Habituation

Definition

Habituation is the reverse process of sensitization, consisting of a waning response to repeated stimulation that can be rapid or gradual. It involves a reduction in excitability, and means that neurons cease to fire when stimulated. However, if the interval between stimuli is altered randomly, and the strength of the stimulus is increased, this process can be reversed.

► Infant Pain Mechanisms
► Migraine Without Aura
► Psychology of Pain, Sensitisation, Habituation and Pain

Hamstring Muscle Strain

Definition

Hamstring muscle strain produces pain in the biceps femoris muscles in the back of the thigh. Stretching the muscle can produce pain, as is found with a straight leg raising maneuver.

► Sciatica

Handicap

► Disability and Impairment Definitions

Hansen's Disease

Aki J. Hietaharju[1], Maija Haanpää;[2]
[1]Department of Neurology and Rehabilitation, Pain Clinic, Tampere University Hospital, Tampere, Finland
[2]Department of Anaesthesiology and Department of Neurosurgery, Pain Clinic, Helsinki University Hospital, Helsinki, Finland
aki.hietaharju@pshp.fi

Synonym

Leprosy

Definition

Hansen's disease is a chronic granulomatous infection of the skin and peripheral nerves caused by ► Mycobacterium leprae. It is associated with marked disabilities which result from the impairment of both sensory and motor nerve function.

Characteristics

Hansen's disease used to be widely distributed all over the world, but now the major part of the global burden of the disease is represented by resource-poor countries, in tropical and warm temperate regions. In 1985, there were an estimated 12 million people with ► leprosy worldwide, resulting in a prevalence of 12 per 10,000 (Britton and Lockwood 2004). At the beginning of 2003, the number of Hansen's disease patients receiving antimicrobial therapy was around 534,000, as reported by 110 countries. About 621,000 new cases were detected during 2002. The six top endemic countries at the start of 2003 were India, Brazil, Madagascar, Mozambique, Nepal, and Tanzania (WHO).

Mycobacterium leprae is an acid-fast gram-positive bacillus, which is supposed to be transmitted mainly by aerosol spread of nasal secretions and uptake through nasal or respiratory mucosa (Noordeen 1994). The infection is not spread by touching, because the bacterium cannot penetrate intact skin. *Mycobacterium leprae* has a peculiar ► tropism for macrophages and ► Schwann cells. After having invaded the Schwann cell, the leprosy bacilli replicate slowly over years. These bacilli show preference for growth in cooler regions of the body causing damage to superficial nerves. Peripheral nerves are affected in fibro-osseous tunnels near the surface of the skin e.g. posterior tibial nerve near the medial malleolus (Britton and Lockwood 2004).

The dynamic nature of the immune response to *Mycobacterium leprae* often leads to spontaneous fluctuations in the clinical state, which are called ► leprosy reaction's. They are divided into two types. ► Leprosy type 1 reaction or reversal reaction is caused by spontaneous increases in T-cell reactivity to mycobacterial antigens (Britton 1998). In type 1 reactions, especially borderline patients may present with reactions to nerve pain, sudden palsies, and many new skin lesions. ► Leprosy type 2 reaction or erythema nodosum

leprosum, is a systemic inflammatory response to the deposition of extravascular immune complexes. It occurs only in borderline-lepromatous and lepromatous leprosy (Lockwood 1996).

Diagnosis of leprosy is clinical and based on patients having at least one of three cardinal signs, which are: (1) hypopigmented or reddish patches with definite loss of sensation, (2) thickened peripheral nerves, and (3) acid-fast bacilli on skin smears of biopsy material (WHO 1998). Leprosy is divided into five subtypes based on histologic and immunologic features: tuberculoid (▶ tuberculoid leprosy), borderline tuberculoid (▶ borderline leprosy), midborderline, borderline lepromatous and ▶ lepromatous leprosy (Ridley and Jopling 1966). These subtypes have been consolidated into two groups, paucibacillary and multibacillary, for assignment to treatment regimens. According to WHO guidelines, the former is treated with ▶ dapsone 100 mg daily and rifampicin 600 mg monthly for 6 months. In multibacillary leprosy, duration of the treatment is a minimum 2 years, and ▶ clofazimine 50 mg daily and 300 mg monthly is added to paucibacillary regimen (Britton and Lockwood 2004).

The most devastating clinical consequence of the intracutaneous nerve damage is the total sensory loss of the extremities (Brand and Fritschi 1985). Pain and temperature sensation are most strikingly decreased in early cases, and later tactile and pressure sense are also lost. Anaesthesia of the extremities predisposes the patient to chronic ulcers and severe secondary deformities, and therefore leprosy remains a significant cause of neurologic disability worldwide.

Since Hansen's disease causes severe sensory loss, it is assumed that pain is uncommon in leprosy. However, peripheral nerve pain, dysesthesias and paraesthesias may complicate leprosy, both during and after treatment. Data on consumption of analgesics by patients with neuropathic pain gives some indication of the extent of the problem. In a Malaysian study of 235 leprosy patients, neuritic pain was the main reason for consumption of analgesic preparations. In 46 patients (19.5%), an overall total intake had been more than 2 kg of analgesics. The duration of intake ranged from 2 to more than 20 years (Segasothy et al. 1986).

Acute pain in one or several nerves may be the presenting feature in Hansen's disease. Pain is a familiar symptom of reactions and neuritis, due to entrapment of the oedematous inflamed nerve in sites of predilection (Nations et al. 1998). Neuritis of cutaneous nerves may also be painful (Theuvenet et al. 1993). Peripheral nerve abscesses, which are often associated with severe acute pain, occur in all types of leprosy and a variety of nerve trunks and cutaneous nerves (Kumar et al. 1997). Leprosy related acute pain can usually be relieved by steroids or other therapeutic measures, such as anti-inflammatory drugs and immobilisation or surgical intervention.

Chronic neuropathic pain in Hansen's disease has received scant attention. Hietaharju et al. (2000) reported on moderate or severe chronic neuropathic pain in 16 patients with treated multibacillary leprosy. In 10 patients, the pain had a glove and stocking-like distribution, and in 2 patients it followed the course of a specific nerve. The quality of pain was burning in 9, biting in 3, pricking in 3, cutting in 2, and electric-shock-like in 2 patients. The occurrence of pain was continuous in 50% of the patients. In an evaluation of 303 patients from a Brazilian referral centre, 174 (57%) patients complained of neuropathic pain (Stump et al. 2002). In 84 patients (48%), pain manifested as bursts. Pain affected one or more peripheral nerve territories; ulnar nerve in 101 (58%) patients and tibial nerve course in 48 (28%). There was a polyneuropathic distribution as glove-like in 47 patients (27%), and sock-like in another 47 patients. At the time of evaluation, pain was present in 47 (27%) patients.

There is little data on the occurrence of sensory disturbances such as dysesthesias, paresthesias or allodynia in patients with leprosy. In a study by Hietaharju et al. (2000), 4 patients complained of a tingling sensation, which was considered as unpleasant and painful, i.e. they had dysesthesia. Dysesthesia followed glove and stocking-distribution in 2 patients, the course of femoral cutaneous nerve in 1 patient, and was located in both legs below mid-thigh in 1 patient. Allodynia, pain due to a stimulus that does not normally provoke pain, was noticed in 2 patients. In both of these patients, enlargement and tenderness of the nerves (cutaneous femoral, common peroneal and posterior tibial) without abscess formation was discovered in clinical examination.

The most typical sensory abnormalities in leprosy patients are severely impaired perception of tactile stimuli and mechanical and thermal pain, indicating damage of Aβ, Aδ and C fibres at the painful site (Hietaharju et al. 2000). The cases with sensory loss associated with pain suggest peripheral deafferentation, i.e. pain due to loss of sensory input into the central nervous system, as occurs with different types of lesions of peripheral nerves. However, in a considerable proportion of the patients with pain the sensory function may be quite well preserved, suggesting other pathophysiological mechanisms. Early involvement of small fibres due to mycobacterial invasion can cause dysfunction and damage leading to paresthesia and pain. Other possible explanations include the impact of previous episodes of reactions, neuritis and inflammation, which may leave the nerve fibrosed, and at risk of entrapment (Negesse 1996). Some patients may have a chronic ongoing neuritis manifesting clinically with pain (Haanpää et al. 2004). Inflammation along nerve trunks has been shown to produce ectopic activity in nerves, and therefore past or present inflammatory conditions represent a source for central sensitisation, which may manifest as chronic neuropathic pain. A delayed ▶ vasculitic

neuropathy, probably precipitated by persisting mycobacterial antigen, is a rare complication of leprosy (Bowen et al. 2000). Vasculitic neuropathies, such as HIV and rheumatoid disease related neuropathies are known to be painful.

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Hargreaves Test

► Thermal Nociception Test

Head Pain

► Headache

Headache

Nikolai Bogduk
Department of Clinical Research Royal Newcastle Hospital, University of Newcastle, Newcastle, NSW, Australia
nbogduk@mail.newcastle.edu.au

Synonyms

Head Pain; Cephalalgia

Definition

H

Headache is pain perceived in the head. Specifically, in order to constitute headache, the pain must be perceived in the occipital, temporal, parietal, or frontal regions of the head, or in some combination of these regions. Pain from these regions may extend to encompass the orbital region, and some forms of headache may particularly affect the orbit. Pain localized to the eye, however, is not generally regarded as headache, and is better described as eye pain. Similar, pain in the face does not conventionally constitute headache; it is regarded separately as facial pain.

Characteristics

There are many varieties of headache, with many possible causes (Headache Classification Subcommittee of the International Headache Society 2004, Olesen et al. 2000). For the most common types of headache, the actual causes are not known. Although several theories are available, they relate rather to the mechanism of pain-production, and do not explain the fundamental reason why the headache occurs. That remains unknown. Headaches are distinguished and defined largely on the basis of their clinical features. These can be described systematically under the categories of enquiry recommended for taking a ► history of a pain problem (see ► medical history):

- Length of Illness
- Site
- Radiation
- Quality
- Intensity
- Frequency
- Duration
- Time of Onset
- Mode of Onset
- Precipitating Features
- Aggravating Features
- Relieving Features
- Associated Features

Length of Illness

This domain pertains to whether or not this is the first episode of headache that the patient has suffered.

Headache for the first time is the cardinal clue for a small set of serious headaches, such as those caused by aneurysm, subarachnoid haemorrhage, meningitis, or sudden, severe hypertension.

Site

The site in which pain is felt is of no diagnostic significance, other than to establish that the complaint is one of headache. However, whether the pain is unilateral or bilateral does bear on the diagnosis of some forms of headache. For example, tension-type headache typically affects the entire head, whereas most other forms of headache are typically, although not always, unilateral. Pain of a neuralgic quality (see below), in the distribution of the nerve affected, is diagnostic of trigeminal neuralgia, glossopharyngeal or vagal neuralgia, and C2 neuralgia.

Radiation

Noting the areas *to which* pain radiates does not help in diagnosis. Different forms of headache may have the same pattern of radiation. However, it can be helpful to recognize sites *from which* pain appears to be referred. Although the pain may be perceived in the forehead, if it appears to have spread from the occiput or neck, a possible cervical source should be considered.

Intensity

All forms of headache can be mild, moderate, or severe in intensity. So, intensity alone does not serve to discriminate different types of headache. However, certain types of headache are characterized by severe headache of sudden onset, sometimes described as "thunderclap" headache. Possible causes include subarachnoid haemorrhage, meningitis, and phaeochromocytoma.

Quality

Most headaches will be dull, aching, or throbbing in quality. These features do not help in making a diagnosis. On the other hand, a lancinating quality of pain establishes that the pain is neuralgic, and is one of the defining features of trigeminal neuralgia, glossopharyngeal or vagal neuralgia, and of C2 neuralgia. Stabbing pain, or jabs of pain, is characteristic of cluster headache, although other features more strongly define this condition.

Frequency

Of all pain problems, headache is the one condition in which frequency is a cardinal diagnostic feature. Short, repeated jabs of pain, recurring in bouts over several minutes are what characterize cluster headache. Periods of pain lasting half a day, or up to three or four days, interspersed with periods free of pain, is what characterizes migraine. Other types of headache occur in paroxysmal bouts, i.e. sustained periods of repeated jabs of intense pain that then switch off. These include chronic paroxysmal hemicrania (CPH), and SUNCT (sudden, unilateral, neuralgiform headache with conjunctival injection and tearing).

Duration

Duration of pain is often inextricably linked to frequency. In cluster headache, and its congeners, the frequency of jabs of pain is high, but the duration of each jab is short, i.e. seconds. In migraine, the headache is established and remains constant, such that its duration is measured in hours or days, but then a pain–free interval appears.

Time of Onset

This is probably an obsolete category of enquiry for diagnostic purposes. Its heritage is that early morning headache was once regarded as pathognomonic of hypertension headache, but this has been disproved. Nevertheless, sometimes the time of onset can provide clues to the cause of headache. For example, headache caused by exposure to chemicals or allergens may occur at only particular times of the day, particular days of the week, or particular seasons of the year. Synchrony with menstrual cycle strongly suggests menstrual migraine.

Mode of Onset

Severe headaches of sudden onset suggest subarachnoid haemorrhage, meningitis, or hypertension as the causes. Otherwise, most headaches come on gradually or in an unremarkable fashion. However, some forms of migraine can have a prodrome. A prodrome of neurological symptoms is virtually diagnostic of classical migraine (now known as migraine with prodrome (Headache Classification Subcommittee of the International Headache Society 2004). Some patients with migraine will suffer cravings for certain types of foods, before the onset of headache. This fits with serotonin mechanisms that on the one hand are involved with pain, and on the other hand are involved with satiety.

Precipitating Factors

Some forms of recurrent headache can be precipitated, inadvertently or consciously, by certain actions. In some patients, the pain of trigeminal neuralgia can be precipitated by touching trigger spots on the face, or in the mouth. Headache precipitated by sexual activity is referred to as "sex headache", and appears to be related to a rapid rise in blood pressure. A rare, but distinctive entity, is colloid cyst of the third ventricle, in which headache can be precipitated by extension of the head, which causes the cyst to occlude the cerebral aqueduct and precipitate a sudden rise in cerebrospinal fluid pressure. "Ice–pick headache" is the term accorded to headache precipitated by exposure to cold foods or liquids.

For headaches of recent onset, not experienced before, an antecedent event may indicate the possible or likely cause. A classical example is post-lumbar puncture headache. A vexatious issue is trauma. Patients may
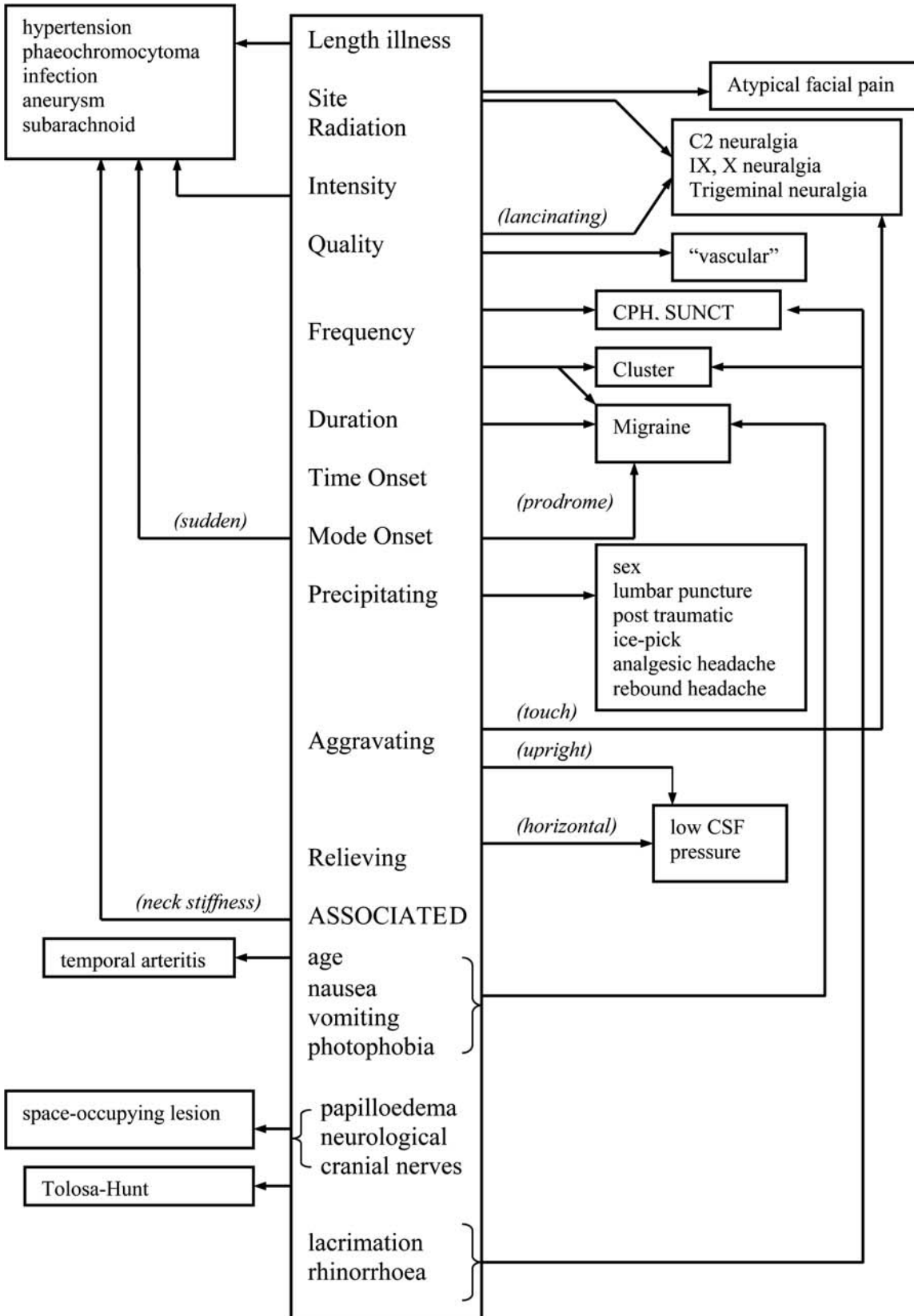
Headache, Figure 1 The differential diagnosis of headache by clinical history and examination.

report an injury that apparently caused the headache. However, a direct link between trauma and headache may be difficult to prove, and is sometimes contentious. Nevertheless, a history of trauma may be the only defining feature of some forms of headache; on which grounds the entity of "post–traumatic headache" is recognized.

Some headaches can be caused by exposure to drugs such as alcohol. Some headaches, paradoxically, can be caused by excessive consumption of analgesics. Withdrawal of analgesics can cause rebound headache.

Aggravating Factors

Few features that aggravate headache help in establishing a diagnosis, for many different forms of headache may be aggravated by activities such as turning the head, or exertion. However, certain features that appear to aggravate the pain are better classified as associated features (see below).

Relieving Factors

Many patients with headache resort to lying down. So, lying down per se is not a discriminating feature. However, when lying down promptly relieves the headache, and when resumption of the upright posture restores it, the leading diagnosis is low-pressure cerebrospinal fluid, which can be idiopathic or secondary to lumbar puncture.

