced in two variants: ASIC1a and ASIC1b, ASIC2a and ASIC2b, ASIC3 and ASIC4 (Chen et al. 1998; Garcia-Anoveros et al. 1997; Grunder et al. 2000; Lingueglia et al. 1997; Waldmann et al. 1997a; Waldmann et al. 1997b). Each subunit is 510 to 560 amino-acids long, with two transmembrane domains and a large extracellular loop, and belongs to the ENaC/DEG/ASIC family (Fig. 2) (Waldmann and Lazdunski 1998). The properties of the channels (i.e. activation and inactivation kinetics, pH sensitivity, ion selectivity) vary according to their subunit composition. For example, ASIC1a opens transiently for pH values from 7.2 and under with a pH_{50} of 6.2, and is sodium selective (Waldmann et al. 1997b) (Fig. 3). ASIC3 generates a biphasic current: the transient current is followed by a sustained current that lasts as long as the pH is low (Waldmann et al. 1997a) (Fig. 3). It has been associated with cardiac ischemic pain (Sutherland et al. 2001), and ASIC3-deficient mice display alterations in the modulation of high-intensity pain stimuli (Chen et al. 2002). Some isoforms have no activity when expressed alone: the isoform ASIC2b modifies the properties of the other subunits when present in heteromeric complexes (Lingueglia et al. 1997); the isoform ASIC4 has absolutely no activity, either alone or with other isoforms (Grunder et al. 2000). The association of ASIC3 and ASIC2b forms a channel with an ion selectivity and a pH sensitivity that is similar to those of an endogenous native current widely expressed on sensory neurons (Benson et al. 2002; Lingueglia et al. 1997), and that can participate in the sustained neuronal activity observed in lasting acidic pain states such as inflammatory and ischemic pain.

ASIC isoforms can be localized exclusively in sensory neurons and particularly nociceptors (ASIC1b and ASIC3), or in both sensory and central neurons (ASIC1a, ASIC2a and 2b). Their role as pH-sensors on sensory neurons occurs particularly in pathophysiological situations when tissue pH decreases. During inflammation, ischemia, around a fracture or a tumor, the extracellular pH can be lower than 6. This acidosis is directly responsible for pain feelings, and bicarbonate solutions used to be infused in arthritic joints to diminish pain.

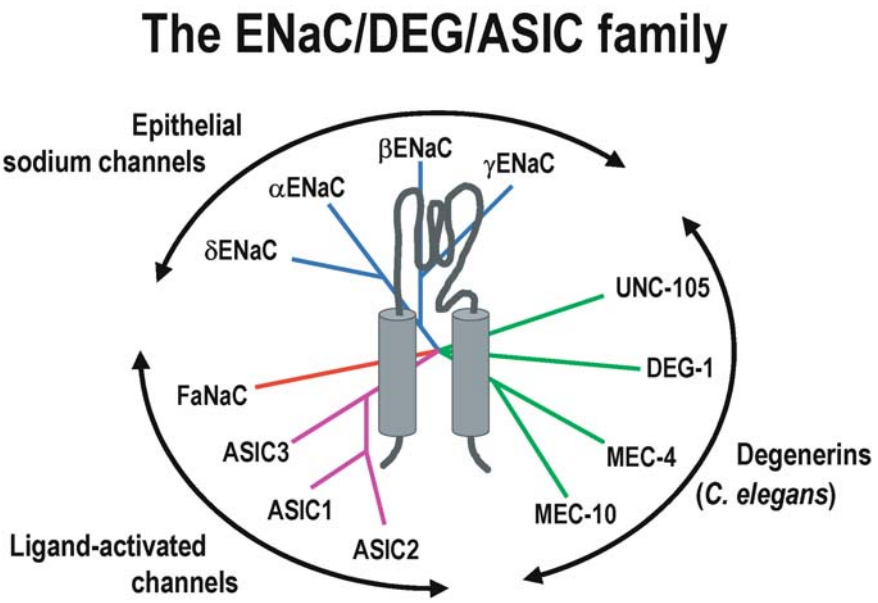
ASIC currents are sensitive to amiloride but with relatively low affinities (around 10 μM). ASIC1a is also potently inhibited by a peptidic toxin isolated from tarantula venom (Escoubas et al. 2000). It has been shown that NSAIDs directly block recombinant and native ASIC currents (Voilley et al. 2001). Ibuprofen and flurbiprofen inhibit ASIC1a-containing channels, and aspirin, salicylate and diclofenac inhibit ASIC3-containing channels. The blocking action of these NSAIDs is direct on ASICs and is independent of cyclo-oxygenase inhibition (Voiley 2004). It prevents sensory neurons from triggering action potentials when submitted to acidic pH (Voilley et al. 2001). The effective concentrations are in the same range as the therapeutic doses necessary for analgesic effect. This pharmacology can explain some of the pain release observed with NSAIDs in experimental tissue acidosis and inflammation (Steen et al. 1996).



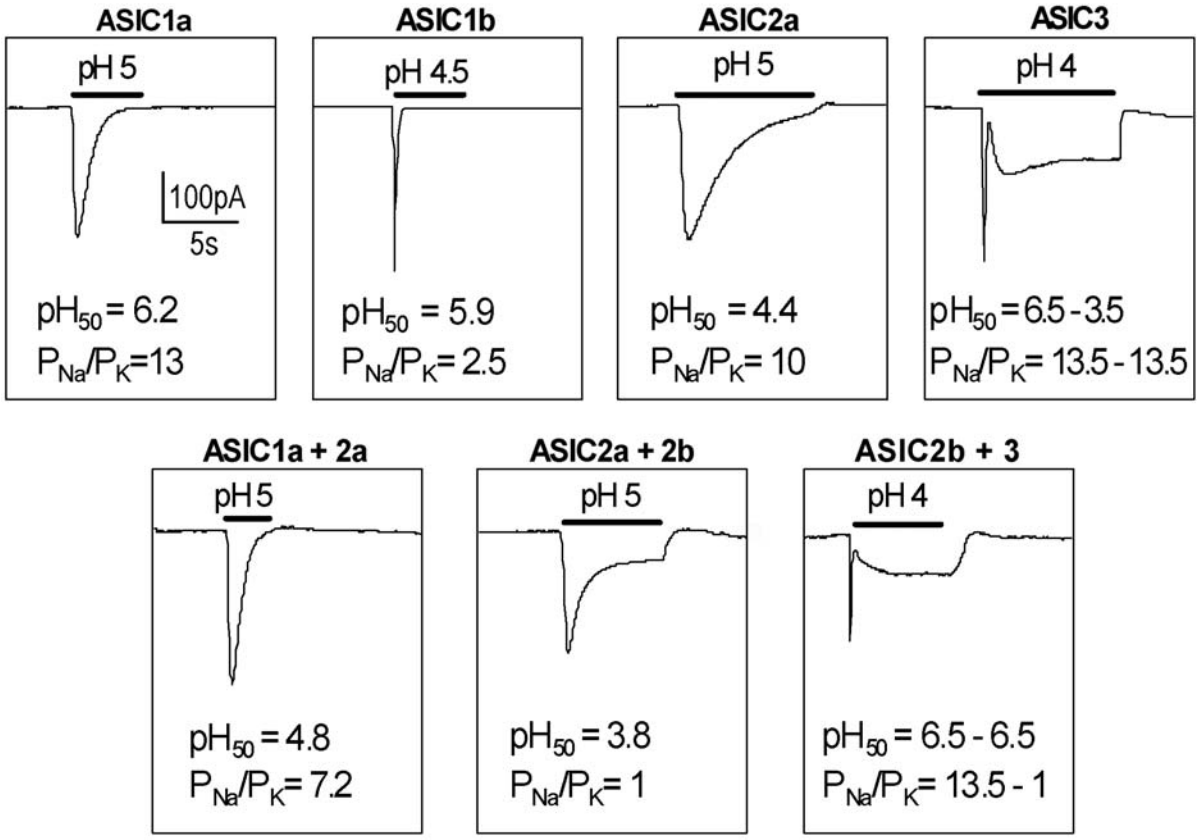
Acid-Sensing Ion Channels, Figure 1 Model of the structure of the acid-sensing ion channel (ASIC) constituted by the assembling of 4 subunits in order to form a functional protein. The channel can be formed by 4 identical subunits (homomer) or by different subunits (heteromer). ASIC1a, 1b, 2a and 3 make functional channels as homomers or heteromers. ASIC2b and ASIC4 have no activity as homomers. However, ASIC2b modifies the current properties of the other subunits when present in a heteromer.

During inflammation, the mRNA levels of the ASICs are increased 6–15 fold, and this *in vivo* increase is completely abolished by treatments with glucocorticoids or NSAIDs (Voilley et al. 2001). This increase is correlated to a higher level of ASIC currents on sensory neurons, and leads to a greater excitability of these cells under pH variations (Mamet et al. 2002). Some pro-inflammatory mediators, and particularly NGF, are directly responsible for the observed increase in ASIC expression and activity. Indeed, NGF controls the expression and the transcriptional regulation of the ASIC3 encoding gene (Mamet et al. 2002; Mamet et al. 2003). Moreover, ASICs are also expressed *de novo* by a greater number of neurons, and participate in the recruiting of sensory fibers that become nociceptive neurons (Mamet et al. 2002; Voilley et al. 2001).

ASICs can also undergo post-translational regulations. Pro-inflammatory mediators like prostaglandins and bradykinin activate protein kinase cascades, which participate in sensory neuron sensitization. ASIC2a protein can be directly phosphorylated by protein kinase C (PKC). This phosphorylation, which is facilitated by an interaction with the PICK–1 protein, has a positive effect on the activity of the channel (Baron et al. 2002).



Acid-Sensing Ion Channels, Figure 2 Phylogenic tree of the ENaC/DEG/ASIC family. The family is constituted mainly by the vertebrate epithelial sodium channel subunits (ENaC), the snail FMRF-amide activated sodium channel (FaNaC), the mammalian acid-sensing ion channels (ASICs) and the nematode *Caenorhabditis elegans* degenerins (MEC and DEG). The proteins share homologies in sequence and structure. Each member protein has a simple structure consisting of 2 transmembrane domains and a large extracellular loop.



Acid-Sensing Ion Channels, Figure 3 Measurement by electrophysiology of the currents generated by ASIC cDNAs transfected in mammalian cells when an acidic stimulus is applied. ASIC1a, ASIC1b and ASIC2a display a transient activation. ASIC3 displays a transient current followed by a sustained phase. ASIC2b and ASIC4 do not bear any activity. In heteromers, ASIC2b confers a plateau phase with a cationic non-selective permeability. For each current type, the half-activation pH (pH_{50}) and the sodium over potassium selectivity (P_{Na}/P_K) are given; when the current is biphasic, both values (peak-plateau) are given.

ASICs present on sensory neurons are thus implicated in acidic pain sensing, neuron sensitization, and onset and maintenance of inflammatory hyperalgesia and allodynia.

References

1. Baron A, Deval E, Salinas M et al. (2002) Protein Kinase C Stimulates the Acid-Sensing Ion Channel ASIC2a Via the PDZ Domain-Containing Protein PICK1. J Biol Chem 277:50463–50468
2. Benson CJ, Xie J, Wemmie JA et al. (2002) Heteromultimers of DEG/ENaC Subunits Form H^+-Gated Channels in Mouse Sensory Neurons. Proc Natl Acad Sci USA 99:2338–2343
3. Chen CC, England S, Akopian AN et al. (1998) A Sensory Neuron-Specific, Proton-Gated Ion Channel. Proc Natl Acad Sci USA 95:10240–10245
4. Chen CC, Zimmer A, Sun WH et al. (2002) A Role for ASIC3 in the Modulation of High-Intensity Pain Stimuli. Proc Natl Acad Sci USA 99:8992–8997
5. Escoubas P, De Weille JR, Lecoq A et al. (2000) Isolation of a Tarantula Toxin Specific for a Class of Proton-Gated Na^+ Channels. J Biol Chem 275:25116–25121
6. Garcia-Anoveros J, Derfler B, Neville-Golden J et al. (1997) BNaC1 and BNaC2 Constitute a New Family of Human Neuronal Sodium Channels Related to Degenerins and Epithelial Sodium Channels. Proc Natl Acad Sci USA 94:1459–1464
7. Grunder S, Geissler HS, Bassler EL et al. (2000) A New Member of Acid-Sensing Ion Channels from Pituitary Gland. Neuroreport 11:1607–1611
8. Lingueglia E, Weille JR de, Bassilana F et al. (1997) A Modulatory Subunit of Acid Sensing Ion Channels in Brain and Dorsal Root Ganglion Cells. J Biol Chem 272:29778–29783
9. Mamet J, Baron A, Lazdunski M et al. (2002) Proinflammatory Mediators, Stimulators of Sensory Neuron Excitability Via the Expression of Acid-Sensing Ion Channels. J Neurosci 22:10662–10670
10. Mamet J, Lazdunski M, Voilley N (2003) How nerve growth factor drives physiological and inflammatory expressions of acid-sensing ion channel 3 in sensory neurons. J Biol Chem 278:48907–48913
11. Steen KH, Reeh PW, Kreysel HW (1996) Dose-Dependent Competitive Block by Topical Acetylsalicylic and Salicylic Acid of Low pH-Induced Cutaneous Pain. Pain 64:71–82
12. Sutherland SP, Benson CJ, Adelman JP et al. (2001) Acid-Sensing Ion Channel 3 Matches the Acid-Gated Current in Cardiac Ischemia-Sensing Neurons. Proc Natl Acad Sci USA 98:711–716
13. Voiley N (2004) Acid-sensing ion channels (ASICs): new targets for the analgesic effects of non-steroid anti-inflammatory drugs (NSAIDs). Curr Drug Targets Inflamm Allergy 3:71–79
14. Voilley N, de Weille J, Mamet J et al. (2001) Nonsteroid Anti-Inflammatory Drugs Inhibit Both the Activity and the Inflammation-Induced Expression of Acid-Sensing Ion Channels in Nociceptors. J Neurosci 21:8026–8033
15. Waldmann R, Bassilana F, de Weille J et al. (1997a) Molecular Cloning of a Non-Inactivating Proton-Gated Na^+ Channel Specific for Sensory Neurons. J Biol Chem 272:20975–20978
16. Waldmann R, Champigny G, Bassilana F et al. (1997b) A Proton-Gated Cation Channel Involved in Acid-Sensing. Nature 386:173–177
17. Waldmann R, Lazdunski M (1998) H(+)-Gated Cation Channels: Neuronal Acid Sensors in the NaC/DEG Family of Ion Channels. Curr Opin Neurobiol 8:418–424

Acinar Cell Injury

► Visceral Pain Model, Pancreatic pain

Acrylamide

An acrylic chemical used in industry and also in the laboratory (gel electrophoresis), with intoxication resulting in peripheral nerve disease (acrylamide neuropathy).

► Toxic Neuropathies

Acting-Out

► Anger and Pain

Action

A readiness to change stage, in which a person is taking concrete steps to change his or her behavior and/or environment.

► Motivational Aspects of 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.

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

Action Potential Conduction of C-Fibres

► Mechano-Insensitive C-Fibres, Biophysics

Action Potential in Different Nociceptor Populations

► Nociceptors, Action Potentials and Post-Firing Excitability Changes

Actiq®

Definition

Actiq® is a transmucosal fentanyl system that produces more significant pain relief at 15, 30, 45, and 60 minutes following administration (over a recommended 15 minutes) in opioid tolerant cancer patients.

► Postoperative Pain, Fentanyl

Activa®

Definition

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.

► Pain Treatment, Spinal Cord Stimulation

Activation Threshold

The current level needed to initiate an action potential in a nerve fiber.

► Pain in Humans, Electrical Stimulation (Skin, Muscle and Viscera)

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 harbour 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 non-specific 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 emphasised that the worst thing they could do would be to act in a guarded, over-cautious way.

Regardless of clinical and radiographic findings, all patients were told to mobilise the affected parts by light, non-specific 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 behaviour. Misunderstandings about musculoskeletal pain were dealt with.

The principal recommendation was to undertake light, normal activities, moving 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 three months and at one 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 five-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 five 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 pre-requisite 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 towards 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 behaviour towards 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 this question 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 short-changing 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 pre-requisite 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.

References

1. Arborelius E, Bremberg S (1994) Prevention in Practice. How do General Practitioners Discuss Life-Style Issues with their Patients? Patient Educ Couns 23:23–31
2. Daltroy LH (1993) Consultations as Educational Experiences Doctor-Patient Communication in Rheumatological Disorders. Baillieres Clin Rheumatol 7:221–239
3. Indahl A, Velund L, Reikeraas O (1995) Good Prognosis for Low Back Pain when Left Untampered: A Randomized Clinical Trial. Spine 20:473–477
4. Indahl A, Haldorsen EH, Holm S et al. (1998) Five-Year Follow-Up Study of a Controlled Clinical Trial using Light Mobilization and an Informative Approach to Low Back Pain. Spine 23:2625–2630
5. Koes BW, Hoogen HMM van den (1994) Efficacy of Bed Rest and Orthoses of Low Back Pain. A Review of Randomized Clinical Trials. Eur J Phys Med Rehabil 4:96–99
6. Kurtz SM, Silverman JD, Benson J et al. (2005) Marrying content and process in clinical method teaching: enhancing the Calgary-Cambridge guides. Acad Med 78(8):802–9
7. McCracken LM, Evon D, Karapas ET (2002) Satisfaction with Treatment for Chronic Pain in a Specialty Service: Preliminary Prospective Results. Eur J Pain 6:387–393
8. McDonald IG, Daly J (2001) On Patient Judgement. Intern Med J 31:184–187
9. McGuirk B, King W, Govind J et al. (2001) The Safety, Efficacy, and Cost-Effectiveness of Evidence-Based Guidelines for the Management of Acute Low Back Pain in Primary Care. Spine 26:2615–2622
10. Miller WR, Rollnick S (2002) Motivational Interviewing: Preparing People for Change, 2nd edn. Guilford Press, New York
11. Roberts L, Little P, Chapman J et al. (2002) Practitioner-Supported Leaflets may Change Back Pain Behaviour. Spine 27:1821–1828
12. Waddell G, Feder G, Lewis M (1997) Systematic Reviews of Bed Rest and Advice to Stay Active for Acute Low Back Pain. Brit J Gen Pract 47:647–652
13. Watson P (1999) The MSM Quartet. Australasian Musculoskeletal Medicine 4:8–9

Active

This refers to movement of a body part using power generated from one's own muscle action.

► Cancer Pain Management, Orthopedic Surgery

Active Inhibition

Definition

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

► Formalin Test

Active Locus

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.

► Dry Needling

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.

► Dry Needling
► Myofascial Trigger Points

Activities of Daily Living

Definition

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

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

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.

► Disability and Impairment Definitions

Activity Limitations

Definition

Difficulties an individual may have in executing activities.

- ► 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, feeding), independent activities of daily living (e.g. cleaning, cooking, shopping, banking), and discretionary activities of daily living (e.g. driving, visiting, leisure activities).

- ► Pain Assessment in the Elderly

Activity Mobilization

Definition

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

- ► Catastrophizing

Activity-Dependent Plasticity

This is an alteration in neuronal structure or function due to activation of the neurons.

- ► Spinothalamic Tract Neurons, Role of Nitric Oxide

Acupuncture

Definition

A system of healing that is part of traditional Chinese medicine. It consists of the insertion of thin solid needles into specific points, usually into muscles, on the body that lie along channels or meridians, in order to treat different symptoms.

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

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 summarised the results of 51 randomised 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 rigour 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 sceptics 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 randomised (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 summarised the evidence from 26 randomised or quasi-randomised 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 randomised clinical trials of all types of acupuncture were included in a systematic review (White and Ernst 1999). Their rigour 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 non-specific back pain (van Tulder et al. 2001). Eleven randomised 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 4 cohort studies and 3 randomised 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 tantalising 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 rigour, e.g. using the novel sham needle devices (Park et al. 2002; Streitberger and Kleinhenz 1998) that have recently become available.

► Acupuncture Mechanisms

References

1. Berman B, Ezzo J, Hadhazy V et al. (1999) Is acupuncture effective in the treatment of fibromyalgia. J Fam Pract 48:213–218
2. Ernst E (1997) Acupuncture as a symptomatic treatment of osteoarthritis. Scand J Rheumatol 26:444–447
3. Ernst E, Pittler MH (1998) The effectiveness of acupuncture in treating acute dental pain: a systematic review. Br Dent J 184:443–447
4. Ernst E, White AR (1998) Acupuncture for back pain. A meta-analysis of randomized controlled trials. Arch Intern Med 158:2235–2241
5. Ernst E, White AR (2001) Prospective studies of the safety of acupuncture: a systematic review. Am J Med 110:481–485
6. Ernst E, Pittler MH, Stevinson C et al. (2001) The desktop guide to complementary and alternative medicine. Mosby, Edinburgh
7. Ezzo J et al. (2000) Is acupuncture effective for the treatment of chronic pain? A systematic review. Pain 86:217–225
8. Jadad AR et al. (1996) Assessing the quality of reports of randomized clinical trials –is blinding necessary? Contr Clin Trials 1996 17:1–12
9. Linde K et al. (2001) Acupuncture for idiopathic headache (Cochrane review). In: The Cochrane Library, Issue 2. Update Software, Oxford, pp 1–46

10. Park J, White A, Stevinson C et al. (2002) Validating a new non-penetrating sham acupuncture device: two randomised controlled trials. Acupunct Med 20:168–174
11. Streitberger K, Kleinhenz J (1998) Introducing a placebo needle into acupuncture research. Lancet 352:364–365
12. Tait PL, Brooks L, Harstall C (2002) Acupuncture: evidence from systematic reviews and meta-analyses. Alberta Heritage Foundation for Medical Research. Edmonton, Canada
13. van Tulder MW, Cherkin DC, Berman B et al. (2001) Acupuncture for low back pain. Available: http://www.cochranelibrary.com
14. White AR, Ernst E (1999) A systematic review of randomized controlled trials of acupuncture for neck pain. Rheumatol 38:143–147

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 ½–2 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 fibres, i.e. 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, Beijing 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 anaesthetics 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 emphasised, 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.

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.

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. Often electro-acupuncture and pain threshold experiments on humans or animals.	Used for clinical pain relief and other symptom relief. Most often manual acupuncture but can also be electro-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 ► 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 DNIC (diffuse noxious inhibitory control) through bulbospinal paths. The involvement of neurochemicals like serotonin, noradrenalin and different endorphins as well as hormones like ACTH and cortisone has been studied in detail.

Acupuncture physiology is often summarised in the following manner (Han 1987; Pomeranz 2000):

For acupuncture needles inserted within the segment of pain:

- Spinal gate-control mechanism (involving enkephalin and dynorphin)

For extrasegmental acupuncture:

- Activation of midbrain structures (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 HPA-axis (hypothalamic-pituitary-adrenal) 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. Probably, the standard neurophysiological model can explain AA, but even so it should be realised that AA is mostly 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 Table 2 below.

Acupuncture Efficacy

In chronic pain patients the improvements are often incomplete with symptom relief for weeks or months. From the first Western descriptions of acupuncture, efficacy was claimed for a lot of different conditions, but mainly for musculoskeletal pain, headaches and nausea. Depending on the technique and the criteria employed,

Acupuncture Mechanisms, Table 2

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

20–40% of patients in pain clinics have been said to benefit from acupuncture. In primary care or private clinics, where experienced practitioners choose who and what they treat, 60–70% of the patients have been reported to benefit. Because of inherent study design problems, especially with double blinding and the use of a proper placebo, the meta-analyses and systematic reviews are very difficult to interpret. However, 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). For a full reference list to all sections of this chapter see (Carlsson 2002).

References

1. Akil H, Watson SJ, Young E et al. (1984) Endogenous opioids: Biology and function. Ann Rev Neurosci 7:223–255
2. Bonica JJ (1974) Acupuncture anesthesia in the Peoples Republic of China. Implications for American medicine. JAMA 229:1317–1325
3. Bossut DF, Mayer DJ (1991) Electroacupuncture analgesia in rats: naltrexone antagonism is dependent on previous exposure. Brain Res 549:47–51
4. Carlsson C (2002) Acupuncture mechanisms for clinically relevant long-term effects –reconsideration and a hypothesis. Acupunct Med 20:82–99
5. Carlsson CPO, Sjölund B (1994) Acupuncture and subtypes of chronic pain: assessment of long-term results. Clin J Pain 10:290–295
6. Carlsson C, Sjölund B (2001) Acupuncture for Chronic Low Back Pain: A Randomized Placebo-Controlled Study With Long-Term Follow-Up. Clin J Pain 17:296–305
7. Foreign Languages Press (1973) Acupuncture anaesthesia. Foreign Languages Press, Beijing
8. Galeano C, Leung CY, Robitaille R et al. (1979) Acupuncture analgesia in rabbits. Pain 6:71–81
9. Han JS (1987) The neurochemical basis of pain relief by acupuncture. A collection of Papers 1973–1987, Beijing
10. Mann F (1974) Acupuncture analgesia. Report of 100 experiments. Br J Anaesth 46:361–364
11. Pomeranz B (2000) Acupuncture Analgesia –Basic Research. In: Stux G, Hammerschlag R (eds) Clinical Acupuncture, Scientific Basis. Springer, Berlin, pp 1–28
12. Price DD, Mayer DJ (1995) Evidence for endogenous opiate analgesic mechanisms triggered by somatosensory stimulation (including acupuncture) in humans. Pain Forum 4:40–43
13. Price DD, Rafii A, Watkins LR et al. (1984) A psychophysical analysis of acupuncture analgesia. Pain 19:27–42
14. Wang JQ, Mao L, Han JS (1992) Comparison of the antinociceptive effects induced by electroacupuncutre and transcutaneous electrical nerve stimulation in the rat. Intern J Neurosci 65:117–129

Acupuncture-Like TENS

Definition

The delivery of TENS 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 100Hz) at a high, but non-painful, intensity to stimulate selectively large diameter muscle efferents. This results in a 'strong but comfortable' muscle twitch that elicits Group III muscle afferent activity.

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

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 Inflammatory Demyelinating Polyneuropathy

► 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 in Children, Post-Operative

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Synonyms

Pediatric Post-Surgical Pain; Acute Post-Operative Pain in Children

Definition

Children who have surgery experience significant postoperative pain for several days. Appropriate pain management should be initiated in the immediate post-operative period and continue until the pain resolves, whether the child is at home or in the hospital. Surgical trauma results from tissue destruction and musculoskeletal strain that causes the release of vaso- and immuno-reactive substrates that promote inflammation, hyperpermeability and pain.

Ineffective pain management increases the incidence of postoperative behavioral disorders in children and the risk of developing persistent or neuropathic pain. In preterm infants and neonates, this effect may be compounded by the lack of descending inhibitory pathways and enhanced neuroplasticity resulting in more extensive, persistent effects (Tachibana et al. 2001). Despite advances in the management of post-operative pain, nearly 70% of patients experience moderate or severe pain after surgery (Apfelbaum et al. 2003).

Effective post-surgical pain management reduces the stress response to surgery, promotes respiratory function, improves wound healing and permits faster return to normal functioning. Surgical invasiveness correlates with the intensity and duration of postoperative pain and analgesic requirements. As surgical invasiveness increases, the interventions employed to manage it escalate.

Characteristics

Good pain management begins with informative preoperative teaching regarding the nature of the surgery, the anticipated level and duration of discomfort and strategies for reducing pain. This is particularly important as more children experience ambulatory surgery that requires parents to manage pain at home. Parents may fail to administer prescribed analgesics due to fear of side effects, addiction or difficulty with administration. Preoperative teaching, improves parental compliance with prescribed analgesic dosing and patient comfort postoperatively (Greenberg et al. 1999). Complementary, non-pharmacological techniques taught preoperatively also reduce anxiety and postoperative pain (Huth et al. 2004).

Postoperative Pain Management Following Ambulatory Surgery

► Local anesthetics improve immediate postoperative comfort and hasten transition through the recovery process. A ► field block, ► installation block or direct peri-neural infiltration (► peri-neural injection) are the safest and easiest analgesic techniques available. Common peripheral nerve blocks employed in children include the ilioinguinal and iliohypogastric nerve block for inguinal herniorrhaphy, ► penile block for circumcision or phallic surgery, femoral, or the ► fascia iliaca

A

Acute Pain

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

Post-operative pain is a major marker of peri-operative 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 recognised 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 post-operative pain is vital to attenuate the stress response to surgery and the accompanying pathophysiological changes in metabolism, respiratory, cardiac, sympathetic nervous system and neuro-endocrine functions. These effects (summarised 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 hypoxaemia from significant ventilation / perfusion mismatching. Continuing hypoventilation predisposes to collapse of lung segments and the supervening infection that follows carries significant morbidity. Psychological and behavioural changes (e.g. yellow flags) also accompany pain states and may need to be recognised and managed. Not only will proper management of post-operative pain result in greater patient comfort and earlier discharge home, but the improved earlier mobilisation and return to function will also reduce serious post-operative complications such as venous thromboembolism.

Neuroendocrine and Metabolic Responses to Surgery (after NH & MRC 1999)

Endocrine

- Catabolic – Due to increase in ACTH, cortisol, ADH, GH, catecholamines, renin, angiotensin II, aldosterone, glucagon, interleukin-1
- Anabolic – Due to decrease in insulin, testosterone

Metabolic

- Carbohydrate – hyperglycaemia, glucose intolerance, insulin resistance
- Due to increase in hepatic glycogenolysis (epinephrine, glucagon) –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 post-operative 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 that with no valid scientific basis (Attard et al. 1992; Zolte and Cust 1986).

Reasons for Ineffective Analgesia (After NH & MRC 1999)

- The common idea that pain is merely a symptom and not harmful in itself
- 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
- Lack of understanding of the pharmacokinetics of various agents

- 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 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 non-specific 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 fibres to the spinal cord at speeds of between 2 m / s in the case of the C type fibres and 10 m / s in the myelinated A delta fibres.
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 centres, 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 fibres whose physiological role is not normally to transmit pain signals to act as nociceptors. For example, while A delta and C fibres are traditionally seen as primary nociceptive fibres, A beta fibres can become nociceptive under certain circumstances.
Coincident with this is the development of peripheral sensitisation. Trauma or other noxious stimuli to tissue results 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 sensitising 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 post-operative 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 optimising 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 post-operative 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 (Rawal and Allvin 1998). While many are headed by consultant anaesthetists, 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 back up 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 organised there must be an efficient method of referral of patients either from the operating theatre or from the various surgical teams.

Clinical Practice Guidelines for Acute Pain Teams (Cousins and Power 1999)

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 individualised proactive pain control plan developed preoperatively by patients and practitioners (since pain is easier to prevent than to treat)
- Assessment and frequent reassessment of the patients pain

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- Use of both drug and non-drug 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' post-operative 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 ► pre-operative 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 post-operative pain prior to surgery do better and use less medication that control groups. A number of studies have consistently pointed out that pain is usually the major fear of patients undergoing surgery. During pre-operative 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 post-operative 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 on-going ► 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 recognise 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.

Post-operative 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).

Pre-emptive Analgesia

Much has been made of the usefulness of ► pre-emptive or preventive analgesia. The concept of providing analgesia prior to a surgical stimulus and thus reducing ► central sensitisation 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 post-operative pain or analgesic use. These include the pre-operative administration of opioids, non-steroidal 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 anaesthesia is employed in a pre-emptive setting, any failure to provide complete blockade will still allow sensitisation to occur (Lund et al. 1987). Another possibility is 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 pre-emptive 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. (1988) 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 ► multi-modal. This implies using a number of agents, sometimes given by different routes, to maximise 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, whilst 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 post-operative attenuation of gastrointestinal function and the possibly 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 revolutionised 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 for example. 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 post-operative monitoring is imperative (Macintyre 2001). While the intramuscular route can be used for intermittent analgesia, the pharmacokinetics are 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 post-operative 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 et al. 2000), it reduces the requirements of opioid analgesics (Niemi and Breivik 1998) and generally allows for a faster return of physiological function, especially gastrointestinal and respiratory status in the post-operative 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 haematoma 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 pre-existing pathologies, which may predispose them to such complications. Lastly, there has been considerable debate about guidelines for epidural placement and removal in patients undergoing peri-operative 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 haematoma 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.

Intrathecal Analgesia

The intrathecal route of drug administration can be useful both as a means of providing anaesthesia and for post-operative analgesia. Both opioids and local anaesthetic 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 post-operative 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).

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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 and ► hydromorphone. None of these drugs are actually "new", having been synthesised in some cases almost 100 years ago, but rather they have been re-discovered
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. 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 non-steroidal anti-inflammatory drugs (NSAIDS), COX-2 inhibitors and ketamine.

Paracetamol

► Paracetamol should be almost the universal basis of acute and post-operative pain control. A number of well controlled trials have clearly demonstrated that regular paracetamol, when given in a dose of 1 gm 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 pro-drug 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. Likewise, although the combination of paracetamol with dextropropoxyphene is widely used to treat more severe pain, many trials suggest that it too has little to offer above paracetamol alone.

Tramadol

Tramadol is unique amongst 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. Its low addiction potential makes it a good choice for long-term use. Because of risk of precipitating serotonin syndrome, tramadol is probably best avoided in combination with many of the different anti-depressant 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 pre-existing history of drug or substance abuse (Brinker et al. 2002; Lange-Asschenfeldt et al. 2002).
In the management of post-operative pain, all efforts should be made to reduce the incidence of post-operative nausea and vomiting, which is not only uncomfortable for the patient, but an 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 (Sil-

vasti et al. 2000; Stamer et al. 1997). However, some strategies have been suggested to attenuate this response including administration of an intra-operative 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 antagonise tramadol's analgesic effects.

Non-Steroidal Anti-Inflammatory Drugs

► NSAIDs, Survey (NSAIDs) 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 reduces 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 post-operative pain is unclear. Even more recently, a parenteral COX-2 inhibitor (parecoxib) has been developed specifically for the management of post-operative pain and initial results of studies are encouraging.
Unfortunately, the cardiovascular safety of these products has recently come under scrutiny that has resulted in at least one (rofecoxib) being withdrawn from the market, owing to an increase in thrombo-embolic events associated with its use (Solomon et al. 2004). There is considerable discussion at present as to wheter this constitutes an individual drug effect or a class effect. These setback have not however prevented the development and release of other members of this group with improved safety profiles.

Ketamine

► Ketamine is an important second line drug in the pain physician's armamentarium. Well known as an anaesthetic agent, it has in the last decade or so found use as an analgesic product when used in sub-anaesthetic 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.

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 post-operative phase (see Features suggestive of neuropathic pain after NHMRC 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 (After NH & MRC 1999)

- Pain can be related to an event causing nerve damage
- 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 sensitisation)
  - Dysaesthesia
- 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

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 ► anti-convulsant medications, notably ► gabapentin and ► carbamazepine,

► anti-depressants and ► membrane stabilising agents such as ► Mexiletine/Mexitil have all been employed with varying success. Local anaesthetics 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 follows recognised 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 or somatic (deep or superficial) pain.

Summary

There have been a number of significant improvements in the management of acute and post-operative 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 post-operative pain management have come about by recognising how to manage pain better with existing drugs, focussing on the use of drug combinations to maximise 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 post-operative 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.

References

1. Albert JM, Talbott TM (1988) Patient-controlled analgesia vs. conventional intramuscular analgesia following colon surgery. Dis Colon Rectum 31:83–86
2. Aromaa U, Lahdensuu M, Cozanitis DA (1997) Severe complications associated with epidural and spinal anaesthesia in Finland 1987–1993. A study based on patient insurance claims. Acta Anaesthesiol Scand 41:445–452
3. Attard AR, Corlett MJ, Kinder NJ et al. (1992) Safety of early pain relief for acute abdominal pain. BMJ 305:554–556
4. Bach S, Noreng MF, Tjellden NU (1998) Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 33:297–301
5. Bergmans L, Snijdelaar DG, Katz J et al. (2002) Methadone for Phantom Limb Pain. Clinl J Pain 18:203–205
6. Bergqvist D, Lindblad B and Matzsch T (1992) Low molecular weight heparin for thromboprophylaxis and epidural / spinal anaesthesia:Is there a risk? Acta Anaesthesiol Scand 36:605–609
7. Bowsher D (1991) Neurogenic pain syndromes and their management. Br Med Bull 47:644–666
8. Brinker A, Bonnel R, Beitz J (2002) Abuse, dependence or withdrawal associated with Tramadol. Am J Psychiatry 159:881
9. Charlton JE (2002) Treatment of Postoprative Pain. In: Giamberardino MA (ed) Pain 2002 – An Updated Review: Refresher Course Syllabus. IASP Press, Seattle
10. Chumbley GM, Hall GM, Salmon P (1999) Why do patients feel positive about patient-controlled analgesia? Anaesthesia 54:38638–38639
11. Cicero T, Adams E, Galler A (1999) Postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend 57:7–22
12. Cousins MJ, Power I (1999) Acute and Post-Operative Pain. In. Wall PD, Melzack R (eds) Textbook of Pain, 4th edn. Churchill Livingstone, Edinburgh, pp 447–492
13. Cousins MJ, Power I, Smith G (2000) 1996 Labat lecture:pain –a persistent problem. Reg Anesth Pain Med 25:6–21
14. Dahl JB, Kehlet H (1993) The value of pre-emptive analgesia in the treatment of postoperative pain. Br J Anaesth 70:434
15. Dahlgren N, Tornebrandt K (1995) Neurological complications after anaesthesia. A follow up of 18,000 spinal and epidural anaesthetics performed over three years. Acta Anaesthesiol Scand 39:872–880
16. Fricke JJ, Karim R, Jordan D et al. (2002) A double-blind, single-dose comparison of the analgesic efficacy of tramadol / acetaminophen combination tablets, hydrocodone / acetaminophen combination tablets, and placebo after oral surgery. Clin Ther 24:953–968
17. Gill P, Kiani S, Victoria B, Atcheson R (2001) Pre-emptive analgesia with local anaesthetic for herniorrhaphy. Anaesthesia 56:414–417
18. Hayes C, Molloy AR (1997) Neuropathic pain in the perioperative period. In: Malloy AR, Power I (eds) International anesthesiology clinics. Acute and chronic pain. Lippincott-Raven, Philadelphia, pp 67–81
19. Horlocker TT and Wedel DJ (1998) Neuraxial blockade and low molecular weight heparins: Balancing perioperative analgesia and thromboprophylaxis. Reg Anesth Pain Med 23(Suppl 2):164–177
20. Horlocker TT, Wedel DJ (2000) Neurologic Complications of Spinal and Epidural Anesthesia. Reg Anesth Pain Med 25:83–98
21. Johnson M (2000) Potential Neurotoxicity of Spinal Anesthesia with Lidocaine. Mayo Clinic Proceedings 75:921–932
22. Kehlet H (1998) Modification of responses to surgery by neural blockade:clinical implications. In: Cousins MJ, Bridenbaugh PO (eds) Neural blockade in clinical anesthesia and management of pain. Lippencott-Raven, Philadelphia, pp 129–178
23. Kehlet H, Holte K (2001) Effect of postoperative analgesia on surgical outcome. Br J Anaesth 87:62–72
24. Kissin I (1996) Preemptive analgesia: why its effect is not always obvious. Anesthesiology 84:1015–1019
25. Lange-Asschenfeldt C, Weigmann H, Hiemke C et al. (2002) Serotonin Syndrome as a result of Fluoxetine in a patient with Tramadol abuse: Plasma level-correlated symptomatology. J Clin Psychopharmacol 22:440–441
26. Lund C, Selmar P, Hensen OB et al. (1987) Effect of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. Anesth Analg 66:343–348
27. Macintyre PE, Ready LB (1996) Acute Pain Management: A Practical Guide. WB Saunders, London
28. Macintyre PE (2001) Safety and efficacy of patient-controlled analgesia. Br J Anaesth 87:36–46
29. Merry A, Power I (1995) Perioperative NSAIDs: towards greater safety. Pain Rev 2:268–291

30. NH&MRC (1999) National Health and Medical Research Council. Acute pain management: scientific evidence. Australian Government Printer
31. Niemi G, Breivik H (1998) Adrenaline markedly improves thoracic epidural analgesia produced by a low-dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. Acta Anaesthesiol Scand 42:897–909
32. Obata H, Saito S, Fujita N (1999) Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. Can J Anaesth 46:1127–1132
33. Pang W-W, Mok M, Huang S et al. (2000) Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. Can J Anaesth 47:968–973
34. Petrone D, Kamin M, Olson W (1999) Slowing the titration rate of tramadol HCI reduces the incidence of discontinuation due to nausea and / or vomiting: a double-blind randomized trial. J Clin Pharm Ther 24:115–123
35. Podder S, Wig J, Malhotra S et al. (2000) Effect of pre-emptive analgesia on self-reported and biological measures of pain after tonsillectomy. Eur J Anaesthesiol 17:319–324
36. Rawall N and Allvin R (1996) Epidural and intrathecal opioids for postoperative pain management in Europe –a 17 nation questionnaire study of selected hospitals. Acta Anaesthesiol Scand 63:583–592
37. Rigg JRA, Jarmrozki K, Myles PS et al. (2002) Epidural anaesthesia and analgesia and outcome of major surgery:a randomised trial. Lancet 359:1276–1282
38. Schmid RL, Sandler AN (2000) Use and efficacy of low-dose ketamine in the management of acute postoperative pain: review of current techniques and outcomes. Pain 82:111–125
39. Senturk M, Ozcan P-E, Talu G-K et al. (2002) The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 94:11–15
40. Silvasti M, Svartling N, Pitkanen M et al. (2000) Comparison of Intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. Eur J Anaesthesiol 17:448–455
41. Solomon DH, Glynn RJ, Levin R et al. (2004) Relationship between selective COX-2 inhibitors and acute myocardial infarction in older adults. Circulation 109:2068–73
42. Stamer U, Maier C, Grondt S et al. (1997) Tramadol in the management of post-operative pain:a double-blind, placebo- and active drug-controlled study. Eur J Anaesthesiol 646–654
43. Uzunkoy A, Coskun A, Akinci O (2001) The value of pre-emptive analgesia in the treatment of postoperative pain after laparoscopic cholecystectomy. Eur Surg Res 33:39–41
44. Webb A, Leong S, Myles P et al. (2002) The addition of a Tramadol Infusion to Morphine Patient-Controlled Analgesia After Abdominal Surgery:A Double-Blinded, Placebo-Controlled Randomized Trial. Anesth Analg 95:1713–1718
45. Wheatley RG, Schug SA, Watson D (2001) Safety and efficacy of postoperative epidural analgesia. Br J Anaesth 87:47–61
46. Woolf CJ, Chong MS (1993) Preemptive analgesia –treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:362–379
47. Young Park W, Thompson JS, Lee KK (2001) Effect of Epidural Anesthesia and Analgesia on Perioperative Outcome:A Randomized, Controlled Veterans Affairs Cooperative Study. Ann Surg 234:560–571
48. Zolte N, Cust MD (1986) Analgesia in the acute abdomen. Annals of the Royal College of Surgeons of England 68:209–210

compartment block for lower extremity procedures and ► digital nerve blocks for toe or finger procedures. Peripheral nerve blocks provide analgesia of similar duration compared to plexus or epidural injections. The duration of the block is determined by the choice of local anesthetic, regional blood flow and use of vasoconstrictor (Table 1). Bupivacaine produces higher peak plasma concentrations in infants than ropivacaine but toxicity from these techniques is exceedingly low due to slow systemic absorption.

► Brachial plexus blockade can provide analgesia following surgery of the hand and / or arm and shoulder. The axillary approach (► axillary block) is most common in children and provides good analgesia of the hand. For surgeries involving the arm or shoulder, an ► interscalene block or ► infraclavicular block provides more reliable postoperative analgesia. The use of interscalene and infraclavicular injections has been limited in children, due to the risks of inadvertent neural or subarachnoid injections in anesthetized patients. The introduction of stimulating catheters and ultrasound guided placement of continuous interscalene and infraclavicular catheters may broaden their application in children undergoing upper extremity surgeries. Catheter techniques are considered safer when performing blocks on anesthetized patients, since catheters are less likely to penetrate the neural sheath and inject with difficulty when positioned within the nerve.

Single shot ► caudal epidural blocks are frequently employed for ambulatory lower abdominal, genitourinary and lower extremity surgeries. Bupivacaine 0.25% or ropivacaine 0.2% without epinephrine provide analgesia for 2–6 h and with the addition of 1:200,000 epinephrine 6–12 h. The inclusion of epinephrine improves the safety of the technique by providing an indicator for inadvertent intravascular or intraosseous injection. The addition of clonidine 1–2 mcg kg^{-1} to the solution significantly prolongs the block but may delay discharge due to excessive duration (Farrar and Lerman 2002). Neuraxial morphine or hydromorphone should not be used for ambulatory patients due to the risk of delayed respiratory depression.

Systemic analgesic therapy must be initiated in order to prevent severe pain (prior to resolution of a local anesthetic block). Nonsteroidal anti-inflammatory agents (NSAIDs) and acetaminophen are the most commonly employed analgesics for children following ambulatory surgery. NSAIDs should be included in the analgesic regimen unless contraindicated (see Contraindications for the Use of NSAIDs) because they reduce the incidence of opioid related side effects and improve recovery characteristics and patient well being (Farrar and Lerman 2002; Gan et al. 2004; Watcha et al. 2003). In addition, they have been associated with a lower incidence of post-surgical behavioral disturbances in children (Kokki 2003).

Acute Pain in Children, Post-Operative, Table 1 Local Anesthetic Maximal Recommended Doses and Usual Duration

Drug	Concentration	Without epinephrine [mg kg^{-1}]	Usual Duration w / o epinephrine	w / epinephrine [mg kg^{-1}]
Chloroprocaine	1–2%	8	½–1	10
Procaine	1–2%	7	½–1	8.5
Bupivacaine	0.25-0.5%	2	4–12 (peripheral Nn)	3
Levo-bupivacaine	0.25–0.5%	2	2–4 (s.c. / epidural)	3
Ropivacaine	0.2–0.5%	2	2–4 (s.c. / epidural)	3
Lidocaine	0.5–2%	5	1–2	7
Mepivacaine	1–1.5%	5	1.5–3	6

Contraindications for the Use of NSAIDs

- Renal Impairment
- Liver Dysfunction
- Hypovolemia
- Thrombocytopenia
- Hypotension
- Coagulation Disorder
- Active Bleeding
- Hypersensitivity / Asthma precipitated by aspirin or other NSAID

A variety of NSAIDs are available for oral, intravenous and rectal administration (Table 2). Comparative trials in children are lacking, however when administered in appropriate doses little variation in their analgesic efficacy is expected with the exceptions of ketorolac and rofecoxib that appear to have stronger analgesic properties (Kokki 2003; Watcha et al. 2003). The volume of distribution and clearance of the NSAIDs are higher in children necessitating slightly higher or more frequent dosing regimens. A ceiling effect limits effectiveness of all NSAIDs. Children are less susceptible to the gastrointestinal side effects of NSAIDs. Caution is advised with renal impairment, asthma, dehydration and bleeding diatheses (Kokki 2003).

Acute Pain in Children, Post-Operative, Table 2 Recommended Doses and Routes of Administration of NSAIDs in Infants >3 months and Children

Drug	Dose	Frequency [h]	Max Daily Dose [mg kg^{-1}]	Preparations Available
Diclofenac	1 mg kg^{-1}	8–12	3	i.v. / pr / PO
Ibuprofen	10 mg kg^{-1}	6–8	4	PO
Flurbiprofen	1 mg kg^{-1}	8–12	5	PO / i.v.
Ketoprofen	1–2 mg kg^{-1}	6–8	5	PO / i.v.
Ketorolac	0.3–0.5 mg kg^{-1}	6–8	2	i.v.

NSAIDs, especially ketorolac, are particularly effective analgesics following dental, oropharyngeal and genitourinary procedures but they are associated with an increased risk of bleeding that limits their use. Selective COX-2 inhibitors were designed to retain the analgesic and anti-inflammatory effects of NSAIDs while reducing the risk of gastric irritation and bleeding. Rofecoxib, 1 mg kg^{-1} day^{-1}, improved post-tonsillectomy pain when compared to placebo and hydrocodone. Evaluations of other COX-2-selective NSAIDs in children are lacking due to the absence of pediatric formulations. Chronic administration of COX-2-selective NSAIDs, in particular rofecoxib, has been associated with an increased incidence of heart attack or stroke in elderly patients. In appropriately selected patients, their short-term use in the peri-operative period has been shown to improve analgesia, recovery and return to normal levels of activity without increasing the risk of bleeding or asthma (Gan 2004).

The role of acetaminophen in the management of post-operative pain in children remains controversial. Confusion regarding the analgesic efficacy of acetaminophen is caused by the diversity of ages, procedures, doses, routes of administration and endpoints studied. Although the early administration of high dose (40–60 mg kg^{-1}) acetaminophen is associated with a reduction in the incidence and severity of post-surgical pain, the result is inconsistent, especially following very painful surgeries. The risk: benefit ratio for escalating doses to achieve faster, higher effect compartment concentrations has not been established. Hepatic failure has occurred with doses lower than those recommended (Table 2) in the presence of dehydration, sepsis and malnutrition. Acetaminophen should be avoided in patients with hepatic dysfunction (Bremerich et al. 2001; Korpela et al 1999).

Opioid analgesics are frequently required following ambulatory surgeries in children. During the recovery phase, fentanyl 0.5–1 mcg kg^{-1} intravenously, repeated every 5–10 min up to 2 mcg kg^{-1}, provides rapid, brief analgesia. Fentanyl is associated with a lower incidence

and severity of postoperative nausea and vomiting (PONV) than morphine and permits the early initiation of oral analgesics so that the adequacy of pain relief can be assessed prior to discharge. Intravenous morphine 0.05–0.2 mg kg^{-1} is employed when pain is more severe or persistent. When larger doses are required, inadequate pain relief after discharge is increasingly likely.

Codeine, the most common oral opioid for mild to moderate postoperative pain is less popular due to the high incidence of side effects. Codeine metabolism to morphine is responsible for its analgesia. Conversion to morphine is impaired in 10% of patients and absent in fetal liver microsomes, rendering it ineffective in 10% of the population and infants <1 month. The usual dose is 1 mg kg^{-1} every 4 h h and is limited by the high incidence of side effects including nausea, vomiting, sedation, urinary retention and constipation.

Hydrocodone, a synthetic opioid agonist, is available alone and in combination with acetaminophen and ibuprofen as an elixir or tablet. Twenty-five percent of the administered dose is converted to active metabolites including hydromorphone. Following ambulatory surgery, the incidence and severity of side effects is reduced when compared to codeine. Analgesia begins within 20–30 min of oral administration and lasts 3–6 h. The usual dose is 0.1–0.15 mg kg^{-1} / dose or 0.6 mg kg^{-1} day^{-1} administered every 4–6 h.

The safety of oxycodone in children following ambulatory surgery has not been established but it is useful during transition from PCA or continuous epidural after major surgery as is hydrocodone.

Adjunctive Analgesics for Ambulatory Surgery

Post-tonsillectomy and genitourinary pain is significantly reduced by ► dexamethasone, 1 mg kg^{-1} up to a maximum 20 mg, intravenously after induction of anesthesia. ► Clonidine is employed preoperatively at a dose of 1–2 mcg kg^{-1} to reduce analgesic requirements. It has limited usefulness in outpatient surgery due its side effects of sedation, bradycardia and hypotension. ► Tramadol offers no advantage in the management of acute pediatric postoperative pain.

Postoperative Pain Management Following Major Surgery

Insertion of a catheter into the ► epidural space permits continuous infusion of opioid or local anesthetics. This provides patients with a baseline, prophylactic analgesic strategy. Studies in adults and most pediatric studies indicate that active pain following major thoracoabdominal, genitourinary, spinal and orthopedic surgeries is more effectively managed by neuraxial analgesia than PCA (Bozkurt 2002; Kokinsky and Thornbert 2003).

In infants, catheters are frequently placed caudally and may often be threaded to the desired dermatomal level in most infants younger than 6 months. Caudally inserted catheters are at greater risk of dislodgement and contamination than those placed at the lumbar or thoracic levels. Infection rates can be reduced and catheter longevity improved by tunneling the catheter to a separate exit site (Kost-Byerly 2002).

When epidural catheters are inserted in anesthetized patients, as in most pediatric situations, the risk of spinal cord or neural injury may be increased. Controversy exists over the safety of anesthetized placement, however, when inserted by experienced anesthesiologists in children, the risk appears to be acceptably low (Krane et al. 1998). Catheters can be placed under direct visualization during spinal instrumentation, so that the catheter tip is located at the level of injury. In addition, two catheter techniques have been employed for extensive spinal surgeries.

Bupivacaine 0.125% at 0.0625% and ropivacaine 0.1–0.2% are the most common solutions employed although 1% lidocaine or 0.125% levobupivacaine are employed in some hospitals. The addition of opioids like fentanyl, 2–10 mcg ml^{-1}, acts synergistically to improve analgesia. At the recommended doses, these solutions provide a band of analgesia. Their safety is quite acceptable but high plasma concentrations can cause seizures and cardiac depression. Neonates are at increased risk of local anesthetic toxicity due to decreased ► alpha-1-acid glycoprotein binding and the accumulation of ► amide local anesthetics. Therefore, infusions should be terminated in infants younger than 3 months after 48 h unless lidocaine is employed and blood levels of lidocaine assessed daily to guide therapy (Kost-Byerly 2002). Motor blockade responds to dose reductions. Dosing guidelines are presented in Table 3.

When neurosensory evaluation is necessary, e.g. following spinal instrumentation, where risk for compartment syndrome exists, or when the catheter tip cannot be located near the surgical site, neuraxial infusions of

Acute Pain in Children, Post-Operative, Table 3 Acetaminophen Dosing Guidelines

	Dose [mg kg^{-1}]	Frequency [h]	Max Daily [mg kg^{-1}]	Route
Acetaminophen				
Preterm Infants / Neonates 1–3 months	15	6	60	PO / pr
Infants >3 months	15–20	6	75	PO / pr
Children [loading dose]	20–40			
15–20	6	90–100	PO	
Propacetamol				
Infants >3 months / Children	30	6	120	i.v.

morphine or hydromorphone provide effective analgesia. Improvement of pain after rate adjustment or bolus requires *ca.* 45 min. Short-acting local anesthetics can be administered when prompt analgesia is needed. The incidence of nausea, pruritus and sedation are comparable to that of intravenous opioids (Kokinsky and Thornbert 2003). The risk of respiratory depression following neuraxial morphine ranges from 0.09–1.1% (Bozkurt 2002).

Patient Controlled Analgesia

When neuraxial techniques are not employed following major surgery, opioids should be administered intravenously whenever possible. Intramuscular injections are painful and result in slow onset of analgesia that cannot be titrated. Nurses should be encouraged to seek painful behavior or elicit pain scores regularly to detect escalation of pain. Early treatment reduces the duration of severe pain, the dose of opioid required to achieve comfort and the risk of inadvertent overdose.

► PCA improves pain relief when compared to intermittent, scheduled dosing. Standard dosing regimens are provided in Table 4. Careful assessment of respiratory function is essential to the safety of this technique since the incidence of serious respiratory depression is between 0.1–1.7% (Bozkurt 2002). The inclusion of a basal infusion rate is associated with a higher incidence of hypoxemia and lower respiratory rates (McNeely and Trentadue 1997). Consideration should be given to provision of a basal infusion at night to improve sleep. Continuous infusion of opioids is recommended for infants and young children. Nurse or family member activation of the ► PCA pump for children who cannot activate it due to cognitive impairment or physical limitations is an innovation that circumvents the main design feature that insures safety. Appropriate monitoring for opioid induced respiratory depression is mandatory.

Nurses trained to assess pain and opioid related side effects can safely employ PCA pumps as an alternative to intermittent bolus dosing. This promotes faster availability of the analgesic, lower incremental doses and improved pain relief. Monitoring protocols following bolus dosing and rate changes are required to maximize safety (Bozkurt 2002; Kokinsky and Thornbert 2003).

Acute Pain in Children, Post-Operative, Table 4 Opioid Infusion and PCA Dosing Guidelines

Medication	Loading Dose	Continuous / Basal Rate	PCA Bolus
Morphine 1 or 5 mg ml-1	0.03 mg–0.05 mg kg^{-1}	0.01–0.03 mg kg^{-1} h^{-1}	0.01–0.03 mg kg^{-1}
Hydromorphone 100 mcg ml-1	5 mcg kg^{-1}	3–5 mcg kg^{-1} h^{-1}	2–5 mcg kg^{-1} h^{-1}
Fentanyl 50 mcg ml-1	0.3 mcg kg^{-1}	0.5–1 mcg kg^{-1} h^{-1}	0.2–1 mcg kg^{-1} h^{-1}

Caregivers can be trained to administer intermittent doses of parenteral opioids. Well-designed, training programs for caregivers and an appropriate level of nursing supervision are required to insure the safety of this innovation (Kost-Byerly 2002). Research regarding the safety of this approach in the acute, post-surgical setting is lacking.

The inclusion of NSAIDs, in particular ketorolac, reduces analgesic requirements and improves analgesia in children with epidurals or PCA (Kokki 2003). The use of NSAIDs following major orthopedic procedures remains controversial since prostaglandins induce lamellar bone formation and animal studies suggest that NSAIDs impair bone healing and fracture repair. No difference in the incidence of curve progression, hardware failure or back pain was found in adolescents following spinal fusion (Farrar and Lerman 2002). Since NSAIDs can result in renal dysfunction they are best avoided during the initial 24 h following major surgeries if ongoing third space losses are anticipated.

References

1. Apfelbaum JL, Chen C, Mehta SS et al. (2003) Postoperative pain experience: results from a national survey suggest postoperative pain continues to be under managed. Anesthe Analg 97:534–40
2. Bremerich DH, Neidhart G, Heimann K et al. (2001) Prophylactically administered rectal acetaminophen does not reduce postoperative opioid requirements in infants and small children undergoing elective cleft palate repair. Anesth Analg 92:907–912
3. Bozkurt P (2002) The analgesic efficacy and neuroendocrine response in paediatric patients treated with two analgesic techniques: using morphine-epidural and patient-controlled analgesia. Paed Anes 12:248–254
4. Farrar, MW, Lerman J (2002) Novel concepts for Analgesia in Pediatric Surgical Patients: cyclo-oxygenase-2 Inhibitors, alpha-2 agonists and opioids. Anes Clin NA 20:59
5. Gan TJ, Joshi GP, Viscusi E et al. (2004) Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. Anesth Analg 98:1665-1673
6. Greenberg RS, Billet C, Zahurak M et al. (1999) Videotape increases parental knowledge about pediatric pain management. Anesth Analg 89:899–903
7. Huth MM, Broome ME, Good M (2004) Imagery reduces children's post-operative pain. Pain 110:439–448
8. Kokinsky E, Thornbert E (2003) Postoperative pain control in children. A guide to drug dose. Paediatr Drugs 5:751–762
9. Kokki, Hannu (2003) Nonsteroidal anti-inflammatory drugs for postoperative pain. A focus on children. Paediatr Drugs 5:103–123
10. Korpela R, Korvenoja P, Meretoja OA (1999) Morphine-sparing effect of acetaminophen in pediatric day case surgery. Anesthesiol 91:442–447
11. Kost Byerly S (2002) New concepts in acute and extended postoperative pain management in children. Anesthesiol Clin North America 20:115–135
12. Krane EJ, Dalens BJ, Murat I et al. (1998) The safety of epidurals placed under general anesthesia. Reg Anesth Pain Med 23:433–438
13. McNeely JK, Trentadue NC (1997) Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. J Pain Symptom Manage 13:268–273

14. Tachibana T, Ling QD, Ruda MA (2001) Increased Fos induction in adult rats that experienced neonatal peripheral inflammation. Neuroreport 12:925–927
15. Watcha MF, Issioui T, Klein KW et al. (2003) Costs and effectiveness of rofecoxib, celecoxib and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. Anesth Analg 96:987–994

Acute Pain in Children, Procedural

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Synonyms

Pediatric Pharmacological Interventions; Pediatric Psychological Interventions; Pediatric Integrated Care for Painful Procedures; Acute Procedural Pain in Children

Definition

Acute procedural pain refers to the pain that infants and children experience as a result of necessary ► invasive diagnostic and therapeutic procedures. Procedural pain management refers to the pharmacological, psychological and physical interventions used to prevent, reduce or eliminate pain sensations in children arising as a result of an invasive or aversive medical procedure.

Characteristics

Acute procedural pain is a significant problem for infants and children and, regrettably, is currently undertreated in many centers. A recent survey of institutions in the Pediatric Oncology Group (Broome et al. 1996) found that 67% of institutions routinely used local anesthesia, 22% used systemic premedication and 11% used different relaxation techniques for management of painful procedures such as lumbar punctures (LPs) and bone marrow aspirations (BMAs). Children (this term refers to all individuals in the pediatric age range, i.e. neonates, infants and adolescents) and their families experience significant emotional and social consequences as a result of pain and the effects of inadequately managed procedure-related pain can be severe and long lasting (Kazak et al. 1997; Young et al. 2005).

The aims of pain management are to 1) optimize pain control during the procedure, recognizing that a pain-free procedure may not be achievable, 2) enhance the patient's physical well-being, 3) enhance the patient's self-esteem and self-efficacy and 4) minimize the short and long term psychological distress of the patient and his / her family.

Invasive Procedures

Children undergo a variety of painful procedures in varied settings such as venipunctures, lumbar punctures, bone marrow aspirations, fracture reduction and orthodontic procedures. Painless procedures (such as CT scanning, MRI positioning for radiotherapy and ultrasonic examination, pelvic examination in young girls) that require patients to lie still, often on a cold, hard surface, may still be aversive and indirectly provoke pain and distress.

Factors that Affect Procedural Pain

Acute procedural pain in children is the result of a dynamic integration of physiological processes, psychological factors and sociocultural context embedded within a developmental trajectory. Consequently, procedural pain management is most probably effective when all components of the child's pain experience are evaluated and addressed. Depending on the nature of the procedure and the characteristics and preferences of the child and his / her family, optimal pain control strategies will range from general anesthesia to ► psychological strategies. In all cases, a multimodal approach may reduce the potential for adverse effects arising from either escalating frequency or dosage levels of a single pharmacological modality (Lang et al. 2000).

In order to address all relevant factors, health care providers must assess the factors that affect a child's pain. A standard nomenclature and a multidimensional approach are essential components of a comprehensive procedural pain assessment. The description of the pain should include its temporal features, intensity, quality and exacerbating and relieving factors. Treatment strategies should be based on the findings of the assessment and should address the inciting and contributing factors. The specific approach to procedural pain is shaped according to the anticipated intensity and duration of expected pain, the type of procedure, the context and meaning as seen by the child and family, the coping style and temperament of the child, the child's history of pain and the available family support system (Liossi 2002; McGrath 1990; Zeltzer et al. 1989).

Procedures that cause pain in a child should be performed by health care professionals with high technical competence, so that pain is minimized to the greatest possible extent. The child and his / her family should be included in the planning and decision-making process regarding the treatment plan. This provides families with control and health care providers with valuable insights into how the child understands and copes with pain. Children and parents should receive appropriate information about what to expect and appropriate preparation about how to minimize distress (Blount et al. 1994). A quiet environment, calm adults and clear, confident instructions increase the likelihood that the specific pain management strategy selected will be effective (McGrath 1990; Zeltzer et al. 1989).

Pharmacological Interventions for Procedural Pain in Children

Local anesthesia is the standard analgesic intervention whenever tissue injury is involved. Topical anesthetics such as EMLA (eutectic mixture of local anesthetics) and amethocaine have recently revolutionized analgesic care but infiltration and regional nerve blocks with lidocaine, bupivacaine and ropivacaine remain in wide use (Finley 2001; Schechter et al. 2003).

For procedural pain that is predictably severe and for which local measures give inadequate relief, such as for bone marrow aspirations, the use of systemic agents is required to reduce or eliminate pain. The use of anxiolytics or sedatives (such as benzodiazepines, propofol, chloral hydrate or barbiturates) alone for painful procedures does not provide analgesia but makes a child less able to communicate distress. The child still experiences pain during the procedure and there are no data on the short- or long-term sequelae of this strategy. These agents are adequate as sole interventions only for nonpainful procedures such as CT or MRI scans (Finley 2001; Schechter et al. 2003).

When it is necessary to use sedation and analgesia for painful procedures, the guidelines issued by the AAP (American Academy of Pediatrics, Committee on Drugs 1992) should be followed. These AAP guidelines recommend that skilled supervision is necessary whenever systemic pharmacologic agents are used for conscious sedation (i.e. the patient maintains a response to verbal and physical stimuli), that sedation should be conducted in a monitored setting with resuscitative drugs and equipment available and that agents should be administered by a competent person. The guidelines further recommend that one person is assigned to monitor the child's condition and another qualified person is present to respond to medical emergencies. After the procedure, monitoring should continue until the patient is fully awake and has resumed the former level of function. Discharged patients should be accompanied by an adult for a time at least as long as two half-lives of the agents used. In contrast to conscious sedation, deep sedation (i.e. when the patient is not responsive to verbal or physical stimuli) is equivalent to general anesthesia and should be performed only under controlled circumstances by a professional trained in its use and skilled in airway management and advanced life support. Despite careful titration of sedative doses, individual responses are variable and patients may occasionally have respiratory compromise or loss of airway reflexes (Zeltzer et al. 1989). Nitrous oxide offers one more analgesic pharmacological option in the management of procedural pain. Its use requires availability of trained personnel and appropriate monitoring procedures. Administered by a mask or tent, nitrous oxide is a potent, short-acting inhalant analgesic. A significant drawback is the high degree of room air contamination, making occupational exposure a serious concern.

Psychological Interventions for Procedural Pain in Children

Psychological interventions for procedural pain management include preparation, deep breathing, distraction, relaxation, play therapy, guided imagery, cognitive therapy and hypnosis. Of these interventions, cognitive therapy and hypnosis have achieved status as empirically validated, efficacious and possibly efficacious interventions respectively, in the management of pediatric procedure-related cancer pain (Liossi 1999; Liossi 2002; Powers 1999), according to the framework developed by the American Psychological Association Division 12 Task Force on Promotion and Dissemination of Psychological Procedures (Chambless and Hollon 1998). The focus in cognitive therapy is on the child's behavior, emotions, physiological reactions and cognitions (i.e. thoughts and visual images). The rationale for cognitive therapy is that a person's understanding of the pain or the illness / procedure causing their pain determines their emotional reactions; therefore it is possible by modifying negative and maladaptive cognitions to reduce pain and distress. Hypnosis is a psychological state of heightened awareness and focused concentration, in which critical faculties are reduced and susceptibility and receptiveness to ideas is greatly enhanced. In all studies conducted to date, cognitive therapy and hypnosis were effective in reducing the pain and anxiety of young patients during procedures (Liossi 2002; Hilgard and LeBaron 1982).

Psychological strategies alone, however, often do not reduce pain sufficiently. A combination of psychological with pharmacological interventions is necessary. To this end, in 1998, the World Health Organization (WHO) developed and published guidelines for the management of pain in children with cancer. For all medical procedures, the use of a combination of a psychological with a pharmacological approach is supported and aggressive, preemptive approaches are emphasized. Preliminary empirical evidence for these guidelines has been offered in a recent randomized controlled clinical trial combining self-hypnosis with local anesthesia (Liossi et al. 2006) and in the development and evaluation of a multidisciplinary psychological and pharmacological protocol for procedure pain in childhood leukemia (APPO) at the Children's Hospital of Philadelphia (Kazak and Kunin-Batson 2001). The general principles for pediatric procedural pain management are as follows:

Before the Procedure

- As far as possible treat procedure-related pain preemptively.
- Provide information regarding the time, frequency, and "clustering" of procedures, if more than one is to be required. For procedures that will be repeated, maximize treatment for the pain and anxiety of the first procedure to minimize the anticipatory anxiety before subsequent procedures.

- Provide the patient and his / her family with education regarding pain and pain management
- Tailor treatment options to the patient's and the family's needs and preferences, to the procedure and to the context.
- Provide adequate preparation of the patient and family. For children, discuss with the child and parents what can be expected and how the child might respond.
- Explore and address concerns regarding the procedure and pain management interventions.
- Minimize delays to prevent escalation of anticipatory anxiety.

During the Procedure

- Integrate pharmacological and nonpharmacological options in a complementary style.
- Allow parents to be with the child during the procedure, if parents choose to remain. Parents should be taught what to do, where to be and what to say to help their child through the procedure.

After the Procedure

- Debrief the patient and his / her family
- Encourage the use of coping skills
- Review with the patient and family their experiences and perceptions about the effectiveness of pain management strategies.

The list below provides an example of how psychological and pharmacological interventions can be integrated in the management of lumbar puncture pain for an older child (>6 years old):

Before the Procedure

- Teach the child self-hypnosis.
- Teach parents how to support their child in the use of self-hypnosis.
- Apply EMLA 60 min before the procedure.

During the Procedure

- Encourage the child to use self-hypnosis and their parents, if they wish, to coach them.

After the Procedure

- Encourage the use of self-hypnosis for the management of possible post lumbar puncture headache.

Summary

Innovations in acute pediatric procedural pain management do not need to be "high tech" In most cases, excellent analgesic results can be achieved through application of standard pharmacological and psychological approaches, continuous patient assessment and patient and family participation in treatment planning. Although financial pressures may slow the adoption of pain control as a priority in acute patient care (and in this regard integrated care is particularly expensive), equally strong social trends demand treatments that enhance patient- and family-centered outcomes. Education of the public will increase societal awareness and support of children in pain and shape appropriate public policy, which in turn will speed up the bridging of the gap between theoretical developments, research evidence and current clinical practice in acute pediatric procedural pain management.

References

1. American Academy of Pediatrics Committee on Drugs (1992) Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 89:1110–1115
2. Blount R, Powers SW, Cotter MW et al. (1994) Making the system work: training pediatric oncology patients to cope and their parents to coach them during BMA / LP procedures. Behav Modif 18:6–31
3. Broome M, Richtmeier A, Maikler V et al. (1996) Pediatric pain practices: a national survey of health professionals. J Pain Symptom Manage11:312–320
4. Chambless DL, Hollon SD (1998) Defining empirically supported therapies. J Consult Clin Psychol 66:7–18
5. Finley GA (2001) Pharmacological management of procedure pain. In: Finley GA, McGrath PJ (eds) Acute and Procedure Pain in Infants and Children. Progress in Pain Research and Management, vol 20. IASP Press, Seattle
6. Hilgard J, LeBaron S (1982) Relief of anxiety and pain in children and adolescents with cancer: Quantitative measures and clinical observations. Int J Clin Exp Hypn 30:417–442
7. Kazak AE, Kunin-Batson A (2001) Psychological and integrative interventions in pediatric procedure pain. In: Finley GA, McGrath PJ (eds) Acute and Procedure Pain in Infants and Children. Progress in Pain Research and Management, vol 20. IASP Press, Seattle, pp 57–76
8. Kazak A, Barakat L, Meeske K et al. (1997) Posttraumatic stress, family functioning, and social support in survivors of childhood cancer and their mothers and fathers. J Consult Clin Psychol 65:120–129
9. Lang EV, Benotsch EG, Fick LJ et al. (2000) Adjunctive nonpharmacological analgesia for invasive medical procedures: a randomised trial. Lancet 29:1486–1490
10. Liossi C (1999) Management of pediatric procedure-related cancer pain. Pain Rev 6:279–302
11. Liossi C (2002) Procedure related cancer pain in children. Radcliffe Medical Press, Abingdon, Oxon, UK
12. Liossi C, White P, Hatira P (2006) Randomised clinical trial of a local anaesthetic versus a combination of self-hypnosis with a local anaesthetic in the management of paediatric procedure-related pain. Health Psychology (in press)
13. McGrath PA (1990) Pain in children: nature, assessment and treatment. The Guilford Press, New York
14. Powers SW (1999) Empirically supported treatments in pediatric psychology: pediatric pain. J Pediatr Psychol 24:131–145
15. Schechter NL, Berde CB, Yaster M (2003) Pain in infants, children, and adolescents. Lippincott Williams & Wilkins, Philadelphia
16. World Health Organization (1998) Cancer pain relief and palliative care in children. World Health Organization, Geneva
17. Young KD (2005) Pediatric procedural pain. Annals Emergency Med 45:160–171
18. Zeltzer LK, Jay SM, Fisher DM (1989) The management of pain associated with pediatric procedres. Pediatr Clin North Am 36:941–964

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Acute Pain Management in Infants

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Synonyms

Infant pain treatment; Infant Pain Reduction/Therapy/Treatment; infant pain therapy; Pain Management in Infants

Definition

Infant pain management is defined as any strategy or technique administered to an infant experiencing pain with the intention of lessening pain sensation and/or perception. Pain management strategies include the drugs described in the essay ► pain management, pharmacotherapy and varied nonpharmacological (contextual, psychological and physical) interventions described in this essay. Pain management during infancy has been almost exclusively focused on acute procedural (including post-operative) pain (although recent work is beginning to focus on assessment and treatment in prolonged and chronic pain), thus the emphasis throughout this essay will be on pain reduction strategies for acute procedural pain.

Characteristics

Developmental and Caregiver Considerations

A sensitive appreciation of infants in pain and their complete reliance on their caregivers is a fundamental starting point for approaching infant pain management (Als et al. 1994). Infants have (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. However, even knowledgeable caregivers often do not recognize and / or adequately manage infants' pain (Simons et al. 2003). The caregivers' difficulty in discerning the state of an infant, the lack of specificity of infant responses to painful procedures and caregiver biases concerning pain assessment and management all contribute to this dilemma. Mixed results have been found regarding the strength of relationship between parental behaviors and infant pain reduction; however, researchers consistently suggest that the influence of parental behaviors on managing infant pain is mediated by the physiological and temperamental qualities of the infant (e.g. Sweet et al. 1999).

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 safest and most effective pain relieving strategy. While an informed understanding of drug therapy is a crucial facet of pain management, psychological, physical and environmental strategies and techniques are also important components and should be included in an integrated pain management approach.

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 non-painful or less painful options should always be explored.

Select the Least Painful Diagnostic or Therapeutic Method

If a painful procedure is unavoidable, the least painful approach incorporating pharmacological (e.g. topical anesthetic), physical (e.g. ► positioning) and cognitive (e.g. distraction) interventions should be undertaken (see Anand et al. 2001 for a review). The onus is on clinicians to familiarize themselves with the current evidence and recommended clinical best practices to minimize procedural pain in infants. Databases such as the Cochrane Collaboration, CINAHL, MEDLINE and EMBASE provide systematic reviews and meta-analyses with recommendations for clinical practice.
For example, venipuncture is recommended as less painful than heel lance for blood sampling in newborns (Shah and Olsson 2004). Other procedural examples may be found in the circumcision context, In addition to dorsal penile nerve blocks, the specific clamp used to hold the foreskin or the type of infant restraint can moderate pain and distress. For example, the Mogen clamp lessens pain in comparison to the Gomco clamp (Kurtis et al. 1999).

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. Preliminary research suggests that infants who are cared for in a developmentally sensitive manner (i.e. low noise and lighting, bundling of procedures to avoid over-handling) have lower pain reactivity (Stevens et al. 1996).

Psychological 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). ► Distraction in the form of play (such as encouraging infant attention to a mobile or mirror) (Cohen 2002) or the combination of music and non-nutritive sucking (Bo and Callaghan 2000) have both been shown to moderate both physiological and behavioral indicators of infant pain (i.e. cry, heart rate, facial grimacing). Another promising cognitive intervention for managing infant pain, adapted from work with older children and adults, was demonstrated by Derrickson et al. (1993). Based on a simple ► signaling paradigm, a 9 month old hospitalized infant was taught to predict the occurrence of painful and invasive procedures.

Physical Strategies

Much of the interventional pain research on infants has been conducted within this domain. Common strategies involve ► non-nutritive sucking (NNS, e.g. pacifiers), ► skin-to-skin contact (e.g. kangaroo care), the administration of sweet substances such as sucrose that are thought to mimic opioid-mediated pain mechanisms or some combination of the above.

The most commonly researched strategy has been the administration of sucrose with and without NNS. Although exact dosage recommendations have not been clearly delineated (a dose range of 0.012 g to 0.12 g was identified), a recent systematic review of the efficacy of sucrose noted that for newborn infants sucrose decreased both physiological and behavioral indices of preterm and full-term infants in response to heel lance and venipuncture (Stevens et al. 2004). Pain responses are further decreased when sucrose and NNS are utilized together for heel lance with the speculation that the opioid-mediated orogustatory (e.g. sweet taste of sucrose), non-opioid-initiated orotactile (e.g. pacifier) and mechanoreceptor mechanisms are complementary in reducing pain (Gibbins and Stevens 2001). The administration of multisensory saturation (i.e. massage, eye contact, gentle vocalization, soothing smell) has also been shown to significantly increase the analgesic efficacy of sucrose (Bellieni et al. 2002). It is noteworthy that the efficacy of sucrose for pain relief tends to decrease with age and is believed to no longer be effective after 6 months of age (Pasero 2004).

Breast milk has also been examined for analgesic properties but has not been found to be as effective as sucrose (Ors et al. 1999). Other physical techniques such as massage, rocking, holding and skin-to-skin contact have also been shown to successfully moderate pain responses through non-opioid mediated pathways (e.g. Johnston et al. 2003).

A further group of pain management strategies relate to the positioning or containing of the infant during painful procedures. ► Swaddling, positioning, ► facilitative tucking, all appear to have some limited efficacy as a pain management technique on their own but appear better as an adjuvant to increase the efficacy of more reliable pain-reducing strategies.

Other types of physical stimulation commonly utilized with children and adults, such as heat, cold, acupuncture, transcutaneous stimulation and acupressure have not yet been investigated adequately with infant populations.

Summary

Understanding that unrelieved pain during infancy can irrevocably 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 strategies available to appropriately manage infant pain.

References

1. Als H, Lawhon G, Duffy FH et al. (1994) Individualized developmental care for the very low-birth-weight preterm infant. Medical and neurofunctional effects. JAMA 272:853–858
2. Anand KJS and International Evidence-Based Group for Neonatal Pain (2001) Concensus statement for the prevention and management of pain in the newborn. Arch Pedistr Adolesc Med 155:173–180
3. Bellieni CV, Bagnoli F, Perrone S et al. (2002) Effect of multisensory stimulation on analgesia in term neonates: A randomized controlled trial. Pediat Res 51:460–463
4. Bo LK, Callaghan P (2000) Soothing pain-elicited distress in Chinese neonates. Pediatrics 105:49
5. Cohen LL (2002) Reducing infant immunization distress through distraction. Health Psychol 21:207–211
6. Derrickson JG, Neef NA, Cataldo MF (1993) Effects of signaling invasive procedures on a hospitalized infant's affective behaviors. J Appl Behav Anal 26:133–134
7. Gibbins S, Stevens B (2001) Mechanisms of sucrose and non-nutritive sucking in procedural pain management in infants. Pain Res Manag 6: 21–28
8. Johnston CC, Stevens B, Pinelli J et al. (2003) Kangaroo care is effective in diminishing pain response in preterm neonates. Arch Pediatr Adolesc Med 157:1084–1088
9. Joint Fetus and Newborn Committee of the Canadian Paediatric Society and American Academy of Pediatrics (2000) Prevention and Management of Pain and Stress in the Neonate Pediatrics105, pp 454–461

10. Kurtis PS, DeSilva HN, Bernstein BA et al. (1999) A comparison of the mogen and gomco clamps in combination with dorsal penile nerve block in minimizing the pain of neonatal circumcision. Pediatrics 103:E23
11. Ors R, Ozek E, Baysoy G et al. (1999) Comparison of sucrose and human milk on pain response in newborns. European J Pediatrics 158:63–66
12. Pasero C (2004) Pain relief for neonates. Am J Nurs 104:44–47
13. Shah V, Ohlsson A (2004) Venepuncture versus heel lance for blood sampling in term neonates. Cochrane Database of Systematic Reviews 4
14. Simons SHP, van Dijk M, Anand KS et al. (2003) Do we still hurt newborn babies?: A prospective study of procedural pain and analgesia in neonates. Arch Pediatr Adolesc Med 157:1058–1064
15. Stevens B, Johnston C, Franck L et al. (1999) The efficacy of developmentally sensitive interventions and sucrose for relieving procedural pain in very low birth weight neonates. Nurs Res 48:35–43
16. Stevens B, Petryshen P, Hawkins J et al. (1996) Developmental versus conventional care: A comparison of clinical outcomes for very low birth weight infants. Can J Nurs Res 28:97–113
17. Stevens B, Yamada J, Ohlsson A (2004) Sucrose for analgesia in newborn infants undergoing painful procedures (Updated Cochrane review). The Cochrane Library 3
18. Sweet SD, McGrath PJ, Symons D (1999) The roles of child reactivity and parenting context in infant pain response. Pain 80:655–661

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 centres.

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 depolarising 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 fibres. Electrophysiological activity in these slow conduction C fibres is characteristically perceived as dull, burning pain. Faster conducting Aδ fibres are coupled to more selective thermal and mechano-thermal 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 sensitised 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 up-regulation of receptor expression, including substance P and brain derived growth factor (BDGF). Morphological changes including sprouting of unmyelinated nerve fibres 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 fibres pass either rostrally or caudally in ► Lissauer's tract. Somatic primary afferent fibres 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 neurons (WDR). The NS neurons are located predominantly in lamina I and respond exclusively to noxious stimuli. They are characterised 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 Sensitisation

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 fibre 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 up-regulated 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 centres *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 tracts), 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 fibres pass to reticular activating system, where they are associated with the arousal response to pain and the periaqueductal grey matter (PAG) where ascending inputs interact with descending modulatory fibres. 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).

1. Localization
   a) primary somatosensory cortex
   b) secondary somatosensory cortex
   c) insula

2. Intensity
   a) prefrontal cortex
   b) right posterior cingulate cortex
   c) brainstem
   d) periventricular grey matter

3. Affective Component
   a) left anterior cingulate cortex

4. Threshold
   a) cingulate cortex
   b) left thalamus
   c) frontal inferior cortex

References

1. Basbaum AI, Jessel TM (2000) The perception of pain. In: Kandel ER, Schwartz JH, Jessell TM (eds) Principles of Neural Science. McGraw-Hill, New York, pp 472–91
2. Fürst S (1999) Transmitters involved in antinociception in the spinal cord. Brain Res Bull 48:129–41
3. Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413:203–7
4. Kidd BL, Urban L (2001) Mechanisms of Inflammatory Pain. Br J Anaesth 87:3–11
5. McBain CJ, Mayer ML (1994) N-methyl-d-aspartic acid receptor structure and function. Physiol Rev 74:723–60
6. Parent A (1996) Carpenter's Human Neuroanatomy. Williams & Wilkins, Baltimore
7. Ready LB, Edwards WT (1992) Management of Acute Pain: A Practical Guide. Taskforce on Acute Pain. IASP Publications, Seattle
8. Smullen DH, Skilling SR, Larson AA (1990) Interactions between Substance P, calcitonin G related peptide taurine and excitatory amino acids in the spinal cord. Pain 42:93–101
9. Treede R-D, Kenshalo DR, Gracely RH et al. (1999) The cortical representation of pain. Pain 79:105–11

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 post-operative 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 post-operative 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.

► Multimodal Analgesia in Postoperative Pain

Acute Pain Team

Synonyms

APT

Definition

A team of nurse(s) and doctors (usually anesthesiologist(s)) that specialize in preventing and treating acute pain after surgery, trauma, due to medical conditions, and in some hospitals also labor pain.

► Postoperative Pain, Acute Pain Management, Principles
► Postoperative Pain, Acute Pain Team

Acute Pain, Subacute Pain and Chronic Pain

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Synonyms

Pain of Recent Origin; Persisting Pain; Subacute Pain; chronic pain

Definition

Acute pain is pain that has been present for less than three months (Merskey 1979; Merskey and Bogduk 1994). ► Chronic pain is pain that has been present for more than three 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 six weeks but less than three 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 aetiological and prognostic.

Acute pain was first defined by Bonica, 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 biological phenomenon resulting from physiological responses to bodily impairment. Pain was recognised as playing the important pathophysiological role of making an individual aware of impairment so they could respond appropriately. Responses include withdrawal from the stimulus causing the pain, to avoid further impairment, and behaviours that minimise the impact of the impairment and facilitate recovery. For example, if a person suffers a fracture the resultant pain warns them to limit activities that might 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 defined by Bonica as "pain that persists a month beyond the usual course of an acute disease or . . . (beyond the) time for an injury to heal, or that is associated with a chronic pathologic process." The implication is 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. One explanation for persistent pain would be that the original insult caused damage beyond the capacity of the natural healing process to repair. Another explanation would be that the insult was recurrent, with each recurrence renewing and prolonging the time required for healing. Yet another would be that the condition involved a chronic pathological process that continues to impair tissue over a long period. Other possible explanations invoke exogenous factors, such as inappropriate interventions applied for treatment, and/or endogenous factors such as cognitions and behaviours that inhibit recovery. Recognition of these endogenous factors lead Engel to develop the biopsychosocial model of chronic pain (Engel 1977), which although originally intended by its author to refer to only some types of chronic pain, is nowadays applied inappropriately by many to chronic pain in general.