Associated Features

It is in the domain of associated features that most headaches can be distinguished. Photophobia, nausea and vomiting are the cardinal diagnostic features of migraine. Lacrimation, rhinorrhoea, and conjunctival injection are reflex parasympathetic effects that occur with a family of headaches. Classically, they are the associated features of cluster headache, but they also occur in paroxysmal hemicrania and SUNCT syndrome. Papilloedema and focal neurological signs are the classic features of space occupying lesion of the cranium. Other important features are neck stiffness and Kernig's sign, which are virtually diagnostic of spread of infection or haemorrhage into the cervical subarachnoid space. Neurological signs affecting the III, IV, and VI cranial nerves are diagnostic of Tolosa–Hunt syndrome, i.e. granuloma of the cavernous sinus.

Age is an important feature. New headache in an elderly patient may be the only warning feature of temporal arteritis.

The diagnosis of acute herpes zoster can be made immediately once the eruption of vesicles occurs, but the pain may precede the eruption by up to three days.

Diagnosis

Figure 1 illustrates how taking a systematic history can allow many types of headache to be diagnosed on the basis of certain clinical features, singly or in combination. Migraine is diagnosed on the basis of periodic pain associated with photophobia, nausea, or vomiting. Cluster headache is defined by paroxysmal pain associated with lacrimation, rhinorrhoea, and conjunctival injection. Its relatives – CPH and SUNCT, only differ essentially with respect to the periodicity and duration of the headache. Intracranial lesions are diagnosed on the basis of associated neurological signs.

Certain entities, however, cannot be recognized clinically, because they do not have any distinctive features. Those entities are: benign intracranial hypertension, sphenoid sinusitis, cervicogenic headache, and tension type headache.

The first three of these entities require investigations. Benign intracranial hypertension requires a CT scan. Sphenoid sinusitis is perhaps the most "impalpable" headache. It exhibits nothing but pain, felt somewhere deep in the centre of the head. The diagnosis is established eventually by medical imaging. The diagnosis of cervicogenic headache requires the establishment of a cervical source of pain, by medical imaging or by diagnostic blocks of cervical structures or nerves.

Tension type headache is notable because there are no positive diagnostic criteria for this entity. It is a diagnosis by exclusion of other possible causes.

Other ill–defined entities include so-called "vascular headache", whose cardinal feature is throbbing pain, but which does not exhibit any of the diagnostic features of migraine.

▶ Chronic Daily Headache in Children

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Headache, Acute Post-Traumatic

MIGUEL JA LÁINEZ-ANDRÉS[1],
ANA M PASCUAL-LOZANO[2]
[1]Department of Neurology, University of Valencia, Valencia, Spain
[2]Clinical Hospital, University of Valencia, Valencia, Spain
jlainez@meditex.es

Synonyms

Post-Traumatic Headache; PTHA

Definition

Post-traumatic headache (PTHA) is usually one of several symptoms of the "post-traumatic syndrome" and therefore may be accompanied by somatic, psychological or cognitive disturbances (Solomon 2001). A variety of pain patterns may develop after head injury and may

closely resemble primary headache disorders. Common headache pathways have been described for primary and post-traumatic headaches but the pathogenesis of PTHA is still not well known (Martelli 1999).

Characteristics

Tension-type is the most common variety of PTHA (more than 80% of the patients suffered a tension-type headache after head or neck trauma), followed by cervicogenic headache. Exacerbations of migraine and cluster-like headaches also occur. Post-traumatic migraine (PTMA) represents approximately 8–10% of PTHA. This is usually a migraine without aura, often found in children, adolescents and young adults with familial history of migraine. Migraine with visual aura has been described in only a few patients (Hachinski 2000).

Mild, moderate and severe head injuries can be associated with a PTHA. Clinical quantification of traumatic brain injury patients should be based on the Glasgow Coma Scale score (GCS), duration of loss of consciousness (LOC) and presence of posttraumatic amnesia (PTA) In addition, a short practicable neuropsychological test may be useful in detecting minor memory and attentional deficits. Paradoxically, mild head injury is often accompanied by headache and additional symptoms, more frequently than moderate or severe head traumas.

To differentiate between a primary and a post-traumatic headache can be difficult in some cases. Patients who develop a new form of headache in close temporal relation to head or neck trauma should be coded as having a secondary headache. Patients in whom this type of headache was pre-existing but significantly worsened in close temporal relation to trauma, without evidence of a causal relationship between the primary headache and the other disorder, receive only the primary headache diagnosis. However, if there is both a very close temporal relation to the trauma and other good evidence that the particular kind of trauma has aggravated the primary headache, that is if trauma in scientific studies of good quality has been shown to aggravate the primary headache disorder, the patient receives the primary and the secondary headache diagnoses. In many cases of secondary headache, the diagnosis is definite only when the headache resolves or greatly improves within a specified time after effective treatment or spontaneous remission of the causative disorder. In such cases, this temporal relation is an essential part of the evidence of causation.

It is easy to establish the relationship between a headache and head or neck trauma when the headache develops immediately or in the first days after trauma has occurred. On the other hand, it is very difficult when a headache develops weeks or even months after trauma, especially when the majority of these headaches have the pattern of tension-type headache and the prevalence of this type of headache in the population is very high.

Such late onset post-traumatic headaches have been described in anecdotal reports but not in case-control studies. In accordance with new IHS Classification, that will soon be published, acute PTHA develops within 7 days after head trauma or regaining consciousness following head trauma and resolves within 3 months.

New Diagnostic Criteria for Acute Post-traumatic Headache: Acute Posttraumatic Headache with Moderate or Severe Head Injury Diagnostic Criteria

a) Headache, no typical characteristics known, fulfilling criteria C and D
b) Head trauma with at least one of the following:

   1. Loss of consciousness for >30 minutes
   2. Glasgow Coma Scale (GCS) <13
   3. Post-traumatic amnesia for >48 h
   4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracerebral and/or subarachnoid haemorrhage, brain contusion and/or skull fracture)

c) Headache develops within 7 days after head trauma or after regaining consciousness following head trauma
d) One or other of the following:

   1. Headache resolves within 3 months after head trauma
   2. Headache persist but 3 months have not yet passed since head trauma

Acute Posttraumatic Headache with Mild Head Injury

Diagnostic Criteria

a) Headache, no typical characteristics known, fulfilling criteria C and D
b) Head trauma with all the following:

   1. Either no loss of consciousness, or loss of consciousness of <30 minutes duration
   2. Glasgow Coma Scale (GCS) >13
   3. Symptoms and/or signs diagnostic of concussion

c) Headache develops within 7 days after head trauma
d) One or other of the following:

   1. Headache resolves within 3 months after head trauma
   2. Headache persists but 3 months have not yet passed since head trauma.

Before new diagnosis criteria, acute-PTHA might begin less than 14 days after head or neck trauma and continue for up to 8 weeks post-injury (Headache Classification Committee of IHS 1988). Headache that develops longer than 14 days after head injury has been termed "delayed-PTHA or late-acquired headache". If such

headaches persist beyond the first 3 months post-injury, they are subsequently referred to as chronic-PTHA

New Diagnostic Criteria for Chronic Post-traumatic Headache: Chronic Posttraumatic Headache with Moderate or Severe Head Injury Diagnostic Criteria

a) Headache, no typical characteristics known, fulfilling criteria C and D
b) Head trauma with at least one of the following:

  1. Loss of consciousness >30 minutes
  2. Glasgow Coma Scale (GCS) <13
  3. Post-traumatic amnesia >48 hours
  4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracerebral and/or sub-arachnoid haemorrhage, brain contusion and/or skull fracture)

c) Headache develops within 7 days after head trauma or after regaining consciousness following head trauma
d) Headache persists for >3 months after head trauma

Chronic Posttraumatic Headache with Mild Head Injury

Diagnostic Criteria

a) Headache, no typical characteristics known, fulfilling criteria C and D
b) Head trauma with all the following:

  1. Either no loss of consciousness, or loss of consciousness of <30 minutes duration
  2. Glasgow Coma Scale (GCS) >13
  3. Symptoms and/or signs diagnostic of concussion

c) Headache develops within 7 days after head trauma
d) Headache persist for >3 months after head trauma

After mild head trauma, laboratory and ▶ neuroimaging investigations are not habitually needed. When the GCS score is less than 13 in the emergency room after head or neck trauma, LOC is longer than 30 min, there is PTA, neurological deficits or personality disturbances, neuroimaging studies (computer tomography scan, CT, or magnetic resonance imaging, MRI) are indicated. MRI (using at least T1 weighted, T2 weighted, proton density and gradient-echo sequence images) is much more sensitive than CT in detecting and classifying brain lesions. Within 1 week of a head injury, MRI can identify cortical contusions and lesions in the deep white matter of the cerebral hemispheres underdiagnosed by CT. MRI thus provides a sounder basis for diagnosis and treatment in patients suffering from late sequelae of cranial injuries (Voller 2001).

Complementary studies (neuroimaging, EEG, evoked potentials, CSF examination, vestibular function tests) should also be considered for patients with ongoing posttraumatic headaches. The relationship between severity of the injury and severity of the post-traumatic syndrome has not been conclusively established. Moreover, there are some controversial data. Most studies suggest that PTHA is less frequent when the head injury is more severe. Differential diagnosis may include a symptomatic headache, secondary to structural lesions and simulation. There is no evidence that an abnormality in the complementary explorations changes the ▶ prognosis or contributes to treatment. Special complementary studies should be considered on a case-by-case basis or for research purposes.

After several months, some patients developed a daily headache. In the majority of patients with episodic headaches after head injury, this condition is self-limited, but a minority of individuals may develop persistent headaches. Neurological factors have been implicated in the initial phase, psychological and legal factors (litigation and expectations for compensation) in the maintenance of them. Premorbid personality can contribute to development of chronic symptoms, affecting adjustment to injury and treatment outcome. Surprisingly, the risk of developing chronic disturbances seems to be greater for mild-moderate head injury.

Age, gender, certain mechanical factors, a low intellectual, educational and socio-economic level, previous history of headache or alcohol abuse and long duration of unconsciousness or neurological deficits after the head or neck injury, are recognized ▶ risk factors for a poor outcome. Women have higher risk of PTHA and increasing age is associated with a less rapid and less complete recovery. Mechanical impact factors, such as an abnormal position of the head (rotation or inclined) increase the risk of PTHA. Other predictor factors are presence of skull fracture, reduced value of Glasgow Scale, elevated serum protein S-100B and dizziness, headache and nausea in the emergency room (De Krujik 2002).

The role of litigation in the persistence of headache is still discussed. The relationship between legal settlements and the temporal profile of chronic-PTHA is not clearly established, but it is important to carefully assess patients who may be malingering and/or seeking enhanced compensation. In general, medico-legal issues should be solved as soon as possible.

Pathophysiology of PTHA

Pathophysiology of post-traumatic headaches is still not well understood but biological, psychological and social factors are included. In the pathogenesis, common headache pathways with primary headaches have been proposed.

During typical migraine, cerebral cortical and brain stem changes occur. The activation of the brainstem monoaminergic nuclei has been demonstrated with functional imaging studies (Bahra 2001). Disturbed neuronal calcium influx and / or hemostatic alterations

have also been involved. However, these events have not been included for PTMA yet.

In recent years, several pieces of research have implicated similar neurochemical changes in both typical migraine and experimental traumatic brain injury, excessive release of excitatory amino acids, alterations in serotonin, abnormalities in catecholamines and endogenous opioids, decline in magnesium levels, abnormalities in nitric oxide formation and alterations in neuropeptides (Packard 1997). Whether these changes are determining, contributing or precipitating factors for headache in each patient is still unknown. In addition, in patients with late-PTMA a sensitization phenomenon is possible. In some patients without previous migraine and history of a recent mild head injury, trigeminal neuron sensitization could be a central cause in relation to focal lesions. Central and peripheral sensitizations have been proposed before by other authors (Malick 2000; Packard 2002).

Further researches are still necessary to clarify the relationship between chronic symptoms after mild head trauma and neuroimaging abnormalities. These abnormalities could provide a pathological basis for long-term neurological disability in patients with post-concussive syndrome. New techniques of MRI (especially diffusion tensor imaging and magnetization transfer ratio) are useful for the detection of small parenchymal brain lesions, diffuse axonal injury secondary to disruption of axonal membranes or delayed cerebral atrophy (Hofman 2002). In normal appearing white matter, magnetic resonance spectroscopy studies detect metabolic brain changes (an early reduction in N-acetyl aspartate and an increase in choline compounds), which correlate with head injury severity (Garnett 2000). Positron-emission tomography (PET), single-photon emission computed tomography (SPECT) and xenon 133 CT may provide evidence of brain perfusion abnormalities after mild head trauma and in the presence of chronic posttraumatic symptoms (Aumile 2002).

Management Strategies

Trauma-induced headaches are usually heterogeneous in nature, including both tension-type and intermittent migraine attacks. Over time, PTHA may take on a pattern of daily occurrence, although if aggressive treatment is initiated early, PTHA is less likely to become a permanent problem. Adequate treatment typically requires both "central" and "peripheral" measures. Delayed recovery from PTHA may be a result of inadequately aggressive or ineffective treatment, overuse of analgesic medications resulting in analgesia rebound phenomena or comorbid psychiatric disorders (posttraumatic stress disorder, insomnia, substance abuse, depression or anxiety) (Lane 2002).

In general, treatment strategies are based upon studies of non-traumatic headache types. Acute-PTHA may be treated with analgesics, anti-inflammatory agents and physiotherapy. PTMA may be also treated with ergotamine or triptans. Chronic-PTHA needs prophylactic medication, chronic-PTMA specific antimigraine medications. Previously amitriptyline or propranolol used alone or in combination and verapamil have been demonstrated to improve all symptoms of postconcussive syndrome, especially the migraine. Recently, Packard has published very good results with divalproex sodium as a preventive option in the treatment of PTMA (Packard 2000). Additional physical therapy, psychotherapy (bio-feedback) and appropriate educational support can be supplied, especially in patients with risk factors for poor prognosis. Explanation of the headache's nature can also improve the patient's evolution. In some cases, when a post-traumatic lesion is identified as a peripheral triggering factor for headache, specific treatment of the triggering lesion can resolve the pain. PTMA poorly treated will affect family life, recreation and employment There is no good evidence that litigation and economical expectation is associated with prolongation of headaches, however litigation should be solved as soon as is possible.

Conclusions

Trauma induced headache and headache attributed to whiplash should be treated early or associated complications will appear (daily occurrence of headache, overuse of analgesic medications and comorbid psychiatric disorders). Preventive and symptomatic treatments may be prescribed according to the clinical pattern of the headache (tension-type, migraine, cluster or cervicogenic headaches) as a primary headache. Physiotherapy, psychotherapy and resolution of litigation can be contributing factors to recovery.

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Headache Associated with Disorders of the Cranium

▶ Headache from Cranial Bone

Headache Associated with Psychotic Disorder

▶ Headache Due to Somatoform Disorder

Headache Associated with Somatisation Disorder

▶ Headache Due to Somatoform Disorder

Headache Attributed to a Substance or its Withdrawal

STEPHEN D. SILBERSTEIN
Jefferson Medical College, Thomas Jefferson University and Jefferson Headache Center, Thomas Jefferson University Hospital, Philadelphia, PA, USA
stephen.silberstein@jefferson.edu

Synonyms

Medication-Induced Headaches; headaches associated with substances or their withdrawal

Definition

The International Headache Society (IHS) previously grouped medication-induced headaches under the rubric "headaches associated with substances or their withdrawal (Headache Classification Committee of the International Headache Society 1988)." The new IHS classification (Headache Classification Committee 2003) now calls these "headaches attributed to a substance or its withdrawal (Monteiro and Dahlof 2000)."

Food, chemical and drug ingestion or exposure can be both a cause of and a trigger for headache (Silberstein 1998). Their association is often based on reports of adverse drug reactions and anecdotal data and does not prove causality. When a new headache occurs for the first time in close temporal relation to substance exposure, it is coded as a secondary headache attributed to the substance. When a pre-existing primary headache is made worse by substance exposure, there are two possibilities. The patient can either be given only the diagnosis of the pre-existing primary headache or be given both this diagnosis and the diagnosis of headache attributed to the substance (Headache Classification Committee 2003).

Headache Attributed to Acute Substance Use or Exposure (Headache Classification Committee 2003)

Diagnostic Criteria
1. Headache fulfilling criteria 3 and 4.
2. Acute use of or other acute exposure to a substance.
3. Headache develops within 12 h of use or exposure.
4. Headache resolves within 72 h after single use or exposure.

Characteristics

Alcohol, food and food additives and chemical and drug ingestion and withdrawal have all been reported to provoke or activate migraine in susceptible individuals. Since headache is a complaint often attributed to placebo, substance-related headache may arise as a result of expectation. The association between a headache and an exposure may be coincidental (occurring just on the basis of chance) or due to a concomitant illness or a direct or indirect effect of the drug and may depend on the condition being treated. Headache can be a symptom of a systemic disease and drugs given to treat such a condition will be associated with headache. Some disorders may predispose to substance-related headache. Alone, neither the drug nor the condition would produce headache. A ▶ NSAIDs, Survey may produce headache by inducing aseptic meningitis in susceptible individuals. The possible relationships between drugs and headache are outlined below (Silberstein 1998).

Drug and Substance Related Headache

A Coincidental
B Reverse causality
C Interaction headache
D Causal

Acute: Primary effect; Secondary Effect

Acute Drug-induced Headache

Whether or not a drug triggers a headache often depends on the presence or absence of an underlying headache disorder. Headaches are usually similar to the preexisting headache. The drugs most commonly associated

with acute headache can be divided into several classes (Monteiro and Dahlof 2000).

Vasodilator's

Headache is a frequent side effect of antihypertensive drugs. It has been reported with the beta-blockers, ► calcium channel blockers (especially nifedipine), ACE inhibitors and methyldopa. Nicotinic acid, dipyridamole and hydralazine have also been associated with headache. The headache mechanism is uncertain (Thomson Healthcare 2003).

Nitric Oxide Donor-induced Headache

Headache is well known as a side effect of therapeutic use of nitroglycerin (GTN) and other ► nitric oxide (NO) donors. They may cause headache by activating the trigeminal vascular pathway. There is an immediate NO donor-induced headache (GTN headache), which develops within 10 min after absorption of NO donor and resolves within 1 h after release of NO has ended. There is also a delayed NO donor-induced headache, which develops after NO is cleared from the blood and resolves within 72 h after single exposure (Ashina et al. 2000).

Phosphodiesterase Inhibitor-induced Headache

Phosphodiesterases (PDEs) are a large family of enzymes that break down cyclic ► nucleotide s (cGMP and cAMP). PDE-5 inhibitors include sildenafil and dipyridamole. The headache, unlike GTN-induced headache, is monophasic. In normal volunteers it has the characteristics of tension-type headache, but in migraine sufferers it has the characteristics of migraine without aura (Headache Classification Committee 2003).