The time factor ascribed by Bonica, i.e. one month longer than the usual time of recovery, would vary from condition to condition. In order to standardise the definitions of acute and chronic pain, attempts were made to ascribe finite durations to them. In 1974, Sternbach (Sternbach 1974) suggested six months as an arbitrary limit, such that pain present for up to six months would be classed as acute, whereas that present for more than six months would be deemed chronic. Others felt six months was too long, and discussion ensued. The International Association for the Study of Pain (IASP) formed a committee chaired by Harold 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, three months. The three month period is arbitrary, but it operationalises 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 applied in the literature (van Tulder et al. 1997) to pain present for between six weeks and three months. As such, it forms a subset of acute pain. The main division between acute and chronic pain remains at three 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 three categories of pain flows from the implicit likelihood of spontaneous recovery, which is crucial to management and prognosis.

The management of acute pain is clear when the condition is understood and known to be likely to resolve within a short time by natural healing. By definition, no therapeutic intervention is necessary for recovery; 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" (Hippocrates. Of the Epidemics, I; II: VI), to which doctors have (supposedly) subscribed for centuries. Cochrane promoted this approach in his farsighted work that lead 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" (Cochrane 1977), and wondered "how many things are done in modern medicine because they can be, rather than because they should be" (Cochrane 1977). The effectiveness of the approach has been shown by Indahl et al. (1995) in the management of subacute low back pain, and by McGuirk et al. (2001) in the management of acute low back pain.

Rational management of chronic pain is quite different. As the circumstances giving rise to chronic pain will not resolve spontaneously, intervention is indicated in virtually every case. The key to the problem is accurate 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, many chronic conditions have specific treatments that will control the pain effectively (Lord et al. 1996; Govind et al. 2003). Nevertheless, psychosocial factors must always be considered as well, 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 it is controversial in pain medicine. Chronic low back and neck pain, in particular, are rarely managed as if precise diagnosis is possible, which these days it is in the majority of cases (Bogduk et al. 1996). If specific treatment is applied and the pain is controlled, associated psychosocial problems can also be expected to remit. There is sound evidence (Wallis et al. 1997) to show this happens, but no sound evidence to show that when pain is controlled effectively, related psychosocial problems persist.

References

1. Bogduk N, Derby R, Aprill C, Lord S, Schwarzer A (1996) Precision Diagnosis of Spinal Pain. In: 8th World Congress on Pain, Refresher Course Syllabus. IASP Press, Seattle, pp 313–323
2. Bonica JJ (1953) The Management of Pain. Lea & Febiger, Philadelphia
3. Cochrane AL (1977) Effectiveness and Efficiency. Random Reflections on Health Services. Cambridge University Press, Cambridge, p 5
4. Engel G (1977) The Need for a New Medical Model: A Challenge for Biomedicine. Science 196:129–136
5. Govind J, King W, Bailey B, Bogduk N (2003) Radiofrequency Neurotomy for the Treatment of Third Occipital Headache. J Neurol Neurosug Psychiat 74:88–93
6. Hippocrates. Of the Epidemics, I; II: VI paraphrased by Galen, in Commentaries
7. Indahl A, Indahl A, Velund L, Reikerås O (1995) Good Prognosis for Low Back Pain when Left Untampered. Spine 20:473–477
8. Lord SM, Barnsley L, Wallis BJ, McDonald GJ, Bogduk N (1996) Percutaneous Radiofrequency Neurotomy for the Treatment of Chronic Cervical Zygapophysial Joint Pain: A Randomized, Double-Blind Controlled Trial. N Engl J Med 335:1721–1726
9. McGuirk B, King W, Govind J, Lowry J, Bogduk N (2001) Safety, Efficacy and Cost-Effectiveness of Evidence-Based Guidelines for the Management of Acute Low Back Pain in Primary Care. Spine 26:2615–2622
10. Merskey H (1979) Pain Terms: A List with Definitions and Notes on Usage Recommended by the IASP Subcommittee on Taxonomy. Pain 6:249–252
11. Merskey H, Bogduk N (1994) Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd edn. IASP Press, Seattle, p xi
12. Sternbach RA (1974) Pain Patients: Traits and Treatment. Academic Press, New York
13. van Tulder MW, Koes BW, Bouter LM (1997) Conservative Treatment of Acute and Chronic Nonspecific Low Back Pain. A Systematic Review of Randomized Controlled Trials of the most Common Interventions. Spine 22:2128–2156
14. Wallis BJ, Lord SM, Bogduk N (1997) Resolution of Psychological Distress of Whiplash Patients following Treatment by Radiofrequency Neurotomy: A Randomised, Double-Blind, Placebo-Controlled Trial. Pain 73:15–22

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.

► Pain Control in Children with Burns

Acute Post-Operative Pain in Children

► Acute Pain in Children, Post-Operative

Acute Postoperative Pain Therapy

Definition

Acute postoperative pain therapy includes the postoperative pain service and pain management, patient controlled epidural analgesia and patient controlled intravenous analgesia.

► 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 one month of exposure to trauma, and whose symptoms are similar to post traumatic distress. They include re-experiencing the event as with flashbacks and nightmares, dissociative symptoms like numbing, avoidance of any reminder of the trauma, and hyperarousal or increased generalized anxiety.

► Pain Control in Children with Burns

Acute-Recurrent Pain

► Postoperative Pain, Acute-Recurrent Pain

Adaptation

Definition

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

► Coping and Pain
► Mechanonociceptors

Adaptation Phase

Definition

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

► Psychophysiological Assessment of Pain

Adaptive Equipment

Equipment designed to increase the abilities of an individual with an impairment or disability.

► Chronic Pain in Children: Physical Medicine and Rehabilitation

ADD Protocol

► Assessment of Discomfort in Dementia Protocol

Addiction

Definition

Addiction is the aberrant use of a substance in a manner characterized by: 1) loss of control over medication use, 2) compulsive use, 3) continued use despite physical, psychological or social harm, and 4) craving, often obtaining supply by deceptive or illegal means. This syndrome also includes a great deal of time used to obtain the medication, use the medication, or recover from its effects. Addiction is not the same as tolerance or dependence. Unlike the other two, which are physiological responses, addiction implies drug seeking behaviors and has a host of psychological factors. Addiction is rare among patients given opioids for the treatment of pain.

- ► 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.

- ► Cancer Pain Management, Orthopedic Surgery

Adenoassociated Virus Vectors

Synonyms

AAV

Definition

Adenoassociated virus (AAV) based vectors are derived from a non-pathogenic parvovirus. AAV are thought to be naturally defective, because of their requirement for co-infection 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.

- ► 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, thyroid, etc. In the majority of cases these neoplasms stay benign, but some transform to malignancy over time.

- ► 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

- ► Dyspareunia and Vaginismus

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 pirimidines. 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.

- ► Purine Receptor Targets in the Treatment of Neuropathic Pain

Adenoviral Vectors

Definition

Adenoviral (Ad) vectors are based on a relatively non-pathogenic 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.

► Opioids and Gene Therapy

Adequate Stimulus

Definition

A term coined by Sherrington in 1890's 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.

► 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.

► Multidisciplinary Pain Centers, Rehabilitation

Adhesion Molecules

Definition

Circulating leukocytes migrate to injured tissue directed by adhesion molecules. The initial step, rolling, is mediated by selectins on leukocytes (L-selectin) and endothelium (P- and E-selectin). The rolling leukocytes are exposed to tissue-derived chemokines. These upregulate the avidity of integrins, which mediate the firm adhesion of cells to endothelium by interacting with immunoglobulin superfamily members such as intercellular adhesion molecule–1. Finally, the cells migrate through the vessel wall, directed by platelet-endothelial cell adhesion molecule-1 and other immunoglobulin ligands. Interruption of this cascade can block immunocyte extravasation.

► Opioids in the Periphery and Analgesia

Adjunctive Drugs

Definition

Adjunctive Drugs are medications employed in the course of therapy to assist in the treatment of side-effects from the prescribed therapy.

► 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.

► Psychiatric Aspects of the Epidemiology of Pain

Adjustment Disorder

Definition

Adjustment Disorder, defined by DSM–IV, includes significant depressive symptoms (with insufficient criteria for a mood disorder) after an identifiable stress, for example, a painful illness, injury, or hospitalization.

► Somatization and Pain Disorders in Children

Adjuvant

Definition

An additive that enhances the effectiveness of medical standard therapy.

► Adjuvant Analgesics in Management of Cancer-Rated Bone Pain
► NSAIDs and Cancer

Adjuvant Analgesic

Definition

Medications that have a primary indication other than pain, but are analgesic in some painful conditions. Examples include antidepressants and anticonvulsants. Adjuvant analgesic drugs are often added to opioids to augment their efficacy.

► Analgesic Guidelines for Infants and Children
► Cancer Pain Management, Adjuvant Analgesics in Management of Pain Due To Bowel Obstruction
► Cancer Pain Management, Non-Opioid Analgesics
► Cancer Pain Management, Principles of Opioid Therapy, Drug Selection
► Opioid Rotation in Cancer Pain Management

Adjuvant Analgesics in Management of Cancer-Rated Bone Pain

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Synonyms

Malignant Bone Pain; boney pain; cancer-related 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.

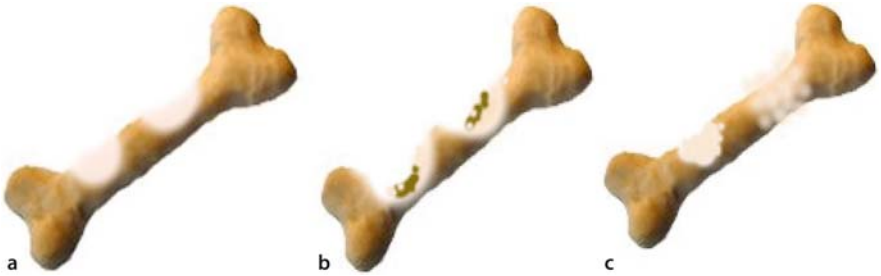
Boney metastases occur in approximately 60–85% of patients who develop metastatic disease from some of the more common cancers, e.g. breast, prostate, and lung. Bone is one of the most common metastatic sites. There are also primary bone cancers, e.g. myeloma, osteosarcoma, Ewing's sarcoma (Mercadante 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 (Mercadante1997; 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 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 one 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 that can be localized or widespread, 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



Adjuvant Analgesics in Management of Cancer-Rated Bone Pain, Figure 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).

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}rhennium (^{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 are 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 two to four hours and 4 mg zoledronic acid administered over 15 min every three to four 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 anti-tumor 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 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.

References

1. Benjamin R (2002) Neurologic complications of prostate cancer. Am Fam Physician 65:1834–1840
2. Bouchet LG, Bolch WE, Goddu SM et al. (2000). Considerations in the Selection of Radiopharmaceuticals for Palliation of Bone Pain from Metastatic Osseous Lesions. J Nucl Med 41:682–687
3. Green JR, Clezardin P (2002) Mechanisms of Bisphosphonate Effects on Osteoclasts, Tumor Cell Growth, and Metastasis. Am J Clin Oncol 25:3–9
4. Hoskin PJ (2003) Bisphosphonates and Radiation Therapy for Palliation of Metastatic Bone Disease. Cancer Treat Rev 29:321–327
5. Lucas LK, Lipman AG (2002) Recent Advances in Pharmacotherapy for Cancer Pain Management. Cancer Pract 10:14–20
6. McQuay HJ, Collins SL, Carroll D et al. (2000) Radiotherapy for the Palliation of Painful Bone Metastases. Cochrane Database Syst Rev:CD001793
7. Mercadante S (1997) Malignant Bone Pain: Pathophysiology and Treatment. Pain 69:1–18
8. Payne R (1997) Mechanisms and Management of Bone Pain. Cancer 80:1608–1613

9. Sabino MA, Ghilardi JR, Jongen JL et al. (2002) Simultaneous Reduction in Cancer Pain, Bone Destruction, and Tumor Growth by Selective Inhibition of Cyclooxygenaseû2. Cancer Res 62:7343–7349
10. Wong R, Wiffen PJ (2002) Bisphosphonates for the Relief of Pain Secondary to Bone Metastases. Cochrane Database Syst Rev:CD002068

Adjuvant Analgesics in Management of Cancer-Related Neuropathic Pain

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Definition

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

Characteristics

Cancer pain caused by neuropathic mechanisms is relatively less responsive to opioid drugs than pain caused by nociceptive mechanisms (Cherny et al. 1994). However, when adjuvant analgesics are appropriately combined with opioid and non-opioid analgesics (anti-inflammatory drugs, acetaminophen), it is possible to obtain a degree of analgesia similar to the one achieved in nociceptive pain (Grond et al. 1999). Several classes of adjuvant analgesics can be used in neuropathic pain. Some are useful in a variety of pain syndromes (nociceptive pain, bone pain, myofascial pain) and are, therefore, termed multipurpose adjuvant analgesics, whereas others are used specifically for neuropathic pain. Although adjuvant analgesics are used extensively to treat cancer-related pain, the scientific evidence is often limited and data from nonmalignant pain must be extrapolated.

Anticonvulsants

Nowadays, anticonvulsants are often favored in the treatment of cancer-related neuropathic pain. Due to its proven analgesic effect, its good tolerability and paucity of drug-drug interactions, gabapentin is now recommended as a first-line agent, especially in the medically ill population (Farrar and Portenoy 2001). It should be started at 100–300 mg at bedtime, and titrated up until analgesia is obtained, which usually occurs with a daily dose of 900–3600 mg. A daily dose higher than 300 mg should be divided into three separate doses. Adverse effects (somnolence, mental clouding, and dizziness) are usually minimal if the titration is gradual, and often abate within a few days.

Although evidence for the analgesic effect of newer anticonvulsants (lamotrigine, levetiracetam, oxcarbazepine, topiramate, pregabalin, tiagabine, zonisamide) is scarce, especially for cancer-related pain, a positive clinical experience justifies a trial of one of these when the pain does not respond to gabapentin (Farrar and Portenoy 2001). The older anticonvulsants, i.e. carbamazepine, phenytoin and valproic acid, can also be analgesic, but caution is required due to their frequent side effects (sedation, dizziness, nausea), narrow therapeutic window, numerous drug interactions and low tolerability in medically ill patients (Farrar and Portenoy 2001).

Antidepressants

Along with anticonvulsants, antidepressants are the adjuvant analgesics most commonly used for neuropathic pain. The tricyclic antidepressants have been proven to be analgesic in several types of neuropathic and non-neuropathic pain (Portenoy 1998). Their frequent adverse effects, especially in elderly and medically ill patients, however, limit their use. The secondary amines (nortriptyline, desipramine) are less anticholinergic than the tertiary amines (amitriptyline, imipramine, doxepin, clomipramine) and are often better tolerated (see ► anticholinergics). All tricyclics are, however, contraindicated in patients with significant cardiac disease and closed angle glaucoma, and should be used with caution in patients with prostate hypertrophy.
The analgesic efficacy of newer antidepressants (selective serotonin reuptake inhibitors, e.g. paroxetine, selective norepinephrine and serotonin reuptake inhibitors, e.g. venlafaxine and duoxetine, and others, e.g. bupropion) has been less well documented than for the tricyclics. However, due to their better tolerability, a few studies supporting their analgesic effect and a favorable clinical experience, a therapeutic trial is often justified (Farrar and Portenoy 2001).

Local Anesthetics

Local anesthetics are known to have analgesic properties in neuropathic pain (Mao and Chen 2000). A brief intravenous infusion of lidocaine has been shown to be effective in nonmalignant neuropathic pain. Despite negative results obtained in randomized controlled trials in neuropathic cancer pain, clinical experience justifies considering its use. Lidocaine infusions can be administered at varying doses within the range of 1–5 mg/kg infused over 20–30 min and should be done under cardiac monitoring. Prolonged pain relief following a brief local anesthetic infusion may be possible. If the pain recurs, long-term systemic local anesthetic therapy is usually accomplished using an oral formulation of mexiletine. Systemic local anesthetics are generally considered second-line, reserved for the treatment of severe intractable or 'crescendo' neuropathic pain (Mao and Chen 2000).

The use of a lidocaine 5% patch is associated with very low systemic absorption and adverse effects. It has been shown to reduce pain and allodynia from postherpetic neuralgia, and clinical experience supports its use in a variety of other neuropathic pain conditions (Argoff 2000).

N-Methyl-D-Aspartate Receptor Blockers

The *N*-methyl-D-aspartate (NMDA) receptor is involved in the sensitization of central neurons following injury and the development of the 'wind-up' phenomenon, a change in the response of the central neurons that has been associated with neuropathic pain. Antagonists at the NMDA receptor may, therefore, offer another approach to the treatment of neuropathic pain in cancer patients.

Ketamine, administered by intravenous bolus or infusion, or orally, has been shown to be effective in relieving pain in cancer patients (Jackson et al. 2001; Mercadante et al. 2000). A subcutaneous or intravenous infusion can be initiated at low doses (0.1–0.15 mg/kg/h). The dose can be gradually escalated, with close monitoring of pain and side effects. Long-term therapy can be maintained using continuous subcutaneous infusion, repeated subcutaneous injections or oral administration. The side effect profile of ketamine can, however, be daunting, especially in medically ill patients, so only clinicians who are experienced in the use of parenteral ketamine should consider this option in patients with refractory pain.

Dextromethorphan is better tolerated, can be used on a long-term basis, and has been reported to reduce phantom limb pain in cancer amputees (Ben Abraham et al. 2003). A prudent starting dose is 45–60 mg/day, which can be gradually escalated until favorable effects occur, side-effects supervene, or a conventional maximal dose of 1 g is reached.

Amantadine and memantine, non-competitive NMDA antagonists, are other options. Amantadine, for example, has been shown to reduce pain, allodynia and hyperalgesia in surgical neuropathic pain in cancer patients (Pud et al. 1998).

Corticosteroids

By decreasing the peritumoral edema, corticosteroid drugs can relieve neuropathic pain from infiltration or compression of neural structures (Watanabe and Bruera 1994). They also have many other indications in cancer and palliative care, including improvement of appetite, nausea, malaise and overall quality of life, as well as treatment of metastatic bone pain. A high-dose regimen (e.g. initial dose of dexamethasone 40–100 mg followed by 16–96 mg/day in divided doses) can be given to patients who experience an acute episode of very severe pain not relieved adequately with opioids, such as that associated with a rapidly worsening malignant plexopathy. More often, a low-dose corticosteroid regimen (e.g. dexamethasone 1–2 mg once or twice daily) is used for patients with advanced cancer who continue to have pain despite optimal dosing of opioid drugs. Although long-term treatment with relatively low doses is generally well tolerated, ineffective regimens should be tapered and discontinued.

Alpha-2-Adrenergic Agonists

Alpha-2-adrenergic agonists are nonspecific multipurpose adjuvant analgesics that can be considered after trials of other adjuvants, mainly antidepressants and anticonvulsants, have failed. Clonidine, administered orally or transdermally, can relieve neuropathic pain, and there is strong evidence that intraspinal administration of clonidine can be effective in neuropathic cancer pain. The occurrence of hypotension may limit its use in medically ill patients.

Tizanidine is an alpha-2-adrenergic receptor agonist with a better safety profile than oral clonidine. Although it is mainly used as an antispasticity agent, it can also be tried as a multipurpose adjuvant analgesic.

Other Adjuvant Analgesics for Neuropathic Pain

Baclofen, an agonist at the gamma aminobutyric acid type B ($GABA_B$) receptor, can also be considered for cancer-related neuropathic pain, notwithstanding very limited evidence of efficacy (Fromm 1994). The effective dose range is very wide (20 to > 200 mg daily), which necessitates careful titration.

Cannabinoids are analgesic, but their utility in the treatment of chronic pain is still uncertain (Campbell et al. 2001). A trial might be considered in refractory neuropathic pain.

Topical therapies may be very useful. The lidocaine patch was described previously. Numerous other drugs – NSAIDs, antidepressants, capsaicin and varied others – have been used. In the cancer population, local application of capsaicin cream can be effective in reducing neuropathic postsurgical pain (postmastectomy, postthoracotomy, postamputation) (Rowland et al. 1997).

Selection of the Most Appropriate Adjuvant Analgesic

When selecting the most appropriate adjuvant for treatment of pain in a cancer patient, a comprehensive assessment is always warranted (Portenoy 1998). This includes: 1) description of the pain, including its etiology and its relationship to the underlying disease, which allows inferences about the predominating type of pain pathophysiology (e.g. nociceptive or neuropathic); 2) assessment of the impact of pain on function and quality of life; 3) identification of any relevant comorbidities that may influence drug selection (e.g. antidepressants will be favored in a patient with concomitant depression); 4) identification of associated symptoms (e.g. corticosteroids may be most appropriate if pain is associated with fatigue, nausea or anorexia); 5) assessment

of the goals of care (e.g. sedation will be better accepted by the patient and family if the patient's comfort is the main objective); 6) evaluation of patient's other medications, looking for potential drug interactions (Bernard and Bruera 2000).

Once the most appropriate adjuvant analgesic has been identified, a few guidelines should be followed in the initial prescription and follow-up of this patient (Portenoy 1998): 1) optimize the opioid and non-opioid analgesic therapy before adding an adjuvant; 2) start only one adjuvant at a time, to decrease cumulative adverse effects; 3) titrate the dose gradually and carefully, according to pain relief and adverse effects; 4) if pain relief is not adequate, consider combining several adjuvant analgesics of different classes; 5) regularly reassess the pain relief as well as the response and adverse effects to analgesic medications and adjust the therapeutic regimen if necessary.

References

1. Argoff CE (2000) New Analgesics for Neuropathic Pain: The Lidocaine Patch. Clin J Pain 16:S62–S66
2. Ben Abraham R, Marouani N, Weinbroum AA (2003) Dextromethorphan Mitigates Phantom Pain in Cancer Amputees. Ann Surg Oncol 10:268–274
3. Bernard SA, Bruera E (2000) Drug Interactions in Palliative Care. J Clin Oncol 18:1780–1799
4. Campbell FA, Tramer MR, Carroll D et al. (2001) Are Cannabinoids an Effective and Safe Treatment Option in the Management of Pain? A Qualitative Systematic Review. Br Med J 323:13–16
5. Cherny NI, Thaler HT, Friedlander-Klar H et al. (1994) Opioid Responsiveness of Cancer Pain Syndromes Caused by Neuropathic or Nociceptive Mechanisms. Neurol 44:857–861
6. Ellison N, Loprinzi CL, Kugler J et al. (1997) Phase III Placebo-Controlled Trial of Capsaicin Cream in the Management of Surgical Neuropathic Pain in Cancer Patients. J Clin Oncol 15:2974–2980
7. Farrar JT, Portenoy RK (2001) Neuropathic Cancer Pain: The Role of Adjuvant Analgesics. Oncol 15:1435–1445
8. Fromm GH (1994) Baclofen as an Adjuvant Analgesic. J Pain Sympt Manage 9:500–509
9. Grond S, Radbruch L, Meuser T et al. (1999) Assessment and Treatment of Neuropathic Cancer Pain following WHO Guidelines. Pain 79:15–20
10. Jackson K, Ashby M, Martin P et al. (2001) 'Burst' Ketamine for Refractory Cancer Pain: An Open-Label Audit of 39 Patients. J Pain Symptom Manage 23:60–65
11. Mao J, Chen LL (2000) Systemic Lidocaine for Neuropathic Pain Relief. Pain 87:7–17
12. Mercadante S, Arcuri E, Tirelli W et al. (2000) Analgesic Effect of Intravenous Ketamine in Cancer Patients on Morphine Therapy: A Randomized, Controlled, Double-Blind, Crossover, Double-Dose Study. J Pain Symptom Manage 20:246–252
13. Portenoy RK (1998) Adjuvant Analgesics in Pain Management. In: Doyle D, Hanks GW, MacDonald N (eds) Oxford Textbook of Palliative Medicine, 2nd edn. Oxford University Press, Oxford, pp 361–390
14. Pud D, Eisenberg E, Spitzer A et al. (1998) The NMDA Receptor Antagonist Amantadine Reduces Surgical Neuropathic Pain in Cancer Patients: A Double Blind, Randomized, Placebo-Controlled Trial. Pain 75:349–354
15. Rowland et al. (1997)
16. Watanabe S, Bruera E (1994) Corticosteroids as Adjuvant Analgesics. J Pain Symptom Manage 9:442–445

Adjuvant Arthritis

► Arthritis Model, Adjuvant-Induced Arthritis

ADLs

► Activities of Daily Living

Adrenergic Agonist

Definition

An adrenergic agonist is a ligand that binds to adrenergic receptors.

► Adrenergic Antagonist
► Sympathetically Maintained Pain, Clinical Pharmacological Tests

Adrenergic Antagonist

Definition

An adrenergic antagonist is a drug that prevents ligands from binding to adrenergic receptors.

► Adrenergic Agonist
► Sympathetically Maintained Pain, Clinical Pharmacological Tests

Adrenoceptors

Definition

Adrenoceptors are receptors that are located pre- and postganglionically on effector tissues, most of which are innervated by postganglionic sympathetic fibers, and are activated by release of norepinephrine, epinephrine, and various adrenergic drugs.

► Sympathetically Maintained Pain in CRPS I, Human Experimentation

Adult Respiratory Distress Syndrome

► ARDS

Adverse Effects

Definition

Unwanted side effects of drug treatment.

► 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.

► Chronic Pelvic Pain, Physical Therapy Approaches and Myofascial Abnormalities

Adverse Selection

Definition

When worse than average risks are most likely to acquire insurance.

► Disability Incentives

Aerobic Exercise

► Exercise

Affective

Definition

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

► McGill Pain Questionnaire

Affective Analgesia

Definition

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

► Thalamo-Amygdala Interactions and Pain

Affective Component (Aspekt, Dimension) of Pain

Definition

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 painful stimulus).

► 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 Responses

Definition

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

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

Affective-Motivational

Definition

Relating to affect and forces that drive behavior.

► 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.

► Nociceptive 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 to a neuron. The cell bodies of afferent fibers in the peripheral nerves reside in the dorsal root and trigeminal ganglion. An afferent neuron is also known as a sensory neuron.

- ► Postsynaptic Dorsal Column Projection, Functional Characteristics
- ► Visceral Nociception and Pain

Afferent Projections

Definition

In nervous systems, afferent signals or nerve fibers carry information toward the brain or a particular brain structure. A touch or painful stimulus, for example, creates a sensation in the brain, only after information about the stimulus travels there via afferent nerve pathways. Efferent nerves and signals carry information away from the brain or a particular brain structure.

- ► Amygdala, Pain Processing and Behavior in Animals

Afferent Signal

Definition

An afferent signal is a neurologic signal that comes from the site of the bone (or any other site of the body) abnormality, and goes towards the central nervous system.

- ► Cancer Pain Management, Orthopedic Surgery

Afterdischarge(s)

Definition

Afterdischarge is the continued nerve response after the stimulus, or inciting event, has ceased. This usually refers to both nerve hypersensitivity and prolonged reactivity.

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

Afterhyperpolarisation

Synonyms

AHP

Definition

For many neuronal cells, an action potential or a burst of action potentials is followed by a hyperpolarisation, where the neuronal membrane potential is lower than the neuron's normal resting membrane potential. In various models, different parts of this AHP with different time constants and different pharmacology have been described and molecular mechanisms, most of them different potassium channels, have been suggested.

- ► Mechano-Insensitive C-Fibres, Biophysics
- ► Molecular Contributions to the Mechanism of Central Pain

After-Pains, Postnatal Pain

- ► Postpartum Pain

Age and Chronicity

- ► Pain in the Workplace, Risk Factors for Chronicity, 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.

- ► Therapy of Pain, Hypnosis

Age-Related Pain Diagnoses

Definition

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

- ► 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.

► Postoperative Pain, Appropriate Management

Agreed Medical Examination

► Independent Medical Examinations

AHP

► Afterhyperpolarisation

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 internis fascia lining the lateral wall of the ischiorectal fossa that transmits the pudendal vessels and nerves.

► Clitoral Pain

Alcohol-Induced Pancreatitis

► Visceral Pain Model, Pancreatic pain

Alcoholism

► Metabolic and Nutritional Neuropathies

Alfentanil

Definition

This is a short acting very potent opioid.

► 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).

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

Algodystrohy

► Complex Regional Pain Syndromes, Clinical Aspects
► Complex Regional Pain Syndromes, General Aspects
► Neuropathic Pain Models, CRPS-I Neuropathy Model
► Sympathetically Maintained Pain in CRPS I, Human Experimentation

Algogen

Definition

Chemical substance with the ability to induce pain and hyperalgesia.

► 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.

► 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).

► Threshold Determination Protocols

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.

► Migraine, Childhood Syndromes

ALIF

Synonyms

Anterior Lumbar Interbody Fusion

Definition

Anterior lumbar interbody fusion are graft/cages placed between the vertebral bodies by anterior approach.

► 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.

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

Allocortex

Definition

The allocortex is a 3–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.

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

Allodynia

Definition

Allodynia is a nociceptive reaction and/or pain due to a stimulus that does not normally evoke pain („allo" – „other"; „dynia" – pain), like mild touch or moderate cold. The definition of allodynia by the International Association for the Study of Pain (IASP) is: "Pain induced by stimuli that are not normally painful" If this definition is taken literally, it means that any drop in pain threshold is allodynia, whereas increases in pain to suprathreshold stimuli are hyperalgesia. Allodynia is based on sensitized central neurons with increased excitability to A-beta fiber input, and is critically dependent on the ongoing activity of nociceptive afferent units, particularly mechano-insensitive C-fibers. It is one of the most distressing symptoms of neuropathic pain.

► Allodynia and Alloknesis
► Anesthesia Dolorosa Model, Autotomy
► Calcium Channels in the Spinal Processing of Nociceptive Input
► Chronic Pelvic Pain, Musculoskeletal Syndromes
► Clitoral Pain
► Cognitive Behavioral Treatment of Pain
► Complex Regional Pain Syndromes, Clinical Aspects
► CRPS-1 in Children
► CRPS, Evidence-Based Treatment
► 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
- ► Percutaneous Cordotomy
- ► PET and fMRI Imaging in Parietal Cortex (SI, SII, Inferior Parietal Cortex BA40)
- ► Postherpetic Neuralgia, Etiology, Pathogenesis and Management
- ► Postherpetic Neuralgia, Pharmacological and Non-Pharmacological Treatment Options
- ► Post-Stroke Pain Model, Thalamic Pain (Lesion)
- ► Psychiatric Aspects of Visceral Pain
- ► Purine Receptor Targets in the Treatment of Neuropathic Pain
- ► Satellite Cells and Inflammatory 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 (Clinical, Experimental)

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Synonyms

Touch Evoked Pain; dynamic mechanical hyperalgesia; obsolete: hyperaesthesia

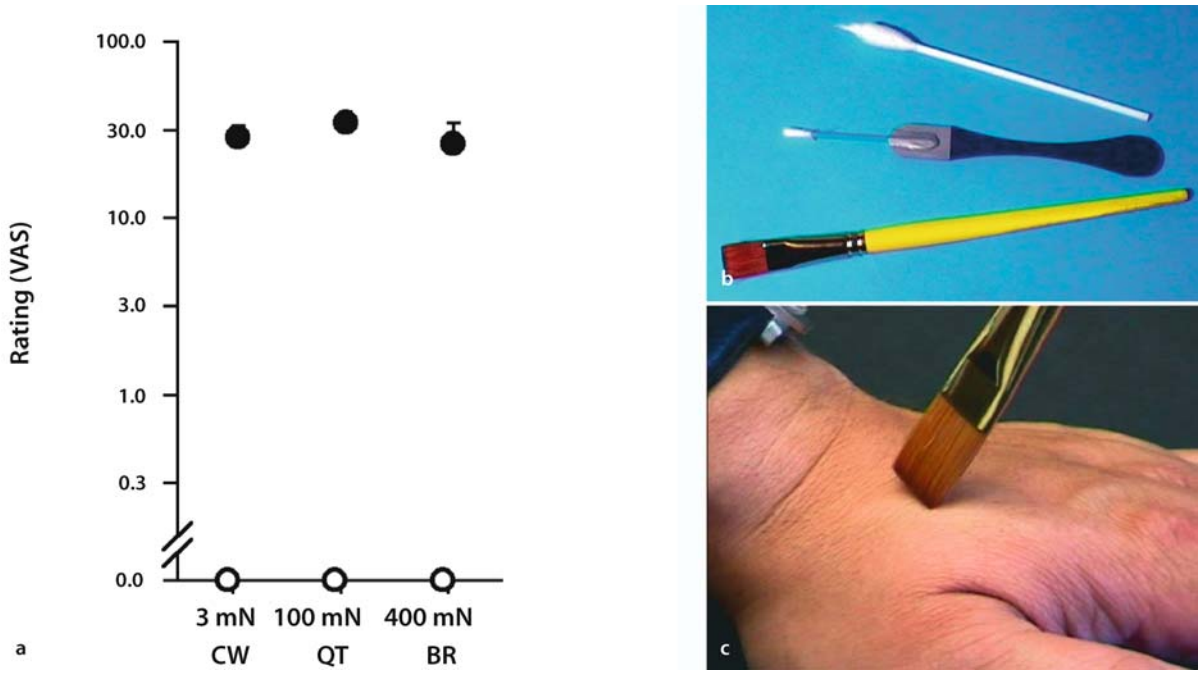
Definition

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



Allodynia (Clinical, Experimental), Figure 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.

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 (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 out-

last 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).

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 towards 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

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

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).

References

1. Baumann TK, Simone DA, Shain CN et al. (1991) Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. J Neurophysiol 66:212–227
2. Campbell JN, Raja SN, Meyer RA et al. (1988) Myelinated afferents signal the hyperalgesia associated with nerve injury. Pain 32:89–94
3. Cervero F, Laird JMA (1996) Mechanisms of touch-evoked pain (allodynia): a new model. Pain 68:13–23
4. Gracely RH, Lynch SA, Bennett GJ (1992) Painful neuropathy: altered central processing, maintained dynamically by peripheral input. Pain 51:175–194
5. Klein T, Magerl W, Hopf HC et al (2004) Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 24:964–971
6. Koltzenburg M, Torebjörk HE, Wahren LK (1994) Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain 117:579–591
7. LaMotte RH, Shain CN, Simone DA et al. (1991) Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms, J Neurophysiol 66:190–211
8. Loh L, Nathan PW (1978) Painful peripheral states and sympathetic blocks. J Neurol Neurosurg Psychiatry 41:664–671
9. Merskey H (1982) Pain terms: a supplementary note. Pain 14:205–206
10. Ochoa JL, Yarnitsky D (1993) Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. Ann Neurol 33:465–472
11. Raja SN, Meyer RA, Ringkamp M et al. (1999) Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R (eds) Textbook of Pain, 4th edn. Churchill Livingstone, Edinburgh, pp 11–57
12. Rolke R, Magerl W, Campbell KA et al. (2006) Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 10:77–88
13. Sandkühler J (2000) Learning and memory in pain pathways. Pain 88:113–118
14. Simone DA, Sorkin LS, Oh U et al. (1991) Neurogenic hyperalgesia: Central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 66:228–246
15. Torebjörk HE, Lundberg LER, LaMotte RH (1992) Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia. J Physiol 448:765–780
16. Treede RD, Meyer RA, Raja SN et al. (1992) Peripheral and central mechanisms of cutaneous hyperalgesia. Prog Neurobiol 38:397–421
17. Treede RD, Handwerker HO, Baumgärtner U et al. (2004) Hyperalgesia and allodynia: taxonomy, assessment, and mechanisms. In: Brune K, Handwerker HO (eds) Hyperalgesia: Molecular Mechanisms and Clinical Implications. IASP Press, Seattle, pp 1–15
18. Wasner G, Schattschneider J, Binder A et al. (2004) Topical menthol –a human model for cold pain by activation and sensitization of C nociceptors. Brain 127:1159–1171
19. Woolf CJ (1983) Evidence for a central component of post-injury pain hypersensitivity. Nature 306:686–688

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.

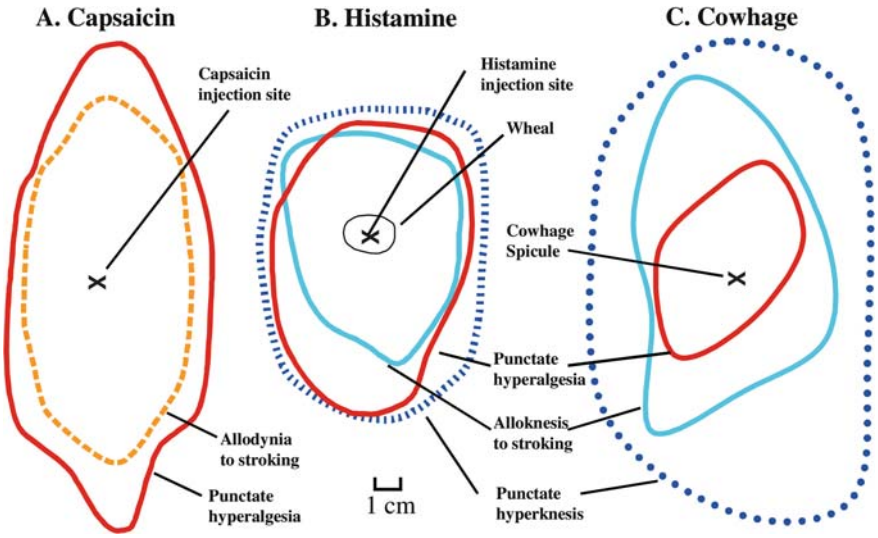
Characteristics

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).

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). 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 (Shelley and Arthur 1957; Graham et al. 1951) (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.



Allodynia and Alloknesis, Figure 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.

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. Subpopulations of mechanosensitive nociceptive peripheral neurons with unmyelinated axons respond, in humans, to histamine (Handwerker et al. 1991) and, in the cat, to cowhage spicules (Tuckett and Wei 1987). Histamine also activates a subpopulation of MIAs with unmyelinated axons in humans (Schmelz et al 1997). Some of these neurons in human and cat exhibited responses that were comparable in time course to the sensation of itch reported by humans in response to the same stimuli. In addition, a few STT neurons with properties similar to the histamine sensitive MIAs were identified in the superficial dorsal horn of the cat (Andrew and Craig 2000). Similarly, a subpopulation of mechanically sensitive, ventrolateral spinal axons with nociceptive properties in the cat responded to cutaneous insertion of cowhage spicules (Wei and Tuckett 1991). However, the primary sensory neurons and spinal neurons responsive to histamine or to cowhage also responded to nociceptive stimuli that do not elicit itch in humans (Schmelz et al. 2003).

In the absence of itch-specific peripheral sensory neurons, it is possible that itch is encoded by pruriceptive central neurons, for example in the spinal dorsal horn, that are activated by peripheral neurons responsive to both pruritic and nociceptive stimuli but inhibited by interneurons that are activated only by noxious but not pruritic stimuli. Such interneurons may well receive input from known nociceptive specific afferents that respond to noxious stimuli such as capsaicin, heat or mechanical stimuli but do not respond to pruritic stimuli such as histamine. This "occlusion theory of itch" (Handwerker 1992) suggests that itch is felt only in the absence of activity in nociceptive neurons that would occlude or inhibit activity in the pruriceptive neurons. Presumably, the pruriceptive neurons would also be inhibited by sensitized central neurons responsible for maintaining a state of allodynia.

References

1. Atanassoff PG, Brull SJ, Zhang JM et al. (1999) Enhancement of experimental pruritus and mechanically evoked dysesthesias with local anesthesia. Somatosen Mot Res 16:299–303
2. Brull SJ, Atanassoff PG, Silverman DG et al. (1999) Attenuation of experimental pruritus and mechanically evoked dysesthesias in an area of cutaneous allodynia. Somatosen Mot Res 16:291–298
3. Graham DT, Goodell H, Wolff HG (1951) Neural mechanisms involved in itch, "itchy skin," and tickle sensations. J Clin Invest 30:37–49
4. Handwerker HO, Forster C, Kirchoff C (1991) Discharge properties of human C-fibres induced by itching and burning stimuli. J Neurophysiol 66:307–315
5. Handwerker HO (1992) Pain and allodynia, itch and alloknesis: an alternative hypothesis. Am Pain Soc J 1:135–138
6. LaMotte RH, Shain CN, Simone DA et al. (1991) Neurogenic hyperalgesia: Psychophysical studies of underlying mechanisms. J Neurophysiol 66:190–211

7. LaMotte RH (1992) Subpopulations of "nocifensor neurons" contributing to pain and allodynia, itch and alloknesis. Amer Pain Soc J 1:115–126
8. Magerl W, Westerman RA, Mohner B et al. (1990) Properties of transdermal histamine iontophoresis: differential effects of season, gender and body region. J Invest Dermatol 94:347–352
9. Nilsson H-JA, Levinsson A, Schouenborg J (1997) Cutaneous field stimulation (CFS) – a new powerful method to combat itch. Pain 71:49–55
10. Schmelz M, Schmidt R, Bickel A et al. (1997) Specific C-receptors for itch in human skin. J Neurosci 17:8003–8008
11. Schmelz M, Schmidt R, Weidner C et al. (2003) Chemical response pattern of dofferent classes of C-nociceptors to pruritogens and algogens. J Neurophysiol 89:2441–2448
12. Shelley WB, Arthur RP (1957) The neurohistology and neurophysiology of the itch sensation in man. Arch Dermatol 76:296–323
13. Simone DA, Oh U, Sorkin LS et al. (1991a) Neurogenic hyperalgesia: Central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 66:228–246
14. Simone DA, Alreja M, LaMotte RH (1991b) Psychophysical studies of the itch sensation and itchy skin ("alloknesis") produced by intracutaneous injection of histamine. Somatosens Motor Res 8:271–279
15. Tuckett RP, Wei JY (1987) Response to an itch-producing substance in cats, II. Cutaneous receptor populations with unmyelinated axons. Brain Res 413:87–94
16. Ward L, Wright E, McMahon SB (1996) A comparison of the effects of noxious and innocuous counterstimuli on experimentally induced itch and pain. Pain 64:129–138
17. Wei JY, Tuckett RP (1991) Response of cat ventrolateral spinal axons to an itch-producing stimulus (cowhage). Somatosens Motor Res 8:227–239

Allodynia in Fibromyalgia

Definition

A lowered pain threshold characterizes the examination findings in fibromyalgia. Allodynia can be caused in animal systems by strategic manipulation of nociceptive neurochemicals. Studies of the nociceptive neurochemicals in FMS spinal fluid have found them to be abnormal in concentration and/or correlated with the symptoms. As a result, FMS can now be identified as chronic, widespread allodynia. These observations change the way FMS is viewed, and identify it as a remarkably interesting human syndrome of chronic central neurochemical pain amplification.

► Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)

Allodynia Test, Mechanical and Cold Allodynia

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A

Synonym

Mechanical Allodynia Test; cold 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. Two different types of stimulation have been used to test allodynia in animal models of neuropathic pain: mechanical and cold. All testing methods rely on foot withdrawal response to stimulus, based on the premise that the animal's avoidance of touching or cooling is an allodynic reaction.

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

Since mechanical allodynia is a major complaint of neuropathic pain patients , testing for signs of mechanical allodynia is an important aspect of behavioral tests for neuropathic pain. Mechanical allodynia, is often tested by quantifying mechanical sensitivity, using a set of von Frey filaments (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

Although there are several ways of measuring mechanical thresholds, we measure foot withdrawal thresholds to mechanical stimuli by using the up-down method (Baik et al. 2003; Chaplan et al. 1994). The rats are placed under a transparent plastic dome (85x80x280mm) 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 (1000xg)], 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 bent for 2 to 3 seconds. 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 6 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: 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 are expressed as VF values (maximum range, 3.54 to 5.27) 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 the 3.54 (0.35 g) range by the 3rd 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.

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 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 1 response from 5 applications was designated as the threshold by Tal & Bennett (1994), while Ma & Woolf (1996) determined that the minimum force required to elicit a reproducible flexor withdrawal reflex on each of 3 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 tactile sensitivity.

In one experiment, mechanical stimuli are applied to the plantar surface of the hind paw with 6 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 g 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 sec period; each trial is repeated 5 times at approximately 3 min. intervals on each hind paw. The occurrence of foot withdrawal in each of 5 trials was expressed as a percent response frequency [number of foot withdrawals/5 (number of trials) x 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 5 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 g and 19.0 g filaments, respectively (Kim and Chung 1992).

In another experimental paradigm, rats are subjected to three sequential series of ten tactile stimulations to the plantar surface of the hind paw using 2 and 12 g VF filaments. Mechanical allodynia is assessed by recording the total number of responses elicited during three successive trials (ten stimulations/each filament), separated by at least 10 min for a total possible score of 30. The terms for the allodynic condition are defined based on the average responses to 12 g von Frey stimulation in each group as follows: minimal (0–5), mild (5–10), moderate (10–15), robust (15 and more) (Hashizume et al. 2000).

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 end 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 half of the plantar surface of the foot and evaporates. On our own volar surface of the forearm, 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 and small withdrawal reflex. After L5/6 spinal

nerve ligation, rats briskly withdraw the hind foot after some delay (about 0.2–0.3 sec) 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 5 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) x 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 (18x28x13 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 noted, and the frequency of hind paw withdrawals and the duration the hind paw is 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 volar forearms are 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 5 and 2-fold, 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. However, complete denervation of the foot does not change this behavior (Choi et al. 1994), making it questionable that the foot lift behavior is related to allodynia, since allodynia would require the presence of functioning sensory receptors.

References

1. Baik EJ, Chung JM, Chung K (2003) Peripheral Norepinephrine Exacerbates Neuritis-Induced Hyperalgesia. J Pain 4:212–221
2. Bennett GJ (1999) Does a Neuroimmune Interaction Contribute to the Genesis of Painful Peripheral Neuropathies? Proc Natl Acad Sci USA 96:7737–7738
3. Bennett GJ, Xie Y-K (1988) A Peripheral Mononeuropathy in Rat that Produces Disorders of Pain Sensation like those Seen in Man. Pain 33:87–107
4. Bonica JJ (1990) Causalgia and Other Reflex Sympathetic Dystrophies. In: Bonica JJ (ed) The Management of Pain. Lea & Febiger, Philadelphia, pp 220–243
5. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL (1994) Quantitative Assessment of Tactile Allodynia in the Rat Paw. J Neurosci Methods 53:55–63
6. Choi Y, Yoon YW, Na HS, Kim SH, Chung JM (1994) Behavioral Signs of Ongoing Pain and Cold Allodynia in a Rat Model of Neuropathic Pain. Pain 59:369–376
7. Dixon WJ (1980) Efficient Analysis of Experimental Observations. Ann Rev Phar Tox 20:441–462
8. Hashizume H, Rutkowski MD, Weinstein JN, DeLeo JA (2000) Central Administration of Methotrexate Reduces Mechanical Allodynia in an Animal Model of Radiculopathy/Sciatica. Pain 87:159–169
9. Kim SH, Chung JM (1992) An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat. Pain 50:355–363
10. Leem JW, Willis WD, Chung JM (1993) Cutaneous Sensory Receptors in the Rat Foot. J. Neurophysiol. 69:1684–1699
11. Lindblom U, Merskey H, Mumford JM, Nathan PW, Noordenbos W, Sunderland S (1986) Pain Terms, A Current List with Definitions and Notes on Usage. Pain Supl 3:215–221
12. Ma Q-P, Woolf CJ (1996) Progressive Tactile Hypersensitivity: An Inflammation-Induced Incremental Increase in the Excitability of the Spinal Cord. Pain 67:97–106
13. Park SK, Chung K, Chung JM (2000) Effects of Purinergic and Adrenergic Antagonists in a Rat Model of Painful Peripheral Neuropathy. Pain 87:171–179
14. Tal M, Bennett GJ (1994) Extra-Territorial Pain in Rats with a Peripheral Mononeuropathy: Mechano-Hyperalgesia and Mechano-Allodynia in the Territory of an Uninjured Nerve. Pain 57:375–382

Alloknesis

Definition

This is the itchy or pruriceptive sensation (from the Latin word *prurire*, to itch) evoked by a stimulus that is normally non-pruriceptive („allo", and „knesis", an ancient Greek word for itching), also referred to as "itchy skin". 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.

► Allodynia and Alloknesis
► Spinothalamic Tract Neurons, Central Sensitization

Alloknesis and Allodynia

► Allodynia and Alloknesis

Allostasis

Definition

Maintaining stability (or homeostasis). Different situations require variations in physiological set points, for which regulatory changes throughout the body are necessary in order to maintain optimal levels of biological function.

► Stress and Pain

Alpha(α) 1-Adrenergic Receptor

Definition

The α^{1}-Adrenergic Receptor is a monoamine neurotransmitter receptor with maximum sensitivity to noradrenaline and blocked by the agonist, phenylephrine.

► Complex Regional Pain Syndrome and the Sympathetic Nervous System

Alpha(α) 2-Adrenergic Agonist

Definition

Drugs that stimulate alpha 2 adrenergic rexceptor subtype of the cathecholamine neurotransmitter, norepinephrine (adrenaline) on nerve endings and inhibit norepinephrine release, resulting in sedative and analgesic actions

► Opioids and Reflexes

► Pain Control in Children with Burns

Alpha(α) 2-Adrenergic Receptor Agonists

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

Alpha(α) 2-Adrenoceptor Agonists

Definition

A drug acting on α_2-adrenoceptors.

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

Alpha(α) 2-Adrenoceptors

Definition

α2-Adrenoceptors are G protein coupled receptors, which inhibit accumulation of cyclic adenosine monophosphate (cAMP), inhibit N-type and P/Q-type calcium channels, and activate potassium channels and Na^{+}/H^{+} antiporter. Three receptor subtypes have so far been identified: α_{2A}, α_{2B} and α_{2C}.

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

Alpha(α) 2-Adrenergic Agonists in Pain Treatment

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Synonyms

Alpha(α) 2-Agonists; α2c-adrenoceptor agonists; α2-receptor agonists; α2-adrenergic agonists; Alpha(α) 2-Adrenergic Receptor Agonists; α-agonists

Definition

$Alpha_2$-adrenergic agonists are drugs that mediate their analgesic (antinociceptive) effects by acting on α2-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 post-operative) 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, labour and during caesarean sections. Furthermore, there is evidence that they provide haemodynamic stability in patients with co-existing cardiovascular diseases during phases of noxious stimulation (e.g. orotracheal intubation) by attenuating the sympathetic response.

Dose and Route of Administration (Table 1)

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. They have been used as

Alpha(α) 2-Adrenergic Agonists in Pain Treatment, Table 1 Alpha2-adrenergic drug dosing: Clonidine

Route		dose	duration
Premedication			
	children elderly patients	2–4 µg/kg 1–2 µg/kg	
Perioperative Analgesia			
intrathecal epidural caudal peripheral nerve block Bier block	with opioid with mepivacaine	max 1 µg/kg up to 75 µg 1–4 µg/kg 0.75–3 µg/kg 0.1–0.5 µg/kg 1–2 µg/kg	long; dose dependent up to 24 h
Postoperative Analgesia			
epidural	clonidine alone	1–4 µg/kg 100–150 µg/hour	
Analgesia for Labour Pain			
intrathecal epidural	with bupivacaine with bupivacaine + fentanyl	50–200 µg max 1 µg/kg 30–150 µg 75 µg	
Chronic Pain			
epidural	Infusion	100–900 µg 30 µg/h	8 h up to 2 weeks

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

Pre-clinical 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. Furthermore, α_2AR agonists have been demonstrated to reduce the ► minimal alveolar concentration (MAC) of volatile anaesthetics and attenuate the pain from propofol injection. Numerous studies have shown that combining α_2AR agonists with local anaesthetics both prolong the sensory blockade and also improve the quality of the block. Therefore, α_2AR agonists may be considered as an adjuvant therapy for both general and local anaesthesia.

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

α_2ARs are present on peripheral nerves, in the spinal cord and at supraspinal pain-modulating centres. They have therefore been applied to all parts of the nervous system in an effort to generate analgesia in patients or antinociception in animals.

Periphery

Although in pre-clinical models peripheral injections of α2AR agonists appeared promising for pain control, 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.

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 hypothesised because of the demonstration of α_2ARs on inflammatory cells, especially macrophages. Peri-neural application of the α_2AR agonist clonidine reduced nerve injury-induced release of the pro-inflammatory 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 pro-inflammatory 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 post-synaptic 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-fibres are positioned to directly modulate pain processing through attenuation of excitatory synaptic transmission (Stone et al. 1997; Stone et al. 1998). 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). 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). These direct actions are concerted with indirect mechanisms by descending noradrenergic pathways, which release noradrenaline that may act via α_{2B}ARs, thought by some to be on spinal ascending nociceptive pathways and interneurons.

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 hypothesised 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).

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 centres 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 behavioural 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 NA 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).

► Thalamic Neurotransmitters and Neuromodulators

References

1. Bie B, Fields HL, Williams JT et al. (2003) Roles of Alpha[1]- and Alpha2-adrenoceptors in the Nucleus Raphe Magnus in Opioid Analgesia and Opioid Abstinence-Induced Hyperalgesia. J Neurosci 23:7950–7957
2. Dawson C, Ma D, Chow A et al. (2004) Dexmedetomidine Enhances Analgesic Action of Nitrous Oxide: Mechanisms of Action. Anesthesiology 100:894–904
3. Duflo F, Li X, Bantel C et al. (2002) Peripheral Nerve Injury Alters the Alpha2 Adrenoceptor Subtype Activated by Clonidine for Analgesia. Anesthesiology 97:636–641
4. Kawasaki Y, Kumamoto E, Furue H et al. (2003) Alpha 2 Adrenoceptor-Mediated Presynaptic Inhibition of Primary Afferent Glutamatergic Transmission in Rat Substantia Gelatinosa Neurons. Anesthesiology 98:682–689
5. Kingery WS, Agashe GS, Guo TZ et al. (2002) Isoflurane and Nociception: Spinal Alpha2A Adrenoceptors Mediate Antinociception while Supraspinal Alpha1 Adrenoceptors Mediate Pronociception. Anesthesiology 96:367–374
6. Lavand'homme PM, Eisenach JC (2003) Perioperative Administration of the Alpha2-Adrenoceptor Agonist Clonidine at the Site of Nerve Injury Reduces the Development of Mechanical Hypersensitivity and Modulates Local Cytokine Expression. Pain 105:247–254
7. Li XH, Eisenach JC (2001) a2A-Adrenoceptor Stimulation Reduces Capsaicin-Induced Glutamate Release from Spinal Cord Synaptosomes. J Pharmacol Exp Ther 299:939–944
8. Ma W, Eisenach JC (2003) Chronic Constriction Injury of Sciatic Nerve Induces the Up-Regulation of Descending Inhibitory Noradrenergic Innervation to the Lumbar Dorsal Horn of Mice. Brain Res 970:110–118
9. Nuseir K, Proudfit HK (2000) Bidirectional Modulation of Nociception by GABA Neurons in the Dorsolateral Pontine Tegmentum that Tonically Inhibit Spinally Projecting Noradrenergic A7 Neurons. Neuroscience 96:773–783
10. Pan HL, Chen SR, Eisenach JC (1999) Intrathecal Clonidine Alleviates Allodynia in Neuropathic Rats: Interaction with Spinal Muscarinic and Nicotinic Receptors. Anesthesiology 90:509–514
11. Paqueron X, Conklin D, Eisenach JC (2003) Plasticity in Action of Intrathecal Clonidine to Mechanical but not Thermal Nociception after Peripheral Nerve Injury. Anesthesiology 99:199–204
12. Sonohata M, Furue H, Katafuchi T et al. (2004) Actions of Noradrenaline on Substantia Gelatinosa Neurones in the Rat Spinal Cord Revealed by *In Vivo* Patch Recording. J Physiol 555:515–526
13. Stone LS, Macmillan L, Kitto KF et al. (1997) The α_2 a-adrenergic Receptor Subtype Mediates Spinal Analgesia Evoked by α_2 Agonists and is Necessary for Spinal Adrenergic/Opioid Synergy. J Neurosci 17:7157–7165
14. Stone LS, Broberger C, Vulchanova L et al. (1998) Differential Distribution of Alpha2A and Slpha2C Adrenergic Receptor Immunoreactivity in the Rat Spinal Cord. J Neurosci 18:5928–5937
15. Stone LS, Vulchanova L, Riedl MS, Wang J, Williams FG, Wilcox GL, Elde R (1999) Effects of Peripheral Nerve Injury on Alpha-2A and Alpha-2C Adrenergic Receptor Immunoreactivity in the Rat Spinal Cord. Neuroscience 93:1399–1407

Alpha(α) 2-Agonists

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

Alpha(α)-Adrenoceptors

A

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.

► Sympathetically Maintained Pain in CRPS II, Human Experimentation

Alpha(α)-Delta(δ) Sleep

Definition

Simultaneous recordings of delta and alpha brainwaves during sleep.

► Fibromyalgia

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.

► Immunocytochemistry of Nociceptors

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 3 & 4.

► Orofacial Pain, Sleep Disturbance

Alpha(α)-I-Acid Glycoprotein

Definition

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

► Acute Pain in Children, Post-Operative

AL-TENS

► Acupuncture-Like TENS

Alternative Medicine

► Alternative Medicine in Neuropathic Pain

Alternative Medicine in Neuropathic Pain

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Synonyms

Complementary Medicine; Alternative Medicine; Holistic Medicine; Unconventional Medicine; Non-Traditional Medicine; Alternative Therapies; Complementary Therapies

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 U.S. 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.

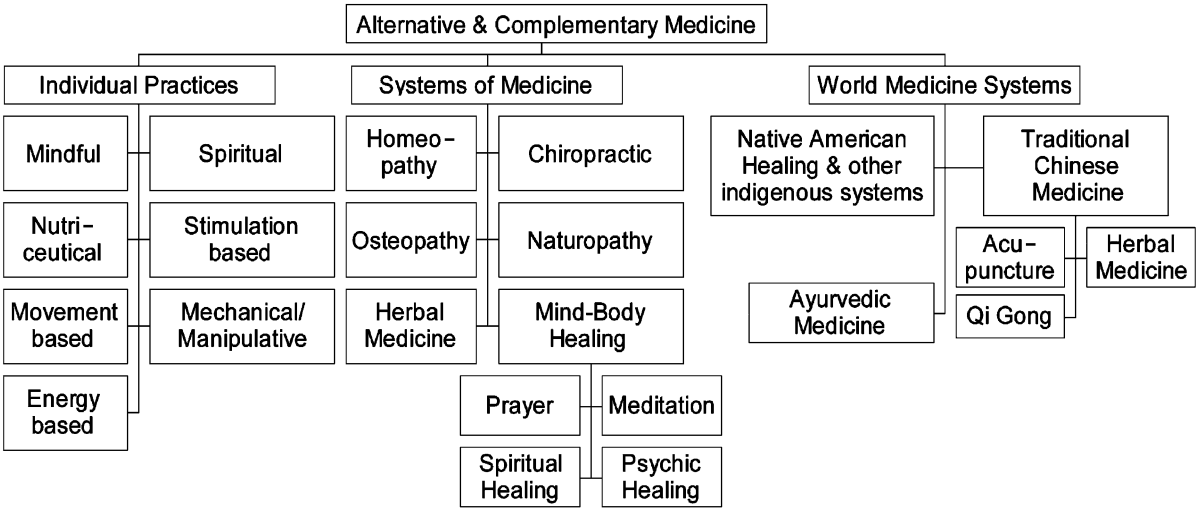
Characteristics

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:



Alternative Medicine in Neuropathic Pain, Figure 1 Organizational chart of alternative and complementary therapies from Belgrade 2003.

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. 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 U.S. 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

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	Prayer	Massage	TENS	Exercise	Chiropractic	Vitamins
Imagery	Spiritual healing	Therapeutic touch	Acupuncture	Dance therapy	Osteopathy	Diet
Meditation	Psychic healing	Homeopathy	Massage	Alexander technique	Massage	Herbal Medicine
Relaxation	Yoga	Acupuncture	Aromatherapy	Tai Chi	Cranio-sacral	Homeopathy
Biofeedback		Qi Gong	Therapeutic touch	Qi Gong	therapy	Aromatherapy
Yoga		Yoga	Music	Yoga	Rolfing	

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 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).

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 to 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 and 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 non-specific 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.

References

1. Belgrade M (1994) Two decades after ping-pong diplomacy: Is there a role for acupuncture in American Pain Medicine? APS Journal 3:73–83
2. Belgrade M (2003) Alternative and Complementary Therapies. In: Rice A, Warfield CA, Justins D, Eccleston C (eds) Clinical Pain Management, 1st edn. Chronic Pain Part 2. Arnold Press, London
3. Brunelli B, Gorson KC (2004) The use of complementary and alternative medicines by patients with peripheral neuropathy. J Neurol Sci 218:59–66
4. Clement-Jones V, McLoughlin L, Tomlin S et al. (1980) Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. Lancet 2:946–949
5. Eisenberg DM, Kesseler RC, Foster C et al. (1993) Unconventional medicine in the United States. New Engl J Med 328:246–252
6. Eisenberg DM, Davis RB, Ettner et al. (1998) Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national survey. JAMA 280:1569–1575
7. Fisher P, Ward A (1994) Complementary medicine in Europe. BMJ 309:107–111
8. Hamza MA, White PF, Craig WF et al. (2000) Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. Diabetes Care 23:365–370
9. Han JS, Terenius L (1982) Neurochemical basis of acupuncture analgesia. Ann Rev Pharmacol Toxicol 22:193–220
10. Hanai F (2000) Effect of electrical stimulation of peripheral nerves on neuropathic pain. Spine 25:1886–1892
11. MacLennon AH, Wilson DH, Taylor AW (1996) Prevalence and cost of alternative medicine in Australia. Lancet 347:569–573
12. Meyer DJ, Price DD, Rafii A (1977) Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Res 121:368–372
13. Millar WJ (1997) Use of alternative health care practitioners by Canadians. Can J Public Health 88:154–158
14. National Institutes of Health on Alternative Medical systems and Practices in the United States (1994) Alternative medicine: Expanding horizons: A report to the National Institutes of Health on Alternative Medical systems and Practices in the United States. US Government Printing Office, Washington DC (017-040-00537-7)
15. Pert A, Dionne R, Ng L et al. (1984) Alterations in rat central nervous system endorphins following transauricular electroacupuncture analgesia in the periaqueductal gray of the rabbit. Brain Res 322:289–296
16. Pomeranz B, Cheng R (1979) Suppression of noxious responses in single neurons of cat spinal cord by electroacupuncture and reversal by the opiate antagonist naloxone. Exp Neurol 64:327–349
17. Rainov NG, Heidecke V (2003) Motor cortex stimulation for neuropathic facial pain. Neurological Research 25:157–161
18. Rainville P, Duncan GH, Price DD et al. (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968–971
19. Shlay JC, Chaloner K, Max MB et al. (1998) Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. JAMA 280:1590–1595
20. Tsunoda Y, Sakahira K, Nakano S et al. (1980) Antagonism of acupuncture analgesia by naloxone in unconscious man. Bull Tokyo Med Dent Univ 27:89–94
21. Wallin J, Fiska A, Tjolsen A et al. (2003) Spinal cord stimulation inhibits long-term potentiation of spinal wide dynamic range neurons. Brain Res 973:39–43
22. Weintraub MI, Wolfe GI, Barohn RA et al. (2003) Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehab 84:736–746

A

Alternative Rat Models of Ureteric Nociceptive Stimulation In Vivo

Definition

Nociceptive stimulation in the ureter has also been obtained with modalities other than stones in past studies. One modality was electrical stimulation of the ureter in the unanesthetized rat (Giamberardino et al. 1988, Neurosci Lett 87:29). This model offered the advantage of a stimulus that could be controlled and modulated in intensity; unfortunately, the aversive reactions of the animals (nocifensive behavior, referred muscle hyperalgesia) were inconstant; furthermore, the stimulation adopted was not natural.

Another modality was distension of the renal pelvis after cannulation of the ureteric-pelvic junction; this produced rather variable pseudo-affective responses that were unrelated to stimulus intensity (Brasch and Zetler 1982, Arch Pharmakol 319:161).

A further modality of stimulation was acute distension of the ureter via a catheter in a preparation involving the anesthetized rat: the ureter was cannulated close to the bladder and graded stimuli applied. Roza and Laird (1995, Neurosci Lett 197:1) have characterized the effects of these stimuli using cardiovascular changes as a measure of the nociceptive reactions. Responses to stimuli less than 25 mmHg were never observed, suprathreshold pressures evoked responses proportional to the 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 neurones 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 to the 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 calculosis rats, allowing the comparison of the neural processing of acute visceral noxious stimulation on normal animals with that of animals with chronic visceral pain and referred hyperalgesia using the same stimulation technique.

► Visceral Pain Model, Kidney Stone Pain

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.

- ► Lower Back Pain, Physical Examination

Amenorrhea

Definition

Amenorrhea is the absence of menstruation, which is normal before puberty, during pregnancy, or after menopause. Congenital abnormalities 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.

- ► 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 hours with or without surgery

- ► 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.

- ► Acute Pain in Children, Post-Operative
- ► Drugs with Mixed Action and Combinations, Emphasis on Tramadol
- ► Postoperative Pain, Methadone

Amide Local Anesthetic

- ► Amide Anesthetic

Aminobisphosphonate

Definition

A class of drugs that block bone resorbing cells (osteoclasts) and prevent bone loss.

- ► 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. Amitriptyline controls chronic facial pain in a relatively low dose (10–25 mg/day), and is also used as a prophylactic drug for migraine.

- ► Atypical Facial Pain, Etiology, Pathogenesis and Management
- ► Fibromyalgia, Mechanisms and Treatment
- ► Migraine, Preventive 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 of 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.

- ▶ Metabotropic Glutamate Receptors in the Thalamus
- ▶ Nociceptive Neurotransmission 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; 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.

- ▶ 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.

- ▶ 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 & basal (main olfactory), medial (accessory olfactory), central (autonomic), basolateral & lateral (frontotemporal & 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.

- ▶ Amygdala, Pain Processing and Behavior in Animals
- ▶ Arthritis Model, Kaolin-Carrageenan Induced Arthritis (Knee)
- ▶ Parabrachial Hypothalamic and Amydaloid Projections

Amygdala, Functional Imaging

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Synonyms

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

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

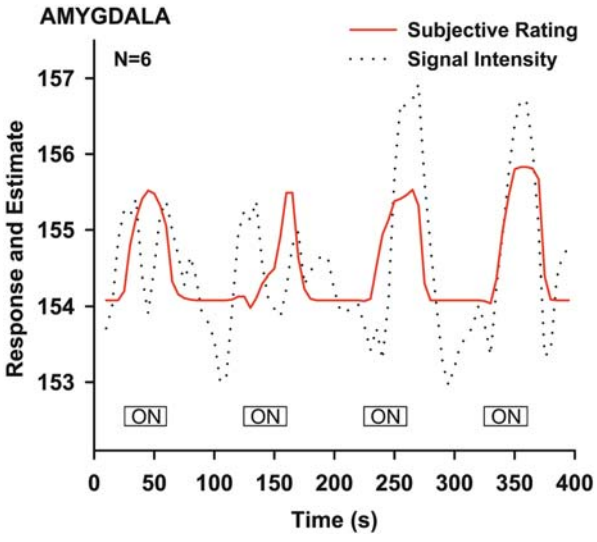
Negative affect is typically evoked by acute pain. Key structures of the ► limbic system have been identified that play an important role in regulating affective behavior; among the most important are the subcortical and cortical areas, the anterior cingulate, the insula and the prefrontal cortex. Most 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 artefacts (see ► inflow artefacts) 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). 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 affect. 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 particular 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 affect. 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 10 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

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

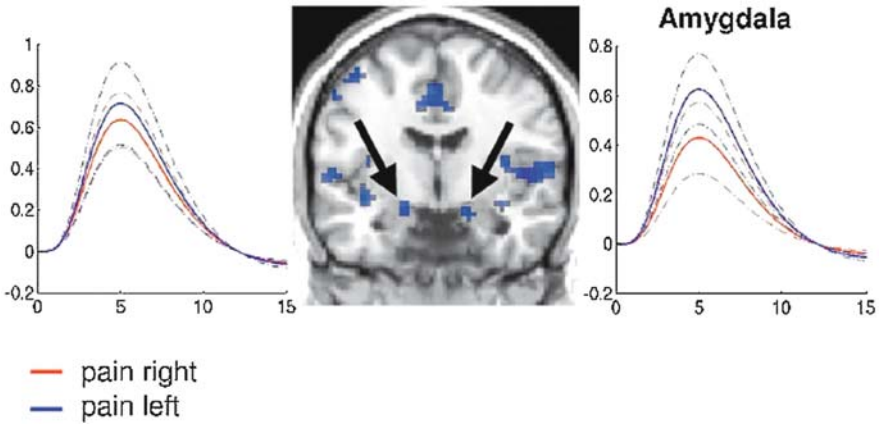
Author	Imaging Method	Painful stimulation	Number of subjects	Amygdala activation/deactivation
Becerra et al. 1999	fMRI (1,5 T)	Thermal stimulation (Peltier based thermode) 46°C	2 groups of 6 healthy subjects	Deactivation of the amygdala
Becerra et al. 2001	fMRI (1,5 T)	Thermal stimulation (Peltier based 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	Non-significant 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



Amygdala, Functional Imaging, Figure 1 Individual signal intensities in the amygdala following correlation with subjective ratings of the six individual participants (from Schneider et al. 2000).

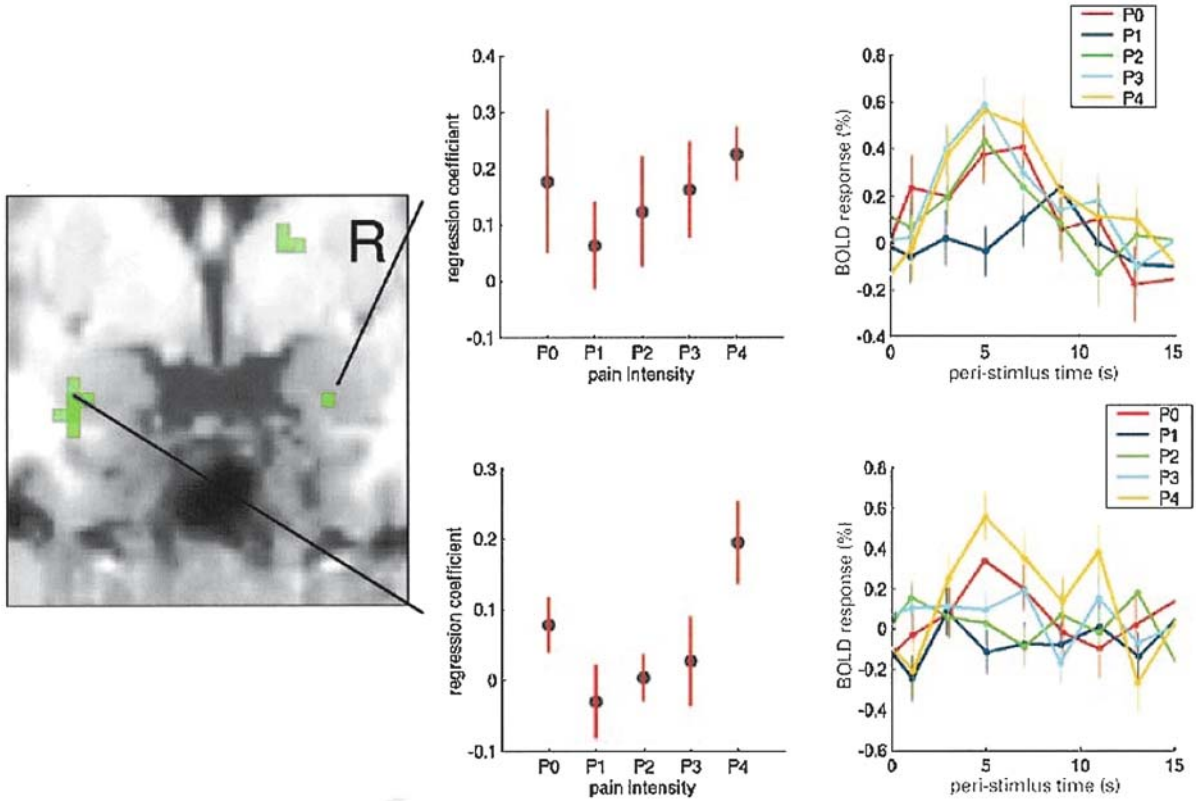
them insula and amygdala. This may once again point especially to the strong affective component of visceral pain. Since visceral pain may be indicative of an urgent and marked system imbalance possible endangering survival, strong affective responses with the objective of initiating adequate adaptations and reactions seem to have an evolutionary purpose and be necessary.

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 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).



Amygdala, Functional Imaging, Figure 2 Amygdala activation emerged bilaterally in response to painful unilateral laser stimulation. Left: Fittet 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).

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 not only demonstrated 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 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 thalamus, somatosensory cortex and insula (Becerra et al. 2001) (Fig. 4). This is in accordance with the activation characteristic of the amygdala during



Amygdala, Functional Imaging, Figure 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).

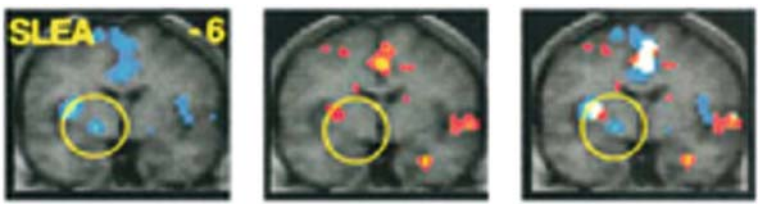
► classical conditioning (Büchel et al. 1998), in which a rapid adaptation to the conditioned stimulus has been observed, pointing to a major role of the amygdala during the early phase of learning, during the establishment of an association between the neutral stimulus and the (un)conditioned response. 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) (Becerra et al. 1999). In this study only 6 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, control condition used for comparison with pain condition etc. 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 with 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



Amygdala, Functional Imaging, Figure 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).

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 (for example *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.

References

1. Aggleton JP, Mishkin M (1986) The amygdala: sensory gateway to the emotions. In Plutchik R, Kellermann H (eds) Emotion: Theory, research, and experience, vol 3. Academic Press, New York, pp 281–299
2. Beccera LR, Breiter HC, Stojanovic M et al. (1999) Human brain activation under controlled thermal stimulation and habituation to the noxious heat: an fMRI study. Magn Res Med 41:1044–1057
3. Becerra L, Breiter HC, Wise R et al. (2001) Reward circuitry activation by noxious thermal stimuli. Neuron 32:927–946
4. Bingel U, Quante M, Knab R et al. (2002) Subcortical structures involved in pain processing: evidence from single-trial fMRI. Pain 99:313–321
5. Bonaz B, Bacin M, Papillon E et al. (2002) Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study. Am J Gastroenterol 97:654–661
6. Bornhövd K, Quante M, Glauche V et al. (2002) Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125:1326–1336
7. Büchel C, Morris J, Dolan RJ et al. (1998) Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron 20:947–957
8. Derbyshire SW, Jones AK, Gyulai F et al. (1997) Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73:431–445
9. Evans KC, Banzett RB, Adams L et al. (2002) BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. J Neurophysiol 88:1500–1511
10. Hsieh JC, Ståhle-Bäckdahl M, Hägermark Ö et al. (1995) Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain 64:303–314
11. Lu CL, Wu YT, Yeh TC et al. (2004) Neuronal correlates of gastric pain induced by fundus distension: a 3T-fMRI study. Neurogastroenterol Motil 16:575–587
12. Morrow TJ, Paulson PE, Danneman PJ et al. (1998) Regional changes in forebrain activation during the early and late phase of formalin nociception: analysis using cerebral blood flow in the rat. Pain 75:355–365
13. Neugebauer V, Li W, Bird GC et al. (2004) The amygdala and persistent pain. Neuroscientist 10:221–234
14. Petrovic P, Carlsson K, Petersson KM et al. (2004) Context-dependent deactivation of the amygdala during pain. J Cogn Neurosci 16:1289–1301
15. Schneider F, Habel U, Holthusen H et al. (2001) Subjective ratings of pain correlate with subcortical-limbic blood flow: an fMRI study. Neuropsychobiol 43:175–185
16. Wilder-Smith CH, Schindler D, Lovblad K et al. (2004) Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 53:1595–1601

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 ► multi-sensory perceptions. This information already 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 1½–2 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).

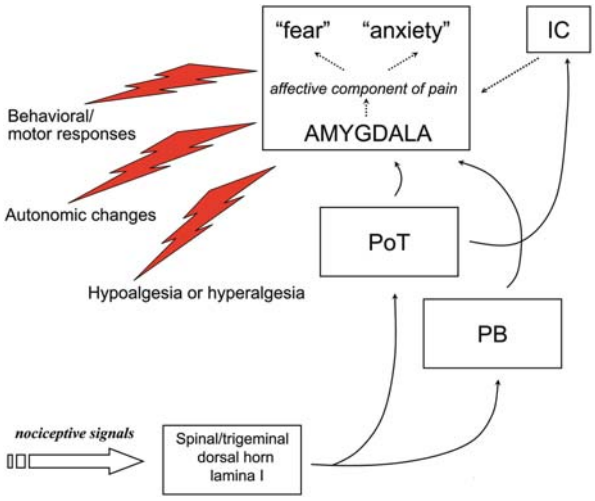
The response characteristics of individual CeA neurons have been studied *in vivo* in rats with or without experimental arthritis in a knee joint (Neugebauer et al. 2004). Prolonged nociception produced by injection of ► carrageenan and ► kaolin into the knee joint results in enhancement of both receptive 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 *vs.* 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 *vs*. rats with persistent pain. In the nociceptive CeA of such rats, it is possible to study ► monosynaptic excitatory post-synaptic 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 intra-colonic 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 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 co-varies with the presence or absence of pain or nociception, but such studies are limited with respect to mechanistic insights and determining cause *vs*. 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 the 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 essay. 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.



Amygdala, Pain Processing and Behavior in Animals, Figure 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.

References

1. Bernard JF, Bester H, Besson JM (1996) Involvement of the spino-parabrachio-amygdaloid and -hypothalamic pathways in the autonomic and affective emotional aspects of pain. Prog Brain Res 107:243–255
2. Bornhovd K, Quante M, Glauche V et al. (2002) Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125:1326–1336
3. Derbyshire SW, Jones AK, Gyulai F et al. (1997) Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73:431–445
4. Gauriau C, Bernard JF (2002) Pain pathways and parabrachial circuits in the rat. Exp Physiol 87:251–258
5. Hebert MA, Ardid D, Henrie JA et al. (1999) Amygdala lesions produce analgesia in a novel, ethologically relevant acute pain test. Physiol Behav 67:99–105
6. Johansen JP, Fields HL, Manning BH (2001) The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. Proc Natl Acad Sci USA 98:8077–8082
7. LeDoux J (2003) The emotional brain, fear, and the amygdala. Cell Mol Neurobiol 23:727–738
8. Monnikes H, Ruter J, Konig M et al. (2003) Differential induction of c-fos expression in brain nuclei by noxious and non-noxious colonic distension: role of afferent C-fibers and 5-HT3 receptors. Brain Res 966:253–264
9. Nakagawa T, Katsuya A, Tanimoto S et al. (2003) Differential patterns of c-fos mRNA expression in the amygdaloid nuclei induced by chemical somatic and visceral noxious stimuli in rats. Neurosci Lett 344:197–200
10. Neugebauer V, Li W, Bird GC et al. (2004) The amygdala and persistent pain. Neuroscientist 10:221–234
11. Paulson PE, Casey KL, Morrow TJ (2002) Long-term changes in behavior and regional cerebral blood flow associated with painful peripheral mononeuropathy in the rat. Pain 95:31–40
12. Shi C-J, Cassell MD (1998) Cascade projections from somatosensory cortex to the rat basolateral amygdala via the parietal insular cortex. J Comp Neurol 399:469–491
13. Tanimoto S, Nakagawa T, Yamauchi Y et al. (2003) Differential contributions of the basolateral and central nuclei of the amygdala in the negative affective component of chemical somatic and visceral pains in rats. Eur J Neurosci 18:2343–2350
14. Ter Horst GJ, Meijler WJ, Korf J et al. (2001) Trigeminal nociception-induced cerebral Fos expression in the conscious rat. Cephalalgia 21:963–975
15. Wilder-Smith CH, Schindler D, Lovblad K et al. (2005) Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 53:1595–1601

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).

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

Analgesia

Definition

A reduced or absent sense of pain response to stimulation that would normally be painful. Can be seen as a decrease in nociceptive threshold or a decrease in pain perception. 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 for an animal to respond to a noxious stimulus is increased above normal. Analgesia is measured in the uninjured stated.

► Cancer Pain, Assessment in the Cognitively Impaired
► 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 1.7 per million live births during the years 1988–1990. The increased use of regional anesthesia for the parturient is in part responsible for this decrease in mortality (Hawkins et al. 1997). Safety is the first and foremost goal of obstetrical anesthesia. For labor analgesia, a secondary goal is to minimize or eliminate maternal lower extremity muscle weakness associated with epidural and subarachnoid ► local anesthetics. Patients with less motor block are more satisfied with their anesthetic experience and decreasing motor block may improve obstetric outcome. Although controversial, motor blockade related to labor epidural analgesia has been implicated as a cause of forceps deliveries and cesarean delivery. Minimizing the motor block may attenuate or eliminate these effects (Chestnut 1997). In addition to ► epidural analgesia (see epidural anesthesia), anesthesiologists are now providing ► spinal anesthesia and the combined spinal-epidural technique for labor analgesia. The purpose of this article 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, 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 10lumbar 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 often added to the local anesthetic to decrease the motor block. But, 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 workload 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) plus an opioid (fentanyl or sufentanil).

Some anesthesiologists use ► patient controlled epidural analgesia (PCEA). This technique allows the patient to self-medicate, controlling their analgesia. Because there are few well-controlled studies regarding PCEA, the optimal dosing regimens have not been determined. Compared with continuous infusion or intermittent bolus techniques, PCEA is associated with fewer anesthetist interventions and less motor block. Less anesthetic also decreases the frequency of maternal hypotension. The total dose of local anesthetic used is less with PCEA, and maternal satisfaction greater than with standard epidural analgesia techniques (Gambling et al. 1990). A commonly used PCEA regimen is bupivacaine 0.0625% with fentanyl 2 $\mu g\ cc^{-1}$ at the following PCEA settings 10 ml h^{-1} basal rate, 5 ml bolus dose, 10 min lockout and a 30 ml h^{-1} 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, but some have suggested that epidural fentanyl may impact on the ability of the neonate to breast-feed (Walker 1997). Although, Halpern et al. did not find any difference in breast-feeding success among neonates whose mothers received epidural fentanyl *vs.* those who did not (Halpern et al. 1999), at least one other study found different results. A recent prospective randomized study (Beilin et al. 2005) found that multiparous women who received >150 μg of epidural fentanyl during labor were more likely to report breastfeeding difficulty on postpartum day one and to have stopped breastfeeding at 6 weeks than women who received less fentanyl or no fentanyl. 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 μg) 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 block.

Subarachnoid opioids offer rapid, intense analgesia with minimal changes in blood pressure or motor func-

tion. 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 either 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, *vs*. 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. Unfortunately, there may be a risk of cauda equina syndrome when placing subarachnoid catheters, especially microcatheters. A study is currently underway to evaluate the safety of subarachnoid microcatheters.

Fentanyl or sufentanil are the most commonly utilized subarachnoid opioid 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 μg of fentanyl and between 2 and 5 μg 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 μg 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. 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 (PDPH) 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. 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 be 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. Norris et al. (Norris et al. 1998) found that the risk of failed epidural catheters was lower in women who received CSE analgesia than those who received epidural analgesia. However, it is 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.

Clarke et al. (1994) 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 do not find any difference in the incidence of fetal heart rate abnormalities with CSE *vs*. epidural analgesia (Albright and Forster 1997; Palmer et al. 1999). If hypertonus occurs, treatment should include subcutaneous terbutaline or intravenous nitroglycerin.

There have been several recent prospective studies evaluating the effects of the CSE technique on the cesarean delivery rate. Nageotte et al. (Nageotte et al. 1997) randomized women to three groups: group 1 received CSE with sufentanil 10 μg, group 2 received the same technique and medication as those in group 1 but were encouraged to ambulate and group 3 received epidural analgesia. They did not find any difference in the cesarean delivery rate between the three groups of patients. Gambling et al. (Gambling et al. 1998) compared women who received CSE analgesia *vs*. those who received intravenous meperidine during labor and they too did not find any difference in the cesarean delivery rate between the 2 groups.