Histamine-induced Headache

Histamine causes an immediate headache in non-headache sufferers and an immediate as well as a delayed headache in migraine sufferers. The mechanism is primarily mediated *via* the H_1 receptor because it is almost completely blocked by mepyramine. The immediate histamine-induced headache develops within 10 min and resolves within 1 h after absorption of histamine has ceased. The delayed histamine-induced headache develops after histamine is cleared from the blood and resolves within 72 h (Krabbe and Olesen 1980).

Nonsteroidal Anti-Inflammatory Drugs

The nonsteroidal anti-inflammatory drugs, especially indomethacin, have been associated with headache. Mechanisms include aseptic meningitis (especially with ibuprofen) and reverse causality.

Serotonin Agonists

M-chlorophenylpiperazine, a metabolite of the antidepressant trazodone, can trigger headache by activating the serotonin (5-hydroxytryptamine [HT]) 2B and 2C receptors (Brewerton et al. 1988). This may be the mechanism of headache induction during early treatment with selective serotonin reuptake inhibitors.

Foods and Natural Products (Headache Induced by Food Components and Additives)

Chocolate, alcohol, citrus fruits, cheese and dairy products are the foods that patients most commonly believe trigger their migraine, but the evidence is not persuasive.

Amino Acids

Monosodium glutamate (MSG) (Schamburg et al. 1969) and aspartame, the active ingredient of "NutraSweet," may cause headache in susceptible individuals (Schiffmann et al. 1987). Phenyl ethylamine, tyramine and aspartame have been incriminated, but their headache-inducing potential is not sufficiently validated.

Monosodium Glutamate-induced Headache (Chinese Restaurant Syndrome)

MSG can induce headache and the Chinese restaurant syndrome in susceptible individuals. The headache is typically dull or burning and non-pulsating, but may be pulsating in migraine sufferers. It is commonly associated with other symptoms, including pressure in the chest, pressure and / or tightness in the face, burning sensations in the chest, neck or shoulders, flushing of the face, dizziness and abdominal discomfort (Schamburg et al. 1969).

Aspartame

Aspartame a sugar substitute is an o-methyl ester of the dipeptide L-α-aspartyl-L-phenylalanine that blocks the increase in brain tryptophan, 5-HT and 5-hydroxyindolacetic acid normally seen after carbohydrate consumption (Schiffmann et al. 1987). It produced headache in two controlled studies but not a third (Silberstein 1998).

Tyramine

Tyramine is a biogenic amine that is present in mature cheeses. It is probably not a migraine trigger (Silberstein 1998).

Phenyl Ethylamine

Chocolate contains large amounts of β-phenyl ethylamine, a vasoactive amine that is, in part, metabolized by monoamine oxidase. The evidence to support it as a trigger is weak (Silberstein 1998).

Ethanol

Alone or in combination with ► congener s (wine), ethanol can induce headache in susceptible individuals. The attacks often occur within hours after ingestion. In the United Kingdom, red wine is more likely to trigger migraine than white, while in France and Italy white wine is more likely to produce headache than red. Headaches are more likely to develop in response to white wine if red coloring matter has been added.

Migraineurs who believed that red wine (but not alcohol) provoked their headaches were challenged either with red wine or with a vodka mixture of equivalent alcoholic content. The red wine provoked migraine in 9 / 11 subjects, the vodka in 0 / 11. Neither provoked headache in other migraine subjects or controls (Littlewood et al. 1988). It is not known which component of red wine triggers headache and the study may not have been blinded to oenophiles.

The susceptibility to hangover headache has not been determined. Migraineurs can suffer a migraine the next day after only modest alcoholic intake, while non-migraineurs usually need a high intake of alcoholic beverages to develop hangover headache. A few subjects develop headache due to a direct effect of alcohol or alcoholic beverages (cocktail headache). This is much rarer than delayed alcohol-induced headache (hangover headache).

Lactose Intolerance

Lactose intolerance is a common genetic disorder, occurring in over two-thirds of African-Americans, native Americans and Ashkenazi Jews and in 10% of individuals of Scandinavian ancestry. The most common symptoms are abdominal cramps and flatulence. How lactose intolerance triggers migraine is uncertain (Silberstein 1998).

Chocolate

Chocolate is the food most frequently believed to trigger headache, but the evidence supporting this belief is inconsistent (Scharff and Marcus 1999). Chocolate is probably not a migraine trigger, despite the fact that many migraineurs believe that it triggers their headache. It is the most commonly craved food in the United States. Women are more likely than men to have migraine and they crave chocolate more than men. Sweet craving is a premonitory symptom of migraine and menses are often associated with an increase in carbohydrate and chocolate craving.

Chemotherapeutic Drugs

▶ Intrathecal methotrexate and diaziquone can produce aseptic meningitis and headache. Methyldichlorophen, interferon B and interleukin 2 are all associated with headache (Boogerd 1995).

Immunomodulating Drugs

Cyclosporine, FK-506, thalidomide and antithymocyte globulin have been associated with headache (Shah and Lisak 1995).

Antimicrobial and Antimalarial Drugs

Amphotericin, griseofulvin, tetracycline and sulfonamides have been associated with headache. Chloroquine and ethionamide are also associated with headache.

Other Substances

Carbon monoxide-induced Headache (Warehouse Workers' Headache)

Typically this is a mild headache without associated symptoms with carboxyhemoglobin levels of 10–20%, a moderate pulsating headache and irritability with levels of 20–30% and a severe headache with nausea, vomiting and blurred vision with levels of 30–40%. When carboxyhemoglobin levels are higher than 40%, headache is not usually a complaint because of changes in consciousness.

Cocaine-induced Headache

Headache is common, develops immediately or within 1 h after use and is not associated with other symptoms unless there is concomitant stroke or TIA (Dhopesh et al. 1991).

Cannabis-induced Headache

Cannabis use is reported to cause headache associated with dryness of the mouth, paresthesias, feelings of warmth and suffusion of the conjunctivae (elMallakh 1987).

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Headache Due to Arteritis

PETER BERLIT
Department of Neurology, Alfried Krupp Hospital, Essen, Germany
peter.berlit@krupp-krankenhaus.de

Synonyms

Vasculitis; Angiitis of the CNS

Definition

Headache is the most common complaint in ► temporal arteritis. The major symptoms of central nervous system arteritis are multifocal neurological symptoms following ► stroke, in combination with headache and some degree of ► encephalopathy, with and without ► seizures. CNS-vasculitis may be part of a systemic autoimmune disease or the only manifestation of angiitis (isolated ► angiitis of the central nervous system – IAN).

Characteristics

Temporal Arteritis

Temporal arteritis (► cranial arteritis, giant cell arteritis) is an autoimmune disease of elderly people, affecting women more frequently than men (3:1). Mean age at the beginning of the disorder is 65 years or more; the disease rarely appears before the age of 50. The incidence is 18 / 100,000; there is a frequent association with HLA-DR4. The diagnosis is confirmed by the histological examination of a ► biopsy specimen from the temporal artery, demonstrating the arteritis with necrosis of the media and a granulomatous inflammatory exsudate containing lymphocytes, leukocytes and giant cells.

Headache is the most common complaint in temporal arteritis, associated with a markedly elevated sedimentation rate. The patient develops an increasingly intense head pain, usually unilateral, sometimes bilateral. It has a non-pulsating often sharp and stabbing character, sometimes with a temporal pronunciation. But the localization of the headache may be frontal, occipital or even nuchal (Pradalier and Le Quellec 2000). The pain increases during the night hours and persists throughout the day. Due to ischemia of the masseter muscles during mastication, ► jaw claudication may appear

Headache Due to Arteritis, Table 1 Frequency of signs and symptoms with temporal arteritis (adapted from Caselli and Hunder 1996)

Symptom	all (%)	initial symptom (%)
headache	72	33
polymyalgia rheumatica	58	25
malaise, weight loss	56	20
jaw claudication	40	4
fever	35	11
cough	17	8
neuropathies (mono-, or multiplex)	14	0
disorders of swallowing	11	2
amaurosis fugax	10	2
permanent loss of vision	8	3
claudication of limbs (legs)	8	0
stroke	7	0
neuro-otologic disorders	7	0
flimmer-scotoma	5	0
pain of the tongue	4	0
depression	3	0.6
diplopia	2	0
myelopathy	0.6	0

(Berlit 1997). The superficial temporal artery may be thickened and tender without pulsation –"cord-sign".

Diagnostic criteria of temporal arteritis

- age 50 years or more
- newly developed headache
- tenderness of the superficial temporal artery
- elevated sedimentation rate, at least 50 mm / h
- giant cell arteritis in a biopsy specimen from the temporal artery

Besides the headache, there may be severe pain, aching and symmetrical stiffness in proximal muscles of the limbs (polymyalgia rheumatica) in as many as 50% of patients. Many patients present the symptoms of a cryptogenic neoplasm, anorexia, loss of weight, anemia, malaise and low-grade fever.

Sudden blindness results from involvement of the posterior ciliary arteries, and blindness of one eye may be followed by the other. Other complications include the affection of intracranial or spinal vessels, necrosis of the scalp or tongue and generalization of the arteritis affecting the coronary arteries, the aorta or the intestines.

The treatment of choice at the earliest suspicion of cranial arteritis is ► prednisone 60–80 mg / day. If ischemic complications are present, a steroid pulse-

therapy for 3 days with at least 500 mg prednisone i.v. is recommended. Patients respond quickly and often very impressively to steroids. The start of this therapy should not be delayed for the biopsy. Depending on the clinical symptoms and the sedimentation rate, steroids are gradually reduced. In the majority of patients, steroid treatment is necessary for at least 20 months; therefore a biopsy is mandatory in all cases. During the long-term course, the CRP is more helpful in the prediction of relapses than the sedimentation rate (Berlit 1997). If necessary, ► azathioprine or ► methotrexate may be used as steroid sparing agents.

Systemic Lupus Erythematosus (SLE)

► Systemic lupus erythematosus (SLE) is the most frequent systemic autoimmune disease, incidence 7 / 100,000 (Ruiz-Irastorza et al. 2001); the prevalence in Europe and the USA is 10 to 60 / 100,000 per year, women : men = 10 : 1. The most common age of manifestation is 15–30 years. Both migraine type headaches (see ► migraine) are frequent. SLE is characterized by a disturbed regulation of T- and B-cell immunity with antinuclear antibodies and autoreactivity against other autoantigens in the progressive relapsing course of the disease. The multilocular manifestations are caused by a thrombotic vasopathy or antibodies interacting with cell membrane functions; a true vasculitis is rare. Antinuclear antibodies are present in 95%, ds-DNA-antibodies in 80%. ► Photosensitivity of the skin with a ► butterfly erythema of the face are typical symptoms of SLE. Arthritis and serositis with pulmonary and cardiac manifestations are frequent. Neurological symptoms are present in about 50% of the patients, encephalopathy (60%), seizures (60%) and stroke (40%). In SLE, strokes are frequently caused by a secondary ► antiphospholipid syndrome (25% of all SLE patients). This diagnosis is made with the detection of lupus anticoagulant and IgG-anticardiolipin antibodies. Stroke may also be caused by cardiogenic embolism with Libmann-Sacks endocarditis or by thrombotic thrombocytopenic purpura. Some autoantibodies (ab) are associated with certain clinical manifestations, ribosomal P –psychosis, Jo 1 – polymyositis, antineuronal – epilepsy, encephalopathy. A classification of the neuropsychiatric SLE-manifestations including headache has been given by the ACR Ad Hoc Committee on Neuropsychiatric Lupus in 1999. In case-control studies, there was no difference between SLE patients and the general population regarding the prevalence and incidence of migraine or tension type headache (Fernandez-Nebro et al. 1999; Sfikakis et al. 1998). In SLE patients with tension type headache, there was an association with personality changes, emotional conflicts and depression (Omdal 2001). Most of these patients have higher disease activity scores (Amit et al. 1999). There was no association between anticardiolipin antibodies and migraine in a prospective study

(Vazquez-Cruz et al. 1990). If a SLE patient develops a new headache, a neurological examination including ► MRI and lumbar puncture is mandatory. The association with a ► pseudotumor cerebri should be excluded. Treatment of idiopathic headache syndromes in SLE is the same as in the general population. A headache as the sole neurological symptom of SLE should not alter the immunosuppressive strategy in the individual patient.

Sjögren's Syndrome

► Sjögren's syndrome is clinically characterized by keratoconjunctivitis sicca and symptomatic xerostomia (the sicca-syndrome) and associated with the detection of anti-Ro (SSA–97%) and anti-La (SSB–78%) autoantibodies. In addition to multifocal CNS symptoms with encephalopathy, depression or headache, a polyneuropathy and myopathy occur frequently. Whenever possible the diagnosis should be verified with a salivary gland biopsy. The incidence of migraine is higher in patients with a sicca syndrome or Raynaud phenomenon (Pal et al. 1989). ► Flunarizin may be helpful for prophylaxis in rheumatologic patients with migraine (Mazagri and Shuaib 1992).

Wegener's Granulomatosis (WG)

► Wegener's granulomatosis (WG) is a rare autoimmune disease (1 per 100,000) associated with antineutrophile cytoplasmic antibodies (c-ANCA); men are affected twice as often as women. In the limited stage of the disease, necrotizing granulomas of the nose and the paranasal sinuses may lead to compression of neighborhood structures with cranial nerve lesions, diabetes insipidus or exophthalmus. With generalization, the systemic necrotizing vasculitis involving small arteries and veins leads to affections of the lung and kidney.
In the limited stage of WG, headaches are frequent and often caused by sinusitis, non-septic meningitis or local granulomas (Lim et al. 2002). MRI may show enhancement of the basal meninges especially of the tentorium (Specks et al. 2000); the development of an occlusive or communicating hydrocephalus is possible (Scarrow et al. 1998) and must be excluded.
Prednisone and ► cyclophosphamide are the treatment of choice in generalized WG. In the limited stage of the disease, the combination of 2×800 mg sulfamethoxazole and 2×160 mg trimethoprim (► Cotrimoxazol) may be sufficient. Headaches are treated symptomatically with paracetamol or non-steroidal antiphlogistics.

Behçet's Disease

► Behçet's disease presents with the trias of iridocyclitis and oral and genital ulcers. The underlying systemic vasculitis of especially the veins may lead to an ► erythema nodosum, a thrombophlebitis, polyarthritis or ulcerative colitis. Behçet's syndrome is rare in the USA and Germany (incidence 1 / 500,000), but

frequent in Turkey (300 / 100,000); men are affected twice as often as women, usually between the ages of 20 and 40. There is an association with HLA-B5. Neurological manifestations occur in approximately 30%, either as ► meningoencephalitis of the brain stem and cerebellum or as a ► sinus thrombosis, which presents often as pseudotumor cerebri (Akman-Demir et al. 1999). Headaches are the most common complaint in ► neuro-Behçet (87%). The holocephal stabbing severe pain does not usually respond to conventional analgetics, but resolves with steroid treatment. MRI and lumbar puncture are diagnostic. Steroids and immunosuppressants like azathioprine are the treatment of choice. In sinus thrombosis, anticoagulants must be given in addition.

Isolated Angiitis of the Central Nervous System – IAN (Granulomatous Arteritis of the Nervous System – GANS)

Isolated angiitis of the central nervous system – IAN (granulomatous arteritis of the nervous system – GANS) is an idiopathic medium and small vessel vasculitis affecting exclusively CNS vessels of the brain or spinal cord. About 350 cases have been documented worldwide (Schmidley 2000). The major symptoms of IAN are multifocal neurological symptoms following stroke, in combination with headache and some degree of encephalopathy, with or without seizures, cranial nerve palsies or ► myelopathy.

The encephalopathy occurs in 40–80%, subacute or chronic headaches in 40–60%, focal symptoms in 40–70% and seizures are present in 30%. An acute beginning of IAN has been described in only 11%; most patients develop the symptoms slowly and progressively. Systemic signs of inflammation (fever, ESR, CRP) are rare (10–20%). On the other hand, there are usually signs of inflammation in the CSF (pleocytosis, elevation of protein, oligoclonal banding). The specificities of cerebral ► angiography or MRI are below 30%. For definitive diagnosis of IAN, a combined leptomeningeal and parenchymal biopsy is necessary, especially in order to exclude infections or tumors (lymphoma!). Before the treatment of choice with prednisone and cyclophosphamide is established, a systemic inflammation or infection must be excluded and leptomeningeal and parenchymal biopsies must demonstrate the vascular inflammation (Moore 1989). Without histological verification of the diagnosis, blind treatment is dangerous and possibly harmful for the patient and must be strictly avoided. With immunosuppressive therapy the headaches resolve completely within a few weeks.

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Headache Due to Brain Metastases

Definition

Intracranial metastases are found in about 25% of all patients who have died of cancer. Some of these tumors are silent, but the majority cause the syndrome consisting of headache, nausea and vomiting, mental change, confusion, seizures and neurological deficit. Some tumors frequently produce brain secondaries (e.g. cancers of the lung and breast as well as melanoma), some only seldomly (e.g. cancer of ovary). Primary tumors, although relatively rare, can produce the same syndrome. Headache may arise from an expanding mass within the skull and distension of meninges. The treatment of choice is skull irradiation accompanied

by the use of dexamethasone. The headache may get worse after morphine.

▶ Cancer Pain

Headache Due to Dissection

MATHIAS STURZENEGGER
Department of Neurology, University of Bern, Bern, Switzerland
matthias.sturzenegger@insel.ch

Synonyms

There are no direct synonyms for headaches resulting from dissections of cervico-cranial arteries. The location of these headaches is variable and mainly dependent on the dissected vessel segment and thus may cause differential diagnostic confusions.

Differential Diagnostic Aspects

The following three pathophysiologically poorly defined and most probably heterogeneous clinical syndromes with a diagnostic eponym may well be caused by dissection.
Sturzenegger 1995).
Carotidynia is a poorly defined syndrome with unilateral anterolateral cervical pain and tenderness. It is good advice to rule out underlying carotid dissection first, since most reports of this entity date from decades ago and the patients' carotid arteries have not been properly studied (no ultrasound, MRI, MRA or angiographic evaluation) (Biousse and Bousser 1994).
Tolosa-Hunt Syndrome (Painful Ophthalmoplegia); variable combination of periorbital pain, ipsilateral oculomotor nerve palsies, oculosympathetic palsy and trigeminal sensory loss) localize the pathological process to the region of the cavernous sinus. The causes may be traumatic, neoplastic, vascular or inflammatory. Within the inflammatory category, there is a specific subset of patients with a steroid responsive relapsing and remitting course – Tolosa-Hunt syndrome in the strict sense. The comprehensive patient evaluation is essential in establishing the correct diagnosis (Kline and Hoyt 2001).
Furthermore, the severe intensity and frequently orbital pain location of headache due to ICAD may at a first glance mimic cluster headache, but there are usually no recurrent short lasting attacks and no clustered bouts.

Definition

As already indicated by the title, the headaches are defined by their underlying pathology, i.e. dissection of the arteries. Since we are talking about headache, it is evident that we talk about dissections of cervico-cranial arteries; it is exceptional that dissection of the subclavian artery or aorta produce headache.

Pathogenesis

We have however to keep in mind that pain is usually a symptom of arterial dissections any where in the body, e.g. also of the aorta, renal or coronary arteries. The question rises why dissections are painful. Other pathologies of arterial walls may also be painful such as arteritis (e.g. giant cell arteritis) whereas atherosclerosis is usually painless.
We know that the walls of extracranial and also basal intracranial arteries are densely supplied with nociceptive, mainly trigeminal nerve fibers (Norregaard and Moskowitz 1985). These fibers are sensitive to inflammatory stimuli such as in vasculitis or to distension of the vessel wall that may take place during balloon dilatation or as a consequence of intramural hemorrhage such as in dissection. In atherosclerosis, although usually considered as an inflammatory process too, the inflammatory activity is probably simply too low to cause nociceptor discharge. It is controversial whether the irritation of the perivascular sympathetic nerve plexus, existing around the carotid as well as the vertebral arteries is another explanation or a contributing etiological factor of dissection-associated pain (De Marinis et al. 1991). In my personal experience, pain may be equally intense in dissections with definite vessel diameter extension as in those dissections without enlargement but merely vessel stenosis or occlusion. Furthermore, also from merely personal experience, pain is not more frequent in patients with Horner's syndrome compared to those without.
Dissection associated pain is usually reported with internal carotid (ICA) or vertebral artery (VA) dissections. We do not have data regarding dissection of extracranial carotid arteries and their branches or subclavian arteries and their branches, nor whether such pathologies exist and how frequently nor whether they may cause any pain. We know, that dissections may take place without causing pain. It seems to be rare, but we usually detect dissections because of their consequences such as pain or cerebral ischemia. That means that asymptomatic dissections may simply go undetected and painless dissections with other complications, such as lower cranial nerve palsy or cerebral ischemia may go unrecognized, since adequate diagnostic methods to detect dissections are not performed. In patients with "painful Horner's syndrome", many physicians have learned to think of ipsilateral internal carotid artery dissection (ICAD), but in what percentage of painless Horner's syndrome is ICAD the cause or is ICAD searched for?
The larger the affected vessel (carotid *versus* vertebral arteries) the more easily dissections are detected, i.e. can be imaged. Yet, without applying fat saturated T1 MRI sequences and, furthermore, that specific method to the appropriate vessel segment (e.g. the high cervical retromandibular ICA segment) painful ICAD without causing vessel stenosis may not be detected even when per-

forming Doppler, Duplex MRA and conventional MRI. In the VA, it is well known that for various reasons MRI, as well as Doppler / Duplex examination are much less sensitive to dissections as compared to angiography, an invasive procedure not completely without risks.

To summarize: pain may herald dissections early on, absence of pain does not exclude dissections, the frequency of painless and asymptomatic dissections is not known but they certainly exist.

Clinical Relevance

The most important aspect of headaches caused by dissections is the fact that they usually herald the onset of dissection and allow early recognition of the underlying pathology. Paying adequate attention to these warning symptoms enables the aversion of the often life-threatening sequelae of cerebral ischemia. 50–80% of patients with a dissection of the cervicocerebral arteries suffer a subsequent stroke; dissections are responsible for 20–30% of all strokes in young (<45 years) persons; warning headaches preceding stroke have been noted in 47–74% of patients with ICAD and in 33–85% of patients with VAD (Fisher 1982; Silbert et al. 1995; Sturzenegger 1994; Sturzenegger 1995).

Characteristics

Headaches caused by dissections have some typical although eventually unspecific features, which are not necessarily present in all cases. Independent of the affected vessel, these are high pain intensity, pain quality not experienced before, continuous more frequent than fluctuating pain over days, constant localization, sharp quality and tenderness of the painful head, face or neck area. Headache onset may be acute or even "thunderclap"-like suggesting subarachnoid hemorrhage, which indeed may be a complication of dissections of intracranial, especially vertebral artery, segments.

Additional characteristics are dependent on the vessel segment affected by the dissection. In the literature there are usually two broad categories, the traumatic and the spontaneous (non traumatic) dissections. This distinction is somewhat arbitrary since in many ▶ spontaneous dissections one will find some kind of so-called "trivial" trauma such as neck thrusting, a fall or certain sports or other violent physical activities with questionable significance.

From the literature one gets the impression that traumatic dissections are more frequently painless; yet this may simple be an assessment bias since in traumatic dissections there are additional injuries readily explaining pain or the health state of the patients is too serious to worry about pain or to make pain assessment possible. In the spontaneous dissection subgroup, the literature reports four major categories, extracranial carotid dissections, intracranial carotid dissections and their branches, extracranial vertebral artery dissections and intracranial vertebral artery dissections and their branches. It may however well be that these categories are human constructions, just for educational reasons, without reflecting the reality of e.g. dissections affecting several segments of one artery or even several arteries. The vessel segments affected by dissections obviously show regional or probably ethnical variations with e.g. dissections of intracranial vertebral artery segments and their branches predominantly reported from Japan.

Spontaneous Internal Carotid Artery Dissection

The most typical clinical syndrome and the most frequent dissection is that of the extracranial segment of the internal carotid artery. Usually the most distal (high cervical, retromandibular) carotid segment just before entering the petrous canal is affected.

Spontaneous Dissection of Extracranial Internal Carotid Artery

Headache is reported in 55–95% of ICAD and was the first symptom in 47–68% (Biousse et al. 1994; Fisher 1982; Schievink 2001; Silbert et al. 1995; Sturzenegger 1995). Headache, facial or orbital pain may be the sole symptom of dissection, probably more frequently than reported so far (5%) and poses a diagnostic challenge. Local neurological manifestations (Horner's sign (35–48%), lower cranial nerve palsies (~10%) or pulsatile tinnitus (up to 30%)) are found in 30–48% of cases (Sturzenegger 1995; Sturzenegger and Huber 1993). Up to one third may complain of unilateral scalp tenderness and hair hypersensitivity. Ischemic cerebral events occur in 86% (stroke in 60% and TIA in 20%) and retinal events in 20% (Biousse et al. 1994; Schievink 2001; Sturzenegger 1995). Headache location is unilateral (79–90%), ipsilateral to the side of dissection (almost all), in the forehead (~70%), temple (~75%), eye or peri-orbital (~60%; ~10% isolated) or ear (~20%; ~10% isolated). The headache quality is steady (~75%), pulsating (25–40%), of severe intensity in 85%, thunderclap-like (14%, mimicking SAB), severe periorbital (10%, mimicking cluster headache), unique and never experienced before (65%). Headache duration is less than 1 week in 90% (range, hours to years). Anterolateral neck pain is reported by 26–60%, usually located in the upper neck behind the angle of the jaw.

Since migraine is a frequent disease, and reported in up to 40% of patients with carotid dissection and even considered a risk factor for dissection (D'Anglejean Chatillon et al. 1989), it is important not to confound migraine headaches with dissection headaches. The patient can usually distinguish these two headache types; dissection headache is a pain he never experienced before, is a continuous and not episodic pain, is not associated with general vegetative symptoms (nausea, vomiting, photophobia) and is usually constant not throbbing. Before assum-

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ing a so-called "migrainous infarct", one should exclude underlying carotid dissection as the cause of the pain and (embolic) brain ischemia. Thus, if a patient with a history of migraine, reports any change in the headache pattern (e.g. unique quality, long-lasting) or clinical characteristic, which he has not experienced before, ICAD should be considered and the appropriate investigation (ultrasound, MRI, MRA) performed soon.

The distinction from cluster headache is usually possible taking into account the duration (repetitive short attacks for cluster) and the autonomic symptoms (hyperhidrosis in cluster, anhidrosis in ICAD).

Spontaneous Dissection of the Intracranial Internal Carotid Artery

Intracranial carotid artery dissection affecting the supraclinoid portion of the ICA and or the middle and anterior cerebral arteries is very rare, especially when compared with dissections of the extracranial ICA. Whether it represents a unique entity, different from the more common extracranial variant, is unclear. Diagnosis is more difficult and usually needs angiography or high quality MRA. According to the literature, it preferentially affects very young patients (between 15 and 25 years) without any vascular risk factors. The clinical presentation comprises severe unilateral retroorbital and temporal headache followed by contralateral hemiparesis usually immediately after headache onset (Chaves et al. 2002).

Spontaneous Vertebral Artery Dissection

Dissections of the VA most frequently affect the mobile and easily distorted V3 segment. The distal extension is frequently difficult to assess and distinction between extracranial and intracranial dissection more difficult in the vertebrobasilar territory than in the carotid.

Yet it could probably be of relevance, since anticoagulation of intracranial dissections, more frequently producing aneurysms, bears a significant risk of subarachnoid hemorrhage, which may accompany intracranial VAD even without anticoagulant treatment.

Headache is reported in 69–85% and was the first symptom in 33–75% (Silbert et al. 1995; Sturzenegger 1994). Headache location is ipsilateral to the side of dissection (almost always), usually in the occiput (~ 80%). Pain always started suddenly, was of sharp quality and severe intensity, different from any previously experienced headache. Headache was steady in about 60% and pulsating in about 40%. The time course of pain was monophasic with gradual remission of a persistent headache lasting 1 to 3 weeks.

Posterior neck pain is reported by 46–80% and may be the only symptom (no associated headache). A delay between onset of head and neck pain heralding onset of dissection and neurological dysfunction is frequent (33–85%) and may be of variable duration (hours to 3 weeks). Report of this distinct type of headache should raise suspicion of an underlying dissection of a vertebral artery. Its early diagnosis and immediate anticoagulation if confined to the extracranial segments may help prevent vertebro-basilar ischemic deficits, which are frequently severe. Presenting clinical features of VAD are extremely variable and include locked-in syndrome, Wallenberg syndrome, which represents the most frequently encountered type of neurological dysfunction, cerebellar syndrome, vestibular syndrome, transient amnesia, tinnitus and hemianopia. Vertebral artery dissection may also occur silently, even without headache and is detected by chance. This seems to happen predominantly in the case of multiple dissections of cervical arteries.

Vertebral artery dissection may be caused by neck manipulation (Williams and Biller 2003). If neck pain is the sole indication for such a treatment, especially in young people who never experienced such a pain before, one should be aware that VAD may be the cause and manipulation might be fatal.

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Headache Due to Hypertension

JOHN EDMEADS
Sunnybrook and Woman's College Health Sciences
Centre, University of Toronto, Toronto, ON, Canada
john.edmeads@sw.ca

Synonyms

Hypertensive Headaches; hypertensive encephalopathy; Reversible Posterior Leucoencephalopathy Syndrome

Definition

Headaches and hypertension have in common the characteristics that both are prevalent, both are caused by multiple factors and both can have acute and chronic phases. The relationships between them are thus multiple and complex.

1. They most often exist coincidentally, with no causal relation between high blood pressure and headache. It is a common lay misconception that chronic hypertension frequently causes headaches. Epidemiological studies show that the prevalence of headache is no higher in patients with mild or moderate hypertension than it is in age-matched normotensive populations (Badran et al. 1970) and, conversely, hypertension is no more common in headache populations than in those without headaches (Waters 1971). When patients with mild to moderate hypertension (diastolic below 120) have headaches, they are likely to be the same migraine and tension-type headaches that bedevil their normotensive brethren. However, severe hypertension (diastolic above 120) may cause headaches by a number of mechanisms.

2. Chronic severe hypertension may cause characteristic recurrent early morning headaches (see section on "Characteristics" for clinical details). It is believed that in chronic severe hypertension the ability of the cerebral circulation to autoregulate itself – that is, to vasoconstrict in order to prevent an increased cerebral blood volume, increased brain capillary hydrostatic pressure and cerebral edema – is impaired and that this, in combination with the effects of the head low position during sleep and perhaps with the vasodilating effects of CO_2 retention during sleep, causes increased intracranial pressure and headache.

3. As a rare complication of chronic hypertension, acute ▶ hypertensive encephalopathy may occur (see section on "Characteristics" for clinical details). In this condition there is segmental failure of protective constriction by some of the brain arterioles with the formation of pockets of paralytic vasodilatation. There is transudation of fluid and perhaps extravasation of blood in these regions, with the production of a pathological picture of multiple foci of cerebral edema with or without hemorrhages and of a clinical picture of increased intracranial pressure with headache, papilledema, obtundation, seizures and / or multifocal deficits. When this vasogenic edema occurs mostly in the distribution of the posterior (vertebrobasilar) circulation, an MRI (magnetic resonance imaging) picture of reversible posterior ▶ leucoencephalopathy may result (see section on "Characteristics" for clinical details).

4. Abrupt marked rises in blood pressure (acute ▶ paroxysmal hypertension) may cause severe paroxysmal headaches, with or without other neurological symptoms (see section on "Characteristics" for clinical details). Here again there is failure of autoregulation with its protective vasoconstriction and headache results from sudden vasodilatation of the intracranial vessels, with or without an element of vasogenic cerebral edema and increased intracranial pressure. Such paroxysms of severe hypertension may occur in response to ingestion of exogenous pressor substances such as amphetamines or cocaine or to the taking of tyramine-containing foods or sympathomimetic medications with monoamine oxidase inhibitors. Endogenous pressor amine secretion, as in sexual intercourse or with pheochromocytoma, may produce ▶ paroxysmal hypertensive headaches. Failure of neurogenic regulation of blood pressure, as in paraplegia or in the Landry-Guillain-Barré syndrome, may lead to acute hypertensive headaches, as may the hypertension of pre-eclampsia and eclampsia.

5. On a more banal note, medications prescribed for the control of hypertension may themselves produce headaches, usually through the mechanism of cranial vasodilatation. These include some calcium channel blockers, enalapril, hydralazine, methyldopa and some beta-blockers (Edmeads 2000)

Characteristics

The morning headache of severe hypertension either awakens the patient early in the morning or is present on spontaneous awakening. It is dull, often vaguely throbbing and is maximal in the posterior part of the head, though on occasion it may be mostly bifrontal. Its characteristic feature is that as the patient gets up and about, the headache begins to abate and within a few hours it is gone – until the next morning. The patient may also complain of feeling "dull" or "muzzy" for the first few hours of the morning and this too clears as the day wears on. The diastolic blood pressure is usually above 120. Often the patient is overweight or is known to snore – factors that predispose to nocturnal CO_2 retention. Otherwise, there are no characteristic findings on examination. The treatment of this headache is that for the high blood pressure.

Acute hypertensive encephalopathy is a rare but dreaded complication of chronic severe hypertension of any etiology. While the diastolic blood pressure (BP) is typically greater (often much greater) than 120, acute hypertensive encephalopathy has been reported with lower blood pressures, such as 150 / 100, particularly in children (whose BP may normally be 90 / 50) and especially in children whose BP has been rapidly elevated by substances which also impair autoregulation, such as cancer chemotherapies or immunosuppressants (Pavlakis et al. 1999).

The patient acutely develops severe generalized headache, sometimes more marked bi-occipitally. Nausea is frequent; vomiting may occur. Visual symptoms are sometimes prominent, perhaps because the parieto-occipital white matter may be particularly edematous (see below) or because of papilledema; this visual impairment may range from non-specific blurring, through transient deficits to blindness. Papilledema, though often present, is no longer considered a prerequisite for the diagnosis. Some degree of confusion or mental obtundation is nearly always present. The foregoing symptoms are consistent with the cerebral edema and increased intracranial pressure that are the basis of this syndrome. Also, there may be focal neurological features such as seizures or hemiparesis.

Stroke (cerebral infarction or hemorrhage) is the major differential diagnosis of acute hypertensive encephalopathy and distinguishing between the two can be difficult. Computerized tomographic (CT) scanning shows multifocal or diffuse cerebral edema, sometimes with scattered small hemorrhages or microinfarcts. Magnetic resonance (MR) imaging may show the appearance of a "reversible posterior leucoencephalopathy" (Hinchey et al. 1996), characterized by increased signal on T_2-weighted and FLAIR sequences found mostly in the posterior parts of the cerebrum, especially the parieto-occipital white matter. The frontal white matter, cerebellum and brainstem may also be involved; there are rare cases of these changes being confined to the brainstem (Gondim and Cruz-Flores 2001). Diffusion-weighted imaging (DWI) can be normal or may demonstrate increased diffusion characteristic of vasogenic edema. This MRI picture is believed to be due to failure of autoregulation, particularly in the posterior (vertebrobasilar) circulation, which has been shown to have a relative paucity of sympathetic vasomotor innervation. Typically these MRI changes reverse when the hypertension is treated and any offending drugs eliminated.

While reduction of blood pressure is the mainstay of treatment for acute hypertensive encephalopathy, it is crucial to avoid precipitous lowering of BP (Weinberger 2003). With autoregulation severely impaired, overly rapid or excessive reduction of perfusion pressure can produce cerebral ischemia and infarction. If systolic blood pressure is greater than 200 mm Hg on presentation, it must not be reduced below 160; if it is less than 200 on presentation, it must not be reduced below 140. In severe hypertensive encephalopathy (obtundation, seizures, visual impairment or major focal deficits), this reduction should be effected over a period of about 15 min. The most controllable regimen is a slow intravenous infusion of sodium nitroprusside with constant BP monitoring, preferably through an arterial line. Alternative regimens include repeated intravenous boluses of labetalol, enalapril or diltiazem; all require continuous BP monitoring for safe use. In patients with lesser degrees of acute hypertensive encephalopathy (awake, with no seizures, visual disturbances or major neurological deficits), more slowly acting (30–45 min) medications can be given by mouth, with intermittent cuff pressures rather than continuous intra-arterial line monitoring. These oral medications include calcium channel blockers, ACE inhibitors and angiotensin receptor blockers.

Acute paroxysmal severe hypertension can produce acute paroxysmal severe headache. The causes of such sudden marked rises are noted above (see section on "Definition"). These headaches are diffuse, severe, often pounding and worse with movement and may be associated with nausea and vomiting. They resemble a very severe migraine headache but, unlike migraine, they do not usually present as multiple recurrent episodes – and, of course, they are accompanied by severe hypertension. The International Headache Society (IHS) has provided diagnostic criteria for some of these acute hypertensive headaches (Headache Classification Committee of the International Headache Society 2004). For a diagnosis of headache caused by an acute pressor response to an exogenous substance, the requirements are evidence of an appropriate toxin or medication, that the headache be accompanied by an acute rise in BP and that the headache clear within 24 h of normalization of BP. For a diagnosis of headache caused by a pheochromocytoma, the IHS requires that the headache be accompanied by an abrupt rise in BP and by at least one adrenergic symptom such as sweating, palpitations, pallor or anxiety, that there be demonstration of the pheochromocytoma by biochemical or imaging procedures and / or at surgery and that the headache clears within one hour of normalization of BP. For a headache to be attributed to pre-eclampsia or eclampsia, the IHS requires that the headache occur during pregnancy (or the puerperium) that there be clinical features of pre-eclampsia or eclampsia (hypertension at least 140/90, and proteinuria), that appropriate investigation rules out other causes of hypertensive headaches such as medications etc and that the headache clears within 7 days of normalization of BP.

The treatment of these acute paroxysmal hypertensive headaches is that of the underlying causes – removal of exogenous toxins and medications and treatment of exogenous conditions such as pheochromocytoma and pre-eclampsia / eclampsia. Where the cause cannot

be identified, treatment is difficult, because the hypertension that causes the headaches is paroxysmal and this makes chronic treatment with hypotensive agents problematic.