The term ► walking epidural has become popular especially in the lay community. The term walking epidural refers to any epidural or spinal technique that allows ambulation. Some have suggested that ambulating or the upright position is associated with a shorter first stage of labor, less pain in early labor and decreased analgesia requirements. These findings have not been confirmed in prospective and randomized studies (Bloom et al. 1998). In most centers, few patients want to ambulate. Most want to rest or sleep once they have pain relief. However, even if patients do not want to ambulate, using a technique that produces minimal motor blockade will

improve maternal satisfaction. Both epidural analgesia using dilute local anesthetic / opioid solutions or 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 refining these drugs and techniques to make obstetric anesthesia even safer and more efficacious so we can better care for our patients.

References

1. Albright GA, Forster RM (1997) Does combined spinal-epidural analgesia with subarachnoid sufentanil increase the incidence of emergency cesarean delivery? Reg Anesth 22:400–405
2. Asokumar B, Newman LM, McCarthy RJ et al. (1998) Intrathecal bupivacaine reduces pruritus and prolongs duration of fentanyl analgesia during labor: a prospective, randomized controlled trial. Anesth Analg 87:1309–1315
3. Beilin Y, Nair A, Arnold I et al. (2002) A comparison of epidural infusions in the combined spinal/epidural technique for labor analgesia. Anesth Analg 94:927–932
4. Bloom SL, McIntire DD, Kelly MA et al. (1998) Lack of effect of walking on labor and delivery. N Engl J Med 339:76–79
5. Beilin Y, Bodian CA, Weiser J et al. (2005) Effect of epidural analgesia with and without fentanyl on infant breast-feeding. A prospective, randomized, double-blind study. Anaesthsiol 103:1211–17
6. Chestnut DH (1997) Does epidural analgesia during labor affect the incidence of cesarean delivery? Reg Anesth 22:495–499
7. Clarke VT, Smiley RM, Finster M (1994) Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of fetal bradycardia? Anesthesiology 81:1083
8. Gambling DR, McMorland GH, Yu P et al. (1990) Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. Anesth Analg 70:256–261
9. Gambling DR, Sharma SK, Ramin SM et al. (1998) A randomized study of combined spinal-epidural analgesia versus intravenous meperidine during labor: impact on cesarean delivery rate. Anesthesiology 89: 1336–1344
10. Halpern SH, Levine T, Wilson DB et al. (1999) Effect of labor analgesia on breastfeeding success. Birth 26:83–88
11. Hawkins JL, Koonin LM, Palmer SK et al. (1997) Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. Anesthesiology 86:277–284
12. Nageotte MP, Larson D, Rumney PJ et al. (1997) Epidural analgesia compared with combined spinal-epidural analgesia during labor in nulliparous women. N Engl J Med 337:1715–1719
13. Norris MC, Fogel ST, Dalman H (1998) Labor epidural analgesia without an intravascular "test dose" Anesthesiology 88:1495–1501
14. Ounsted MK, Boyd PA, Hendrick AM et al. (1978) Induction of labour by different methods in primiparous women. II. Neurobehavioural status of the infants. Early Hum Dev 2:241–253
15. Palmer CM, Maciulla JE, Cork RC et al. (1999) The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia. Anesth Analg 88:577–581
16. Walker M (1997) Do labor medications affect breastfeeding? J Hum Lact 13:131–137

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.

► Analgesia During Labor and Delivery

Analgesic Effect of Oxycodone

Definition

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

► Postoperative Pain, Oxycodone

Analgesic Gap

Definition

The increase in pain levels sometimes associated with withdrawal of high-level input (usually via a Pain Service) to analgesic strategies.

► Postoperative Pain, Transition from Parenteral to Oral

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, non-steroidal 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 non-drug 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). 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 non-steroidal 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 health-care providers can relieve pain in the majority of children with a few drugs. 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 health care 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 (SSRI's), may be beneficial to treat depression in a child with pain, but have not been shown to be beneficial for pain management. 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 recently and the use of gabapentin has increased. We still await published studies to support the wide use of gabapentin. Non-steroidal 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 chapter are based on guidelines from our institution (The Hospital for Sick Children 2004–2005). Recommended starting doses for analgesic medications to control children's disease-related pain are listed in Table 1 and Table 2; starting doses for adjuvant analgesic medications to control pain, drug related side effects and other symptoms are listed in Table 3. (For further review of analgesics and adjuvant analgesics in children, see (McGrath and Brown 2004; 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

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 2400 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

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 (Reprinted from McGrath and Brown 2004)

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
Meperidine[a]	75 mg	0.5–1.0 mg kg^{-1} every 3–4 h	1:4	1.0–2.0 mg kg^{-1} every 3–4 h (dose limit 150 mg)	1–3 h
Fentanyl[b]	100 µg	1–2 µg kg^{-1} h^{-1} as continuous infusion		25 µg patch	72 h (patch)

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 6 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.
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.
[a]Avoid use in renal impairment. Metabolite may cause seizures.
[b]Potentially highly toxic. Not for use in acute pain control.
Abbreviations: PO, by mouth; I.V., intravenous
(Modified from McGrath and Brown 2004)

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

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. Titrate upward by 0.25 mg kg^{-1} every 2–3 days. Maintenance: 0.2–3.0 mg kg^{-1} Alternatives: nortriptyline, doxepin, imipramine.	► Neuropathic pain (i.e., vincristine-induced, radiation plexopathy, tumor invasion, CRPS–1). Insomnia.	Usually improved sleep and pain relief within 3–5 days. 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. 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. Alternatives: phenytoin, clonazepam.	Neuropathic pain, especially shooting, stabbing pain.	Side effects: gastrointestinal upset, ataxia, dizziness, disorientation, and somnolence. Monitor for hematological, hepatic and allergic reactions with carbamazepine.
Sedatives, hypnotics, anxiolytics	Diazepam, 0.025–0.2 mg kg^{-1} PO every 6 h. Lorazepam, 0.05 mg kg^{-1}/dose SL Midazolam, 0.5 mg kg^{-1}/dose PO administered 15–30 min prior to procedure; 0.05 mg kg^{-1}/dose IV for sedation.	Acute anxiety, muscle spasm. Premedication for painful procedures.	Sedative effect may limit opioid use. Other side effects include depression and dependence with prolonged use.
Antihistamines	Hydroxyzine, 0.5 mg kg^{-1} PO every 6 h. Diphenhydramine, 0.5–1.0 mg kg^{-1} PO/IV every 6 h.	Opioid-induced pruritus, anxiety, nausea.	Sedative side effects may be helpful.
Psychostimulants	Dextroamphetamine, Methylphenidate, 0.1–0.2 mg kg^{-1} BID. Escalate to 0.3–0.5 mg kg^{-1} as needed.	Opioid-induced somnolence. Potentiation of opioid analgesia.	Side effects include agitation, sleep disturbance and anorexia. 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 McGrath and Brown 2004)

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 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 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

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 mid–day so as not to interfere with night–time 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 McGrath and Brown 2004)

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 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 a recent alert by the Joint Commission on Accreditation of Health Care 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.

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 a fairly recently employed 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.

References

1. Ahmedzai S, Brooks D (1997) Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manage 13:254–261
2. Berde CB, Solodiuk J (2003) Multidisciplinary Programs for Management of Acute and Chronic Pain in Children. In: Schechter NL, Berde CB, Yaster M (eds) Pain in Infants, Children, and Adolescents, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 471–486
3. Bray RJ, Woodhams AM, Vallis CJ et al. (1996) A double-blind comparison of morphine infusion and patient controlled analgesia in children. Paediatr Anaesth 6:121–127
4. Christensen ML, Wang WC, Harris S et al. (1996) Transdermal fentanyl administration in children and adolescents with sickle cell pain crisis. J Pediatr Hematol Oncol 18: 372–376
5. Hunt A, Goldman A, Devine T et al. (2001) Transdermal fentanyl for pain relief in a paediatric palliative care population. Palliat Med 15:405–412
6. Krane EJ, Leong MS, Golianu B et al. (2003) Treatment of pediatric pain with nonconventional analgesics. In: Schechter NL, Berde CB, Yaster M (eds) Pain in Infants, Children, and Adolescents, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 225–241
7. McDonald AJ, Cooper MG (2001) Patient-controlled analgesia: an appropriate method of pain control in children. Paediatr Drugs 3: 273–284
8. McGrath PA, Brown SC (2004) Paediatric palliative medicine - Pain control. In: Doyle D, Hanks G, Cherny N et al. (eds) Oxford Textbook of Palliative Medicine, 3rd edn. Oxford University Press, Oxford, pp 775–789
9. McNeely JK, Trentadue NC (1997) Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. J Pain Symptom Manage 13:268–273
10. Noyes M, Irving H (2001) The use of transdermal fentanyl in pediatric oncology palliative care. Am J Hosp Palliat Care 18:411–416
11. Rodgers BM, Webb CJ, Stergios D et al. (1988) Patient-controlled analgesia in pediatric surgery. J Pediatr Surg 23:259–262
12. Schechter NL, Berde CB, Yaster M (2003) Pain in infants, children, and adolescents, 2nd edn. Lippincott Williams & Wilkins, Philadelphia
13. Sentinel Event Alert (2004) Patient controlled analgesia by proxy: Joint Commission of Healthcare Organizations
14. The Hospital for Sick Children (2005) The 2004–2005 Formulary, 23rd edn. The Hospital for Sick Children, Toronto
15. World Health Organization (1990) Cancer Pain Relief and Palliative Care. World Health Organization, Geneva

Analgesic Ladder

Definition

In 1986 WHO proposed a three step analgesic ladder. Non-opioids (step 1) are administered in case of mild pain. If this is not enough, weak opioids (step 2) are being added. They may be exchanged by strong opioids (step 3). The analgesics from the ladder frequently need to be co-administered with other drugs aiming either reduction of adverse effects (e.g. laxatives) of increase of activity and widening the spectrum of analgesic activity (e.g. tricyclic antidepressants).

► Cancer Pain

Analgesic Tolerance

► Opioids, Clinical Opioid Tolerance

Analgesic Treatment

Definition

A treatment used to reduce pain or its perception, without causing loss of consciousness.

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

Analgesics

Definition

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

► NSAIDs, COX-Independent Actions
► Opioids, Clinical Opioid Tolerance
► Opioids in Geriatric Application

Analgesics, History

► History of Analgesics

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.

► 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.

► Thalamic Nuclei Involved in Pain, Cat and Rat

Anesthesia Dolorosa

Definition

Spontaneous pain felt in a body part that has been denervated or deafferented, which is therefore numb and unresponsive to applied stimuli. It is usually the result of a surgical lesion of a peripheral nerve (usually the trigeminal) intended to relieve pain.

► 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

Model of Spontaneous Neuropathic Pain; Neuroma Model of Neuropathic Pain; Denervation Model of Neuropathic Pain; deafferentation model of neuropathic pain; autotomy model of neuropathic pain

Definition

"Anesthesia dolorosa" ("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 by either: 1) cutting all peripheral nerves that serve

it (► denervation), or 2) 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). Anesthesia dolorosa differs from phantom limb pain in that the body part in which the pain is felt is still present; it has not been amputated. Since it is unlikely that the presence of the insensate limb contributes materially to the spontaneous pain, this model is also useful for studying amputation phantom pain, and spontaneous pain in neuropathy in general.

Characteristics

Spontaneous ► dysesthesia and pain is probably the most common and troublesome element 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). Although in recent years it has been largely superseded by partial denervation models based on the evaluation of allodynia and hyperalgesia, autotomy remains the most important behavioral probe of ongoing painful dysesthesia in experimental animals.

Background and Ethical Considerations

Although it had been recognized previously that animals, from 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). Actually, investigators rarely witness actual autotomy behavior. Rather, the accumulated amount of tissue loss is scored. Long-term observations and video monitoring indicate that autotomy usually occurs in brief "attacks", separated by hours or days, in which no further tissue loss occurs. This suggests that autotomy may reflect paroxysmal pain events, perhaps overlaid on a continuous ongoing pain. Across-strains genetic analysis in mice indicates that autotomy behavior is part of a pain family ("type") that includes thermal nociception (Mogil et al. 1999). Perhaps, in mice at least, the 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 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. Autotomy is prevented by "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 that 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, but not in animals. Moreover, compulsive autotomy-like behavior does occur in some people with ongoing dysesthesias (including itch) and pain (Mailis 1996; Devor and Seltzer 1999). As for the second critique, rendering a limb numb by sustained local anesthetic nerve block does not trigger autotomy (Blumenkopf and Lipman 1991).

There are many positive indicators that autotomy reflects spontaneous pain. These include:

- Limb denervation and deafferentation frequently cause ongoing neuropathic pain in humans. As in

humans, palpating neuromas in rats evokes distress vocalization and struggling (Levitt 1985)

- 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 reforms (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, opiates, corticosteroids, tricyclics, NMDA receptor antagonists). Likewise, analgesics minimally effective against neuropathic pain, such as NSAIDs, do not suppress autotomy (Coderre et al. 1986; Seltzer 1995; Kaupilla 1998; Devor and Seltzer 1999)
- Spinal injection of excitants such as strychnine, tetanus toxin, alumina cream, penicillin, and substance P, which almost certainly cause pain, induces scratching and biting of the corresponding limb, and sometimes frank autotomy (Coderre et al. 1986; Kaupilla 1998; Devor and Seltzer 1999)
- Blockade of descending antinociceptive control by appropriate brainstem or spinal tract lesions augments autotomy (Coderre et al. 1986; Saade et al. 1990), while midbrain or dorsal column stimulation, and dorsal root entry zone (DREZ) lesions, suppress it (Levitt 1985; Kauppila and Pertovaara 1991; Rossitch et al. 1993; Devor and Seltzer 1999)
- 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 are consistent differences in autotomy behavior among inbred strains of mice and rodent selection lines, despite identical denervation and sensory loss. There is clear evidence that genes, as well as environmental factors, determine the level of autotomy. One such pain susceptibility gene is located on mouse chromosome 15 (Mogil et al. 1999; Devor and Seltzer 1999; Seltzer et al. 2001)

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. 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) survive, as do sensory endings in the skin. The limb is not denervated.

It is generally presumed that pain and the resulting autotomy due to denervation and deafferentation result from different mechanisms, although this conjecture has not been proved definitively.

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 (Devor and Seltzer 1999).

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. 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 the pain (Rossitch et al. 1993; Devor and Seltzer 1999).

References

1. Basbaum AI (1974) Effects of Central Lesions on Disorders Produced by Dorsal Rhizotomy in Rats. Exp Neurol 42:490–501
2. Bennett G, Xie Y-K (1988) A Peripheral Mononeuropathy in Rat that Produces Disorders of Pain Sensation Like Those Seen in Man. Pain 33:87–107

3. Blumenkopf B, Lipman JJ (1991) Studies in Autotomy: Its Pathophysiology and Usefulness as a Model of Chronic Pain. Pain 45:203–210
4. Coderre TJ, Grimes RW, Melzack R (1986) Deafferentiation and Chronic Pain in Animals: An Evaluation of Evidence Suggesting Autotomy is related to Pain. Pain 26:61–84
5. Devor M, Inbal R, Govrin-Lippmann R (1982) Genetic Factors in the Development of Chronic Pain. In: Lieblich I (ed) The Genetics of the Brain. Elsevier-North Holland, Amsterdam, pp: 273–296
6. Devor M, Seltzer Z (1999) Pathophysiology of Damaged Nerves in Relation to Chronic Pain. In: Wall PD and Melzack R (eds) Textbook of Pain, 4th edn, Churchill Livingstone, London pp: 129–164
7. Kauppila T, Pertovaara A (1991) Effects of Different Sensory and Behavioral Manipulations on Autotomy Caused by a Sciatic Lesion in Rats. Experimental Neurology 111:128–130
8. Kauppila T (1998) Correlation between autotomy-behavior and current theories of neuropathic pain. Neurosci Biobehav Rev 23:111-129
9. Levitt M (1985) Dysesthesias and Self-Mutilation in Humans and Subhumans: A Review of and Experimental Studies. Brain Res Reviews 10:247–290
10. Mailis A (1996) Compulsive Targeted Self-Injurious Behaviour in Humans with Neuropathic Pain: A Counterpart of Animal Autotomy? Four Case Reports and Literature Review. Pain 64:569–578
11. Mogil JS, Wilson SG, Bon K et al. (1999) Heritability of Nociception. II. "Types" of Nociception Revealed by Genetic Correlation Analysis. Pain 80:83–93
12. Raber P, Devor M (2002) Social variables affect phenotype in the neuroma model of neuropathic pain. Pain 97:139-150
13. Rossitch EJ, Abdulhak M, Olvelmen-Levitt J et al. (1993) The Expression of Deafferentation Dysesthesias Reduced by Dorsal Root Entry Zone Lesions in the Rat. Journal of Neurosurgery 78:598–602
14. Saadé NE, Atweh SF, Tabbur SJ and Wall PD (1990) Effects of Lesions in the anterolateral columns and dorsolateral funiculi on self-mutilation behavior in rats. Pain 42:313-321
15. Seltzer Z (1995) The Relevance of Animal Neuropathy Models for Chronic Pain in Humans. Seminars in Neuroscience 7:31–39
16. Seltzer ZWT, Max MB, Diehl SR (2001) Mapping a Gene for Neuropathic Pain-Related Behavior following Peripheral Neurectomy in the Mouse. Pain 93:101–106
17. Wall PD, Devor M, Inbal R et al. (1979) Autotomy following Peripheral Nerve Lesions: Experimental Anaesthesia Dolorosa. Pain 7:103–111
18. Zeltser R, Zaslansky R, Beilin B et al. (2000) Comparison of Neuropathic Pain Induced in Rats by Various Clinically-Used Neurectomy Methods. Pain 89:19–24

Anesthesiological Interventions

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

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.

► 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.

► 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.

► Primary Cough Headache

Anger and Pain

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Synonyms

Frustration; hostility; Aggression; Acting-Out; Anger-In

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 chapter, 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, and duration, intensity of the experience, expression styles, and target of the anger. The earlier studies mostly focused on anger levels, or one's tendency to become angry. 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. Some early clinical studies with chronic pain patients suggest that high levels of anger exacerbate pain severity (Gaskin et al. 1992), whereas the experimental studies show higher frustration and hostility as a result of noxious stimulation (Berkowitz and Thorme 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. Various studies have shown that anger-in and pain intensity in chronic pain patients are positively related (e.g. Kerns et al. 1994). 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. Those who tend to readily express their anger and hostility may sabotage the effectiveness of rehabilitative effort (Fernandez and Turk 1995).

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 somatic 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. This psychodynamic concept of hysteria has been applied to pain conditions, when the conditions cannot be understood from the medical findings.

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. Moreover, 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, is 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 re-experience/recall anger, chronic back patients who tended to suppress their anger, seemed to show reduced paraspinal muscle reactivity (Burns 1997). These results suggest that anger, stress response, and pain seem to form a complex relationship. Janssen et al. (2001) showed the positive relationship between cardiovascular reactivity in response to anger provocation and pain threshold, yet the participants reported increased pain reports under such conditions.

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). The mediation effect is modest and certainly does not completely explain the relationship; nevertheless, this line of research has just begun, and further research may help uncover the psychophysiological-neurological patterns associated with pain and anger.

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 inversed relationship between the pre-treatment 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. Given the salient effects of poorly managed anger, future research is warranted to evaluate the enhancement effects of such approaches for pain rehabilitation.

References

1. Berkowitz L, Thome P (1987) Pain, Expectation, Negative Affect, and Angry Aggression. Motivation Emo 11:183–193
2. Bruehl S, Burns JW et al. (2002) Anger and Pain Sensitivity in Chronic Low Back Pain Patients and Pain-Free Controls: The Role of Endogenous Opioids. Pain 99:223–233
3. Bruehl S, Chung OY et al. (2003) The Association between Anger Expression and Chronic Pain Intensity: Evidence for Partial Mediation by Endogenous Opioid Dysfunction. Pain 106:317–324
4. Burns J, Higdon L et al. (1999) Relationships among Patient Hostility, Anger Expression, Depression and the Working Alliance in a Work Hardening Program. Annals Behav Med 21:77–82
5. Burns JW (1997) Anger Management Style and Hostility: Predicting Symptom-Specific Physiological Reactivity among Chronic Low Back Pain Patients. J Behav Med 20:505–522
6. Burns JW, Johnson BJ et al. (1998) Anger Management Style and the Prediction of Treatment Outcome among Male and Female Chronic Pain Patients. Behav Res Ther 36:1051-1062
7. Fernandez E (2002) Anxiety, Depression, and Anger in Pain. Toronto, University of Toront Press
8. Fernandez E, Turk DC (1995) The Scope and Significance of Anger in the Experience of Chronic Pain. Pain 61:165–175
9. Flor H, Turk DC (1989) Psychophysiology of Chronic Pain: Do Chronic Pain Patients Exhibit Symptom-Specific Psychophysiological Responses? Psychol Bull 105:215–259
10. Gaskin ME, Greene AF et al. (1992) Negative Affect and the Experience of Chronic Pain. J Psychosom Res 36(8):707–713
11. Janssen SA, Spinhoven P et al. (2001) Experimentally Induced Anger, Cardiovascular Reactivity, and Pain Sensitivity. J Psychosom Res 51:479–485
12. Kerns RD, Rosenberg R et al. (1994) Anger Expression and Chronic Pain. J Behav Med 17:57–67
13. Okifuji AD, Turk DC et al. (1999) Anger in Chronic Pain: Investigations of Anger Targets and Intensity. J Psychosom Res 47:1–12
14. Smedslund J (1992) How Shall the Concept of Anger be Defined? Theory Psychol 3:5–34
15. Wade JB, Price DD et al. (1990) An Emotional Component Analysis of Chronic Pain. Pain 40:303–310

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.

- ► 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

Visceral Sensation; interoceptive sensation; Sympathetic Afferents

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 pathways DC) 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 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, micro-stimulation 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.

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 micro-stimulation 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; Lenz et al. 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 (Chatrianet 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).

References

1. Apkarian AV, Hodge CJ (1989) Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways. J Comp Neurol 288:493–511
2. Berthier M, Starkstein S, Leiguarda R (1988) Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann Neurol 24:41–49
3. Blair RW, Weber N, Foreman RD (1982) Responses of thoracic spinothalamic neurons to intracardiac injection of bradykinin in the monkey. Circ Res 51:83–94
4. Blair RW, Ammons WS, Foreman RD (1984) Responses of thoracic spinothalamic and spinoreticular cells to coronary artery occlusion. J Neurophysiol 51:636–648
5. Bruggemann J, Shi T, Apkarian AV (1998) Viscerosomatic interactions in the thalamic ventral posterolateral nucleus (VPL) of the squirrel monkey. Brain Res 787:269–276
6. Chatrian GE, Canfield RC, Knauss TA et al. (1975) Cerebral responses to electrical tooth pulp stimulation in man. An objective correlate of acute experimental pain. Neurology 25:745–757
7. Dong WK, Salonen LD, Kawakami Y et al. (1989) Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. Brain Res 484:314–324
8. Foreman RD, Blair RW, Ammons WS (1986) Neural mechanisms of cardiac pain. In: Cervero F, Morrison JFB (eds) Progress in Brain Research. Elsevier Science Publishers BV, New York, Amsterdam, Oxford, pp 227–243
9. Friedman DP, Murray EA, O'Neill JB et al. (1986) Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol 252:323–347
10. Greenspan JD, Winfield JA (1992) Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. Pain 50:29–39
11. Halgren E, Walter RD, Cherlow DG et al. (1978) Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain 101:83–117
12. Horie H, Yokota T (1990) Responses of nociceptive VPL neurons to intracardiac injection of bradykinin in the cat. Brain Res 516:161–164
13. Jones EG (1985) The Thalamus. Plenum, New York
14. Lenz FA, Seike M, Richardson RT et al. (1993) Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. J Neurophysiol 70:200–212
15. Lenz FA, Gracely RH, Hope EJ et al. (1994) The sensation of angina can be evoked by stimulation of the human thalamus. Pain 59:119–125
16. Lenz FA, Gracely RH, Romanoski AJ et al. (1995) Stimulation in the human somatosensory thalamus can reproduce both the affective and sensory dimensions of previously experienced pain. Nat Med 1:910–913
17. Locke S, Angevine JB, Marin OSM (1961) Projection of magnocellular medial geniculate nucleus in man. Anat.Rec 139:249–250
18. Mehler WR (1962) The anatomy of the so-called "pain tract" in man: an analysis of the course and distribution of the ascending fibers of the fasciculus anterolateralis. In: French JD, Porter RW (eds) Basic Research in Paraplegia. Thomas, Springfield, pp 26–55
19. Meller ST, Gebhart GF (1992) A critical review of the afferent pathways and the potential chemical mediators involved in cardiac pain. Neurosci 48:501–524
20. Mishkin M (1979) Analogous neural models for tactual and visual learning. Neuropsych 17:139–151
21. Taguchi H, Masuda T, Yokota T (1987) Cardiac sympathetic afferent input onto neurons in nucleus ventralis posterolateralis in cat thalamus. Brain Res 436:240–252

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).

► NSAIDs and Cancer

Angiography

Definition

An Angiography is necessary for the diagnosis of CNS vasculitides.

► Headache Due to Arteritis

Animal Models for Mononeuropathy

Definition

Experimental procedures that produce partial lesion of the nerves supplying one appendage (fore leg or hind leg). Several animal models are available and are known to produce increased nociception.

► Thalamotomy, Pain Behavior in Animals

Animal Models of Inflammatory Bowel Disease

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Animal Models and Experimental Tests to Study Nociception and Pain

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Introduction

Animal models and experimental tests are the fundamental tools that make studying nociception and pain possible. In fact, it would not be an exaggeration to say that progress in pain research has been made only to the degree that these essential research tools are available. Perhaps, the oldest and the most commonly used nociceptive test would be the ► tail flick test that was developed by D'Amour and Smith in 1941 (D'Amour and Smith 1941). Following this early test, which is a test for acute pain in normal rodents, many other tests and models for chronic or persistent pain using various animals have been developed. The availability of these new tests and models has made it possible for research on persistent pain to flourish during the last decade. The present section attempts to document the majority of commonly used animal models and experimental tests. Hence, this section would be a good reference source for those who want to know about these basic tools for pain research.

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 the 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 decade. These include various musculoskeletal pain models (► arthritis model, kaolin-carrageenan induced arthritis (knee); ► arthritis model, adjuvant-induced arthritis; ► cancer pain model, bone cancer pain; ► 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 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.

In particular, 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 that 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 3 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 gun shot 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.

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), over-distension 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 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 make-up 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.

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.

Conclusion

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 ones representing other painful conditions.

References

1. Bennett GJ, Xie Y-K (1988) A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33:87–107
2. D'Amour FE, Smith DL (1941) A method for determining loss of pain sensation. J Pharmacol Exp Ther 72:74–79
3. Decosterd I, Woolf CJ (2000) Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain 87:149–158
4. Hargreaves K, Dubner R, Brown F et al. (1988) A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 32:77–88
5. Kim SH, Chung JM (1991) Sympathectomy alleviates mechanical allodynia in an experimental animal model for neuropathy in the rat. Neurosci Lett 134:131–134
6. Kim SH, Chung JM (1992) An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 50:355–363
7. Kim KJ, Yoon YW, Chung JM (1997) Comparison of three rodent neuropathic pain models. Exp Brain Res 113:200–206
8. Mitchell SW (1872) Injuries of nerves and their consequences. JB Lippincott, Philadelphia, pp 252–281
9. Na HS, Han JS, Ko KH et al. (1994) A behavioral model for peripheral neuropathy produced in rat's tail by inferior caudal trunk injury. Neurosci Lett 177:50–52
10. Seltzer Z, Dubner R, Shir Y (1990) A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. Pain 43:205–218

Synonyms

Colitis; Crohn's Disease; Inflammatory Bowel Disease, Animal Models; Ulcerative Colitis

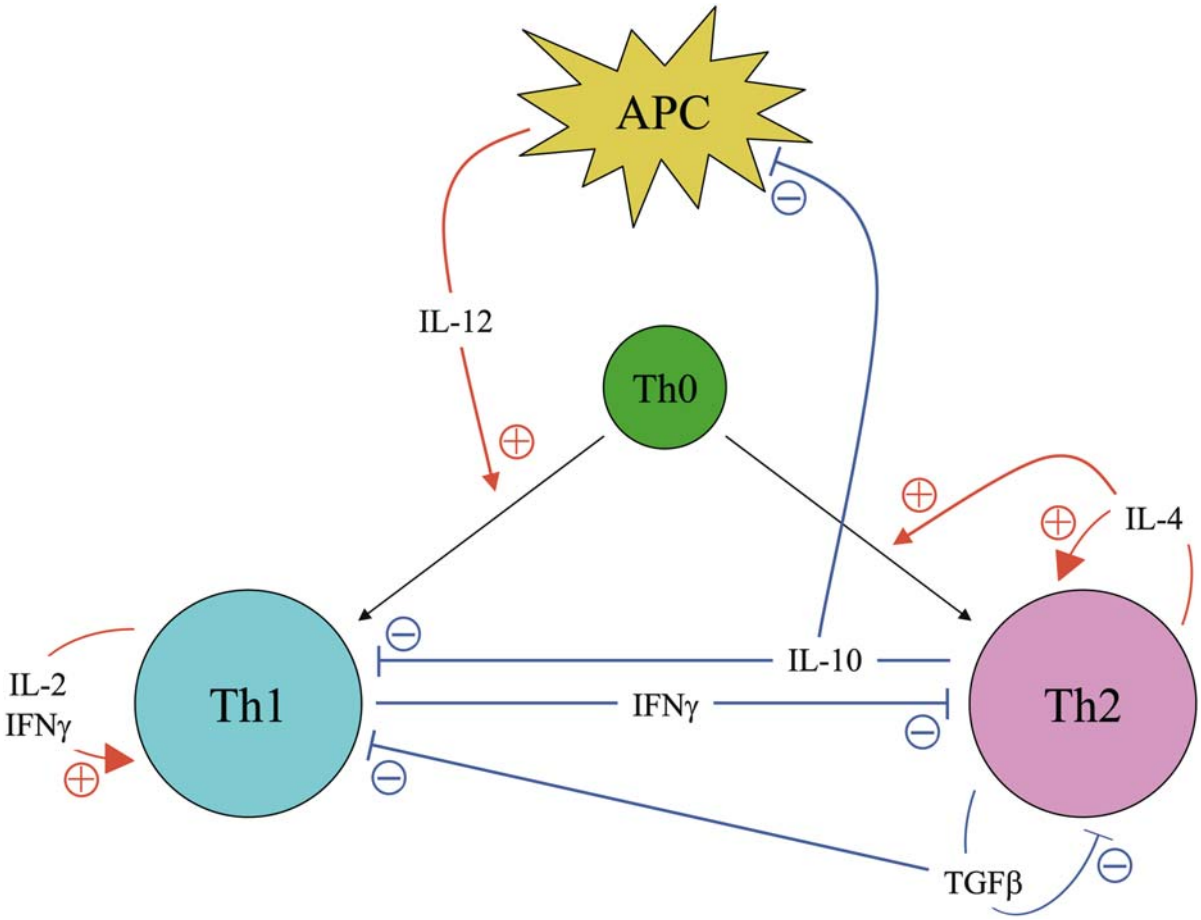
Definition

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 affect 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



Animal Models of Inflammatory Bowel Disease, Figure 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 up-regulating 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 down-regulating IL-12 production.

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 3–6 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, 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. Over-expression of HLA-B27 or STAT-4 both increase 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, over-expression 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 over-expresses 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.

References

1. Bhan AK, Mizoguchi E, Smith RN et al. (1999) Colitis in transgenic and knockout animals as models of human inflammatory bowel disease. Immunol Rev 169:195–207
2. Blumberg RS, Saubermann LJ, Strober W (1999) Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. Curr Opin Immunol 11:648–656
3. Bush TG, Savidge TC, Freeman TC et al. (1998) Fulminant jejuno-ileitis following ablation of enteric glia in adult transgenic mice. Cell 93:189–201
4. Elson CO, Beagley KW, Sharmanov AT et al. (1996) Hapten-induced model of murine inflammatory bowel disease: mucosa immune responses and protection by tolerance. J Immunol 157:2174–2185
5. Fiocchi C (1998) Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 115:182–205
6. Hendrickson BA, Gokhale R, Cho JH (2002) Clinical aspects and pathophysiology of inflammatory bowel disease. Clin Microbiol Rev 15:79–94
7. Kamp EH, Jones RC 3rd, Tillman SR et al. (2003) Quantitative assessment and characterization of visceral nociception and hyperalgesia in mice. Am J Physiol Gastrointest Liver Physiol 284:434–444
8. Kim HS, Berstad A (1992) Experimental colitis in animal models. Scand J Gastroenterol 27:529–537
9. Mahler M, Bristol IJ, Leiter EH et al. (1998) Differential susceptibility of inbred mouse strains to dextran sulfate sodium-induced colitis. Am J Physiol 274:G544–551
10. Martinez V, Thakur S, Mogil JS et al. (1999) Differential effects of chemical and mechanical colonic irritation on behavioral pain response to intraperitoneal acetic acid in mice. Pain 81:179–186
11. Mashimo H, Wu DC, Podolsky DK et al. (1996) Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor. Science 274:262–265
12. Ribbons KA, Currie MG, Connor JR et al. (1997) The effect of inhibitors of inducible nitric oxide synthase on chronic colitis in the rhesus monkey. J Pharmacol Exp Ther 280:1008–1015
13. Sengupta JN, Snider A, Su X et al. (1999) Effects of kappa opioids in the inflamed rat colon. Pain 79:175–185
14. Wirtz S, Neurath MF (2000) Animal models of intestinal inflammation: new insights into the molecular pathogenesis and immunotherapy of inflammatory bowel disease. Int J Colorectal Dis 15:144–160
15. Yamada T, Deitch E, Specian RD et al. (1993) Mechanisms of acute and chronic intestinal inflammation induced by indomethacin. Inflammation 17:641–662

Animal Models of Inflammatory Muscle Pain

► Muscle Pain Model, Inflammatory Agents-Induced

Animal Models of Inflammatory Myalgia

► Muscle Pain Model, Inflammatory Agents-Induced

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).

- ► 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 results in reduced mobility or stiffness of the joint.

- ► 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.

- ► Lumbar Traction
- ► Whiplash

Anorexia

Definition

Loss of appetite.

- ► Clinical Migraine with Aura

Antecedents and Consequences of Behaviour

Definition

The set of factors that occurred temporally before and after a behavioral event or experience. The antecedents may contribute to an individuals 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, the antecedents and consequences play a role in determining the onset, maintenance, and exacerbation of inappropriate behaviours, or contribute to appropriate and adaptive responses to similar situations and sensations in the future.

- ► Psychological 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. It's 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.

- ► 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.

- ► Pain Treatment, Spinal Nerve Blocks

Anterior Pulvinar Nucleus

Definition

The Anterior Pulvinar Nucleus extends from the medial pulvinar and posterior nuclei, situated between the centre median and ventral posterior nuclei.

- ► 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, 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.

► Parabrachial Hypothalamic and Amydaloid 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.

► 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.

► Cancer Pain Management: Neurosurgical Interventions
► Percutaneous Cordotomy
► Spinothalamic Neuron

Antiarrythmics

► 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.

► Cancer Pain Management, Adjuvant Analgesics in Management of Pain Due To Bowel Obstruction

Anticipatory Anxiety

Definition

Anticipatory anxiety refers to the perceived dangerousness or threat-value of an impending 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. With respect to pain, it tends to lead to hyperalgesia and to an attentional focus on pain.

► Experimental Pain in Children
► Respondent Conditioning of Chronic Pain

Anticonvulsant (Agent)

Definition

Antiepileptics. An agent that prevents or arrests seizures, which are primary used in the management of epilepsy.

► Drugs Targeting Voltage-Gated Sodium and Calcium Channels
► Migraine, Preventive Therapy
► Postoperative Pain, Anti-Convulsant Medications
► Post-Seizure Headache

Antidepressant Analgesics in Pain Management

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Synonyms

Tricyclic-Type Antidepressants
More noradrenergic (N): e.g. nortriptyline, desipramine, maprotiline (tetracyclic)
More serotonergic (S): e.g. clomipramine
Monamine Oxidase Inhibitors
Selective serotonin reuptake inhibitors (SSRIs) e.g. fluoxetine, fluvoxamine, sertraline, paroxetine
Atypical Antidepressants
Serotonin Norepinephrine Reuptake Inhibitors

Definition

Antidepressants are a broad category of drugs originally aimed at treating depressed mood; however, there is an independent analgesic effect that occurs at lower doses than the antidepressant effect. They are categorized in different ways, based on structure (tricyclic, tetracyclic) and their putative mechanism of action (serotonin and norepinephrine reuptake inhibition, monoamine oxidase inhibition).

Charateristics

Historical

There is a large body of scientific evidence that a variety of pain disorders are relieved by antidepressant therapy. The roots of this information have been neglected to-date, and historical studies of seminal importance have been omitted from reviews of these drugs. In the early 1960s, publications of case series in the French literature reported relief of pain (in some cases neuropathic), by injectable and oral imipramine. Although responses seemed most pronounced in patients with psychological disorders, a few were described as having no psychiatric diagnosis. The mechanism of action was unclear to these investigators, but a leucotomy-like action and an antihistaminic effect were suggested. Lance and Curran (1964) studied amitriptyline in chronic tension headache by controlled trial, and noticed that most patients were not depressed and stated that "there was no evidence that amitriptyline influenced selectively those patients who had some degree of depression" They said that "amitriptyline seems unlikely to exert a significant analgesic effect in tension headache" despite their finding of a lack of effect on depression. They thought that an effect on vasodilation may have resulted in the benefit seen. The French authors' results with imipramine were referred to in a study of amitriptyline in postherpetic neuralgia (PHN) by Woodforde (1965) and appeared to have influenced him. Woodforde described the relief of PHN with amitriptyline in intractable cases of long duration and with prolonged follow-up. He thought patients were depressed, and that pain relief was associated with relief of depression. Merskey and Hester (1972), aware of the 1964 Lance and Curran report, published a report of patients with chronic pain, including 7 patients with PHN treated successfully with a tricyclic (usually amitriptyline) and a phenothiazine (usually pericyazine). They stated that they thought that these drugs had an analgesic effect independent of a mood-altering action. Taub (1973, 1974) chose amitriptyline to treat PHN because of its sedative and antidepressant effect. He added a phenothiazine because of persistent pain and anxiety. He described eventually using perphenazine because of its better side effect profile. He observed that this latter drug seemed to him to be the pain-relieving agent in the combination. Taub's regimen of amitriptyline 75 mg and perphenazine 1 mg TID came into widespread use in North America and, along with clinical experience, led Watson and others to conduct the initial randomized controlled trial (RCT) of amitriptyline alone vs placebo in PHN (Watson et al. 1982), and because of Merskey's work (1972), to investigate the possibility of an independent analgesic action for this drug.

Pharmacodynamics

The original reason for the treatment of chronic pain with antidepressants appears to have been for the relief of concomitant depression.A proportion of chronic pain patients have been shown to be depressed and show an increased incidence of familial depression and response to tricyclic antidepressants. RCTs have demonstrated that relief of pain occurs as well as depression relief with these agents. Pain relief, separate from the antidepressant effect, suggesting an analgesic action, has been reported since the 1960's. RCTs have repeatedly and clearly demonstrated the separation of the analgesic and antidepressant effects.
The earliest concept of the mechanism of antidepressant analgesia was that this occurred via pain-inhibiting systems that descend from the brainstem onto the dorsal horn of the spinal cord. The earliest candidate involved an endorphin link from the periaqueductal gray area to the raphe nucleus in the mid-pons, and then a serotonergic (S) connection from the raphe to the dorsal horn of the spinal cord. Another inhibitory system extends from the locus coeruleus in the lateral pons to the dorsal horn which involves noradrenaline(N). RCTs have indicated that the selective S drugs appear either to be ineffective or less effective than N agents and those with a mixed effect on S + N. The N agent maprotiline has been shown to be effective, but comparative trials indicate that it is probably less effective than amitriptyline (S + N). The more effective antidepressants for chronic pain appear to be amitriptyline and its metabolite nortriptyline. A meta-analysis of 39 placebo-controlled trials of antidepressant analgesia in chronic pain has found that a larger effect size occurs with the agents that combine

Antidepressant Analgesics in Pain Management, Table 1 Number needed to treat (NNT) data in some neuropathic pain conditions

DRUG	CONDITION				COMMENTS
	Postherpetic Neuralgia	Diabetic Neuropathy	Painful Pain	Central Neuropathy	
ANTIDEPRESSANTS					
McQuay et al. 1996	2.3	3.0		1.7	systematic review
Sindrup and Jensen 1999	2.3	2.4		1.7	review
Collins et al. 2000	2.1	3.4			systematic review
Sindrup et al. 2003					
IMIPRAMINE					
Sindrup et al. 2003			2.7		RCT
VENLAFAXINE					
Sindrup et al. 2003			5.2		RCT
GABAPENTIN					
Sindrup and Jensen 1999	3.2	3.7			systematic review
PREGABALIN					
Dworkin et al. 2003	3.4				RCT
OXYCODONE					
Watson et al. 1998	2.5				RCT
Watson et al. 2003		2.6			RCT
TRAMADOL					
Sindrup and Jensen 1999			3.4		systematic review

N and S effects than the more specific drugs (Onghena and Van Houdenhove 1992). The older antidepressants are, however, relatively "dirty drugs" and act on multiple receptors and have multiple effects. It has been suggested that relief of pain might be due to an anxiolytic or sedative effect. This seems unlikely. Other actions that possibly could contribute are the anticholinergic effect, an antihistaminic effect, an anti-inflammatory effect due to the inhibition of prostaglandin synthetase or a calcium channel blocking action. Recent attractive ideas, in light of current thinking, are that these drugs may be n-methyl d-aspartate (NMDA) antagonists, or that they have a sodium channel blocking effect.

Evidence-Based Studies

In terms of the published RCTs, favourable trials are more likely to be found in arthritis headache, PHN, and painful diabetic neuropathy (PDN), in which all published trials are favourable. Only 40–50% of trials were positive in other kinds of chronic non-malignant pain such as fibromyalgia and low back pain.This finding may simply be due to a failure to report negative trials in some conditions. A summary of published literature on the effect of anti-depressants on pain is presented in Table 1.

Acute Pain Studies

The acute pain studies are few in number, with mainly negative studies of amitriptyline and desipramine in postoperative pain (Kerrick et al. 1993; Levine et al. 1986), although the potentiation of morphine by desipramine and not amitriptyline is of interest (Levine et al. 1986). The duration and dose may have been inadequate to show an effect in these trials. The solitary positive trial (Stein et al. 1996) was in acute low back pain and used a higher dose of amitriptyline than is commonly used for pain relief (150 mg).