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Headache Due to Intracranial Bleeding

SEYMOUR SOLOMON

Montefiore Medical Center, Albert Einstein College of Medicine, New York, Bronx, NY, USA
ssolomon@montefiore.org

Synonyms

Intracerebral Hematoma: Apoplexy; Blood Clot in Brain; Hemorrhagic Stroke
Subdural Hematoma
Epidural Hematoma: Acute Traumatic Epidural Hematoma

Definition

Intracerebral Hematoma

Bleeding within the brain due to rupture of a blood vessel.

Subdural Hematoma

Hemorrhage between the brain and the dura matter, the covering of the brain, usually due to trauma.

Epidural Hematoma

Bleeding between the outer layer of the dura, the covering of the brain and the skull, due to trauma that fractures the skull and tears the artery within the bone.

Characteristics

Intracerebral Hematoma

Primary intracerebral hemorrhages are the third most common cause of stroke, after cerebral arterial thrombosis and embolism. (Hemorrhage may also be secondary to trauma, tumor or hemorrhagic diseases.) Cerebral infarcts may become hemorrhagic particularly those caused by embolism. In recent years, hemorrhagic transformation of a cerebral infarct may be a complication of early thrombolysis therapy (Fiorelli et al. 1999). A spontaneous brain hemorrhage is usually the result of long standing hypertension and associated degenerative changes in cerebral arteries (Fang et al. 2001). In recent decades, with widespread understanding of the need to control blood pressure, the incidence of intracerebral hemorrhage has decreased. In the vast majority of cases the hemorrhage/stroke occurs while the person is up and about rather than during sleep (Caplan 1993). The neurological symptoms and signs are dependent on the location and size of the hemorrhage. About 50% of hemorrhages are deep in the brain. Seepage or rupture of blood into the ventricular system is common with resultant bloody cerebrospinal fluid. Less common sites of hemorrhage are the cerebral lobes and the cerebellar hemisphere. If the hematoma is in the cerebral lobes, the focal signs will be appropriate to the function of the cerebral site. Typically there is the sudden onset of headache and vomiting. If the cerebral hemorrhage is large and deep, there is depression of consciousness, hemiplegia, coma and death.

If the hemorrhage is in the cerebellum, the initial symptoms of headache may be subacute or sudden. Inability to stand and walk may be the only signs and the diagnosis may be missed if the patient is examined only in bed or stretcher (Ropper and Brown 2005). As the hematoma grows, brain stem compression results in depressed consciousness, paralysis of gaze, other brain stem signs and finally pinpoint pupils, decerebrate posture, coma and death. Computerized tomography will allow almost immediate visualization of the blood. Prompt surgical evacuation of the cerebellar hematoma is often life saving but the value of surgery for cerebral hemorrhages is more problematic. Surgery is almost always futile once the patient has become comatose (Rabinstein et al. 2002).

High plasma levels of proinflammatory biochemicals within 24 h of the hemorrhage are predictive of a poor outcome (Castillo et al. 2002). The prognosis for large and deep hemorrhages is grave (Arboix et al. 2002). About one-third of patients will die during the first few days to 1 month. In those who survive there may be a surprising degree of recovery since, contrary to cerebral infarction, the hemorrhage stretches brain tissue rather than destroys it. Nevertheless only one third of patients regain independent functional status after 3 months (Weimar et al. 2003).

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Headache is not invariable in patients with intracerebral hematoma. The frequency ranges from one-third to two thirds of patients (Mitsias and Jensen 2006). The frequency of headache is highest in cerebellar and occipital hemorrhages and when the hematoma is large. The pain is presumably due to the stretching and stimulation of pain sensitive structures by the mass effect of the hematoma and the irritation of blood (if subarachnoid bleeding is associated). The site of the headache often overlies the cerebral hematoma; occipital headache often is associated with cerebellar or occipital hematoma.

Subdural Hematoma

The course of neurological events may be acute or chronic, more or less corresponding to the degree of trauma. The location of the hematoma is usually over one or both cerebral hemispheres but rarely it may form in the posterior fossa.

In people who develop an acute subdural hematoma, the symptoms may be similar to those of acute epidural hematoma and the two conditions often occur together. Headache or loss of consciousness may be immediate, due to cerebral concussion following the blow to the head. Recovery from concussion is often associated with a lucid interval, but soon the effects of the mass of blood compressing the brain become evident with increasing headache and decreasing consciousness. Computerized tomography is used to visualize the hemorrhage. Prompt surgical evacuation of the hematoma is essential (Koc et al. 1997).

Chronic subdural hematoma is less clearly associated with head trauma (Iantosca and Simon 2000). The slowly developing blood clot is over one or sometimes both cerebral hemispheres. The trauma may be trivial or may have been forgotten. This is particularly true in the elderly when the brain shrinks and the veins bridging the skull and brain traverse a longer distance. For this reason the veins are more easily sheared by slight trauma. The symptoms develop slowly over weeks or months. Headache is most common along with depression of mentation, drowsiness, inattentiveness and confusion; focal signs are usually minor or absent. The initial symptoms are often subtle and may be mistaken for depression, Alzheimer's disease, drug intoxication or brain tumor. Symptoms often fluctuate in severity, sometimes suggesting transient ischemic events. The hematoma eventually becomes encysted by a fibrous membrane (LaBadie and Glover 1976). As blood contents dissipate, computerized tomography may no longer reveal the striking density of blood, rather the diagnosis is made by the space occupying effect of the mass. Contrast material used during the study will show the surrounding fibrous membrane. The hematoma may spontaneously reabsorb. But if it continues to grow surgical drainage is necessary.

Subdural hematoma causes headache in about two thirds of patients and is related more to the location in the head and irritation of the meninges than to the volume of the hematomas (Melo et al. 1996). Because the hematoma is due to venous bleeding the symptoms as well as the course may range from acute to chronic. The time between injury and headache may range from hours to months. The headache is almost always ipsilateral to the hematoma but the qualities of the headache are not specific.

Epidural Hematoma

Because of arterial bleeding the course of epidural hemorrhage is acute (Castillo et al. 2002). Typically the blow to the head causes loss of consciousness due to cerebral concussion. Recovery of consciousness after a few minutes is followed by a lucid interval of minutes or hours. The epidural hematoma, rapidly expanding against the brain, causes headache, vomiting, drowsiness, coma, and (if not treated) death. Compression of the brain may cause hemiparesis and eventual compression of the brain stem causes generalized spasticity of the limbs and a dilated pupil on the side of the hematoma. Fracture of the skull is seen on standard roentgenograms and computerized tomograms reveal a lens-shaped clot. Usually the middle meningeal artery is sheared within the fractured temporal bone. Surgical drainage of the hematoma is the only life saving treatment.

If loss of consciousness is not immediate, head pain will be associated with trauma. Headache first on the side of the trauma, progresses in intensity as the clinical course progresses. The qualities of the headache are not specific.

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Headache Due to Low Cerebrospinal Fluid Pressure

ANDREAS R. GANTENBEIN, PETER S. SÁNDOR
Headache & Pain Unit, University Hospital Zurich, Zurich, Switzerland
peter.sandor@usz.ch

Synonyms

Spontaneous Intracranial Hypotension; Symptomatic Intracranial Hypotension; Post-Lumbar Puncture Headache; Low Intracranial Pressure Headache; Spontaneous Aliquorhea; Ventricular Collapse; Hypotension of Spinal Fluid

Definition

There are 3 types of headache attributed to low ▶ cerebrospinal fluid (CSF) pressure in the new classification of the International Headache Society (IHS, Headache Classification Committee of the International Headache Society 2004): Post-dural puncture headache (7.2.1), CSF fistula headache (7.2.2), and headache related to spontaneous low CSF pressure (7.3.3). They have in common an ▶ orthostatic component, as the headache usually begins within 15 min of standing or sitting up. The headache mainly improves in the recumbent position; however, this is a diagnostic criterion only for post- ▶ lumbar puncture in the IHS classification. The headache is associated with at least one of the following symptoms: neck stiffness, tinnitus, hypacusis, photophobia, or nausea. The aetiology is different for the 3 types. See Table 1 for compared classification criteria (Headache Classification Committee of the International Headache Society 2004).

Characteristics

In 1938, Schaltenbrand, a German neurologist, wrote about two conditions regarding cerebrospinal fluid:

a) 'Liquorrhea' involving headache and ▶ papilloedema, which later became known as pseudotumor cerebri, and
b) 'Spontaneous aliquorhea', presenting with orthostatic headaches and features of intracranial hypotension. He explained the syndrome of low CSF

pressure by three possible pathological mechanisms: decreased production, increased absorption or leakage, e.g. after a lumbar puncture (Schaltenbrand 1938).

The brain is 'swimming' in the CSF. The average weight of 1500 g is reduced to 50 g by the intracranial pressure. The remaining weight is held by the meningeal blood vessels, the outgoing cranial nerves, and microstructures. If the CSF pressure decreases, there is traction on the supporting structures of the brain. Recent MRI studies have even shown the "descending" brain (Pannullo et al. 1993). It is thought that traction on the cranial nerves (V, IX, X), on the three upper cervical nerves, and on bridging veins which are pain-sensitive structures, causes the headache and its associated features. However, there are contradictory reports to this so called 'sagging theory' (Levine and Rapalino 2001). As long as magnetic imaging cannot be performed in the erect position, it will probably be difficult to bring an end to that discussion.

Magnetic imaging of the head and spine has revolutionized the knowledge and the detection of this disorder (Fishman and Dillon 1993; Mokri 2001; Sable and Ramadan 1991). It was not until the 1990s that investigators demonstrated that the production of about 500 ml per day is relatively constant, and therefore is rarely a cause for the problems. The CSF volume is estimated to be between 150–210 ml, this means the total volume is renewed 2–3 times per day. CSF volume is smaller in women, younger, and obese persons. Most of the CSF is absorbed via the arachnoid villi into the venous sinuses and cerebral veins, and only a very small part is absorbed through simple diffusion. On this background, the most obvious and common reason for low intracranial pressure is CSF leakage. The spontaneous leaks are mostly located on the thoracic or cervical level (Sencakova et al. 2001).

Post-lumbar puncture headache happens in up to one-third of patients with lumbar puncture (Adams et al. 2002). Patients with preceding headaches, and young women with low BMI, may be at higher risk of developing headaches. Patients with postural headaches should be imaged before lumbar puncture, and if there are MRI signs of ▶ pachymeningeal enhancement, a lumbar puncture should not be performed.

Symptoms

Low CSF pressure usually causes orthostatic headaches, which develop in the upright position and improve when lying down (recumbency). The onset of the headache is usually sudden or gradual. The character of the pain is often described as severe and throbbing or dull, and it can be diffuse or focal, with a frontal or occipital localisation. The headache typically has orthostatic features in the beginning (e.g. onset within 30 min after standing up), however, these features may blur with

Headache Due to Low Cerebrospinal Fluid Pressure, Table 1   Compared diagnostic criteria of the International Headache Classification 2nd Edition regarding headache attributed to low CSF pressure

Post-dural puncture headache	CSF fistula headache	Spontaneous low CSF
Headache within 15 min of sitting or standing		
Resolving within 15 min after lying		
Associated symptoms (1 of the following):		
Neck stiffness Tinnitus Hypacusis Photophobia Nausea		
Etiology		
Dural puncture	CSF leakage: MRI evidence (pachymengial enhancement) Conventional or CT myelography, cysternography OP <60 mm CSF in sitting position	
Onset		
Within 5 days after lumbar puncture	Close relation to CSF leakage	No lumbar puncture or leakage
Resolving		
Spontaneously within 1 week or Within 48 h after treatment	Within 1 week of sealing leak	Within 72 h after blood patch

chronicity and result in a chronic daily headache which is worse when the patient is in an upright position and improves when lying down. Other exaggerating factors include movements of the head, sneezing, coughing, straining, and jugular venous compression. In general pain killers do not sufficiently improve the headache. Recumbency is often the only measure which can relieve the pain; usually within 10–15 min. Associated features can be manifold: anorexia, nausea, vomiting, vertigo, dizziness, neck stiffness, blurred vision, and even photophobia are commonly described. Tinnitus, bilateral hyp(er)acusis, unsteadiness, staggering gait, diplopia, transient visual obscuration, hiccups, and dysgeusia have been reported.

Examination

The neurological examination is typically normal. However, mild neck stiffness is frequently noted.

The CSF opening pressure is typically below 70 mm, however, it can be low normally. Fluid is typically clear and colourless, occasionally ▶ xanthochromic. The CSF protein level is usually normal, but may be high, mostly still below 100 mg/dl. Cell counts give variable results: erythrocytes and leukocytes may be normal or elevated. Cytologic and microbiologic tests are always negative, and glucose rate CSF/plasma is always between 0 and 1.

The standard diagnostic investigation for low CSF pressure and CSF leaks is MR imaging with Gadolinium. The most common abnormality is diffuse pachymeningeal enhancement (Mokri 2004). According to the Monro-Kellie doctrine (brain volume + CSF + intracranial blood = constant) the CSF loss is compensated by venous hyperaemia. Whereas the leptomeninges have blood brain barriers, the pachymeninges (dura mater) do not and therefore accumulate the contrast medium. The enhancement is typically linear, thick and uninterrupted, and diffuse, including supra- and infratentorial meninges. Furthermore, there is commonly sinking or sagging of the brain, which can sometimes mimic Chiari I malformation, subdural fluid collections (they may be unilateral), and decrease in size of ventricles. Less common abnormalities include pituitary enlargement, engorged venous sinuses, and elongation of the brain stem. MRI of the spine can show spinal pachymeningeal enhancement, engorgement of venous plexus, and extraarachnoidal fluid, but only rarely reveal the site of the leak. The most accurate technique to find the exact site of CSF leaks is CT myelography. It is to be mentioned that different leaks and diverticles of different sizes can be found in the same patient. An exact identification of the site of the leak, however, is only necessary when surgical intervention is needed.

A CT scan of the head is usually unremarkable and therefore not very useful. Older diagnostic techniques include radioisotope cisternography with Indium-111, myelography without CT, and meningeal biopsy.

Differential-Diagnosis

Most patients present with a new onset daily headache following a lumbar puncture or another dural trauma, or, if developing spontaneously present as new daily persistent headache, which would act as a working diagnosis, unless low CSF pressure headache is diagnostically clas-

sified using imaging techniques (▶ MRI, CT myelography).

The orthostatic component is a salient feature. It is therefore hard to understand that in a recent study (Schievink 2003) spontaneous intracranial hypotension (SIH) was misdiagnosed in 94% of the reviewed cases, with a mean diagnostic delay of 13 months (median 5 weeks, range 4 days to 13 years). Sometimes associated features, such as nausea or photophobia, can mimic migraine. Especially when there is a personal or family history of headaches, the picture can be diluted. Furthermore, the orthostatic feature becomes less prominent with time. Obviously, the diagnosis of low CSF pressure headache is easier when the patient is seen at the beginning of the problem, and when there is a close temporal relationship to a lumbar puncture or another trauma affecting the spine. The differential diagnosis to the other orthostatic headache due to raised intracranial pressure should be fairly easy. Interestingly, almost all patients with low CSF pressure develop headaches, but only 30–80% of the patients with increased intracranial pressure do so (Mokri 2001).

Whereas both, low and high pressure headaches can be aggravated by coughing or straining, intracranial hypertension typically develops when lying down, especially in the morning, and is mostly present with transient visual loss or papilloedema in the neurological examination.

Management & Treatment

Fortunately, many low pressure headaches dissolve spontaneously within days. Treatments vary for the three different types of low CSF pressure headache. Conservative strategies include bed rest, fluid intake and an abdominal binder. Caffeine (250–500 mg i.v.), theophylline and to a lesser part steroids can be effective. When conservative treatments give no sufficient pain relieve within 24 h, an epidural ▶ blood patch (10–15 ml of autologous blood into the epidural space) would be indicated. Blood patches seem to have not only an immediate effect, through simple volume replacement, but also a delayed sealing of the leak. Post-lumbar puncture headaches are often relieved after the first (rarely the second) blood patch, while patients with spontaneous CSF leaks may need up to 4 or more. Instead of a second or third blood patch an epidural saline infusion could be attempted, using a catheter placed at the L2-3 level and a flow rate of 20ml/h for 72 h. If a leak is clearly located with imaging techniques and the headache is treatment refractory a surgical closure may be considered.

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Headache Due to Sinus-Venous Thrombosis

VOLKER LIMMROTH, HANS-CHRISTOPH DIENER
Department of Neurology, University of Essen, Essen, Germany
volker.limmroth@uni-essen.de,
h.diener@uni-essen.de

Definition

Cerebral venous sinus thrombosis (CVST) is a rare but challenging condition and is therefore often unrecognised. Its clinical presentation may vary significantly from case to case. Headache, however, is often the very first and leading symptom. The headache is mostly described as dull holocephalic pain, of increasing intensity and can easily be mistaken for tension type headache, migraine headache or other disorders such as pseudotumor cerebri. Along with headache, additional symptoms typical to increasing intracranial pressure such as papilloedema, nausea, vomiting and cognitive decline may be present. Further symptoms are focal deficit and seizures. The headache does not typically respond to classical anti-headache drugs, which should be taken as an important sign that further evaluation is necessary. Classical patients with CVST are young females with risk factors such as oral contraceptive pill, nicotine abuse, being overweight or during pregnancy, but all age groups can be affected and CVST can evolve secondary to an adjacent infectious process; dehydration, hypercoagulable state, inflammatory disorders, malignancies or head traumas. The diagnosis can be easily confirmed by MRI with venography or modern spiral-CAT-scan.

The treatment of choice is intravenous heparin followed by oral anticoagulation for 3–6 months. The prognosis is good if treatment is initiated early but can be fatal when the condition is overlooked. Despite its low incidence, CSVT is, therefore, one of the most important differential diagnosis clinicians must bear in mind when evaluating patients with headache.

Characteristics

Pathophysiology

Venous blood drains through small cerebral veins into larger veins that empty into dural sinuses and eventually into the internal jugular veins. Pre-existing anastomoses between cortical veins allow the development of collateral circulation in the event of an occlusion. The main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%). In about one-third of cases more than one sinus is affected, in a further 30–40% both sinuses and cerebral or cerebellar veins are involved (Ameri and Bousser 1992; Bousser and Barnett 1992; Villringer et al. 1994). In contrast to arterial thrombus, a venous thrombus evolves slowly, due good collateralisation of the venous vessels, which probably explains the usually gradual onset of symptoms, frequently over weeks and months. Sudden onset, however, may occur and may then cause predominating focal deficits rather than headache. Haemorrhagic infarction occurs in approximately 10–50% of cases, principally affecting the cortex and adjacent white matter (Bousser et al. 1985; de Bruijn et al. 1996; Buonanno et al. 1982; Provenzale et al. 1998). This is thought to be primarily due to elevated venous and capillary pressure caused by the persistence of thrombosis.

Predisposing Factors

An overview of predisposing factors is given below. In most of the cases one or more of these factors can be identified. In general, a distinction can be made between infective and non-infective causes or, as suggested by Bousser and Barnett, between local and systemic causes (Bousser and Barnett 1992). Within recent decades, infective causes have declined and are now responsible for less than 10% of cases and are mostly caused by staphylococcal infection of the face. Amongst the non-infective causes, systemic conditions such as connective tissue diseases, other granulomatous or inflammatory disorders and malignancies are the most common. Other risk factors in otherwise healthy subjects are overweight, hormonal therapy, smoking and underlying – mostly unknown – clotting disorders. In many cases several of these factors can be found.

Local causes

- penetrating head injury
- intracranial infection
- regional infection
- stroke and haemorrhage
- space occupying lesions
- neurosurgery

Systemic causes

- severe dehydration
- hormonal and endocrine causes
- cardiac disease
- red blood cell disorders
- thrombocythaemia
- coagulation disorders (acquired or hereditary)
- infusions *via* central venous catheter
- surgery with immobilisation
- malignancies
- inflammatory bowel disease
- connective tissue diseases
- Behcet's disease
- sarcoidosis
- nephrotic syndrome
- drugs (L-asparaginase, epsilonaminocaproic acid, ecstasy)
- sepsis and systemic infection

Clinical Presentation

Depending on the sinus involved and the extent of the venous thrombus, CVST presents with a wide spectrum of symptoms and signs. Headache is the leading symptom and present in 70–90% of cases. Other important symptoms are focal deficits such as hemiparesis and hemisensory disturbance, seizures, impairment of level of consciousness and papilloedema (Ameri and Bousser 1992; Bousser et al. 1985). The onset may also vary a great deal from acute, subacute or insidious, but most patients develop symptoms over days or weeks.

In a series of 110 cases, Ameri and Bousser (1992) found several typical clinical constellations; up to 75% of cases are characterised by a focal neurological deficit and headache, 30%–50% may present with seizures often followed by a Todd's paresis and 18–38% of cases present with a syndrome resembling benign intracranial hypertension with headache, papilloedema and visual disturbances. As indicated above, symptoms also depend on the location of the thrombus. The (isolated) thrombosis of the superior sagittal sinus (which occurs in less than 5% of the cases) presents with bilateral or alternating deficits, particularly in the lower limbs and/or seizures, the (isolated) thrombosis of the cavernous sinus (3% of the cases) with chemosis, proptosis and painful ophthalmoplegia. Patients with lateral sinus thrombosis may present with a pseudotumor cerebri-like syndrome. Recently, Farb et al. (2003), using a technique called auto-triggered elliptic-centric-ordered 3-dimensional gadolinium-enhanced MR venography, found that 27 of 29 patients with idiopathic intracranial hypertension suffered from a bilateral sinovenous stenosis which was only seen in 4 of 59 control subjects. Severe cases with the involvement of the superior

sagittal sinus, the cavernous sinus and the lateral sinus, however, may present with a rapidly progressive condition including headache, nausea, pyramidal signs and deepening coma.

CVST appears to be slightly more frequent in women with a suggested female-to-male ratio of 1.29:1. Interestingly, while 61% of women with CVST were aged 20–35 years, a uniform age distribution has been suggested for men with CVST. The most likely explanation for this specific age distribution in women is the use of oral contraceptives and fact that CVST is frequently observed during pregnancies.

Diagnosis

Patients with a suspected CVST must undergo specific cranial imaging immediately. Magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) have largely replaced invasive cerebral angiography and conventional computed tomography (CT). Modern subsecond spiral CT and multi-detector-row-CT-scanners (MDCT), however, are now able to obtain whole-brain CT venograms in less than a minute. Unlike the conventional CT scanner, MDCT scanners have sufficient speed for high resolution images of the entire brain and all dural sinuses during the peak venous enhancement (Casey et al. 1996; Wetzel et al. 1999). The technique can therefore – if available – be used as a first line diagnostic tool since the procedure is cheaper and faster than MRI/MRV. Moreover, using a CT scanner of the latest generation, a recent study has been shown that CT venography may be superior to MRV in visualising sinuses or smaller cerebral veins or cortical veins with low flow. However, it goes without saying that MRI/MRV are the imaging techniques of choice for pregnant women. Some doubtful cases may still require cerebral angiography. One of the common problems is the absence or hypoplasia of the anterior portion of the superior sagittal sinus, a normal variant that can simulate thrombosis on MRV (Provenzale et al. 1998; Wang 1996). Also, contrast enhancement along the edge of the thrombus can be mistaken for normal contrast material accumulating within a patient's sinus. Aside from confirming the diagnosis by cranial imaging, it is mandatory to search for the underlying causes including the search for local infection, head injury, malignancies, connective tissue diseases with inflammatory markers, autoantibodies and markers of coagulation disorders such as Factor V Leiden mutation if resistance to activated protein C is abnormal, activities of proteins C and S, antithrombin III, plasminogen, fibrinogen and anticardiolipin antibodies (de Bruijn et al. 1998; Deschiens et al. 1996; Kellett et al. 1998) All these investigations should probably be performed twice, i.e. before starting anticoagulation, and 6 months later after finishing since the acute status of the disease may influence the expression of these parameters.

Treatment

Only a few therapeutic trials have evaluated potential therapeutic agents in CVST. Antithrombotic treatment modalities include heparin, thrombolysis and oral anticoagulants. Einhäupl et al. (1991) in a randomised and placebo-controlled trial, demonstrated the benefits of heparin in a series of 20 patients. There was a significant difference in favour of intravenous heparin with respect to neurological recovery and mortality compared to placebo. Interestingly, in an additional retrospective analysis on 102 patients with CVST the same authors suggested heparin to be beneficial, even in those patients who had an intracranial haemorrhage prior to treatment initiation. A few years later, de Bruijn et al. (1999) compared low-molecular-weight heparin followed by warfarin, or placebo. A significant difference between the groups could not be detected in this study (de Bruijn and Stam 1999).

Several groups (Frey et al. 1999; Horowitz et al. 1995; Kim and Suh 1997; Smith et al. 1994) addressed the question of whether additional benefit could be achieved by thrombolysis via selective catheterisation of the occluded sinus. Although all studies included a small number of patients (n = between 7 and 12 patients per study), all studies suggested that the majority of patients undergoing catheterisation and thrombolysis with urokinase recovered well, and only a few patients suffered from an additional cerebral haemorrhage. Since there is no direct comparative trial between heparin and thrombolysis, the question if this approach provides an additional benefit and an acceptable benefit-to-risk ratio when compared to i.v. heparin is not answered. The disadvantage of catheterisation in patients with CVST is the significant logistic effort and expertise necessary to have this intervention always available.

There is a general agreement that oral anticoagulants should follow as treatment of the acute phase for 3–6 months. In patients with known prothrombotic conditions anticoagulation may be a life-long requirement. No agreement has been reached regarding the question whether patients who present with seizures should undergo anti-epileptic treatment after the acute phase. This decision remains to be made from case to case and under the consideration of the individual circumstances. Taken together, intravenous heparin is the first-line treatment in a dosage sufficient to increase the apTT to 2–3 times of the control value. Several authors suggest a start with a heparin bolus of 5000 U and to continue according to the apTT elevation, which mostly requires dosages between 1000 and 1600 U/h for adults. Heparin is the first-line treatment, even in the presence of haemorrhagic infarction (Bousser 1999). In case of clinical deterioration despite adequate heparinisation, selective local thrombolysis should be considered, in spite of the increased haemorrhagic risk.

H

Prognosis

Mortality in untreated cases of venous thrombosis has been reported to range from 13.8–48% (Preter et al. 1996). A recent Portuguese study suggested a morbidity of around 8% despite adequate treatment in a group of 91 prospectively analyzed consecutively admitted patients with a mean 1 year follow-up interval (Ferro et al. 2004). Interestingly, 82% of the patients recovered completely, but 59% developed thrombotic events during the follow-up, 10% had seizures and 11% complained of severe headaches. Recently Buccino et al. (2003) found a good overall outcome in a series of 34 patients with CSVT. Still, 10 patients (30%) suffered from episodic headaches, 3 patients (8.8%) from seizures, 4 patients (11.7%) from pyramidal signs and 2 (5.9%) from visual deficits and 6 patients (17.6%) from working memory deficit and depression. All these studies clearly emphasize that CSVT is a treatable condition in the majority of cases and that early diagnosis and immediate initiation of heparin treatment are the key components for a good overall outcome.

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Headache Due to Somatoform Disorder

RETO M. AGOSTI
Headache Center Hirlsanden, Zurich, Switzerland
reto.agosti@kopfwww.ch

Synonyms

Headache Associated with Somatisation Disorder; Headache Associated with Psychotic Disorder

Definition

Headaches of no typical characterisation (such as migraine or cluster headaches) with close temporal association with undifferentiated somatoform disorder (as defined by DSM IV).

Characteristics

This type of headache does not have any characteristic symptoms that are unique to these types of headaches. Any other headache type, primary (such as migraine, cluster headaches, etc) or secondary, must be excluded. By definition, there must be a close temporal relationship with the multiple symptoms of an undifferentiated somatoform disorder as defined by DSM-IV: a) A physical complaint, plus headache, that, after appropriate investigation, cannot be fully explained by a known general medical condition, or by the direct effects of a substance or medication or, when there is a related medical condition, that complaint or impairment is in excess of what would be expected from the history, examination and/or laboratory findings; and b) The physical com-

plaint and headaches cause distress or impairment and last at least 6 months. The headache occurs exclusively during the course of the other physical complaint, and resolves after the undifferentiated somatoform disorder remits. A similar condition with clearly more stringent criteria regarding the somatoform symptoms and complaints are headaches associated with somatisation disorder, for which DSM-IV requires a minimum of eight somatoform symptoms or complaints and age of onset under 30. Both types of headaches (associated with somatoform and somatisation disorder) only entered the IHS classification of headaches in 2004, and are highly debated regarding their existence as proper diagnoses, with the persistent lack of a biological marker for primary headaches as one of the major obstacles. The diagnosis is fully based on phenomenology, and the treatment symptomatic towards treating the headaches or the underlying psychiatric disorder. A causal relationship in any direction is under debate. Association of headaches with other psychiatric disturbances such as depression, phobias etc. are classified separately. Headaches associated with somatisation disorder are rare, but headaches associated with somatoform disorder are more frequent.

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Headache, Episodic Tension Type

ANDREAS R. GANTENBEIN, PETER S. SÁNDOR
Headache & Pain Unit, University Hospital Zurich, Zurich, Switzerland
andy.gantenbein@gmx.ch, peter.sandor@usz.ch

Synonyms

Episode Tension Type Headache; Idiopathic Headache; Muscle Contraction Headache; Ordinary Headache; Psychogenic Headache; Psychomyogenic Headache; Tension Headache

Definition

The new classification of the International Headache Society (IHS) distinguishes an infrequent (less than 1 day per month) and a frequent form (at least 1 day but less than 15 days per month) of episodic tension type headache. Duration varies from minutes to days. The pain is typically bilateral, of mild to moderate intensity, and has a ▶ pressing/tightening character. There is no worsening with routine physical activity. There is no nausea, but ▶ photophobia or ▶ phonophobia may be present. Both infrequent and frequent types can be subdivided according to the presence or absence of pericranial ▶ tenderness (jaw, scalp and neck muscles). See Table 1 for the classification criteria (Headache Classification Subcommittee of the International Headache Society 2003).

Characteristics

With a lifetime prevalence of 30–78% in general population, tension type headache is the most common primary headache and has a high socio-economic impact. The male to female ratio is 1:1.5. The prevalence in childhood ranges from 0.5–12% (Anttila et al. 2002; Rasmussen et al. 1991; Rasmussen 2001; Schwartz et al. 1998). Tension headache was first defined by the IHS classification committee in 1988. This type of headache previously had a psychological label and was thought to be caused exclusively by mental conflicts, stress, tension, or emotional overload. There was exciting little interest from research and pharmaceutical companies. However, more recently a number of studies have investigated neurobiological mechanisms. Peripheral pain mechanisms, such as myofascial tenderness, hyperalgesia and muscle hardness have been implicated in the episodic type, and dysfunction of central sensitisation in the chronic type. Overall tension-type headache appears to be a central disinhibitory phenomenon, probably with involved neurotransmitter changes, defective nociceptive control, increased sensitivity to both myofascial and vascular input, and associated personality traits (Jensen and Olesen 2000). Whether tension type headache and migraine are separate entities, as suggested by epidemiological data, or rather represent a continuum with shared pathophysiology remains controversial (Rasmussen 1996; Ulrich et al. 1996).

Symptoms

The headache can be described in simple terms as pain in the head without associated symptoms. Unlike migraine there is no sensory hypersensitivity, e.g. to sound, light, or movements. Unlike cluster headache autonomic features (tearing, redness of the eye and blocked nose) are not present. Due to the usually mild and short lasting character, patients with less frequent tension headache often view their symptoms as a nuisance and rarely seek the advice of a specialist. Accordingly, these patients often treat their headache with standard over-the-counter pain killers (often containing caffeine) or with non-pharmacological treatments, such as hot or cold packs, or massage. If the headache is more frequent it may well become distressing and interfere with daily life. This may be associated with regular intake of non-specific analgesics, and can lead to further problems, including chronification of the headache.

Headache, Episodic Tension Type, Table 1 Compared diagnostic criteria frequent episodic tension-type headache and migraine without Aura from the International Headache Classification 2nd edn

Diagnosis:	Frequent episodic tension type headache	Migraine without Aura
Number of episodes:	At least 10	At least 5
Number of days with such headache:	≥ 1 day and < 15 days per month (for at least 3 months)	< 15 days/month (untreated or unsuccessfully treated)
Duration of the headache:	30 min to 7 days	4–72 h
Pain characteristics:	At least two of the following:	At least two of the following:
	Pressing/tightening (non-pulsating) quality	Pulsating quality
	Mild or moderate intensity	Moderate or severe pain intensity
	Bilateral location	Unilateral location
	No aggravation by walking stairs or similar routine physical activity	Aggravation by or causing avoidance of routine physical activity
Accompanying Symptoms:	Both of the following:	At least one of the following:
	No nausea or vomiting (anorexia may occur).	Nausea and/or vomiting
	Photophobia or phonophobia or none	Photophobia and phonophobia

Episodic tension type headache has a high intra- and interindividual variability with respect to frequency and intensity. Additionally, the duration of each attack may range from 30 minutes to 7 days. It usually has a diffuse pressing character, often described by patients as a 'tight band around the head'. The pain is dull, persistent and often diurnal. The headache is bilateral in 80–90% of cases. Most commonly intensity is mild to moderate and may interfere with (though not usually prevent) performance of daily activities. Characteristically it is not aggravated by routine physical activity. Nausea and vomiting are absent. Patients may complain of mild intolerance to loud sound or bright light, though true photophobia or phonophobia is rare and strongly suggest migraine (certainly when both present). There is no blurred vision and no focal neurological disturbance. Patients may complain of a feeling of giddiness or light-headedness, sometimes as a consequence of hyperventilation in association with anxiety. Many patients report difficulties in concentrating and lack of interest in work and hobbies. With age, tension-type headache can increases in frequency and duration, and there tends to be more variability of localization and rarely nausea may develop (Wober-Bingol et al. 1996).

Examination

Tension type headache patients require thorough neurological examination, including inspection and palpation of ► pericranial muscles. Pericranial tenderness is easily recorded by small rotating movements and a firm pressure with two fingers on the frontal, temporal, masseter, pterygoid, sternocleidomastoid, splenius and trapezius muscles. A local tenderness score from 0–3 on each muscle can be summated to a total tenderness score for each

individual. The use of a palpometer (pressure sensitive device) can improve validity and reproducibility. Palpation is also a useful guide for treatment strategy, and adds value and credibility to the explanations given to the patient.

Differential-Diagnosis

An accurate diagnosis is essential, and migraine, as well as secondary headache, should be excluded. Tension-type headache is sometimes difficult to distinguish from migraine in patients who have both tension headache and migraine with or without aura. It is important to educate patients in the differentiation between these headaches, as the right treatment for the right headache can be administered and medication overuse headache can be avoided. A diagnostic headache diary can be helpful to identify different patterns, since patients often describe only the characteristics of recent or the most severe attacks. In favour of tension type headache is a highly variable temporal profile and pain improvement with exercise. Unsuccessful treatment with ergotamins or triptans for acute attacks, or with beta-blockers or Flunarizin for prevention, also suggest a diagnosis of tension type headache. (Kaniecki 2002) See Table 1 for the comparison of classification criteria for migraine without aura and tension-type headache.

If headache is new (particularly over the age of 50), has a sudden onset, changes significantly in established pattern or characteristics, or does not fit a classical scheme, then secondary causes need to be excluded. Head trauma, vascular disorder, nonvascular intracranial disorder, substance abuse, noncephalic infection, metabolic disorder, and cranial structure defects can sometimes imitate tension type headache. If the neu-

Headache, Episodic Tension Type, Table 2 Acute treatment options in episodic tension-type headache

List of effective acute drugs			
Paracetamol/ Acetaminophen	1000 mg		
Aspirin	1000 mg	Steiner et al. Cephalalgia 2003	
Ibuprofen	400 mg	Packman et al. Headache 2000	
Ketoprofen	25 mg	Steiner et al. Cephalalgia 1998	
Naproxen	750 mg	Autret et al. Cephalalgia 1997	
Diclofenac	12.5–25 mg	Kubitzek et al. EurJPain 2002	
Metamizol	1000 mg	Martinez et al.	Cephalalgia 2001
Medications for children			
Ibuprofen	10 mg/KG		
Paracetamol	15 mg/KG		

H

rological examination is normal and the headache has no worrisome characteristics, there is no need for further investigations such as neuroimaging or lumbar puncture, and the patient can be reassured.

A number of precipitating factors have been described, including oromandibular dysfunction, non-psychological motor stress, local myofascial release of irritants, sleep deprivation, and coexisting migraine (Spierings et al. 2001). More controversial is the role of psychological factors, although the triggering of attacks by psychological stress is recognised. Up to one third of tension type headache patients show associated symptoms of depression or anxiety, though surveys of personality profiles have not demonstrated significant abnormalities (Holroyd 2002; Merikangas et al. 1994; Mitsikostas and Thomas 1999).

Management and Treatment

As yet there is no specific treatment for tension-type headache. Episodic and mild headaches are often successfully treated with non-specific analgesics, without the involvement of specialists. Drugs with evidence based benefit for acute treatment include aspirin, paracetamol and NSAIDs (Table 2). Compound analgesics should be used with caution, as repeated self-medication can yield to dependency, rebound headache and chronification. The use of drugs for more than 2–3 days per week (> 10 days per month) with associated chronic headache suggests an additional medication-overuse headache (IHS classification). The following rules apply for the acute treatment of ▶ episodic tension-type headache :

1. The analgesics should be taken at relatively high dose!
2. The intake should be as early as possible! *
3. Drugs should not be taken on more than 2 days a week!*

4. The use of compound analgesics (codeine, caffeine, etc.) should be avoided, or at least limited and carefully monitored!

*cave: balance!