Cancer Pain

The cancer pain RCTs were also few and notable because of the relief of neuropathic pain in breast cancer by amitriptyline (Kalso et al. 1995) and venlafaxine (Tasmuth et a1 2002), the amitriptyline dose in the favourable trial (Kalso et al. 1995) being higher (50–100 mg) than that in an unfavourable study in the same condition (30–50 mg) (Mercadante 2002).

Chronic Non-Malignant, Non-Neuropathic Pain

Results in a number of chronic nonmalignant, non-neuropathic disorders (CNMNNP) have demonstrated that a variety of antidepressants with a mixed effect

Antidepressant Analgesics in Pain Management, Table 2 Comparative studies on the effect of anti-depressants on pain

Outcome of Trial	Author(s) of study
Effect on chronic, malignant, non-neuropathic disorders (CNMNNP)	
Only amitriptyline (N+S) relieved arthritic pain compared to desipramine(N) and trazodone(S)	Frank et al. (1988) Journal of Rheumatology 15:1632–1638
Combination of fluoxetine(S) and amitriptyline better than either alone in fibromyalgia; however, the dose of amitriptyline was low at 25 mg	Goldenberg (1996) Arthritis and Rheumatism 39:1852–1859
Fluoxetine (S) better than amitriptyline(S+N) in a variety of rheumatic conditions but again the dose of amitriptyline was only 25 mg	Usha et al. (1996) Anaesthesia Analgesia 83: 371–375
Effect on Neuropathic Pain	
Amitriptyline (S+N) is more effective than maprotiline (N)	Watson et al. (1992) Pain 48:29–36
Nortriptyline (N) has less significant adverse effects than amitriptyline	Watson et al. (l998) Neurology 51:1166–1171
Opioids thought to be more effective than tricyclic antidepressants in a comparative study in PHN	Raja et al. (2002) Neurology 59:1015–1021
Comparison RCTs in PDN indicate that amitriptyline (S+N) and desipramine (N) relieve pain but fluoxetine (S) does not.	Max et al. (1992) New England Journal of Medicine 326:1250–1256
In PDN, amitriptyline(S+N) appears more effective than maprotiline (N), an identical result to that in PHN	Vrethem et al. (1997) Clinical Journal of Pain 12:313–323
An RCT in PHN (Morello et al. 1999) has shown amitriptyline to be equal to gabapentin in pain relief and adverse events.	Morello et al. (1999) Archives of Internal Medicine 159:1931–1937
S agent clomipramine may be more effective than desipramine(N).	Sindrup et al. (1990) Br J Clin Pharmacol 30:683–691
Favourable response of NP to topical doxepin	McLeane (2000) British Journal of Clinical Pharmacology 49(6):574–579
Favourable response of NP to bupropion	Semenchuk et al. (2001) Neurology 57:1583–1588
Favourable response of NP to venlafaxine, although study indicated that venlafaxine is less effective than imipramine	Sindrup et al. (2003) Neurolgy 60:1284–1289
Favourable response of central pain to amitriptyline (S+N)	Leijon and Boivie (1989) Pain 36:27–36
Favourable response of central pain to clomipramine(S) and nortriptyline(N)	Panerai et al. (1990) Acta Neurologica Scandnavica 82:34–38
Negative trials in HIV neuropathy pain	Kieburtz et al. (1998) Neurology 51:1683–1688 Shlay et al. (1998) JAMA 289:1590–1595
Negative trails of nortriptyline in cis-platinum neuropathy	Hammack et al. (2002) Pain 91:195–203

on S and N were associated with favourable results (amitriptyline, imipramine, trimipramine,dothiepin, dibenzepin), as was a drug with a predominantly N action (nortriptyline). More selective S agents were also more effective than placebo (fluoxetine, fluvoxamine, sertraline) (Watson et al. 2004). (For studies on the effect of antidepressants on CNMNNP, the reader is referred to Table 2).

The data in CNMNNP do not allow us to draw conclusions as to the relative effectiveness of different antidepressants, nor have they been compared to other analgesic drugs. Neither is there information about clinical meaningfulness such as number needed to treat (NNT)(Laupacis et al. 1988) information in these studies.

Neuropathic Pain (NP)

Most of the antidepressant research in neuropathic pain (NP) has been carried out in PHN and painful diabetic neuropathy (PDN), both of which have proven to be good clinical experimental models for antidepressant research (Watson 2000). The results in the two conditions have been reasonably similar, except that there is evidence of an effect of S agents in PDN; however, but there are no RCTs of these agents in PHN. In both PHN and PDN trials, amitriptyline (N+S) and the N agents, i.e. maprotiline, desipramine, and nortriptyline, have been repeatedly shown to be better than placebo. More of these drugs have been studied in PDN, and there are positive trials with imipramine (S+N), as well as S agents e.g. paroxetine, clomipramine, and citalopram in this disorder. There are also negative trials of mianserin (Sindrup et al. 1992) and fluoxetine(S) (Max et al. 1992). (For trials on the effect of antidepressants on neuropathic pain, the reader is referred to Table 2).

What are we to conclude about the relative efficacy of these different antidepressants? It is probable that the mixed N and S agents amitriptyIine and imipramine are more effective than the N agents desipramine and maprotiline (although nortriptyline appears equal in pain relief

but superior to amitriptyline in having less significant adverse effects). Selective S agents appear less effective in some cases or not effective at all. Recent studies indicate that opioids may be more effective than antidepressants (Raja et al. 2002), and that amitriptyline is equal to gabapentin in the relief of pain and in causing adverse effects is of interest. NNT data from systematic reviews and single RCTs (Table 1) may help to give us some insight as to the relative efficacy of antidepressants versus other agents, but probably must be interpreted with caution. A comparison of NNT is problematic, especially given the use of intent-to-treat analyses in the gabapentin trials but not in the crossover trials of tricyclic antidepressants and opioids.(Dworkin et al. 2003). It is also probable that the generalization of these NNT data to clinical practice is problematic because of the selection that goes into RCTs.

Practical Guidelines

Practical guidelines for the use of antidepressants and NP pain are to start with nortriptyline (less significant adverse events) or amitriptyline in a low dose, that is 10 mg in those over 65 and 25 mg in those under 65, and to slowly increase the dose every week or two by similar amounts until an end point of satisfactory pain relief or a significant adverse event occurs. The average dose is around 75 mg for appreciable pain relief, and this occurs in about 1/2 to 2/3 of patients. It may be helpful to try different antidepressants, moving from those with a mixed effect on S and N such as amitriptyline and imipramine to the more N ones such as desipramine and maprotiline, to an S agent. Individual differences in pain-inhibitory mechanisms may mean that one drug is more efficacious for an individual patient. It is important to try to deal with some side effects pre-emptively such as a mouth spray for dry mouth and stool softeners for constipation. Caution regarding possible weight gain is important as well. Combination therapy is reasonable, that is combining an antidepressant with an opioid and/or gabapentin and/or the lidocaine patch.

Conclusions

In conclusion, antidepressants have repeatedly been shown to have an analgesic effect and to relieve different components of neuropathic pain, which is the stabbing pain, steady pain, and skin sensitivity, and that this effect is independent of an antidepressant action. Adverse events are often problematic and some can be dealt with pre-emptively. There is evidence that the drugs with a mixed effect on S and N such as amitriptyline and imipramine, may be more effective than the N agents desipramine and maprotiline (except for nortriptyline which seems equal to amitriptyline and to have less significant adverse events). S agents appear least efficacious, but may have an effect in individual instances. More comparative studies are needed to determine the relative efficacy of the antidepressants and how they compare with other agents such as gapapentin, pregabalin, and other anticonvulsants and opioids. Some agents require further study (topical doxepin, bupropion), clinical meaningfulness data such as NNT should be incorporated in future studies, and new drugs and approaches are needed.

References

1. Collins SL, Moore RA, McQuay JH (2000) Antidepressants and Anticonvulsants for Diabetic Neuropathy and Postherpetic Neuralgia: A Quantitative Systematic Review. J Pain Symptom Manage 20:449–458
2. Dworkin RH, Corbin AE, Young JP (2003) Pregabalin for the Treatment of Postherpetic Neuralgia. Neurology 60:1274–1283
3. Kalso E, Tasmuth T, Neuvonen PJ (1995) Amitriptyline Effectively Relieves Neuropathic Pain following Treatment of Breast Cancer. Pain 64:293–302
4. Kerrick JM, Fine PG, Lipman AG et al. (1993) Low Dose Amitriptyline as an Adjunct to Opioids for Postoperative Orthopaedic Pain: A Randomized Controlled Trial. Pain 52:325–330
5. Lance JW, Curran DA (1964) Treatment of Chronic Tension Headache. Lancet I:1236–1239
6. Langohr HD, Stohr M Petruch F (1982) An Open End, Double-Blind, Crossover Study on the Efficacy of Clomipramine in Patients with Painful Polyneuropathies. Eur Neurol 21:309–317
7. Laupacis A, Sackett DL, Roberts RS (1988) An Assessment of Clinically Useful Measures of the Consequences of Treatment. New Engl J Med 318:1728–1733
8. Levine JD, Gordon NC, Smith R et al. (1986) Desipramine Enhances Opiate Postoperative Analgesia. Pain 27:45–49
9. Max MB, Lynch SA, Muir J et al. (1992) Effects of Desipramine, Amitriptyline, and Fluoxetine on Pain in Diabetic Neuropathy. New Engl J Med 326:1250–1256
10. McQuay H, Trainer M, Nye BA et al. (1996) A Systematic Review of Antidepressants in Neuropathic Pain. Pain 68:217–227
11. Mercadante S, Arcuri E, Tirelli W et al. (2002) Amitriptyline in Neuropathic Cancer Pain in Patients on Morphine Therapy: A Randomized, Placebo-Controlled, Double-Blind, Crossover Study. Tumori 88:239–242
12. Merskey H, Hester RA (1972) The Treatment of Pain with Psychotropic Drugs. Postgraduate Medical Journal 48:594–598
13. Onghena P, van Houdenhove B (1992) Antidepressant-Induced Analgesia in Chronic Non-Malignant Pain: A Meta-Analysis of 39 Placebo Controlled Studies. Pain 49:205–219
14. Raja SN, Haythornethwaite JA, Pappagallo M et al. (2002) Opioids versus Antidepressants in Postherpetic Neuralgia: A Randomized, Placebo-Controlled Trial. Neurology 59:1015–1021
15. Sindrup SH, Jensen TS (1999) Efficacy of Pharmacological Treatment of Neuropathic Pain: An Update and Effect Related to Mechanism of Drug Action. Pain 83:389–400
16. Sindrup SH, Tuxen C, Gram LF et al. (1992) Lack of Effect of Mianserin on the Symptoms of Diabetic Neuropathy. Eur J Clin Pharmacol 43:251–255
17. Sindrup SH, Bach FW, Madsen C et al. (2003) Venlafaxine versus Imipramine in Painful Neuropathy: A Randomized Controlled Trial. Neurolgy 60:1284–1289
18. Stein D, Floman Y, Elizur A et al. (1996) The Efficacy of Amitriptyline and Acetaminophen in Acute Low Back Pain. Psychosomatics 37:63–70
19. Tasmuth T, Brita H, Kalso E (2002) Venlafaxine in Neuropathic Pain following Treatment of Breast Cancer. Eur J Pain 6:17–24
20. Usha PU, Naidi MUR, Prasad V (1996) An Evaluation of Antidepressants in Rheumatic Pain Conditions. Anaesth Analg 83:371–375
21. Watson CPN, Vernich L, Chipman M et al. (1998) Amitriptyline versus Nortriptyline in Postherpetic Neuralgia. Neurology 51:1166–1171

22. Watson CPN, Evans RJ, Reed K et al. (1982) Amitriptyline versus Placebo in Postherpetic Neuralgia. Neurology 32:671–673
23. Watson CPN (2000) The Treatment of Neuropathic Pain: Antidepressants and Opioids. Clin J Pain 16:49–55
24. Watson CPN, Moulin D, Watt-Watson JH et al. (2003) Controlled Release Oxycodone Relieves Neuropathic Pain: A Randomized Controlled Trial in Painful Diabetic Neuropathy. Pain 105:71–78
25. Watson CPN, Chipman M, Monks RC (2004) Textbook of Pain, Churchill Livingstone Woodforde JM, Dwyer B, McEwen BW et al. (1965) The Treatment of Postherpetic Neuralgia. Medical Journal of Australia 2:869–872

Antidepressant Drugs

Definition

Antidepressant drugs are primarily used in the management of depressive disorders.

► Diabetic Neuropathy, Treatment
► Migraine, Preventive Therapy
► Postoperative Pain, Anti-Depressants

Antidepressants in Neuropathic Pain

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Definition

Neuropathic pain is pain caused by a lesion or dysfunction in the 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 and citalopram (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 some data on SNRIs, SSRIs and a DNRI (Sindrup et al. 2005).

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 1997). 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 (Baldessarini 2001; 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 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

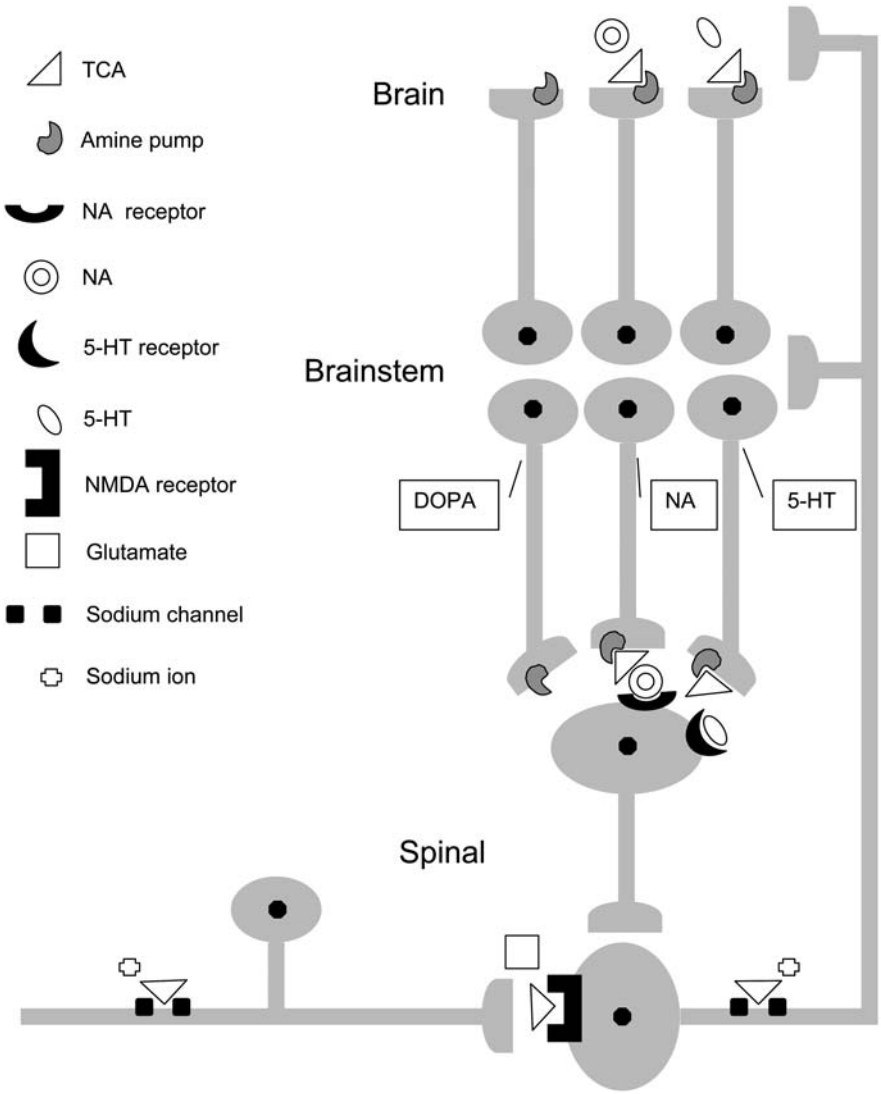
Numerous ► randomised, ► double-blind, placebo-controlled clinical trials have shown that TCAs relieve painful polyneuropathies and post-herpetic neuralgia, and a few trials have indicated that TCAs also have the potential to relieve central post-stroke pain and post-mastectomy pain syndrome (Sindrup et al. 2005). 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 (Sindrup et al. 2005). In a study including a mixture of different types of peripheral neuropathic pain, bupropion provided astonishing pain relief (Semenchuck 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

Antidepressants in Neuropathic Pain, Table 1 Pharmacological profile of antidepressant drugs tried in neuropathic pain

		TCA		SNRI	DNRI	SSRI
		Amitriptyline Imipramine Clomipramine	Nortriptyline Desipramine Maprotiline	Venlafaxine Duloxetine	Bupropion	Fluoxetine Paroxetine Citalopram
Reuptake inhibition	Serotonin	+	-/(+)	+	-	+
	Noradrenaline	+	+	+	+	-
	Dopamine	-	-	-	+	-
Receptor Blockade	α-adrenergic	+	+	-	-	-
	H^1−histaminergic	+	+	-	-	-
	Musc. cholinergic	+	+	-	-	-
	NMDA	+	+	-	?	-
Ion channel blockade	Sodium	+	+	-/(+)	?	-/(+)/?
	Calcium	+	+	?	?	?



Antidepressants in Neuropathic Pain, Figure 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)	4.6	2.9–10.6	112
SSRI (fluoxetine, paroxetine, citalopram)	6.8	3.4–441	81
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

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). 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 SNRI venlafaxine seems to have lower efficacy than TCA in painful polyneuropathy, whereas preliminary reports have indicated that duloxetine, another SNRI, has the potential to relieve painful diabetic polyneuropathy more efficiently. The SSRIs have been tested in painful diabetic polyneuropathy and appear to have rather low efficacy, with an NNT value of 6.8. 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; Max et al. 1991).

Dosing of Antidepressants in Neuropathic Pain

TCAs exhibit a large interindividual variability in pharmacokinetics (Baldessarini 2001), 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 50 mg/d 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/d was ineffective, whereas 225 mg/d 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 preliminary data on duloxetine indicate that 60–120 mg/d provides pain relief, whereas 20 mg/d is ineffective.

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 SNRI venlafaxine 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 21.5 (11.2–270) for SNRIs and bupropion together. 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.

References

1. Baldessarini RJ (2001) Drugs for the Treatment of Psychiatric Disorders. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th edn. McGraw Hill, New York, pp 447–483
2. Kishore-Kumar R, Max MB, Schafer SC et al. (1990) Desipramine Relieves Postherpetic Neuralgia. Neurology 47:305–312
3. Max MB, Culnane M, Schafer SC et al. (1987) Amitriptyline Relieves Diabetic Neuropathy in Patients with Normal and Depressed Mood. Neurology 37:589–596
4. Max MB, Schafer SC, Culnane M et al. (1988) Amitriptyline, but not lorazepam, Relieves Postherpetic Neuralgia. Neurology 38:1427–1432
5. Max MB, Kishore-Kumar R, Schafer SC et al. (1991) Efficacy of Desipramine in Painful Diabetic Neuropathy: A Placebo-Controlled Trial. Pain 45:3–9
6. Rasmussen PV, Jensen TS, Sindrup SH et al. (2004) TDM-Based Imipramine Treatment in Neuropathic Pain. Ther Drug Monit 26:352–360
7. Rowbotham MC, Goli V, Kunz NR et al. (2004) Venlafaxine Extended Release in the Treatment of Painful Diabetic Polyneuropathy: A Double-Blind, Placebo-Controlled Study. Pain 110:697–706
8. Semenchuk MR, Sherman S, Davis B (2001) Double-Blind, Randomized Trial of Bupropion SR for the Treatment of Neuropathic Pain. Neurology 57:1583–1588
9. Sindrup SH (1997) Antidepressants as Analgesics In: Yaksh TL, Lynch C, Zapol WM et al. (eds). Anesthesia. Biological Foundations. Lippencott-Raven Publishers, Philadelphia, pp 987–997
10. Sindrup SH, Bach FW, Madsen C et al. (2003) Venlafaxine versus Imipramine in Painful Polyneuropathy. A Randomized, Controlled Trial. Neurology 60:1284–1289
11. Sindrup SH, Otto M, Finnerup NB et al. (2005) Antidepressants in Neuropathic Pain. Basic Clin Pharmacol Toxcicol 96:399–409
12. Woolf CJ, Mannion RJ (1999) Neuropathic Pain. Aetiology, Symptoms, Mechanisms and Management. Lancet 353:1959–1964

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 criterion (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.

- ► Corticothalamic and Thalamocortical Interactions
- ► Nociceptor, Fatigue
- ► Nociceptors in the Orofacial Region (Temporomandibular Joint and Masseter Muscle)
- ► Parabrachial Hypothalamic and Amydaloid Projections
- ► Spinothalamic Neuron
- ► Spinohypothalamic Tract, Anatomical Organization and Response Properties

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.

- ► Spinothalamic Input, Cells of Origin (Monkey)

Antiepileptic Drugs (Agents)

Definition

Antiepileptic drugs are primarily used in the management of epilepsy.

- ► Diabetic Neuropathy, Treatment
- ► Postoperative Pain, Anti-Convulsant Medications
- ► Postoperative Pain, Gabapentin

Antihyperalgesic Effect

Definition

An effect leading to the attenuation of hyperalgesia, usually produced by surgical or pharmacological methods.

- ► 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.

- ► Cytokines, Regulation in Inflammation

Antinociception

Definition

Attenuation of nociceptive processing in the nervous system, and the reduction of inhibition of nociceptive transmission. In animal models of pain, a decrease in a response to a stimulus that is perceived as painful to humans.

- ► 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.

- ► Thalamic Nuclei Involved in Pain, Cat and Rat

Antinociceptive Models

Definition

Animal models of experimental pain include the tail flick test, ► Hot Plate Test (Assay), warm water tail withdrawal, abdominal constriction, 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 is monitored. For instance, thermal stimuli typically produce a pre-determined response within a latency time; antinociception is determined by the prolongation of the latency time. A chemical stimulus such as phenylquinone or acetic acid typically induces abdominal constrictions, which can be suppressed by analgesic drugs.

- ► Nitrous Oxide Antinociception and Opioid Receptors

Antiphospholipid Syndrome

Definition

Diagnosis with the detection of lupus anticoagulant and IgG-anticardiolipin antibodies; primary or secondary in collagene vascular disease (SLE).

- ► Headache Due to Arteritis

Antipyretic Analgesics

- ► NSAIDs and their Indications

Antisense Oligonucleotide

Synonyms

ASO

Definition

A DNA sequence, typically 15 to 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.

► Purine Receptor Targets in the Treatment of Neuropathic Pain

Anxiety

Definition

Anxiety is the subjective feeling of apprehension, dread, or foreboding ranging from excessive concern about the present or future to feelings of panic, 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 seems to place the defensive physiological mechanisms in a heightened state of preparedness, thereby facilitating and stimulating the fight-flight response only in case the threatening event occurs. Anxiety is often distinguished from fear in that fear is a more appropriate word to use when threat or danger exists in the real world. Anxiety is more reflective of a threat that is not apparent or imminent in the real world, at least not to an experienced degree.

► Amygdala, Pain Processing and Behavior in Animals
► Fear and Pain
► Pain in the Workplace, Risk Factors for Chronicity, 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.

► Fear and Pain

Anxiolysis

► Minimal Sedation

Apamin

Definition

Bee venom inhibiting some Ca dependant K channels (SK type).

► Mechano-Insensitive C-Fibres, Biophysics

Apoplexy

► Headache Due to Intracranial Bleeding

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.

► NSAIDs and Cancer
► NSAIDs, COX-Independent Actions

Apoptotic Degeneration

Definition

Programmed cell death, which involves a tightly controlled death pathway. It avoids tissue inflammation, which usually accompanies cell death though cell damage.

► GABA and Glycine in Spinal Nociceptive Processing

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.

► Catastrophizing
► Psychology of Pain, Assessment of Cognitive Variables

APS

► Acute Pain Service

APT

► Acute Pain Team

Arachadonic Acid

Definition

Arachidonic Acid is a C_{20} carboxylic acid with 4 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 arachadonic 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 haemostasis). Metabolites are named "eicosanoids", referring to the common structural feature of 20 carbon atoms.

► 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, non-vascular membrane that is closely attached to the outermost layer, the dura mater. The epidural space surrounds the dura mater sac.

► Postoperative Pain, Intrathecal Drug Administration

Archispinothalamic Tract

Definition

Part of the Paleo-spinothalamic tract, it is an intersegmental nerve fiber tract that travels for 2–4 segments.

► Parafascicular Nucleus, Pain Modulation

ARDS

Synonyms

Adult Respiratory Distress Syndrome

Definition

ARDS is a severe form of acute lung failure requiring mechanical ventilation.

► 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.

► Brainstem Subnucleus Reticularis Dorsalis Neuron

Area under the Curve

Synonyms

AUC

Definition

The area under the curve (AUC) is the integral of drug blood level over time from zero to infinity, and is a measure of the quantity of drug absorbed and in the body.

► NSAIDs, Pharmacokinetics

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.

► Spinothalamic Tract Neurons, Descending Control by Brainstem Neurons

Arterial Spasm

Definition

Arterial constriction, vasospasm.

► Primary Exertional Headache

Arthralgias

Definition

Neuralgic pain in a joint or joints.

► Animal Models of Inflammatory Bowel Disease

Arthritis

Definition

Arthritis is defined as inflammation of a joint, usually a synovial joint, which is characterized by specific features. Clinically, these features are often radiographic (that is, only detectable on radiograph) and include loss of bone in the joint, narrowing of the space between opposing bones in the joint, and thickening of the lining of the joint, the synovium. Histologically, features that are often present include inflammatory cell infiltrate, usually of monocytes, synovial hyperplasia and pannus formation, bone erosion and new bone formation, and in the more extreme situations, ankylosis of the joint.. The two most common forms of arthritis are osteoarthritis and rheumatoid arthritis. Osteoarthritis is a degenerative condition characterized by progressive loss of cartilage, leading to joint pain and loss of motion. Weight bearing joints, particularly the hips and knees, commonly used joints, and hands (distal and proximal interphalangeal joints), are the most commonly affected. Importantly, the pain of osteoarthritis is worse with use and better with rest, and most common in older adults. Rheumatoid arthritis is an inflammatory polyarthritis that involves peripheral joints in a symmetric distribution. Characteristic signs are morning stiffness and pain that improves with movement, with joint swelling and tenderness.

► 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 two 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 oedematous 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.

Behaviourally rats show weight loss, reduced mobility, increased vocalisation 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 localised 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).

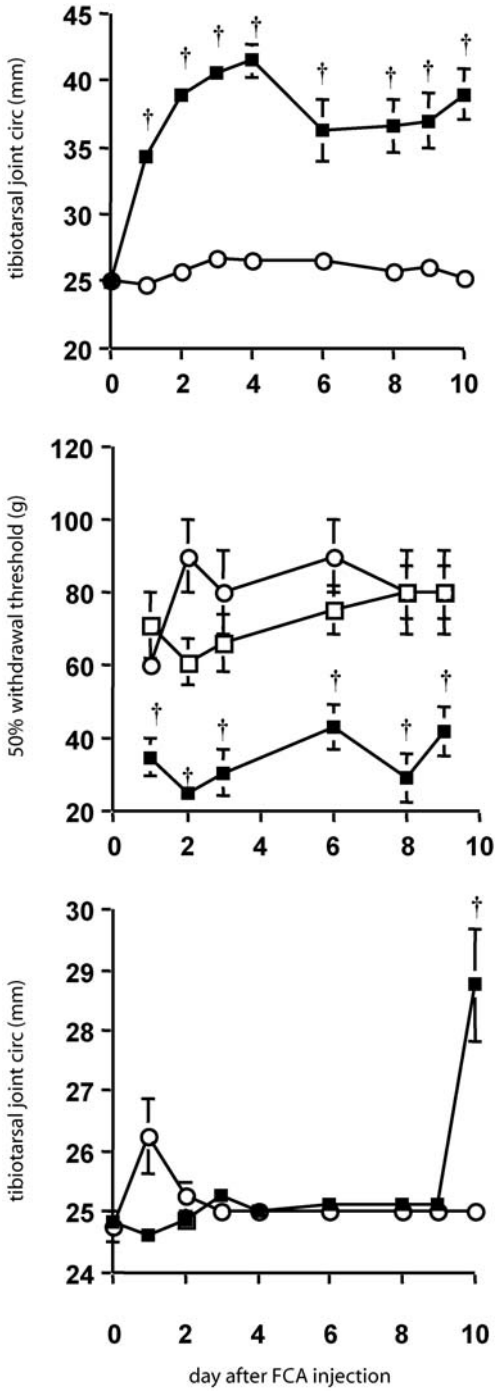
Modified Adjuvant-Induced Arthritis Models

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.

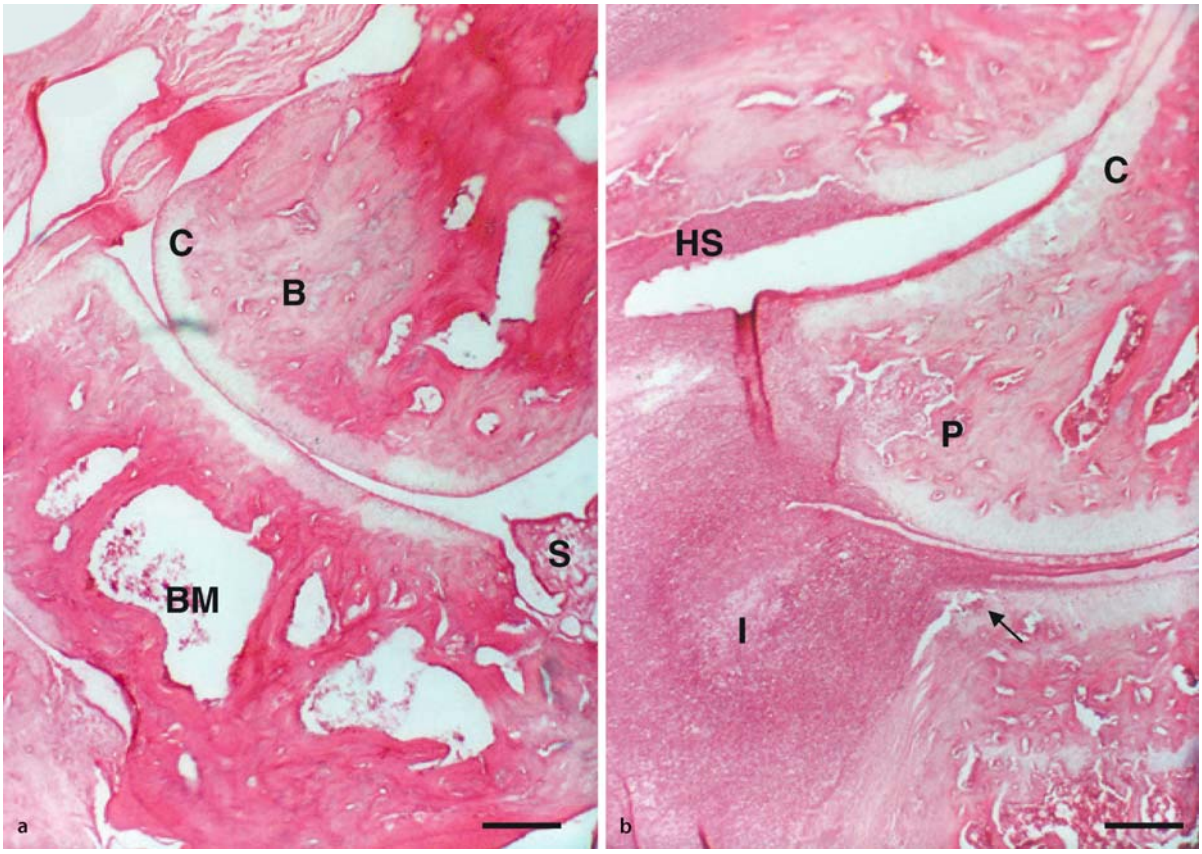
Injection of FCA into the skin around the tibiotarsal joint results in a reproducible arthritis after 14 days, which is maintained as a unilateral arthritis for at least 60 days post-injection (Donaldson et al. 1993). Gross features of this monoarthritis include tibiotarsal joint swelling, often resulting 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 behaviours, 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 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).



Arthritis Model, Adjuvant-Induced Arthritis, Figure 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 ($^{\dagger}p<0.001$).



Arthritis Model, Adjuvant-Induced Arthritis, Figure 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), 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 = 100μm.

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.

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 hypothesised 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 behavioural (pain behaviours) 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 immunisation. 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 hours), 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 versus 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.

References

1. Audibert F, Chedid L (1976) Adjuvant Disease Induced by Mycobacteria, Determinants of Arthritogenicity. Agents Actions 6:75–85
2. Butler SH, Godefroy F, Besson JM, Weil-Fugazza J (1992) A Limited Arthritic Model for Chronic Pain Studies in the Rat. Pain 48:73–81
3. Chillingworth NL, Donaldson LF (2003) Characterisation of a Freund's Complete Adjuvant-Induced Model of Chronic Arthritis in Mice. J Neurosci Meth 128:45-52
4. Colpaert FC, Meert T, De Witte P, Schmitt P (1982) Further Evidence Validating Adjuvant Arthritis as an Experimental Model of Chronic Pain in the Rat. Life Sci 31:67–75
5. De Castro Costa M, De Sutter P, Gybels J, Van Hees J (1981) Adjuvant-Induced Arthritis in Rats: A Possible Animal Model of Chronic Pain. Pain 10:73–185
6. Decaris E, Guingamp C, Chat M, Philippe L, Grillasca JP, Abid A, Minn A, Gillet P, Netter P, Terlain B (1999) Evidence for Neurogenic Transmission Inducing Degenerative Cartilage Damage Distant from Local Inflammation. Arthritis Rheum 42:1951–1960
7. Donaldson LF, McQueen DS, Seckl JR (1994) Endogenous Glucocorticoids and the Induction and Spread of Monoarthritis in the Rat. J Neuroendocrinol 6:649–654
8. Donaldson LF, McQueen DS, Seckl JR (1995) Neuropeptide Gene Expression and Capsaicin-Sensitive Primary Afferents: Maintenance and Spread of Adjuvant Arthritis in the Rat. J Physiol 486:473–482
9. Donaldson LF, Seckl JR, McQueen DS (1993) A Discrete Adjuvant-Induced Monoarthritis in the Rat: Effects of Adjuvant Dose. J Neurosci Methods 49:5–10
10. Gauldie SD, McQueen DS, Clarke CJ, Chessell IP (2004) A robust model of adjuvant-induced chronic unilateral arthritis in two mouse strains. J Neurosci Meth 139(2):281-29
11. Hood VC, Cruwys SC, Urban L, Kidd BL (2001) The Neurogenic Contribution to Synovial Leucocyte Infiltration and Other Outcome Measures in a Guinea Pig Model of Arthritis. Neurosci Lett 299:201–204
12. Larson AA, Brown DR, el-Atrash S, Walser MM (1986) Pain Threshold Changes in Adjuvant-Induced Inflammation: A Possible Model of Chronic Pain in the Mouse. Pharmacol Biochem Behav 24:49–53
13. Pearson CM, Wood FD (1959) Studies of Polyarthritis and Other Lesions in Rats by Injection of Mycobacterial Adjuvant. I. General Clinical and Pathological Characteristics and some Modifying Factors. Arthritis Rheum 2:440–45
14. Pettipher ER, Henderson B (1988) The Relationship between Cell-Mediated Immunity and Cartilage Degradation in Antigen-Induced Arthritis in the Rabbit. Br J Exp Pathol 69:113–122
15. Rainsford KD (1982) Adjuvant Polyarthritis in Rats: Is this a Satisfactory Model for Screening Anti-Arthritic Drugs? Agents Actions 12:452–458.
16. Ratkay LG, Tait B, Tonzetich J, Waterfield JD (1994) Lpr and MRL Background Gene Involvement in the Control of Adjuvant Enhanced Arthritis in MRL-lpr Mice. J Autoimmun 7:561–573
17. Sarlis NJ, Chowdrey HS, Stephanou A, Lightman SL (1992) Chronic Activation of the Hypothalamo-Pituitary-Adrenal Axis and Loss of Circadian Rhythm During Adjuvant-Induced Arthritis in the Rat. Endocrinology 130:1775–1779
18. van Eden W, Holoshitz J, Nevo Z, Frenkel A, Klajman A, Cohen IR (1985) Arthritis Induced by a T-Lymphocyte Clone that Responds to Mycobacterium Tuberculosis and to Cartilage Proteoglycans. Proc Natl Acad Sci USA 82:511701–5120
19. Wakesman BH, Pearson CM, Sharp JT (1960) Studies of Arthritis and other Lesions Induced in Rats by Injection of Mycobacte-

rial Adjuvant. II. Evidence that the Disease is a Disseminated Immunologic Response to Exogenous Antigen. Proc Natl Acad Sci USA 85:403–417

Arthritis Model, Kaolin-Carrageenan Induced Arthritis (Knee)

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Synonyms

Kaolin-Carrageenan induced arthritis; K/C Arthritis; Acute Experimental Monoarthritis; Acute Knee Joint Inflammation; Acute Experimental Synovitis

Definition

Aseptic inflammatory monoarthritis induced by injections of kaolin and carrageenan into the synovial cavity of one knee joint, resulting 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) and mice (Zhang et al. 2001) to study pain mechanisms in the peripheral and central nervous system. The K/C arthritis 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.

Induction of Arthritis

This experimental arthritis is induced in one knee by intraarticular injections of kaolin and carrageenan into the one 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 intraarticular 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.

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 are injected intraarticularly, 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).

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).

Rat

Kaolin and carrageenan are injected either sequentially or together according to the following protocols: 1) 80–100 µl of a 4% kaolin suspension are 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 are 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 are injected into one knee joint.

Histopathology

The intraarticular 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 intraarticular pressure, hyperthermia of the knee, and edema with marked cellular infiltration (polymorphnuclear leucocytes) (Schaible and Grubb 1993; Schaible et al. 2002; Sluka and Westlund 1993).

Pain Behavior

The K/C arthritis 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. Whereas in the acute stage of the K/C arthritis evoked pain behavior is strictly unilateral, secondary allodynia and hyperalgesia can occur bilaterally in the more chronic phase (> 1 week).

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 intraarticular pressure
- Increased temperature of arthritic (but not contralateral) knee
- Cellular infiltration (neutrophils)

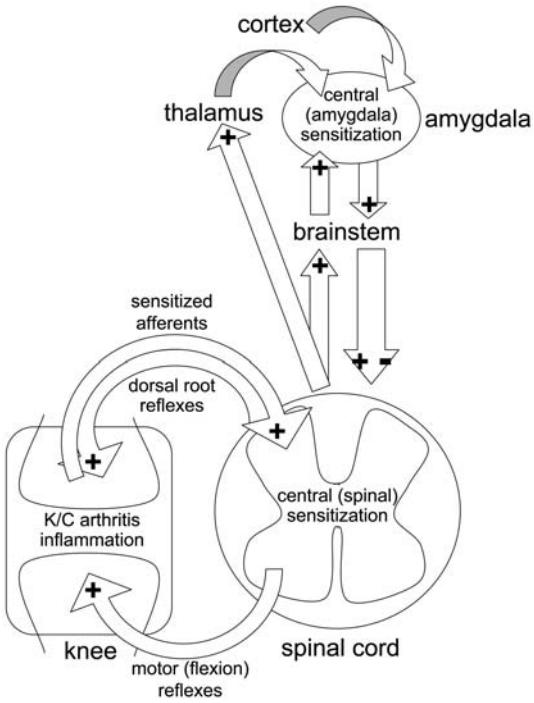
Pain Behavior

- 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)



Arthritis Model, Kaolin-Carrageenan Induced Arthritis (Knee), Figure 1 Peripheral and central pain mechanisms in the K/C arthritis model. The 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 (plasticity in other brain areas has not yet been analyzed in the K/C model) and enhanced descending control of spinal nociceptive processing.

- **Spinal Cord**

EAA (Glutamate, glutamine, aspartate)
NO metabolites (citrulline)
Substance P
NKA
Calcitonin gene-related peptide (CGRP)
Prostaglandins (PGE2)

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, non-responsive types)

- **Brainstem/Brain**

Increased descending inhibition and facilitation
Sensitization of neurons in the central nucleus of the amygdala (multi-receptive and non-responsive but not nociceptive-specific)

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, Nicotinic cholinergic receptor
Inhibitory: $GABA_A$ (but not $GABA_B$) receptor

- **Amygdala**

Excitatory: NMDA receptor (but not non-NMDA receptor), Metabotropic glutamate receptor (mGluR) group I, II and III

Peripheral Sensitization

Physical (increased intraarticular pressure; increased temperature) and chemical (low pH, inflammatory mediators, peptides, and amino acids) factors lead to the enhanced excitability and responsiveness of articular afferent nerve fibers to mechanical and chemical stimuli (sensitization). 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 normally ► Innocuous Input/Stimulus compression (see ► innocuous input/stimulus) 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 for 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 postsynaptic 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 negatively 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: multi-receptive neurons (comparable to spinal wide-dynamic-range neurons) and non-responsive 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). 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, 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. Pain-related plasticity in these areas, however, remains to be studied in the K/C arthritis model.

References

1. Coggeshall RE, Hong KA, Langford LA et al. (1983) Discharge Characteristics of Fine Medial Articular Afferents at Rest and during Passive Movements of Inflamed Knee Joints. Brain Res 272:185–188
2. Dougherty PM, Sluka KA, Sorkin LS et al. (1992) Neural Changes in Acute Arthritis in Monkeys. I. Parallel Enhancement of Responses of Spinothalamic Tract Neurons to Mechanical Stimulation and Excitatory Amino Acids. Brain Res Rev 55:1–13
3. Lawand NB, McNearney T, Westlund KN (2000) Amino Acid Release into the Knee Joint: Key Role in Nociception and Inflammation. Pain 86:69–74
4. Neugebauer V, Li W (2003) Differential Sensitization of Amygdala Neurons to Afferent Inputs in a Model of Arthritic Pain. J Neurophysiol 89:716–727
5. Neugebauer V, Li W, Bird GC et al. (2003) Synaptic Plasticity in the Amygdala in a Model of Arthritic Pain: Differential Roles of Metabotropic Glutamate Receptors 1 and 5. J Neurosci 23:52–63
6. Neugebauer V, Lucke T, Schaible H-G (1993) N-methyl-D-aspartate (NMDA) and Non-NMDA Receptor Antagonists Block the Hyperexcitability of Dorsal Horn Neurons during Development of Acute Arthritis in Rat's Knee Joint. J Neurophysiol 70:1365–1377
7. Schaible H-G, Grubb B (1993) Afferent and Spinal Mechanisms of Joint Pain. Pain 55:5–54
8. Schaible H-G, Ebersberger A, von Banchet GS (2002) Mechanisms of Pain in Arthritis. Ann N Y Acad Sci 966:343–354
9. Sluka KA (1996) Pain Mechanisms Involved in Musculoskeletal Disorders. J Orthop Sports Phys Ther 24:240–254
10. Sluka KA, Rees H, Westlund KN et al. (1995) Fiber Types Contributing to Dorsal Root Reflexes Induced by Joint Inflammation in Cats and Monkeys. J Neurophysiol 74:981–989
11. Sluka KA, Westlund KN (1993) Behavioral and Immunohistochemical Changes in an Experimental Arthritis Model in Rats. Pain 55:367–377
12. Urban MO, Zahn PK, Gebhart GF (1999) Descending Facilitatory Influences from the Rostral Medial Medulla Mediate Secondary, but not Primary Hyperalgesia in the Rat. Neurosci 90:349–352
13. Yang LC, Marsala M, Yaksh TL (1996) Characterization of Time Course of Spinal Amino Acids, Citrulline and PGE_2 Release after Carrageenan/Kaolin-Induced Knee Joint Inflammation: A Chronic Microdialysis Study. Pain 67:345–354
14. Yu YC, Koo ST, Kim CH et al. (2002) Two Variables that can be used as Pain Indices in Experimental Animal Models of Arthritis. J Neurosci Methods 115:107–113
15. Zhang L, Hoff AO, Wimalawansa SJ et al. (2001) Arthritic Calcitonin/[alpha] Calcitonin Gene-Related Peptide Knockout Mice have Reduced Nociceptive Hypersensitivity. Pain 89:265–273

Arthritis Model, Osteoarthritis

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Synonyms

Degenerative Joint Disease; Arthritis; 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.

Characteristics

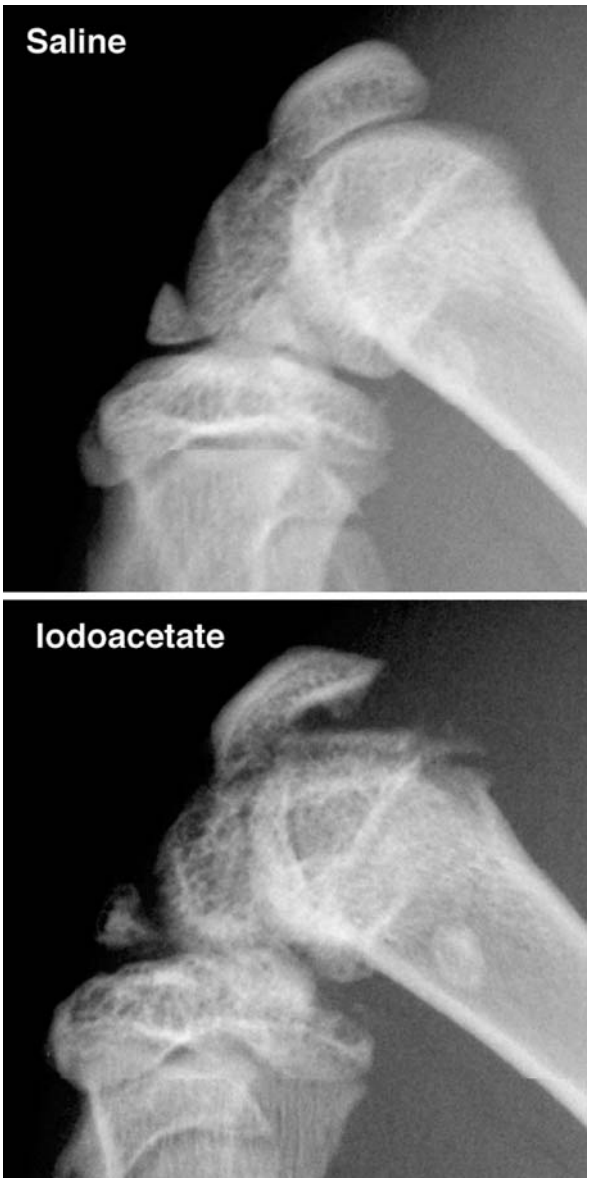
Osteoarthritis (OA) and other degenerative joint diseases affect almost one third of all adults, equaling nearly 70 million adults in the United States and 34 million adults in Europe. It is the leading cause of disability in the United States. The most important risk factor for OA is age (Elders 2000), and as the aging population is dramatically increasing, the prevalence of the disease is likewise expected to increase. OA is distinct from rheumatoid arthritis, which is a systemic inflammatory disease, and is much less prevalent.

OA is frequently associated with severe pain, but the sources of this pain are not fully understood, which has presented many obstacles for its treatment and the development of novel therapies. The generation and maintenance of OA-related pain is so poorly understood largely because OA itself is not a single disease entity, but rather a group of diseases with different origins that share a common pathology. This pathology is characterized by damage of the cartilage in synovial joints, alterations in the physiology of ► chondrocytes, and profound changes in the ► subchondral bone including sclerosis, cyst formation, and the formation of bony spurs beneath the affected cartilage. 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). Aside from the radiological evidence for the presence of the disease, the main symptom of the disease is pain, in particular, pain associated with use of the affected joint. Current treatment for OA–related pain can be divided

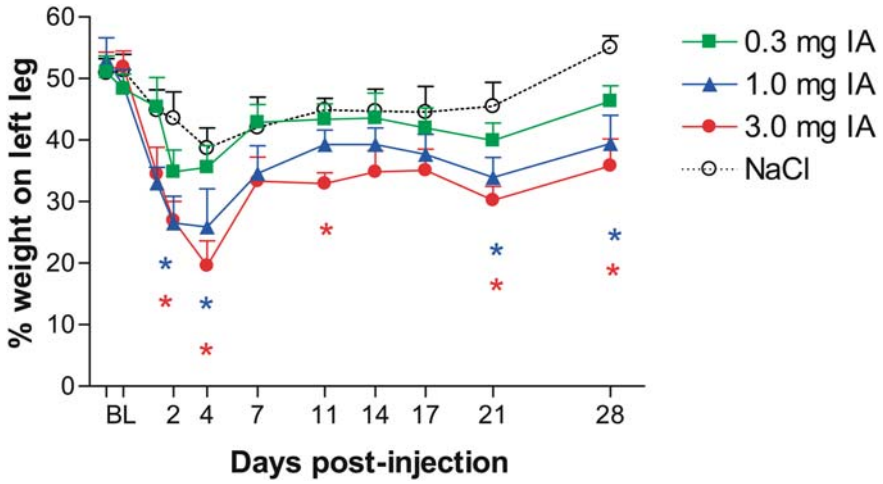
into three categories: physical/occupational therapy and devices, pharmacological treatment, and surgical intervention. The use of physical therapy can maintain muscle strength around the joint and can assist by increasing joint stability. Therapeutic intervention is most commonly achieved by using ► NSAIDs, Survey (NSAIDs). Although these drugs have been shown clinically to provide pain relief in OA patients, this pain relief is often incomplete (Altman et al. 2000), and they are often accompanied by unwanted side effects including the induction of ulcers (Scheiman 2003). However, the relatively recent development of selective ► Cyclooxygenase-2 Inhibitors such as rofecoxib and celecoxib, has led to equal or superior pain relief with a lower incidence of gastrointestinal toxicity (Scheiman 2003). Other pharmacological therapies include injections of steroids or high molecular weight hyaluronate into the affected joints. Finally, surgical intervention has grown rapidly over the past 25 years, but is only considered when the pain associated with OA has become intractable.

Several animal models of OA have been developed over the years. Just as OA itself has multiple distinct origins, different types of animal models have been developed. These animal models can be broadly classified as one of three types. The first type is a 'chemical' model of osteoarthritis and will be the focus of this chapter. Briefly, chemical models involve injection of one of a number of substances into a joint (typically the knee), which ultimately results in perturbations of the cartilage of the joint. The second type of model is a surgical model and mimics OA that develops secondary to an injury. These models typically involve severing one or more ligaments in the knee, but can also involve damaging the ► meniscus. The third type of model involves specific strains of mice or other animals that are prone to spontaneously develop OA. Each type of model has its own benefits and limitations, but like the human disease shares a similar pathology, namely damage to the cartilage and subchondral bone.

Initial studies using these models focused primarily on the biological processes that mediate the development of the disease, but they rarely addressed the pain associated with the disease. As the pain associated with OA significantly decreases the quality of life for OA sufferers, treatment of this pain has become of significant interest to the research community. Thus, these models have become the subject of recent investigation for studying the potential of novel therapeutics for OA–related pain. The monosodium iodoacetate (MIA) model in particular has received considerable attention for studying OA related pain. MIA is a metabolic inhibitor that blocks the activity of glyceraldehyde–3–phosphate dehydrogenase, preventing ► glycolysis. This inhibition ultimately leads to the death of the affected cells. When injected into a joint space, MIA preferentially acts on chondrocytes, causing damage to the cartilage of the joint. As the cartilage that normally protects the underlying bone is destroyed, subsequent damage to this bony tissue occurs, and a pathology similar to that seen in humans develops. This is evident by histological analysis showing significant loss of cartilage and death of chondrocytes as well as alterations in the subchondral bone, and infiltration of inflammatory cells (van der Kraan et al. 1989; Guingamp et al. 1997; Guzman et al. 2003). The pathology is also evident when the knee joint is visualized using x-rays, which show severe damage to the bones in the knee joint (Fig. 1). Similarly, injection of MIA results in a concentration-dependent decrease in bone mineral



Arthritis Model, Osteoarthritis, Figure 1 Radiograph showing the effect of iodoacetate on the bones of the rat knee joint. Injection of 3 mg iodoacetate (bottom panel) leads to profound deformation of the bones relative to saline-injected control of the knee joint (top 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.



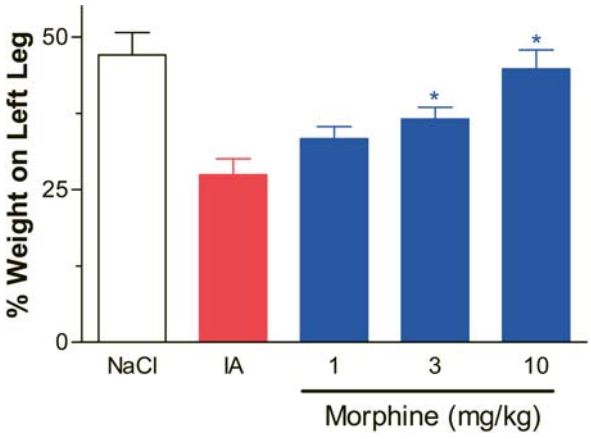
Arthritis Model, Osteoarthritis, Figure 2 Injection of iodoacetate (IA) into the left knee of male rats leads to a concentration dependent alteration in hind limb weight bearing, indicative of joint pain. Note the biphasic nature of the response, and the critical late phase that begins around day 11, and does not appear to resolve. Asterisks denote significant differences between treatment groups for the respective colors compared to saline (NaCl)–injected control rats.

density in the affected joint (Pomonis et al. 2005) and marked joint swelling (Fernihough et al. 2004).

Although the MIA model of OA has been used for some time to study the pathology associated with the model, its use to study pain associated with OA has only recently been investigated. Injection of MIA results in a concentration-dependent decrease in spontaneous activity in rats (Guingamp et al. 1997). However, this study did not investigate whether compounds that are known to provide pain relief altered these behaviors, and as such, it was unclear whether the decreased activity actually reflected the pain associated with the disease. Subsequent advances in behavioral assessment more conclusively demonstrated the utility of the MIA model for studying OA–associated pain. Several investigators have begun to measure hind limb weight bearing (WB) as a measure of OA–associated pain in rats. This technique simultaneously measures the weight borne by each hind limb of a rat. Rats with experimentally-induced OA show profound alterations in WB in a concentration-dependent manner (Bove et al. 2003; Kobayashi et al. 2003; Pomonis et al. 2005). As shown in Figure 2, the alterations in WB are biphasic in nature, with an intense acute phase that lasts approximately 4 days, followed by a period of restored WB. Eventually, a chronic phase of altered WB emerges that does not appear to resolve (Pomonis et al. 2005).

The alterations in WB can be reversed upon administration of pain relieving agents such as morphine (Fernihough et al. 2004; Pomonis et al. 2005), acetaminophen, naproxen, rofecoxib (Bove et al. 2003), and celecoxib (Pomonis et al. 2005). The reversal of the MIA–induced alterations in WB is important, as it demonstrates that these behaviors are pain-related (and do not simply reflect alterations in joint stability). This also indicates that this technique is amenable to testing novel therapeutic agents for the treatment of OA–associated pain. Assessment of altered WB has not been the only reported pain behaviors observed in the MIA model, as mechanical hypersensitivity has been reported in the corresponding hind paw (Fernihough et al. 2004), although these behaviors have not been observed by all experimenters (Pomonis et al. 2005).

Measurement of alterations in WB has also allowed other experimental models of OA to be examined for pain behaviors. Surgical transection of the meniscus leads to alterations in WB and mechanical hypersensitivity, but to a lesser extent than what is seen with MIA injection, despite similar changes in joint pathology (Fernihough et al. 2004). Intra-articular injection of papain (a protease derived from papaya) leads to concentration-dependent alterations in WB, but the alterations are relatively short-lasting and not as robust as those seen with injection of MIA (Pomonis et al. 2005). While the implications of the differences in pain behaviors in the various models of OA are not completely clear, it appears that several factors including the



Arthritis Model, Osteoarthritis, Figure 3 Morphine reverses pain associated with experimental osteoarthritis. Twenty one days after an injection of 1 mg iodoacetate (IA), rats received a single dose of morphine or vehicle, and hind limb weight bearing was assessed one hour later. Asterisks denote that the 3 and 10 mg/kg doses of morphine produced significant reversal of IA-induced pain. Adapted from Pomonis et al. (2005).

region of damage to the joint, the source of pathology, and the extent of the pathology can all have profound effects on the subsequent pain behaviors. This suggests that there may be distinct mechanisms responsible for the generation and maintenance of OA–associated pain, and that considerable work will need to be done to more fully understand these mechanisms.

References

1. Altma R, Hochberg M, Moskowitcz RW, Schnitzer TJ (2000) Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee: 2000 Update. Arthritis and Rheumatism 43:1905–1915
2. Bove S, Calcaterra S et al. (2003) Weight Bearing as a Measure of Disease Progression and Efficacy of Anti-Inflammatory Compounds in a Model of Monosodium Iodoacetate-Induced Osteoarthritis. Osteoarthritis and Cartilage 11:821–830
3. Cushnaghan J, Cooper C et al. (1990) Clinical Assessment of Osteoarthritis of the Knee. Annals of the Rheumatic Diseases 49:768–770
4. Elders MJ (2000) The Increasing Impact of Arthritis on Public Health. J Rheumatol 60:6–8
5. Fernihough J, Gentry C et al. (2004) Pain Related Behaviour in Two Models of Osteoarthritis in the Rat Knee. Pain 112:83–93
6. Guingamp C, Gefout-Pottie P et al. (1997) Mono-Iodoacetate-Induced Experimental Osteoarthritis: A Dose-Response Study of Loss of Mobility, Morphology, and Biochemistry. Arthritis and Rheumatism 40:1670–1679
7. Guzman R, Evans M et al. (2003) Mono-Iodoacetate-Induced Histologic Changes in Subchondral Bone and Articular Cartilage of Rat Femorotibial Joints: An Animal Model of Osteoarthritis. Toxicologic Pathology 31:619–624
8. Kobayashi K, Imaizumi R et al. (2003) Sodium Iodoacetate-Induced Experimental Osteoarthritis and Associated Pain Model in Rats. J Vet Med Sci 65(11):1195–1199
9. Pomonis JD, Boulet J et al. (2005) Development and Pharmacological Characterization of a Rat Model of Osteoarthritis Pain. Pain: 114:339–346
10. Scheiman JM (2003) Gastroduodenal Safety of Cyclooxygenase-2 Inhibitors. Current Pharmaceutical Design 9:2197–206
11. van der Kraan P, Vitters E et al. (1989) Development of Osteoarthritic Lesions in Mice by "Metabolic" and "Mechanical" Alterations in the Knee Joints. Am J Pathol 135:1001–1014

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.

► 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, 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 either classified 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 19th 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 20th 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; Hildebrand 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 1200, 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 (Hildebrand 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 arthritis caused significant upregulation of the number of CGRP - but not SP-positive neurons (Hanesch et al. 1997). 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, while in 10% of afferents these two neuropeptides seemed to be colocalized (Tamura et al. 1998).

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, Heppelmann 1997). In this paragraph general ultrastuctural 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. 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. 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.

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 cat 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, whilst 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. It has been hypothesized that the sensitivity of fine sensory receptors is reflected by the number of energy-providing mitochondria within the sensory axons, which is significantly different between individual sensory group III endings (Heppelmann et al. 1994).

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 6 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.

References

1. Andres KH, von Düring M. (1973) Morphology of Cutaneous Receptors. In: Iggo A (ed) Handbook of Sensory Physiology, vol 2, Somatosensory System. Springer, Berlin, pp 3–28
2. Ebinger M, Schmidt RF, Heppelmann B (2001) Composition of the Medial and Posterior Articular Nerves of the Mouse Knee Joint. Somatosens Mot Res 18:62–65
3. Freeman MAR, Wyke B (1967) The Innervation of the Knee Joint. An Anatomical and Histological Study in the Cat. J Anat 101:505–532
4. Halata Z, Rettig T, Schulze W (1985) The Ultrastructure of Sensory Nerve Endings in the Human Knee Joint Capsule. Anat Embryol 172:265–275
5. Hanesch U, Heppelmann B, Schmidt RF (1991) Substance P- and Calcitonin Gene-Related Peptide Immunoreactivity in Primary Afferent Neurons of the Cat's Knee Joint. Neuroscience 45:185–193
6. Hanesch U, Heppelmann B, Schmidt RF (1995) Somatostatin-Like Immunoreactivity in Primary Afferents of the Medial Articular Nerve and Colocalization with Substance P in the Cat. J Comp Neurol 354:345–352
7. Hanesch U, Heppelmann B, Schmidt RF (1997) Quantification of Cat's Articular Afferents Containing Calcitonin Gene-Related Peptide or Substance P Innervating Normal and Acutely Inflamed Knee Joint. Neurosci Lett 233:105–108
8. Heppelmann B (1997) Anatomy and Histology of Joint Innervation. J Peripher Nerv Syst 2:5–16
9. Heppelmann B, Heuss C, Schmidt RF (1988) Fiber Size Distribution of Myelinated and Unmyelinated Axons in the Medial and Posterior Articular Nerves of the Cat's Knee Joint. Somatosens Res 5:273–281
10. Heppelmann B, Messlinger K, Neiss WF et al. (1990) Ultrastructural Three-Dimensional Reconstruction of Group III and Group IV Sensory Nerve Endings ("Free Nerve Endings") in the Knee Joint Capsule of the Cat: Evidence for Multiple Receptive Sites. J Comp Neurol 292:103–116
11. Heppelmann B, Messlinger K, Neiss WF et al. (1994) Mitochondria in Fine Afferent Nerve Fibres of the Knee Joint in the Cat: A Quantitative Electron-Microscopical Examination. Cell Tissue Res 275:493–501
12. Heppelmann B, Messlinger K, Neiss WF et al. (1995) Fine Sensory Innervation of the Knee Joint Capsule by Group III and Group IV Nerve Fibers in the Cat. J Comp Neurol 351:415–428
13. Hildebrandt C, Oqvist G, Brax L et al. (1991) Anatomy of the Rat Knee Joint and Fibre Composition of a Major Articular Nerve. Anat Rec 229:545–555
14. Hinsey JC (1927) Some Observations on the Innervation of Skeletal Muscle of the Cat. J Comp Neurol 44:87–195
15. Langford LA, Schmidt RF (1983) Afferent and Efferent Axons in the Medial and Posterior Articular Nerves of the Cat. Anat Rec 206:71–78
16. Messlinger K, Pawlak M, Steinbach H et al. (1995) A New Combination of Methods for Localization, Identification, and Three-

Dimensional Reconstruction of the Sensory Endings of Articular Afferents Characterized by Electrophysiology. Cell Tissue Res 281: 283–294
17. Messlinger K (1996) Functional Morphology of Nociceptive and other Fine Sensory Endings ("Free Nerve Endings") in Different Tissues. In: Kumazawa T, Kruger L, Mizumura K (eds) The Polymodal Receptor – a Gateway to Pathological Pain – Progress in Brain Research, vol 113. Elsevier, Amsterdam, pp 273–298
18. Salo PT, Theriault E (1997) Number, Distribution and Neuropeptide Content of Rat Knee Joint Afferents. J Anat 190:515–522
19. Tamura R, Hanesch U, Schmidt RF et al. (1998) Examination of Colocalization of Calcitonin Gene-Related Peptide- and Substance P-Like Immunoreactivity in the Knee Joint of the Dog. Neurosci Lett 254:53–56
20. Weddell G, Harpman JA (1940) The Neurohistological Basis for the Sensation of Pain Provoked from Deep Fascia, Tendon, and Periosteum. J Neurol Neurosurg Psychiat 3:319–328
21. Zimny ML (1988) Mechanoreceptors in Articular Tissues. Am J Anat 182:16–32

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.

Characteristics

Pain in Joints

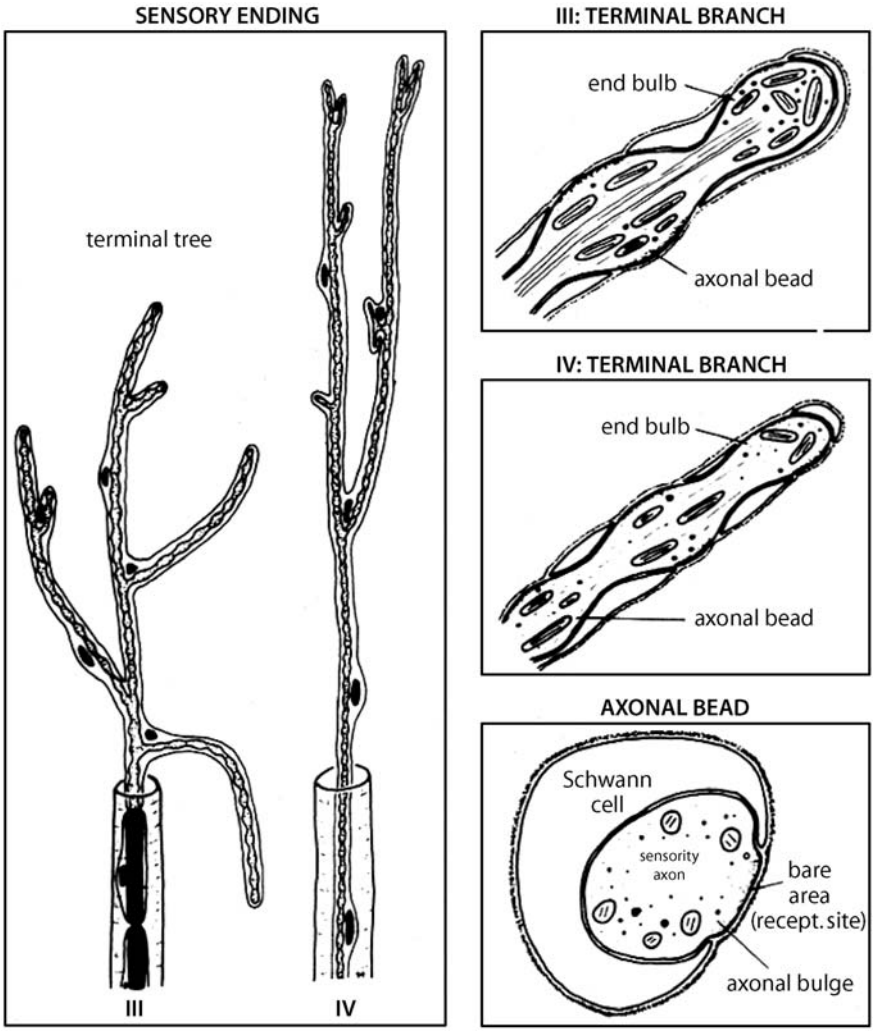
Pain in a normal joint is commonly elicited by twisting or hitting the joint. In conscious humans, pain in the normal joint can be elicited when noxious mechanical or chemical stimuli are applied to the fibrous structures, such as ligaments and fibrous capsule. No pain is elicited by stimulation of cartilage. Stimulation of normal synovial tissue rarely evokes pain. Stimulation of fibrous structures with innocuous mechanical stimulation can evoke pressure sensations.
Joint inflammation 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 2005).

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) fibres. The latter are either sensory afferents or sympathetic efferents (each ~ 50%). While Aβ fibres 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 fibres are nociceptive. Aδ and C fibres terminate as unencapsulated ("free") nerve endings in the fibrous capsule, adipose tissue, ligaments, menisci, and the periosteum. Using staining for nerve fibres 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 and Grubb 1993; Schaible 2005).
Figure 1 shows the reconstruction of peripheral nerve endings of joint afferents of cat's knee joint. Typical 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 fibres (Heppelmann et al. 1990).

Mechanosensitivity of Joint Afferents

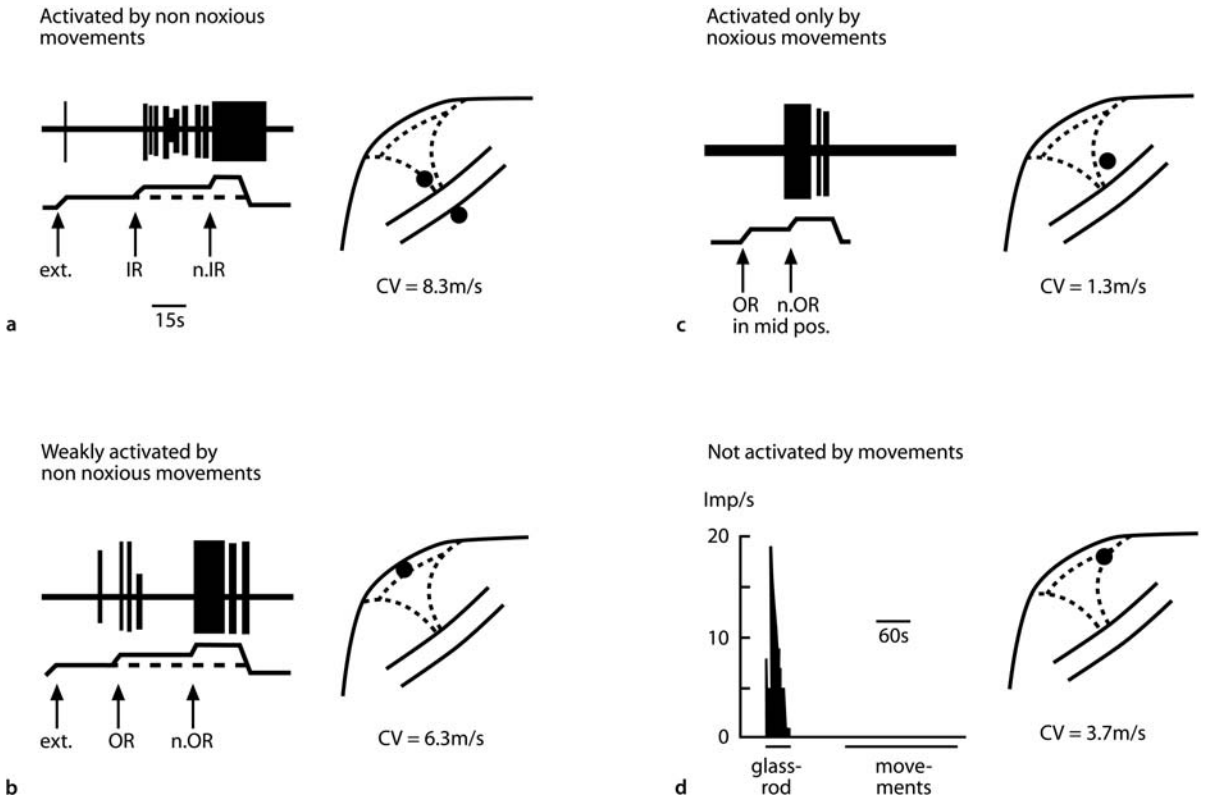
Joint afferents have been mainly recorded in articular nerves supplying cat knee and rat knee and ankle joints. They were characterized by their responses to innocuous and noxious mechanical stimuli. Light to moderate pressure applied to the joint, and movements within the working range of the joint, 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 (Schaible and Schmidt 1983a; Schaible and Schmidt 1983b).
Figure 2 shows four typical joint afferents of cat's knee joint with different sensitivities to movements. Figure 2a displays a low threshold Aδ fibre. This fibre 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 fibre was thus activated by innocuous movements, i.e. the threshold was in the innocuous range. However, the 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 fibres in the fibrous capsule and in ligaments, including the anterior cruciate ligament.



Articular Nociceptors, Figure 1 Schematic drawings of a group III (Aδ) and group IV (C) fibre 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).

Although these units have their 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 fibre types shown in Figure 2 respond mainly or exclusively to noxious mechanical stimuli. Figure 2b shows an Aδ fibre with a receptive field in the patellar ligament (dot). This unit responded weakly, with only a few spikes during outward rotation in the working range (OR), but it had a strong response to noxious outward rotation (n.OR). The C fibre in Figure 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 also require high pressure intensity to elicit a response by probing the receptive field. Figure 2D displays an Aδ fibre 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 Figure 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 conditions no receptive field is found, and no response is elicited by innocuous or 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. It is estimated that about one third of the sensory C fibres and a small proportion of Aδ fibres 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



Articular Nociceptors, Figure 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).

many more silent nociceptors than the medial articular nerve.

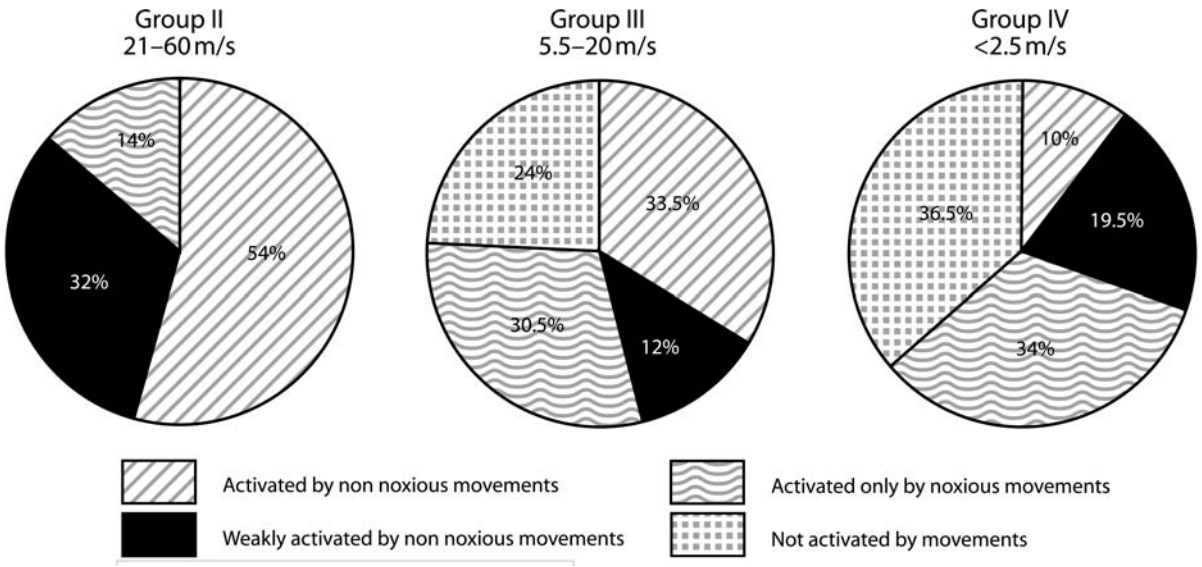
Figure 3 displays the medial articular nerve of cat's knee joint, and the proportions of Aβ, Aδ and C fibres in the categories defined in Figure 2. Only those neurons that had a detectable receptive field, and that were activated by innocuous and/or noxious mechanical stimuli applied to the normal joint (initially mechanoinsensitive sensory neurons are not included) are included. It is shown that most Aβ fibres were either strongly or weakly activated by innocuous stimuli. More than 50% of the Aδ fibres and about 70% of the sensory C fibres were classified as high threshold units (Schaible and Grubb 1993; Schaible 2005).

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 fibres show increased responses to movements in the working range. Most strikingly, a large proportion of high threshold afferents (see Figs. 2c and d) are sensitized, such that they respond to movements in the working range of the joint (Schaible and Schmidt 1985). Increased mechanosensitivity has also been found 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). Furthermore, initially mechanoinsensitive afferents (silent nociceptors) are sensitized and become mechanosensitive (Schaible and Schmidt 1988). Thus, silent nociceptors are recruited for the encoding of noxious events during an inflammatory process.

Chemosensitivity of Joint Afferents

The vast majority of sensory Aδ and C fibres in the joint nerve are chemosensitive for endogenous compounds that are produced and released during pathophysiological conditions. Mediators are able to excite and/or sensitize primary afferent neurons for mechanical stimuli and for chemical stimuli. These mediators also usually produce vascular and other changes in the tissue (i.e. they contribute to the inflammatory process itself). Concerning chemosensitivity, the following aspects should be noted: first, these mediators only affect Aδ and C fibres of the joint nerve, not Aβ fibres, second, an effect is typically elicited only in subpopulations of the articular units (i.e. not all units express the full range of



Articular Nociceptors, Figure 3 Mechanosensitivity of primary afferent neurons supplying normal cat's knee joint. The graph shows the proportions of Aβ, Aδ, and C fibres in the different sensitivity classes. From Schaible and Grubb (1993).

chemosensitivity), and 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 2005).

Effects of mediators can be described as follows. Some mediators can induce firing of neurons and/or an increase of their responses to movements. Such effects have been observed for bradykinin, prostaglandins E_2 and I_2, and serotonin. However, after bolus injections of the compounds into the joint artery, differences in the pattern of effects were noted. The excitatory effect of bradykinin on joint afferents is short (less than 1 min), whereas the sensitization for mechanical stimuli of joint afferents lasts minutes, even when 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, whereas 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, regardless of whether 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. Serotonin also sensitizes Aδ and C fibres of the joint nerve to excitation by mechanical stimuli (Schaible and Grubb 1993; Schaible 2005). Excitation of articular afferents has also been observed following administration of capsaicin, ATP and adenosine (Dowd et al. 1998a; Dowd et al. 1998b). Effects have also been found for neuropeptides. While substance P increased (Herbert and Schmidt 2001) and somatostatin reduced mechanosensitivity in numerous afferents (Heppelmann and Pawlak 1997), the peptides galanin (Heppelmann et al. 2000), neuropeptide Y (Just et al. 2001), and nociceptin (McDougall et al. 2000) sensitized some neurons and reduced responses in other neurons. Whether the different patterns of peptide effects (excitation or inhibition) are dependent on the functional state of the neuron is not known at the moment. In general, it was proposed that the simultaneous presence of different neuropeptides regulates excitability of the afferent fibres.

References

1. Dowd E, McQueen DS, Chessell IP, Humphrey PPA (1998a) P2X Receptor-Mediated Excitation of Nociceptive Afferents in the Normal and Arthritic Rat Knee Joint. Br J Pharmacol 125:341–346
2. Dowd E, McQueen DS, Chessell IP, Humphrey PPA (1998b) Adenosine A1 Receptor-Mediated Excitation of Nociceptive Afferents Innervating the Normal and Arthritic Rat Knee Joint. Br J Pharmacol 125:1267–1271
3. Guilbaud G, Iggo A, Tegner R (1985) Sensory Receptors in Ankle Joint Capsules of Normal and Arthritic Rats. Exp Brain Res 58:29–40
4. Heppelmann B, Messlinger K, Neiss W, Schmidt RF (1990) Ultrastructural Three-Dimensional Reconstruction of Group III and Group IV Sensory Nerve Endings (Free Nerve Endings) in the Knee Joint Capsule of the Rat: Evidence for Multiple Receptive Sites. J Comp Neurol 292:103–116
5. Heppelmann B, Just S, Pawlak M (2000) Galanin Influences the Mechanosensitivity of Sensory Endings in the Rat Knee Joint. Eur J Neurosci 12:1567–1572
6. Heppelmann B, Pawlak M (1997) Inhibitory Effect of Somatostatin on the Mechanosensitivity of Articular Afferents in Normal and Inflamed Knee Joints of the Rat. Pain 73:377–382
7. Herbert MK, Schmidt RF (2001) Sensitisation of Group III Articular Afferents to Mechanical Stimuli by Substance P. Inflamm Res 50:275–282

8. Just S, Heppelmann B (2001) Neuropeptide Y Changes the Excitability of Fine Afferent Units in the Rat Knee Joint. Br J Pharmacol 132:703–708
9. McDougall JJ, Pawlak M, Hanesch U, Schmidt RF (2000) Peripheral Modulation of Rat Knee Joint Afferent Mechanosensitivity by Nociceptin/Orphanin FQ. Neurosci Lett 288:123–126
10. Schaible H-G (2005) Basic Mechanisms of Deep Somatic Pain. In: McMahon SB, Koltzenburg M (eds) Textbook of Pain (in press)
11. Schaible H-G, Grubb BD (1993) Afferent and Spinal Mechanisms of Joint Pain. Pain 55:5–54
12. Schaible H-G, Schmidt RF (1983a) Activation of Groups III and IV Sensory Units in Medial Articular Nerve by Local Mechanical Stimulation of Knee Joint. J Neurophysiol 49:35–44
13. Schaible H-G, Schmidt RF (1983b) Responses of Fine Medial Articular Nerve Afferents to Passive Movements of Knee Joint. J Neurophysiol 49:1118–1126
14. Schaible H-G, Schmidt RF (1985) Effects of an Experimental Arthritis on the Sensory Properties of Fine Articular Afferent Units. J Neurophysiol 54:1109–1122
15. Schaible H-G, Schmidt RF (1988) Time Course of Mechanosensitivity Changes in Articular Afferents during a Developing Experimental Arthritis. J Neurophysiol 60:2180–2195

Articular Nociceptors, Sensitization

► Sensitization of Muscular and Articular Nociceptors

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.
► Opioid Rotation

Aseptic Meningitis

► Headache in Aseptic Meningitis

ASICs

Synonyms

Acid sensing ion channels

Definition

A family of proteins combined to form acid sensing ion channels (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 *C. 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.
► 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.
► Somatic Pain

Aspirin-Like Drugs

► Non-Steroidal 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

A

Ascending Nociceptive Pathways

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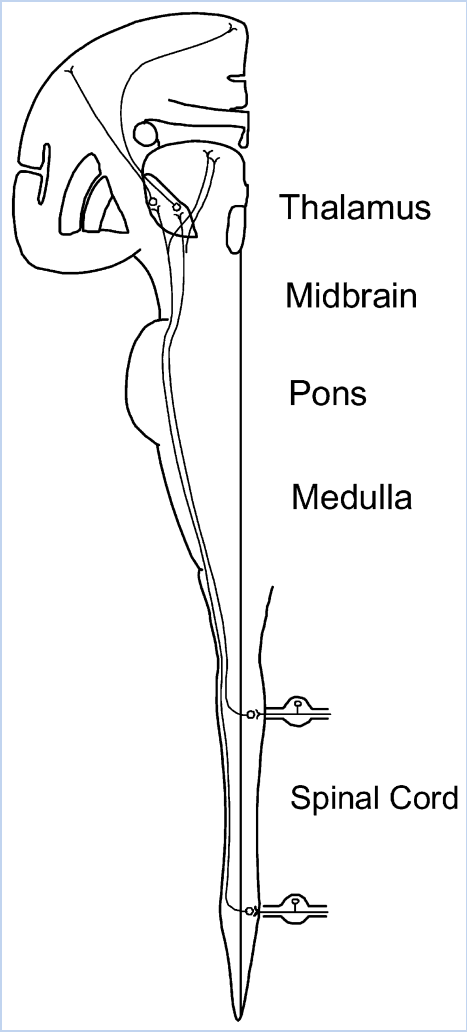
Nociceptive neurons in the spinal cord and trigeminal nuclei send their axons to terminate within a large number of regions in the upper cervical spinal cord, brainstem and diencephalon. The precise roles of each of these pathways in nociception have not yet been established with certainty and it is likely that their roles vary among species. This overview 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 Encyclopedia of Pain. These are referred to throughout this overview.

Spinothalamic Tract

The most widely studied ascending nociceptive pathway originating in the spinal cord is the spinothalamic tract. Nearly 100 years ago, anatomical studied 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 in humans 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 neurons. It has been estimated, based on retrograde tracing studies, that there are between 10 and 20 thousand 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 (Andrew and Craig 2001; Craig et al. 1994; Willis et al. 1979). STT cell bodies and dendrites receive glutamatergic (see ► spinothalamic tract neurons, glutamatergic input) and several types of peptidergic inputs (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 brainstem neurons). Axons of STT neurons decussate at a level near the cell body and the majority turn and ascend 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 brainstem. 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 brainstem. 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



Ascending Nociceptive Pathways, Figure 1 Schematic representation of spinothalamic tract and thalamic projection to primary somatic sensory cortex from the ventral posterior lateral nucleus of thalamus.

lesions to be made. Cordotomies are now frequently done percutaneously under local anesthesia.