As a preventative treatment for frequent tension-type headaches a typical first choice is a tricyclic antidepressant, such as Amitriptyline. High dose Magnesium may be effective. Combination with a non-pharmacological treatment, such as cognitive behavioural therapy, progressive muscle relaxation, or psychological counselling may be useful. In addition, advice may be also needed about the mechanisms of hyperventilation. Management must include elimination of exacerbating factors, such as dental pathology, sinus disease, depressive disorders, un-physiological working conditions, and disturbed sleep patterns. Physiotherapy, physical treatment (hot and cold packs), ultra-sound, electrical stimulation, posture improvement, relaxation and exercise programs are helpful in certain cases. Some patients report beneficial effects of muscle relaxants, tiger balm, and peppermint oil. (Stillman 2002)

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Headache from Cranial Bone

HARTMUT GÖBEL
Kiel Pain Center, Kiel, Germany
hg@schmerzklinik.de

Synonyms

Headache Associated with Disorders of the Cranium; Facial Pain Associated with Disorders of the Cranium

Definition

Pain in the head or face caused by a lesion within the cranial bone.

Characterisitics

Most disorders of the skull (e.g. congenital abnormalities, fractures, tumours, metastases) are not usually accompanied by headache. Exceptions of importance are osteomyelitis, multiple myeloma and Paget's disease. Headache may also be caused by lesions of the mastoid, and by petrositis. No epidemiological data are available on headaches due to lesions of the cranial bone.

The bone of the skull has limited sensitivity to pain because only a few nerve fibers enter it from the overlying periosteum. The periosteum is more pain sensitive, and skull lesions therefore produce headache, chiefly by involving it. The lesions of the skull most likely to do this are those that are rapidly expansile, aggressively osteoclastic, or have an inflammatory component.

Most skull lesions are asymptomatic and are discovered as incidental findings on roentgenograms or other imaging procedures done to investigate unrelated complaints, including fibrous dysplasia, osteomas, epidermoid cysts, metastatic cancers, hemangiomas, eosinophilic granulomas, and Paget's disease of the skull. Some of these lesions, notably hemangiomas and eosinophilic granulomas and the rare aneurysmal bone cysts, may present with a tender swelling on the calvarium but not with spontaneous headache.

Relatively few skull lesions produce headache. Multiple myeloma often presents with bone pain anywhere in the body, and skull deposits are sometimes a source of such pain. The multiplicity of the deposits, and the proclivity of the myeloma cells to produce osteoclast activating factor, are likely to account for the production of head pain by this particular bone tumor. Osteomyelitis produces spontaneous head pain because of its rapid evolution and its inflammatory component. Although most cases of Paget's disease of the skull are asymptomatic, remodeling of bone, by producing basilar invagination, may cause headache either through traction on the upper cervical nerve roots, or by the production of cerebrospinal fluid pathway distortion with hydrocephalus. Skull lesions as a cause of headache are infrequent, but usually require neurosurgical treatment. If necessary, surgical excision can serve to confirm the diagnosis and retard the progression of neurological dysfunction and head pain. Apart from specific medication, non-opioid and opioid analgesics may be used for pain relief.

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Headache in Aseptic Meningitis

K. RAVISHANKAR
The Headache and Migraine Clinic, Jaslok Hospital and Research Centre, Lilavati Hospital and Research Centre, Mumbai, India
dr_k_ravishankar@vsnl.com

Synonyms

Viral Meningitis; Serous Meningitis; Abacterial Meningitis; Aseptic Meningitis

Definition

▶ Aseptic Meningitis is the term applied to an acute clinical syndrome that comprises headache, fever, signs of

meningeal inflammation and a predominantly lymphocytic pleocytosis with normal glucose and normal to elevated proteins in the cerebro-spinal fluid (CSF).

Historically, the word 'aseptic' was introduced to denote the nonbacterial aetiology of this syndrome, and included forms of infective meningitis (viral and fungal) that were negative on routine bacteriologic stains and culture. With the introduction of polymerase chain reaction (PCR) based investigations and improved diagnostic techniques, the yield has improved, and the list of conditions that can present with a clinical picture like aseptic meningitis has expanded considerably. Although often used interchangeably, this term is therefore no longer synonymous with ► Viral Meningitis.

Characteristics

Introduction

Both infective and noninfective conditions may present with a picture that fits the definition of aseptic meningitis. Infective causes (Table 1) are mostly viral in origin and less commonly of fungal, parasitic, nonpyogenic bacterial, rickettsial or mycoplasmal origin; non-infective causes (Table 2) include tumours of the central nervous system, carcinomas, leukaemias, sarcoidosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, certain drugs, vaccines, immunoglobulins, intrathecal agents and rarely some disorders of unproven aetiology like Behcets syndrome, Vogt-Koyanagi-Harada syndrome.

Aseptic meningitis is common and seen more often in children and young adults, especially during the summer months. Except in the neonatal period, the mortality and morbidity rates are low (Norris et al. 1999; Cherry 1998). Most patients with aseptic meningitis due to viral causes have a benign course and spontaneously improve, while others may run a complicated course unless specifically

Headache in Aseptic Meningitis, Table 1   Viral Conditions that may present with aseptic meningitis

Infectious Etiologies	Non-Infectious Causes
	Drugs:-
Enteroviruses, Polio, coxsackievirus, echovirus	NSAIDs
HSV types 1 and 2	Trimethoprim
Varicella-zoster virus	Azathioprine
Adenovirus	Intravenous immunoglobulin
Epstein-Barr virus	Isoniazid
LCMV	Intrathecal
HIV	Methotrexate
Influenza A and B	Vaccines
	Allopurinol

Headache in Aseptic Meningitis, Table 2   Non-Viral Conditions that may present with aseptic meningitis

Infectious Etiologies	Non-Infectious Causes
Bacteria:-	**Other Diseases:-**
M.tuberculosis	Sarcoidosis
Borrelia burgdorferi	Leptomeningeal carcinoma
Treponema pallidum	SLE
Brucella	CNS vasculitis
Mycopl.pneumoniae	Behcet disease
Fungi:-	Vogt-Koyanagi-Harada syndrome
Crypto. Neoformans	Migraine
Histo. capsulatum	
Coccidiodes immitis	
Blasto. Dermatitides	
Parasites:-	
Toxoplasma gondii	
Taenia solium	

treated. World-wide prevalence varies depending on geographic factors, seasonal influence, epidemiologic patterns of diseases and vaccination policies.

Clinical Features

Aseptic meningitis is characterized by abrupt onset of headache, fever and neck stiffness. Additional clinical symptomatology may vary depending on the underlying cause. Focal signs and seizures are rarely seen in aseptic meningitis, but mumps, certain arboviruses, and lymphocytic choriomeningitis virus may cause a meningoencephalitis (Rice 2001).

The headache of aseptic meningitis has no typical characteristics. It is severe, most often bilateral and may be associated with fever and vomiting. Lamonte et al. (1995), in their retrospective review of 41 patients with aseptic meningitis, noted that headache was present in all, started or worsened abruptly in 24; in 39 the headache was severe and in 6 it was the worst headache. There was no consistent pattern of location or type of pain. In all cases the headache was different from the usual headache. Systemic prodromal symptoms preceded the onset of headache in 19 patients. Nausea, vomiting, cognitive changes, back pain, blurred vision, phonophobia, photophobia and tinnitus were the associated symptoms seen in their series (Marian et al. 1995).

Migraine headache may mimic aseptic meningitis, but if a patient presents acutely with fever and headache that is bilateral, throbbing not relieved with analgesics and different from their earlier headaches, then aseptic meningitis needs ruling out. Rarely migraine itself can cause

aseptic meningitis. Bartleson et al. (1981) reported a series of patients with complicated migraine and CSF pleocytosis preceded by a viral-like illness (Gomez-Aranda et al. 1997). Other causes of similar headache that may confuse include subarachnoid haemorrhage and other acute headaches.

The cell count in aseptic meningitis is usually less than 1000 per cu. mm, and there may be an early predominance of polymorphonuclear leucocytes. Repeated lumbar puncture in 8-12 hours frequently shows a change from neutrophil to lymphocyte predominance. CSF glucose levels are normal and CSF proteins may be normal or elevated. CSF culture for viruses and PCR studies help in further confirming the diagnosis.

Differential Diagnosis

Viruses are the most common causative agents, but even when all viral diagnostic facilities are available, the causal agent may be difficult to identify in a good proportion of cases. Viral pathogens may enter the CNS through the haematogenous or neural route. Neural penetration is limited to herpes viruses (HSV–1, HSV–2 and varicella zoster virus) and some enteroviruses. Exposure to mosquito or tick vectors is a risk factor for transmission (Adams and Victor 2001). Over 80% of aseptic meningitis are caused by enteroviruses (coxsackie A or B, enterovirus 68 to 71, echovirus and poliovirus), followed by the mumps virus, HSVû2, HIV, and less commonly HSV–1, varicella zoster virus (VZV), Epstein-Barr virus and cytomegalovirus (CMV). Rarely arbovirus, lymphocytic choriomeningitis virus (LCMV) and adenovirus may be responsible for similar symptoms. Influenzal and parainfluenzal illnesses can also cause aseptic meningitis. The incidence of polio and mumps in the vaccination era has decreased significantly in developed countries. In younger people, measles virus may cause aseptic meningitis that is associated with a rash (Waisman et al. 1999).

Human Immunodeficiency Virus (HIV) infection may present with aseptic meningitis, particularly at the time of seroconversion (Levy et al. 1990). Patients may present with CSF pleocytosis, elevated protein level and high intracranial pressure. Besides the usual meningeal signs, patients with HIV infection may have neurological deficits and may need imaging. Adenovirus may be a major cause of meningitis in patients with HIV infections. Varicella zoster virus can affect the immunocompromised.

Arbovirus accounts for approximately 5% of cases of aseptic meningitis in North America, and the incidence varies depending on the life cycle of arthropod vectors, animal reservoirs and their contact with humans. Some of the important viruses include Eastern and Western equine encephalitis viruses, St Louis Encephalitis virus, West Nile virus, Japanese B virus and Colorado tick fever. LCMV affects those at risk who come in contact with rodents or their excreta (Nelsen et al. 1993).

The immediate concern in practice should not be aimed at establishing a particular virus as the cause of the illness, but more importantly to exclude the few conditions with aseptic meningitis like picture, but having another underlying non-viral cause warranting specific management. In every patient with aseptic meningitis one has to look beyond viruses as the causative factor

Non-viral causes have a more complicated course but can be managed with specific treatment. Tuberculous, fungal, syphilitic, spirochaetal, rickettsial, parasitic and other mycoplasmal infections can cause aseptic meningitis, which should be suspected in the appropriate clinical setting. In the early stages, tuberculous meningitis may appear like aseptic meningitis and can be difficult to diagnose. The glucose levels are reduced only in the later stages and the organism is difficult to find. CSF features of aseptic meningitis, but without fever, may be seen with acute syphilitic meningitis. Cryptococcal infections, other fungal infections, and some rare conditions like Mycoplasma pneumonia, Brucellosis and Q fever can also present like aseptic meningitis. Brucellosis is common in specific geographic locations.

Conjuctival suffusion with transient erythema, severe leg and back pain, pulmonary infiltrates and aseptic meningitis should suggest leptospiral infection. Infection is acquired by contact with soil or water contaminated by the urine of rats, dogs, or cattle. Lyme borreliosis is a common spirochaetal cause of aseptic meningitis and meningoencephalitis. The spirochaete is tick borne, common in north eastern United States from May to July (Eppes et al. 1999).

Leukaemias in children and lymphomas in adults are common sources of meningeal reactions with aseptic meningitis like CSF picture. In these disorders, and in meningeal carcinomatosis, neoplastic cells are found throughout the leptomeninges with additional root involvement. Features of the aseptic meningitis syndrome can also be caused by brain abscess, parameningeal infections and partially treated bacterial meningitis, when it may be mistakenly diagnosed as viral aseptic meningitis. A careful history of previous antibiotic administration must therefore be obtained in all patients with meningitis.

Sarcoidosis, Behcets syndrome, vasculitis and granulomatous angiitis can present with aseptic meningitis syndrome by infiltrating the leptomeninges. These conditions, however, rarely present with a clinical picture of meningitis alone, more often they are seen with other neurological accompaniments (Gullapalli and Phillips 2002; Nelsen et al. 1993). Some chronic diseases like systemic lupus erythematosus, serum sickness and Vogt-Koyanagi-Harada syndrome, may present with aseptic meningitis (Adams and Victor 2001).

Drug induced aseptic meningitis (DIAM), either by: 1) direct irritation of the meninges with intrathecal administration, or by 2) immunological hypersensitivity to the drug, has been reported as an uncommon

adverse reaction with numerous agents (Chaudhry and Cunha 1991). The major categories of causative agents are non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobials, intravenous immunoglobulins, isoniazid, allopurinol and vaccines for measles, mumps and rubella. In addition to headache, there may be signs of a hypersensitivity reaction. Trimethoprim-sulphamethoxazole, azathioprine and intrathecal injections can result in the clinical findings of aseptic meningitis. The association between SLE and ibuprofen as a cause of DIAM is important to recognise. A high index of suspicion is necessary to make the diagnosis. Treatment is to withhold the drug. There are no long-term sequelae of DIAM.

Besides the typical CSF picture, it is essential to isolate the virus in CSF, stool, saliva and throat swabs using PCR and other serologic tests (Jeffery et al. 1997). It is important to enquire about a past history of infectious disease, immunisations, contact with animals, insect bites, recent respiratory or gastro-intestinal infection and recent travel. The season during which the illness occurs and the geographical location are helpful pointers.

Recurrent aseptic meningitis is also known as Mollarets meningitis and can be a diagnostic dilemma. There is spontaneous remission and no causative agent has been consistently found. It is difficult to identify the virus in the CSF. These patients need detailed investigations with repeat lumbar punctures, cytology or CSF bacterial cultures, PCR, HIV testing and MRI with contrast if necessary. Recurrence in a few cases is caused by HSV–1 and HSV–2 infections (Cohen et al. 1994).

Conclusion

Most patients with aseptic meningitis need only supportive care. It may be prudent to start antibiotics until cultures are shown to be negative, or a second examination of CSF shows a more typical picture. Most patients recover completely and rapidly when the aetiology is viral, unless there is an associated encephalitic component. Precautions should be taken when specific viruses are identified. Effective antiviral therapy is available against HSV–1, varicella and CMV. For HSV–2, acyclovir is the drug of choice. Other causes need appropriate management. Rarely, patients may have persistent headache, mild mental impairment, incoordination or weakness that lasts for months. Although aseptic meningitis is an acute illness, most patients eventually improve.

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Health Informatics

▶ Information and Psychoeducation in the Early Management of Persistent Pain

Heart Pain

▶ Visceral Pain Model, Angina Pain

Heat Hyperalgesia

Definition

Heat hyperalgesia is increased pain produced by a normally painful heat stimulus.

▶ Neuropathic Pain Model, Partial Sciatic Nerve Ligation Model
▶ Sympathetically maintained Pain and Inflammation, Human Experimentation

Heat Lesion

▶ Radiofrequency Neurotomy, Electrophysiological Principles

H

Heat Sensor

▶ Capsaicin Receptor

Heightened Attention

▶ Hypervigilance and Attention to Pain

Heightened Vigilance

▶ Hypervigilance and Attention to Pain

Helical CT

▶ CT Scanning

Helicobacter Pylori

Definition

Helicobacter Pylori are bacteria that cause inflammation and ulcers in the stomach.
▶ NSAIDs, Adverse Effects

Heliotherapy

Definition

Heliotherapy is the exposure to sun rays and ultraviolet rays.
▶ Spa Treatment

Helplessness

Definition

Helplessness is a belief in one's inability to adequately manage or cope with a stressful situation and to exert any control over ones circumstances, symptoms, and life.
▶ Catastrophizing
▶ Cognitive-Behavioral Perspective of Pain

Hemianesthesia

Definition

Hemianesthesia is the sensory loss in the left or right side of the body.
▶ Central Nervous System Stimulation for Pain

Hemibody Radiation

Definition

Hemibody radiation is an external beam of radiation administered to half of the body, i.e. above or below the diaphragm, for systemic metastatic disease.
▶ Adjuvant Analgesics in Management of Cancer-Rated Bone Pain

Hemicrania Continua

Lawrence C. Newman
Albert Einstein College of Medicine, New York, NY, USA
lnewman@chpnet.org

Definition

An under-recognized, primary headache disorder that is characterized by a constant, one-sided headache with fluctuating intensity. In general, the headache is present as a persistent background discomfort of mild to moderate intensity, but exacerbations of more severe pain, superimposed upon the baseline pain, occurs periodically. During these painful flare-ups, patients experience one or more symptoms on the side of the headache. These symptoms include, drooping of the eyelid, reddening or tearing of the eye, constriction of the pupil, and stuffiness or dripping of the nostril. Recognition of the disorder is important, because the headache responds dramatically to treatment with the anti-inflammatory medication indomethacin.

Characteristics

Hemicrania continua (HC) is an under-recognized primary headache disorder. Initially, HC was believed to be a very rare disorder, however, in headache subspecialty practices, HC is a common cause of refractory, ▶ unilateral, chronic daily headache. (Peres et al. 2001) Sjaastad and Spierings initially described the disorder in two patients with continuous headaches from onset (Sjaastad and Spierings 1984). Since that initial description, approximately 150 cases have been described in the literature.
Hemicrania continua demonstrates a marked female preponderance, with a female to male ratio of approximately 2:1. The condition most often begins during adulthood. The age of onset ranges from 5-67 years (mean 28 years) (Peres et al. 2001; Matharu et al. 2003). Most sufferers describe strictly unilateral pain, without side-shift. Rarely, bilateral pain (Pasquier et al. 1987; Iordanidis and Sjaastad 1989; Trucco et al. 1992), or pain that alternated sides, has been described (Newman et al. 1992; Newman et al. 2004). The maximal pain

is experienced in the eye, temple and cheek regions. On occasion, the pain may radiate into the ▶ ipsilateral occiput, neck and retro-orbital areas.

The pain is usually described as a steady ache or throbbing pain. Superimposed upon the continuous baseline low-level discomfort, the majority of patients report exacerbations of more intense pain lasting from 20 minutes to several days. Although significantly more intense than the usual background discomfort, the painful exacerbations never reach the level experienced by ▶ cluster headache sufferers. These exacerbations may occur at any time of the day or night, and frequently awaken the patient from sleep. Migraine-like associated symptoms such as nausea, vomiting, ▶ photophobia and ▶ phonophobia often accompany these exacerbations. Rarely, painful exacerbations may be preceded by a migrainous visual aura (Peres et al. 2002). ▶ Autonomic features of cluster headache, including ipsilateral ▶ ptosis, ▶ conjunctival injection, ▶ lacrimation and nasal congestion, often accompany exacerbations of pain. When present, however, these associated features are usually much less pronounced than those seen in cluster headaches. Painful exacerbations are also associated with a sensation of ocular discomfort, often likened to a foreign body in the eye (typically reported as sand or hair). Concurrent ▶ primary stabbing headaches ("jabs and jolts") are reported by many patients, occasionally occurring only in association with the painful exacerbations. During exacerbations of pain, patients assume the pacing activity usually seen with cluster headaches. The International Headache Society (IHS) diagnostic criteria for HC are as follows:

Diagnostic Criteria

a) Headache for > 3 months fulfilling criteria B–D
b) All of the following characteristics:
   1. unilateral pain without side-shift
   2. daily and continuous, without pain-free periods
   3. moderate intensity, but with exacerbations of severe pain
c) At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
   4. conjunctival injection and/or ▶ lacrimation
   5. nasal congestion and/or ▶ rhinorrhea
   6. ptosis and/or miosis
d) Complete response to therapeutic doses of indomethacin
e) Not attributed to another disorder

Three temporal profiles of HC have been reported (Newman et al. 1994, Goadsby and Lipton 1997). A chronic form in which headaches persist unabated for years, an episodic form in which distinct headache phases are separated by periods of pain-free remissions, and an initially episodic form that over time evolves into the chronic, unremitting form. HC is chronic from onset in 53%, chronic evolved from episodic in 35%, and episodic in 12% of sufferers (Matharu et al. 2003). There are also individual case reports of atypical presentations; one patient initially experienced the chronic form that over time became episodic (Pareja 1995), another patient with the episodic form experienced headaches with a clear seasonal pattern (Peres et al. 2001).