STT axons terminate in three principle regions of the thalamus including the ventral posterior lateral (VPL), central lateral and adjacent parts of the medial dorsal nucleus, and posterior thalamic nuclei (Cliffer et al. 1989; Craig 2004; Graziano and Jones 2004; Mehler 1969; Craig et al. 1994; Willis et al. 1979). 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 the 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 (Giesler et al. 1981). 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 responses to nociceptive stimulation. 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 and 55°C (Kenshalo et al. 1979). Repeated applications of noxious heat stimuli lead 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 with 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,

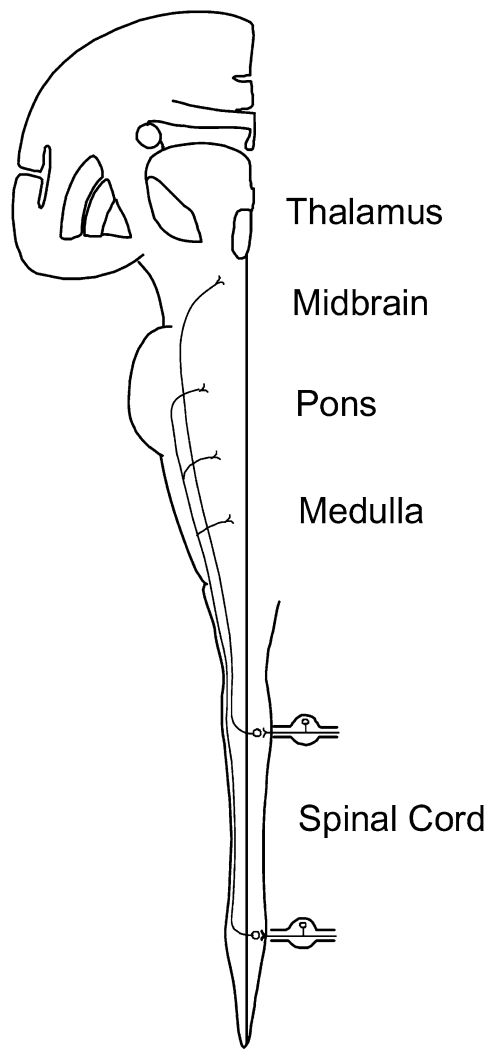
vagina, colon, rectum, gall bladder and bile duct (see ► spinothalamic tract neurons, visceral input). In almost all cases, STT neurons that respond to stimulation of a visceral organ have somatic receptive fields as well. Frequently the somatic receptive fields were found to be located in areas in which 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

In the late 1980's, 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 brainstem. 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 brainstem 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 the 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 is probably involved in providing nociceptive information that is used in producing cortical arousal (Villanueva et al. 1990).



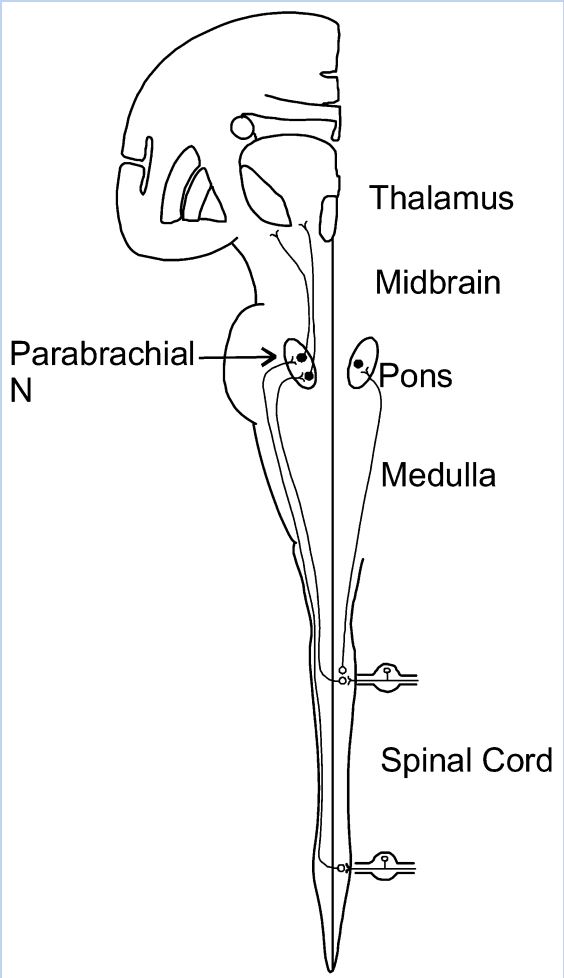
Ascending Nociceptive Pathways, Figure 2 Schematic illustration of spinoreticular tract.

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 brainstem 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 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 frequently been recorded deep within the spinal gray matter and have large complex receptive fields, often 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 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 amydaloid 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. 1995). Studies in which antidromic activation has been used to identify spinoparabrachial tract neurons in cats indicate that the overwhelming majority are 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 amydaloid projections). Therefore, this projection appears well suited for providing nociceptive information that is used for producing cognitive, emotional or affective responses to pain.

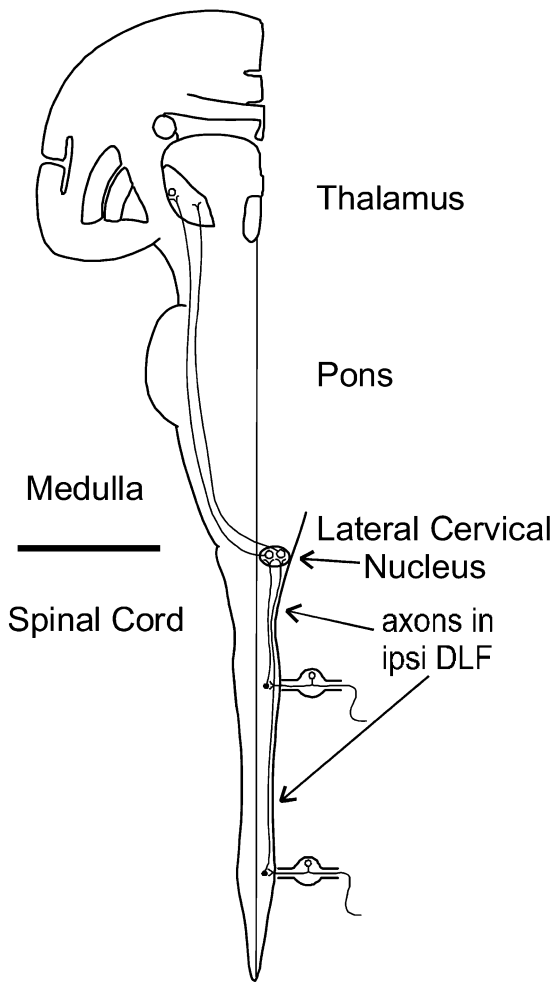


Ascending Nociceptive Pathways, Figure 3 Schematic representation of spinoparabrachial tract projection.

Spinocervicothalamic Tract

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 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 (Brown 1981; Cervero et al. 1977; Kniffki et al. 1977). These SCT neurons respond to noxious mechanical and thermal stimuli.



Ascending Nociceptive Pathways, Figure 4 Schematic representation of postsynaptic dorsal column projection.

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 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 the ascending axons of LCN neurons give off branches that terminate within the midbrain.

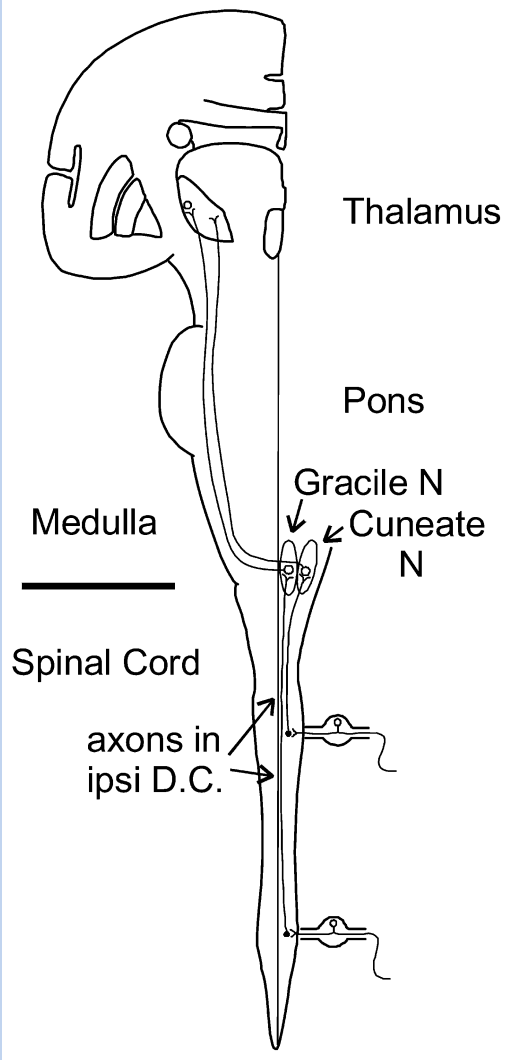
Postsynaptic Dorsal Column Projection

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 the PSDC neurons can

be driven exclusively by innocuous mechanical stimulation and the remainder can be classified as WDR neurons (Angaut-Petit 1975; Uddenberg 1968), 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 in 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 unlikely 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 (Esteves et al. 1993; Menetrey and Basbaum 1987). Spinosolitary neurons were founding 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.



Ascending Nociceptive Pathways, Figure 5 Schematic depiction of spinocervicothalamic projection.

References

1. Al-Chaer ED, Lawand NB, Westlund KN et al. (1996) Pelvic visceral input into the nucleus gracilis is largely mediated by the postsynaptic dorsal column pathway. J.Neurophysiol 76:2675–2690
2. Al-Chaer ED, Feng Y, Willis WD (1998) A role for the dorsal column in nociceptive visceral input into the thalamus of primates. J Neurophysiol 79:3143–3150
3. Andrew D, Craig AD (2001) Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nat Neurosci 4:72–77
4. Angaut-Petit D (1975) The dorsal column system: II. functional properties and bulbar relay of the postsynaptic fibres of the cat's fasciculus gracilis. Exp Brain Res 22:471–493

5. Applebaum AE, Beall JE, Foreman RD et al. (1975) Organization and receptive fields of primate spinothalamic tract neurons. J Neurophysiol 38:572–586
6. Apkarian AV, Hodge CJ (1989) Primate spinothalamic pathways: I. a quantitative study of the cells of origin of the spinothalamic pathway. J Comp Neurol 288:447–473
7. Bennett GJ, Seltzer Z, Lu G-W et al. (1983) The cells of origin of the dorsal column postsynaptic projection in the lumbosacral enlargement of cats and monkeys. Somatosens Res 1:131–149
8. Bernard J., Peschanski M, Besson JM (1989) A possible spino(trigemino)-ponto-amygdaloid pathway for pain. Neurosci Letters 100:83–88
9. Bernard JF, Dallel R, Raboisson P et al. (1995) Organization of the efferent projections from the spinal cervical enlargement to the parabrachial area and periaqueductal gray: A PHA-L study in the rat. J Comp Neurol 353:480–505
10. Boivie J (1970) The termination of the cervicothalamic tract in the cat. An experimental study with silver impregnation methods. Brain Res 19:333–360
11. Brown AG (1981) Organization in the Spinal Cord: The Anatomy and Physiology of Identified Neurones. Springer-Verlag, Berlin, pp 17–72
12. Burstein R, Cliffer KD, Giesler GJ Jr (1987) Direct somatosensory projections from the spinal cord to the hypothalamus and telecephalon. J Neurosci 7:4159–4161
13. Cervero F, Iggo A, Molony V (1977) Responses of spinocervical tract neurones to noxious stimulation of the skin. J Physiol 267:537–558
14. Cliffer KD, Giesler GJ Jr (1989) Postsynaptic dorsal column pathway of the rat. III. distribution of ascending afferent fibers. J Neurosci 9:3146–3168
15. Craig AD Jr (1978) Spinal and medullary input to the lateral cervical nucleus. J Comp Neurol 181:729–744
16. Craig AD (2004) Distribution of trigeminothalamic and spinothalamic lamina I terminations in the Macaque monkey. J Comp Neurol 477:119–148
17. Craig AD Jr, Tapper DN (1978) Lateral cervical nucleus in the cat: Functional organization and characteristics. J Neurophysiol 41:1511–1534
18. Craig AD, Bushnell MC, Zhang ET et al. (1994) A thalamic nucleus specific for pain and temperature sensation. Nature 372:770–773
19. Esteves F, Lima D, Coimbra A (1993) Structural types of spinal cord marginal (lamina I) neurons projecting to the nucleus of the tractus solitarus in the rat. Somatosensory and Motor Res 10:203–216
20. Fields HL, Wagner GM, Anderson SD (1975) Some properties of spinal neurons projecting to the medial brainstem reticular formation. Exp Neurol 47:118–134
21. Foreman RD, Schmidt RF, Willis WD (1979) Effects of mechanical and chemical stimulation of fine muscle afferents upon primate spinothalamic tract cells. J Physiol 286:215–231
22. Giesler GJ Jr, Yezierski RP, Gerhart KD et al. (1981) Spinothalamic tract neurons that project to medial and / or lateral thalamic nuclei: evidence for a physiologically novel population of spinal cord neurons. J Neurophysiol 46:1285–1308
23. Giesler GJ Jr, Nahin RL, Madsen AM (1984) Postsynaptic dorsal column pathway of the rat. I. Anatomical studies. J Neurophysiol 51:260–275
24. Graziano A, Jones EG (2004) Widespread thalamic terminations of fibers arising in the superficial medullary dorsal horn of monkeys and their relation to calbindin immunoreactivity. J Neurosci 24:248–256
25. Haber LH, Moore BD, Willis WD (1982) Electrophysiological response properties of spinoreticular neurons in the monkey. J Comp Neurol 207:75–84
26. Hylden JHK, Hayashi H, Dubner R et al. (1986) Physiology and morphology of the lamina I spinomesencephalic projection. J Comp Neurol 247:505–515
27. Kajander KC, Giesler GJ Jr (1987) Responses of neurons in the lateral cervical nucleus of the cat to noxious cutaneous stimulation. J Neurophysiol 57:1686–1702
28. Kniffki K-D, Mense S, Schmidt RF (1977) The spinocervical tract as a possible pathway for muscular nociception. J Physiol 73:359–366
29. Kenshalo DR, Leonard RB, Chung JM et al. (1979) Responses of primate spinothalamic neurons to graded and to repeated noxious heat stimuli. J Neurophysiol 42:1370–1389
30. Light AR, Sedivec MJ, Casale EJ et al. (1993) Physiological and morphological characteristics of spinal neurons projecting to the parabrachial region of the cat. Somatosensory and Motor Res 10:309–325
31. Mehler WR (1969) Some neurological species differences –A posteriori. Ann NY Acad Sci 167:424–468
32. Menetrey D, Basbaum AI (1987) Spinal and trigeminal projection to the nucleus of the solitary tract: A possible substrate for somatovisceral and viscerovisceral reflex activation. J Comp Neurol 255:439–450
33. Menetrey D, Roudier F, Besson JM (1983) Spinal neurons reaching the lateral reticular nucleus as studied in the rat by retrograde transport of horseradish peroxidase. J Comp Neurol 220:439–452
34. Truex RC, Taylor MJ, Smythe MQ et al. (1970) The lateral cervical nucleus of the cat, dog, and man. J Comp Neurol 139:93–104
35. Uddenberg N (1968) Functional organization of long, second-order afferents in the dorsal funiculus. Exp. Brain Res 4:377–382
36. Villanueva L, Cliffer KD, Sorkin LS et al. (1990) Convergence of heterotopic nociceptive information onto neurons of caudal medullary reticular formation in monkey (*Macaca fascicularis*). J Neurophys 63:1118–1127
37. Willis WD Jr, Coggeshall RE (2004) Sensory Mechanisms of the Spinal Cord, 3rd edn. Kluwer Academic / Plenum, New York
38. Willis WD, Kenshhalo DR Jr, Leonard RB (1979) The cells of origin of the primate spinothalamic tract. J Comp Neurol 188:543–573
39. Yezierski RP, Schwartz RH (1986) Response and receptive-field properties of spinomesencephalic tract cells in the cat. J Neurophys 55:76–95
40. Zhang X, Kostarczyk E, Giesler GJ Jr (1995) Spinohypothalamic tract neurons in the cervical enlargement of rats: Descending axons in the ipsilateral brain. J Neurosci 15:8393–8407
41. Zhang X, Wenk HN, Honda CN et al. (2000) Locations of spinothalamic tract axons in cervical and thoracic spinal cord white matter in monkeys. J Neurophysiol 83:2869–2880

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.

► Psychological 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.
► Cancer Pain, Assessment in the Cognitively Impaired

Assessment of Hypoalgesia

► Hypoalgesia, Assessment

Assessment of Pain Behaviors

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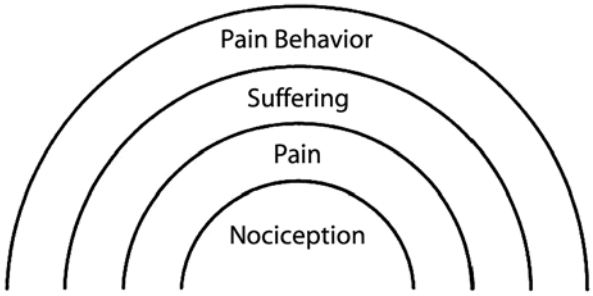
Synonyms

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, or 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.



Assessment of Pain Behaviors, Figure 1 Fordyce's (1979) behavioral model of pain.

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, and
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, or pain-related body postures). Second, the model serves to guide treatment efforts designed to improve adjustment to persistent pain by modifying pain behavior. Behavioral treatments based on this model include graded activation programs in which:

- patients learn to gradually increase their activity level, and time-contingent medication scheduling, and
- 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,

Assessment of Pain Behaviors, Figure 2 Keefe and Lefebvre's (1994) systems model of pain behavior.

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, a patient directly records 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 individual 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. A patient, for example, who shows 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 session was 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, and
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 eval-

uate 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, a patient who reports 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.

References

1. Buckelew SP, Parker JC, Keefe FJ et al. (1994) Self-Efficacy and Pain Behavior among Subjects with Fibromyalgia. Pain 56:191–201
2. Fordyce WE (1976) Behavioral Methods for Chronic Pain and Illness. CV Mosby, Saint Louis
3. Fordyce WE (1979) Environmental Factors in the Genesis of Low Back Pain. In: Bonica JJ, Liebeskind JE, Albe-Fessard DG (eds) Proceedings of the Second World Congress on Pain. Advances in pain Research and Therapy, vol 3. Raven Press, New York, pp 659–666
4. Keefe FJ, Affleck G, Lefebvre JC et al. (1997) Coping Strategies and Coping Efficacy in Rheumatoid Arthritis: A Daily Process Analysis. Pain 69:43–48
5. Keefe FJ, Block AR (1982) Development of an Observation Method for Assessing Pain Behavior in Chronic Low Back Pain Patients. Behav Ther 13:363–375
6. Keefe FJ, Crisson JE, Trainor M (1987) Observational Methods for Assessing Pain: A Practical Guide. In: Blumenthal JA, McKee DC (eds) Applications for Behavioral Medicine and Health Psychology. Professional Resources Exchange, Sarasota, pp 67–94
7. Keefe FJ, Lefebvre J (1994) Pain Behavior Concepts: Controversies, Current Status, and Future Directions. In: Gebhart G, Hammond DL, Jensen TS (eds) Proceedings of the VIIth World Congress on Pain. Elsevier, New York, pp 127–148
8. Keefe FJ, Lefebvre J (1999) Behavioral Therapy. In: Melzack R, Wall P (eds) Textbook of Pain fourth edition. Churchill Livingstone, London, pp 1445–1461
9. Keefe FJ, Wilkins RH, Cook WA (1984) Direct Observations of Pain Behavior in Low Back Pain Patients during Physical Examination. Pain 20:59–68
10. Keefe FJ, Wilkins RH, Cook WA et al. (1986) Depression, Pain, and Pain Behavior. J Consult Clin Psychol 54:665–669
11. McDaniel LK, Anderson KO, Bradley LA et al. (1986) Development of an Observation Method for Assessing Pain Behavior in Rheumatoid Arthritis Patients. Pain 24:185–184
12. Richards R, Nepomuceno C, Riles M et al. (1982) Assessing Pain Behavior: The UAB Pain Behavior Scale. Pain 14:393–398
13. Romano JM, Turner JA, Friedman LS et al. (1992) Sequential Analysis of Chronic Pain Behaviors and Spouse Responses. J Consult Clin Psychol 60:777–782
14. Sugimoto A, Hara Y, Findley TW et al. (1997) A Useful Method for Measuring Daily Physical Activity by a Three-Direction Monitor. Scand J Rehabil Med 29:37–42
15. Turner JA (1996) Educational and Behavioral Interventions for Back Pain in Primary Care. Spine 21:2851–2857

Assimilation

Definition

Giving up the values, beliefs, material culture and practices of their native group, and adopting those of the host culture.

► Cancer Pain, Assessment of Cultural Issues

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.
► Alleles
► Opioid Analgesia, Strain Differences

Astrocytes

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.
► Cord Glial Activation
► Diencephalic Mast Cells

Asymmetric Junctions

Definition

Gray (1962) divided the central synapse into two types, based on the differences in synaptic density between the pre- and post-synaptic membranes, asymmetric (type I) and symmetric (type II).
► 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.
► Diabetic Neuropathies

Atenolol

Definition

Beta-blocker.
► Migraine, Preventive 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.
► 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.
► 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, the 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 to 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.
► Migraine, Childhood Syndromes

ATrP

► Attachment Trigger Point

Attachment Trigger Point

Synonyms

ATrP

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.
► Myofascial Trigger Points

Attentional Bias

Definition

The tendency to selectively attend to threatening information in comparison to neutral information.
► 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.
► Spinothalamic Tract Neurons, Descending Control by Brainstem Neurons

Attributable Effect

► Effect Size

Attributable Effect and Number Needed to Treat

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Synonyms

Efficacy; effectiveness; number needed to treat; NTT

Definition

The ► Attributable Effect of a treatment is the extent to which it achieves its outcomes, beyond that achieved by non-specific 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 non-specific 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 non-specific effects. The larger the number, the more the treatment works by non-specific effects. The smaller the number, the more the treatment has a specific effect.

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 non-specific 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 non-specific effects.
Mathematically:
$AE=P_{index}-P_{control}$

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

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 non-specific 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 non-specific 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 non-specific effects of treatment. There is no way of determining which particular patient or patients responded to the attributable effect or to non-specific 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 patient: those whose outcome was due to the attributable effect (N_{AE}), and those who had non-specific 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 non-specific effects. All that is required to determine the ratio between attributable and non-specific 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 3 patients with a successful outcome, 1 can be attributed to the specific effects of the treatment, while the other 2 outcomes were due to non-specific effects. If 30 patients were to have a successful outcome, 10 would be due to the attributable effect, and 20 due to non-specific 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 5 patients with a successful outcome, 1 is due to the specific effects of treatment, and 4 are due to non-specific 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 non-specific 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 over all. It is a measure of how much a particular outcome is due to specific effects of the treatment, compared with non-specific 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 non-specific effects. Less powerful treatments may nevertheless be effective, but their outcomes are due less to the attributable effect, and more to non-specific 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 non-specific 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 non-specific, 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 the 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 minutes" the NNT for that outcome would be recorded as
$NNT_{\text{ability to walk 1 km in 10 minutes}}$.
If the success in question is "achieving a reduction of at least 50% in VAS score" the NNT for that outcome would be
$NNT_{\text{reduction in VAS by 50\%}}$.
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 realisation 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 realises 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 totalled 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. $NNT_{\text{complete relief}}$; $NNT_{\text{50\% relief}}$; and $NNT_{\text{return to work}}$.

References

1. Cook RJ, Sackett DL (1995) The Number Needed to Treat: A Clinically Useful Measure of Treatment Effect. BMJ 310:452–454
2. Laupacis A, Sackett DL, Roberts RS (1988) An Assessment of Clinically Useful Measures of the Consequences of Treatment. New Engl J Med 318:1728–1733
3. McQuay HS, Moore A (1996) Epidural Steroids for Sciatica. Anaesth Intens Care 24:284–286

Atypical Antidepressants

► Antidepressant Analgesics in Pain Management

Atypical Facial Neuralgia

► Atypical Facial Pain, Etiology, Pathogenesis and Management
► Trigeminal, Glossopharyngeal, and Geniculate Neuralgias

Atypical Facial Pain, Etiology, Pathogenesis and Management

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Synonyms

Atypical Facial Neuralgia; atypical odontalgia; Phantom Tooth Pain; Stomatodynia; burning mouth syndrome; Idiopathic Orofacial Pain; complex regional pain syndrome

Definition

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 (Sharav 1999; Woda and Pionchon 1999). 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, 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. 1987a). All reports of atypical oral and facial pain indicate 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 two 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. (1987a) 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. 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 very 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.

References

1. Feinmann C, Harris M, Cawley R (1984) Psychogenic Facial Pain: Presentation and Treatment. BMJ 288:436–438
2. Grushka M, Sessle BJ, Miller R (1987a) Pain and Personality Profiles in Burning Mouth Syndrome. Pain 28:155–167
3. Loeser JD (1989) Tic Douloureux and Atypical Facial Pain. In: Wall PD, Melzack R (eds) Textbook of Pain, 2nd edn. Churchill Livingstone, pp 535–543
4. Marbach JJ (1978) Phantom tooth pain. Journal of Endodontics 4:362–372
5. Sharav Y, Singer E, Schmidt E, Dionne RA, Dubner R (1987) The Analgesic Effect of Amitriptyline on Chronic Facial Pain. Pain 31:199–209
6. Sharav Y (1999) Orofacial pain. In: Wall PD, Melzack R (eds) Textbook of Pain, 4th edn. Churchill Livingstone, pp 711–738
7. Vickers ER, Cousins MJ, Walker S, Chisholm K (1998) Analysis of 50 Patients with Atypical Odontalgia. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics 85:24–32
8. Woda A, Pionchon PA (1999) Unified Concept of Idiopathic Orofacial Pain: Clinical Features. J Orofac Pain 13:172–184

Atypical Odontalgia

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Definition

Atypical odontalgia 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, 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. ► Vascular orofacial pain (VOP) may be especially relevant to the diagnosis of atypical intraoral pain (atypical odontalgia). VOP, possibly a new diagnostic entity (Sharav 1999), shares many of the signs and symptoms common to other ► vascular-type craniofacial pain. It was found to be associated with atypical toothache (Benoliel et al. 1997) and to mimic ► pulpitis (Cherninsky 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.

Treatment

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).

► Atypical Facial Pain
► Atypical Facial Pain, Etiology, Pathogenesis and Management

References

1. Benoliel R, Elishoov H, Sharav Y (1997) Orofacial Pain with Vascular-Type Features. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics 84:506–512
2. Hu JW, Sharav Y, Sessle BJ (1990) Effect of One- or Two-Stage Deafferentation of Mandibular and Maxillary Tooth Pulps on the Functional Properties of Trigeminal Brainstem Neurons. Brain Research 516:271–279
3. Marbach JJ (1978) Phantom tooth pain. Journal of Endodontics 4:362–372
4. Sharav Y (1999) Orofacial pain. In: Wall PD, Melzack R (eds) Textbook of Pain, 4th edn. Churchill Livingstone, pp 711–738
5. Woda A, Pionchon PA (1999) Unified Concept of Idiopathic Orofacial Pain: Clinical Features. J Orofac Pain 13:172–184

Atypical Trigeminal Neuralgia

► Trigeminal Neuralgia, Etiology, Pathogenesis and Management

AUC

► Area Under the Curve

Audit Report

Definition

An audit report refers to conclusions made by grouping data according to criteria, so that inferences can be made from them.

► Postoperative Pain, Data Gathering and Auditing

Aura

Definition

Aura is a transient disturbance in neurological function that may precede an attack of migraine headache. These disturbances usually last 20–30 minutes, but may persist for as long as 1 hour. The classical migraine aura that precede attacks in about 30% of migraine sufferers is visual, and characterized by an arc of brightly colored lights that flicker and change shapes. These visual disturbances often surround an area of dimmed or absent vision.

► 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, historical events that have occurred in one's lifetime.

► Pain Memory

Autogenic Feedback

Definition

A combination of autogenic training and thermal biofeedback, used for the purpose of promoting hand warming and generalized relaxation.

► 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.

► 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.

► Cell Therapy in the Treatment of Central Pain

Autologous Thrombocyte Injection as a Model of Cutaneous Pain

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Synonyms

Blood Platelets; Intracutaneous Injection Pain; hyperalgesia; Cutaneous Pain Model

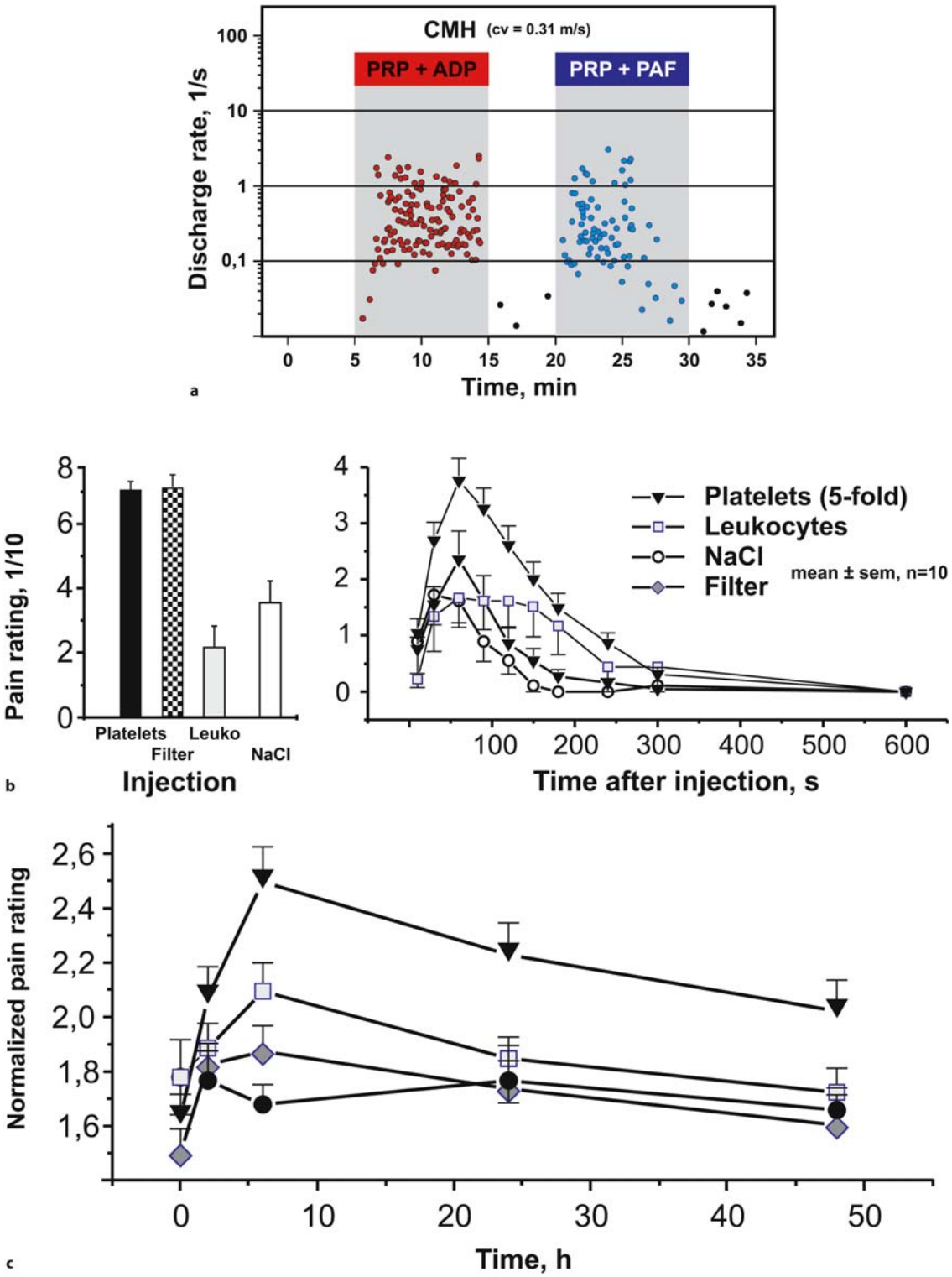
Definition

Thrombocytes are usually associated with the hemostasis or with vascular inflammatory processes. Little is known about the role of corpuscular components like white blood cells or platelets in the excitation and sensitization of nociceptors in human tissue. Injections of autologous preparations of human thrombocytes into the dermal layer of the skin are able to directly excite nociceptors and to induce an inflammatory ► induration, showing prolonged primary mechanical and thermal hyperalgesia (► primary hyperalgesia). Neuronal and vascular reactions following platelet injections have been assessed by videography, ► Laser-Doppler Flowmetry (LDF), and various other psychophysical methods to measure primary hyperalgesia. Injections of platelet preparations into the skin are intended to further increase the pathophysiological relevance of hyperalgesia models.

Characteristics

Inflammatory processes are often associated with pain and hyperalgesia (Koltzenburg and Torebjörk 1995). Even though a multitude of algogenic substances, such as ► bradykinin, could be identified as mediators in inflammatory processes (Reeh and Kress 1995), little is known about the origin of mechanical hyperalgesia in inflamed tissue. A variety of algogenic substances and combinations of mediators have been thoroughly tested in various cutaneous pain models. Nevertheless, only a very few models inducing subacute or chronic inflammatory pain in humans exist. All of these models are based on the physical or noxious stimulation of the skin (heat, UV-irradiation, ► capsaicin injection) (Bickel et al. 1998; LaMotte et al. 1992). Yet, there is only limited information about the role of corpuscular elements in the activation and sensitization of nociceptors in these models. Every trauma, be it a laceration, scalding (Lofgren et al. 1997), UV-irradiation, blunt tissue injury or even inflammatory, immunological diseases (Alstergren and Kopp 1997; Maeda et al. 1998), usually results in the disruption, or at least in the alteration, of the vascular system, inducing the activation of the coagulation system.

The first electrophysiological studies employing *in vitro* skin nerve preparations of the rat hind paw have verified acute activation of nociceptive C-fibers exposed to activated platelets (Ringkamp et al. 1995). These studies clearly show, that only activated human



Autologous Thrombocyte Injection as a Model of Cutaneous Pain, Figure 1 Platelet injections as cutaneous pain model. Effects of thrombocyte superfusion of in vivo rat skin and of injections of autologous platelet preparations into human skin of volunteers. (a) In a nerve-skin preparation activated platelets (ADP and PAF) induce severe discharge of a mechano-heat sensitive C-unit (CMH), reversible during washout periods. (b) In humans, injections of platelet preparations induced pronounced injection pain (rated on a numerical rating scale of 0 "no pain" to 10 "most severe pain"), which gradually receded over the observation period of 10 minutes. (c) Six hours after the injection, mechanical hyperalgesia developed directly at the induration at the injection site. This was significantly increased for 3 days. Filtered platelets were only able to induce severe injection pain. Hyperalgesia did not develop. Leukocytes, like saline injections, produced unspecific effects.

platelets were able to excite these isolated nociceptive units. Platelets contain a considerable amount of ► serotonin, an algogenic substance that is secreted upon activation of the cell fragment. This substance is known to activate nociceptive nerve endings (Reeh and Kress 1995). Further studies employing serotonin antagonists and prostaglandin inhibitors underlined that serotonin discharged from activated thrombocytes was not the crucial mediator (Ringkamp et al. 1994b). The activation of platelets not only resulted in the activation of nociceptive nerve endings in the rat, but was equally able to induce dose dependent pain and ► axon reflex flare reactions after the injection of autologous platelet preparations into the skin of human subjects (Schmelz et al. 1997). The pain subsided within minutes after the injection, but, within only a few hours, a local induration developed. This induration was hypersensitive to mechanical and thermal stimuli and gradually dissolved after about three days. This hyperalgesic reaction was linked to membrane bound mediators, as injection of filtered platelets did evoke acute pain, but no hyperalgesia (Blunk et al. 1999). Therefore, acute pain is probably induced by the secretion of a water-soluble algogenic substance, whereas the development of mechanical and thermal primary hyperalgesia is probably due to a cyto-attractant substance bound to the platelet membrane. The activation of platelets and subsequent release of ► Beta(β)-Thromboglobulin (Blunk et al. 1998) in the human burn model has already been shown by intracutaneous microdialysis, suggesting a role for platelets in this pain and hyperalgesia model. Interestingly, activated platelets have also been proposed to be linked to myocardial pain (Fu and Longhurst 2002), whereas the proposed link to migraine might not be valid (Migraine Pathophysiology 2004).

Injections of pure leukocyte preparations do not have an algogenic effect on nociceptors, but synergistically enhance the ability of platelets to induce pain and inflammation in the skin (Blunk et al. 1999). The interaction of platelets and leukocytes is of major interest, as it is the basis of transcellular synthesis resulting in mediators such as lipoxins (Kantarci and Van Dyke 2003). In summary, platelets are a most interesting source of mediators that can excite and sensitize nociceptors in the human.

References

1. Alstergren P, Kopp S (1997) Pain synovial fluid concentration of serotonin in arthritic temporomandibular joints. Pain 72:137–143
2. Bickel A, Dorfs S, Schmelz M et al. (1998) Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man. Pain 76:317–325
3. Blunk J, Schmelz M (1998) Beta-thromboglobulin is secreted by platelets in heat-induced skin inflammation. Abstract in Pflügers Archiv, Eur J Physiol, Suppl 435:25–5
4. Blunk J, Osiander G, Nischik M et al. (1999) Pain and inflammatory hyperalgesia by intradermal injections of human platelets and leukocytes. Eur J Pain 3:247–259
5. Fu LW, Longhurst JC (2002) Activated platelets contribute to stimulation of cardiac afferents during ischaemia in cats: role of 5-HT(3) receptors. J Physiol 544:897–912
6. Kantarci A, Van Dyke TE (2003) Lipoxins in chronic inflammation. Crit Rev Oral Biol Med 14:4–12
7. Koltzenburg M, Torebjörk HE (1995) Pain and hyperalgesia in acute inflammatory and chronic neuropathic conditions. Lancet 345:1111
8. LaMotte RH, Lundberg LER, Torebjörk HE (1992) Pain, hyperalgesia and activity on nociceptive-C units in humans after intradermal injection of capsaicin. J Physiol Lond 448:749–764
9. Lofgren O, Gazelius B, Lundeberg T (1997) Acute microcirculatory changes after scalding of the rat hind paw. Acta Physiol Scand 161:289–294
10. Maeda M, Kachi H, Mori S (1998) Ultrastructural observations of platelets from patients with progressive systemic sclerosis (PSS). J Dermatol 25:222–230
11. Reeh PW, Kress M (1995) Effects of classical algogens. Semin Neurosci 7:221–226
12. Ringkamp M, Schmelz M, Kress M et al. (1994a) Activated human platelets in plasma excite nociceptors in rat skin, in vitro. Neurosci Lett 170:103–106
13. Ringkamp M, Schmelz M, Allwang M et al. (1994b) Nociceptor excitation by platelets is not due to 5-HAT or prostanoids released. Soc Neurosci Abstr 20:1569
14. Schmelz M, Osiander G, Blunk J et al. (1997) Intracutaneous injections of platelets cause acute pain and protracted hyperalgesia. Neurosci Lett 226:171-174
15. No authors listed (2004) Migraine Pathophysiology. Headache 44:735-739

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 and the parasympathetic nervous system.

► Psychiatric Aspects of Visceral Pain

Autonomic Dominant Cramping Disease

Definition

Familial forms of idiopathic cramps. In most cases, a central, neuronal origin of the cramps at the level of the motoneuron somata has been hypothesized.

► Muscular Cramps

Autonomic Dysreflexia

Definition

Autonomic dysreflexia is the inappropriate autonomic function that results from spinal cord injury at or above the level of T6

► Spinal Cord Injury Pain

Autonomic Features

Definition

A variety of symptoms referable to activation of the autonomic nervous system. When activated, symptoms include ptosis, miosis, lacrimation, conjuctival injection, nasal congestion and rhinorrhea. These autonomic symptoms classically accompany attacks of cluster headache, but also occur during painful exacerbations of hemicrania continua.

► 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.

► 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 blood pressure, pulse rate, operation of the bowel and bladder and body temperature. It includes the sympathetic, parasympathetic and enteric nervous system.

► Amygdala, Pain Processing and Behavior in Animals
► Diabetic Neuropathies
► Hereditary Neuropathies

Autonomic Phenomena

Definition

Signs and symptoms associated with vascular-type craniofacial pain. Local autonomic signs include: tearing, redness of eye, nasal congestion and rhinorrhea, cheek swelling and redness. Symptoms include: nausea, photophobia and phonophobia.

► Atypical Facial Pain

Autonomic Reactions/Symptoms

Definition

Variation of blood pressure, cardiac rhythm, blood circulation, respiration, pupil diameter, visceral motility and visceral secretion triggered by a noxious stimulus.

► Autonomic Functions
► Hypnic Headache
► Parabrachial Hypothalamic and Amydaloid 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.

► Primary Exertional Headache

Autotomy

Definition

Self-injurious behavior in which a body part, usually denervated or deafferented, is compulsively licked, bitten and chewed (self mutilation), and is commonly observed in animals following neurectomy. 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.

► Anesthesia Dolorosa Model, Autotomy
► Dietary Variables in Neuropathic Pain

Autotraction

► Lumbar 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.

- ► 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.

- ► 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.

- ► 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 seconds. Subjects remain in sleep and are not usually aware of external influences. They could complain of non-refreshing sleep on the following day.

- ► 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.

- ► Acute Pain in Children, Post-Operative

Axolemma

Definition

Membrane around the nerve cell; the membranous sheath that encloses the long thin extension of a nerve cell (axon).

- ► Perireceptor Elements

Axon

Definition

A process (and its eventual collaterals) of a neuron that conducts electrical impulses (action potentials) away from the soma (orthodromically) to its presynaptic ending(s) (forming synaptic contacts with other neurons, muscles or glands). Axons and their sheaths are called nerve fibers.

- ► 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 towards the CNS, but also along its branching fibers back towards the skin. This leads to the release of the vasoactive substances CGRP (calcitonin-gene-related peptide) and substance P. These neuropeptides subsequently induce protein extravasation and vasodilation, which is reddening and weal formation of the skin (neurogenic inflammation).

- ► Autologous Thrombocyte Injection as a Model of Cutaneous Pain
- ► Nociceptor, Axonal Branching
- ► Nociceptors in the Dental Pulp

Axonal Arborization

Definition

Terminal domain of an axon, exhibiting numerous branches and varicosities where the synaptic events take place.

► Spinothalamic Tract Neurons, Morphology

Axonal Degeneration

Definition

The pathologic term to describe destruction of nerve fibers (axons).

► 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.

► Dietary Variables in Neuropathic Pain
► Neuropathic Pain Model, Diabetic Neuropathy Model
► Opioids and Inflammatory Pain
► Toxic Neuropathies

Axotomy

Definition

When the axon of a neurone is transacted, the neurone is said to be axotomized. This occurs when the nerve trunk is cut, crushed, ligated or frozen. The stump of the axon becomes swollen with accumulated organelles originally destined for the nerve terminals. The soma responds within ~ 6 hours, 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 by scar formation or another impediment, a neuroma forms. Axotomy of the sciatic nerve, particularly in rats or mice, is frequently used as an animal model for nerve injury and neuropathic pain.

► 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 immunosuppressant agent, purine derivate. Steroid sparing agent in cranial arteritis; treatment of choice in Behçet's disease.

► Headache Due to Arteritis
► Vascular Neuropathies