Organic mimics of HC have been reported to occur in association with brain tumors involving the bones of the skull and skull base (Matharu et al. 2003). HC has been reported to occur in a patient diagnosed with HIV, although a causal relationship was not definitively established (Brilla et al. 1998). Rarely, the diagnosis of HC is masked by a concurrent medication rebound headache. In these instances, discontinuation of the overused analgesic is not associated with headache cessation, and the diagnosis of HC is made by exclusion (Matharu et al. 2003). In rare instances, HC followed head trauma (Lay and Newman 1999).

Hemicrania continua is often misdiagnosed. Although it is not a true cluster headache variant, HC may be mistaken for cluster if the physician focuses on the painful flare-ups with associated autonomic features. A careful history should reveal the presence of the continuous, low-level baseline discomfort in addition to the more disabling exacerbations. Additionally, the autonomic features of HC, when present, tend to be much less pronounced than those of cluster. Similarly, the associated nausea, vomiting, photophobia and phonophobia that accompany exacerbations of pain may be misdiagnosed as chronic migraine headaches. HC is distinguished from migraine by the presence of the persistent dull background discomfort.

Like all primary headache disorders, HC is diagnosed based on the patients' history, medical and neurological examinations. As it is a relatively uncommon headache disorder, and because there have been serious disorders that mimic HC, all patients with features of HC should undergo an MRI scan of the brain prior to initiating therapy.

The treatment of HC is with the medication ▶ indomethacin. In fact, the diagnosis of HC is predicated on response to treatment with indomethacin. The initial dosage is 25 mg, three times daily. If clinical response is not seen within 1–2 weeks, the dosage should be increased to 50–75 mg, three times daily. Complete response to treatment with indomethacin is prompt, usually within 1–2 days of reaching the effective dose. The typical maintenance dose ranges from 25–100 mg, daily. Skipping or delaying the dose often results in headache recurrence. An intramuscular injection of indomethacin, 50–100 mg (the "indotest") has been proposed as a diagnostic procedure for HC (Antonaci et al. 1998). Total resolution of the pain of HC was

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reported to occur within 2 hours of the injection. Injectable indomethacin is not available in the United States.

Patients suffering with the episodic form should be instructed to continue the medication for 1–2 weeks longer than their typical headache phase and then gradually taper the dose. For those patients with the chronic form, medication tapering should be attempted every 6 months. Patients requiring long-term indomethacin therapy should be given medications such as antacids, misoprostol, histamine H_2 blockers or proton pump inhibitors to mitigate the gastrointestinal side effects of this agent.

In patients who do not respond to treatment with adequate doses of indomethacin, another diagnosis should be considered. Other agents, which may have partial success in the treatment of HC, include naproxen and paracetamol, paracetamol in combination with caffeine, ibuprofen, piroxicam, and reficoxib (Matharu et al. 2003). Six patients who met the clinical criteria for HC, yet failed to respond to treatment with indomethacin, have been reported (Matharu et al. 2003). Nonetheless, the IHS clinical criteria for HC specify that indomethacin responsiveness is necessary for the diagnosis.

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Hemicrania Continua Headache

Definition

Hemicrania continua is a continuous (always present) but fluctuating unilateral headache, moderate to severe in intensity, and accompanied by of one of the following during pain exacerbations: conjuntival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, or eyelid edema. It is uniquely responsive to indomethacin.
▶ Chronic Daily Headache in Children
▶ New Daily Persistent Headache
▶ Paroxysmal Hemicrania

Hemicrania Simplex

▶ Migraine Without Aura

Hemipain

Definition

Hemipain is pain that is situated in one half of the body.
▶ Diagnosis and Assessment of Clinical Characteristics of Central Pain

Hemisection Model

▶ Spinal Cord Injury Pain Model, Hemisection Model

Hemisphere

Definition

The hemisphere is either half of the cerebrum or brain; the human brain has a left and a right hemisphere.
▶ PET and fMRI Imaging in Parietal Cortex (SI, SII, Inferior Parietal Cortex BA40)

Hemorrhagic Stroke

▶ Headache Due to Intracranial Bleeding

Hereditary Motor and Sensory Neuropathy

Definition

Hereditary motor and sensory neuropathy is an alternative name for Charcot-Marie-Tooth Disease.
▶ Hereditary Neuropathies

Hereditary Neuropathies

WILLIAM N. KELLEY, STEVEN S. SCHERER
Department of Neurology, The University of
Pennsylvania Medical School, Philadelphia, PA, USA
sscherer@mail.med.upenn.edu

Synonyms

Charcot-Marie-Tooth disease (CMT); Hereditary Motor and Sensory Neuropathy (HMSN); Dejerine-Sottas neuropathy (DSN); Congenital Hypomyelinating Neuropathy; Hereditary Neuropathy with Liability to Pressure Palsies

Definition

Hereditary neuropathies are inherited diseases that injure peripheral nerves.

Characteristics

Classification of Hereditary Neuropathies

Inherited neuropathies can be separated according to whether they are syndromic (i. e., one of a number of affected tissues), and whether they are "axonal" or "demyelinating" (whether the primary abnormality appears to affect axons/neurons or myelinating ▶ Schwann cells). Non-syndromic inherited neuropathies (Tab. 1) are usually called ▶ CMT or ▶ HMSN. Different kinds are recognized clinically, aided by electrophysiological testing of peripheral nerves (Dyck et al. 1993; Lupski and Garcia 2001; Kleopa and Scherer 2002). If the forearm motor nerve conduction velocities (NCVs) are greater or less than 38 m/s, then the ▶ neuropathy is traditionally considered to be "axonal" (CMT2/HMSN II) or "demyelinating" (CMT1/HMSN I), respectively. Some non-syndromic inherited neuropathies have been given different names because their phenotypes differ; these may be milder (e.g. HNPP) or more severe (DSN CHN). Mutations in different genes can cause a similar phenotype, and different mutations in the same gene can cause different phenotypes (Lupski and Garcia 2001; Suter and Scherer 2003; Wrabetz et al. 2004). For most of these mutations, the evidence favors the idea that the more severe phenotypes are caused by a gain of function and that (heterozygous) loss of function alleles cause milder phenotypes.

The Biology of Myelinated Axons and Neuropathies

The structure and function of myelinating Schwann cells is the basis for understanding how mutations cause inherited demyelinating neuropathies. The ▶ myelin sheath itself can be divided into two domains, compact and non-compact myelin, each of which contains a non-overlapping set of proteins (Fig. 1). Compact myelin forms the bulk of the myelin sheath. It is largely composed of lipids, mainly cholesterol and sphingolipids,
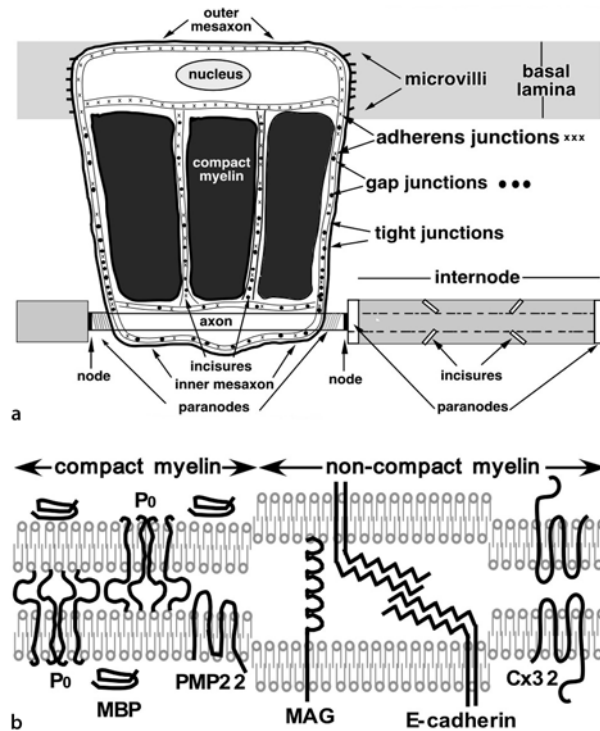
Hereditary Neuropathies, Figure 1 The architecture of the myelinated axon in the PNS. In (a) one myelinating Schwann cell has been "unrolled" to reveal the regions forming compact myelin, as well as paranodes and incisures, regions of non-compact myelin. In (b) note that P_0, PMP22, and MBP and are found in compact myelin, whereas Cx32, MAG and E-cadherin are localized in non-compact myelin. Modified from (Kleopa and Scherer 2002), with permission of Elsevier Science.

including galactocerebroside and sulfatide, and three proteins – MPZ/P_0, PMP22, and myelin basic protein (MBP). Found in the paranodes and incisures, non-compact myelin contains tight junctions, gap junctions, and adherens junctions. In most cell types, these junctions join adjacent cells, whereas in Schwann cells, they are found between adjacent layers of non-compact myelin (Scherer et al. 2004). Gap junctions formed by Cx32 may form a radial pathway, directly across the layers of the myelin sheath; this would be advantageous as it provides a much shorter pathway (up to 1000-fold) than a circumferential route.

Genetic evidence supports the long-standing doctrine that neuropathies are length-dependent, because the longest axons are the most vulnerable to defects in axonal transport (Suter and Scherer 2003). Neurofilaments and microtubules comprise the axonal cytoskeleton. Neurofilaments are composed of three subunits, termed heavy, medium, and light. Dominant mutations in the gene encoding the light subunit (*NEFL*) cause an axonal neuropathy (CMT2E, Tab. 1). Most proteins are synthesized in the cell body and transported down the axon. Microtubule-activated ATPases, known as kinesins, which are molecular motors that use microtubules as tracks, mediate axonal transport.

Hereditary Neuropathies, Table 1 Non-syndromic inherited neuropathies with a genetically identified cause The neuropathies are classified by MIM (http://www.ncbi.nlm.nih.gov/Omim/); the references for the individual mutations are compiled in the CMT mutation database (http://molgen-www.uia.ac.be/ CMTMutations/DataSource/MutByGene.cfm). Bolded diseases have pronounced affects on pain.

Disease (MIM)	Mutated gene/linkage	Clinical features
Autosomal or X-linked dominant demyelinating neuropathies		
HNPP (162500)	Usually deletion of one *PMP22* allele	Episodic mononeuropathies at typical sites of compression; also mild demyelinating neuropathy
CMT1A (118220)	Usually duplication of one *PMP22* allele	Onset 1st–2nd decade; weakness, atrophy, sensory loss; beginning in the feet and progressing proximally
CMT1B (118200)	*MPZ*	Similar to CMT1A; severity varies according to mutation (from "mild" to "severe" CTM1)
CMT1C (601098)	*LITAF/SIMPLE*	Similar to CMT1A; motor NCVs about 20 m/s
CMT1D (607687)	*EGR2*	Similar to CMT1A; severity varies according to mutation (from "mild" to "severe" CTM1)
CMT1X (302800)	*GJB1*	Similar to CMT1A, but distal atrophy more pronounced; men are more affected than are women
Autosomal dominant axonal neuropathies		
CMT2A (118210) CMT2A2 (609260)	*KIF1B*β *MFN2*	Onset of neuropathy by 10y; progresses to distal weakness and atrophy in legs; mild sensory disturbance
CMT2B (600882)	*RAB7*	Onset 2nd–3rd decade; severe sensory loss with distal ulcerations; also length-dependent weakness
CMT2C (606071)	*12q23-24*	Prominent vocal cord and diaphragmatic weakness
CMT2D (601472)	*GARS*	Arm more than leg weakness; onset of weakness 2nd–3rd decade; sensory axons involved
CMT2E (162280)	*NEFL*	Variable onset and severity; ranging from DSS-like to CMT2 phenotype; pain sensation may be diminished
CMT2-P$_0$ (118200)	*MPZ*	Late onset (30y or older); but progressive neuropathy; pain; hearing loss; abnormally reactive pupils
Severe demyelinating neuropathies (autosomal dominant or recessive; "CMT3 or HMSN III")		
DSS (Dejerine-Sottas Syndrome (145900)	Dominant (*PMP22*; *MPZ*; *GJB1*; *EGR2*; *NEFL*) and recessive (*MTMR2*; *PRX*) mutations	Delayed motor development before 3y; severe weakness and atrophy; severe sensory loss particularly of modalites subserved by large myelinated axons; motor NCVs less than 10 m/s; dysmyelination on nerve biopsies
CHN (Congenital Hypomyelinating Neuropathy; 605253)	Dominant (*EGR2*; *PMP22*; *MPZ*) &recessive (*EGR2*) mutations	Clinical picture often similar to that of Dejerine-Sottas syndrome; but hypotonic at birth
Autosomal recessive demyelinating neuropathies ("CMT4")		
CMT4A (214400)	*GDAP1*	Early childhood onset; progressing to wheelchair-dependency; mixed demyelinating and axonal features
CMT4B1 (601382)	*MTMR2*	Early childhood onset; may progress to wheelchair-dependency; focally-folded myelin sheaths
CMT4B2 (604563)	*MTMR13*	Childhood onset; progression to assistive devices for walking; focally-folded myelin sheaths; glaucoma
CMT4C (601596)	*KIAA1985*	Infantile to childhood onset; progressing to wheelchair-dependency; severe to moderate NCV slowing
CMT4D (601455)	*NDRG1*	Childhood onset; progression to severe disability by 50y; hearing loss and dysmorphic features
CMT4F (605260)	*PRX*	Childhood onset; usually progression to severe disability; prominent sensory loss
CMT4 (605253)	*EGR2*	Infantile onset; progressing to wheelchair-dependency

Hereditary Neuropathies, Table 1 (continued)

Disease (MIM)	Mutated gene/linkage	Clinical features
Autosomal recessive axonal neuropathies ("AR-CMT2" or "CMT 2B")		
AR-CMT2A(605588)	*LMNA* mutations	Onset of neuropathy in 2nd decade; progresses to severe weakness and atrophy in distal muscles
Hereditary Motor Neuropathies (HMN or "distal SMA")		
SMARD1 (604320)	Recessive *IGHMBP2* mutations	Distal infantile spinal muscular atrophy with diaphragm paralysis
HMN 5 (600794)	Dominant *GARS* mutations	Arm more than leg weakness; onset of weakness 2nd–3rd decade; no sensory involvement
Hereditary Sensory (and Autonomic) Neuropathies/Neuronopathies (HSN or HSAN)		
HSN-1 (162400)	Dominant *SPTLC1* mutations	Onset 2nd–3rd decade (often with phase of lacinating pain); severe sensory loss (including nociception) with distal ulcerations; also length-dependent weakness
HSN-2 (201300)	Recessive *HSN2* mutations	Childhood onset of progressive numbness in hands and feet, exacerbated by cold; reduced pain sensation; no overt autonomic dysfunction
HSN-3 (Riley-Day syndrome; 223900)	Recessive *IKBKAP* mutations	Congenital onset; dysautonomic crises; decreased pain sensation; absent fungiform papilla; overflow tears
HSN-4 (CIPA; 256800)	Recessive *NTRKA*	Dysautonomia and loss of pain sensation caused by congenital absence of sensory and sympathetic neurons
HSN-5 (608654)	Recessive *NGFB* mutations	Childhood onset; unheeded pain leads to development of Charcot joints; deceased sensation to multiple modalities
HSN with cough and gastroesophageal reflux (608088)	3p22-p24	Adult onset cough and sensory neuropathy; with sensory loss; painless injuries; and/or lacinating pains

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A mutation in the gene encoding kinesin KIF1Bβ causes CMT2A1 a dominantly inherited axonal neuropathy. Mutations in the genes encoding gigaxonin and the p150 subunit of dynactin also disrupt axonal transport and cause neuropathy/neuronopathy. Defective axonal transport has been implicated in a host of other inherited neurological diseases, including the inherited spastic paraplegias, which appear to be length-dependent CNS axonopathies.

CMT and Pain

The best examples of a dominantly inherited neuropathy that is associated with pain are *MPZ* mutations, which cause a CMT2-like phenotype (CMT2-P$_0$), particularly the Thr124Met mutation. Several families have been found to have an adult-onset neuropathy with painful lacinations and hearing loss. Nerve biopsies from clinically affected patients show axonal loss, clusters of regenerated axons, and some thinly myelinated axons. In spite of a late onset, many patients progress relatively rapidly to the point of using a wheelchair. Neuropathic pain is not a prominent symptom in most patients with *MPZ* mutations (CMT1B).

Neuropathic pain can be a prominent feature in some CMT2 (e.g. CMT2-P$_0$) patients (Gemignani et al. 2004), but the genetic cause(s) of these cases is not yet known. CMT2B patients have the opposite problem –

they do not feel pain, and insensitivity to pain commonly leads to distal ulcerations in the feet, even toe amputations. CMT2B is caused by dominant mutations in *RAB7*, which encodes a member of the Rab family of Ras-related GTPases that are essential for proper intracellular membrane trafficking. RAB7 is widely expressed, including in motor and sensory neurons. A similar, ulceromutilating neuropathy has been reported in an Austrian family, which did not link to the CMT2B locus, indicating further genetic heterogeneity in this phenotype.

Hereditary Sensory (and Autonomic) Neuropathies (HSN or HSAN)

They were initially classified together for their shared characteristics - the loss of sensory (especially of small fibers) and ▶ autonomic fibers, resulting in severe sensory loss to the point that the hands and feet became mutilated from unheeded trauma. They proved to be genetically heterogeneous (Tab. 1). HSN-1 is an autosomal dominant trait and manifests in adolescence with small fiber sensory loss, burning pain (distal>proximal and legs>arms), pedal deformity, acromutilation, and distal weakness. It is caused by mutations in the gene encoding serine palmitoyl transferase, long-chain base subunit 1 (*SPTLC1*). The mutations that cause HSN-1 reside in a conserved region, and the corresponding mu-

tations in the yeast enzyme act as dominants because the enzyme is part of a heterodimer.

HSN-2, HSN-3 and HSN-4 are autosomal recessive. HSN-2 begins in early childhood with similar phenotype to HSN-1. HSN-3, also known as the Riley-Day syndrome or familial dysautonomia with congenital indifference to pain, is usually caused by a mutation that leads to missplicing of IKBKAP (inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein) (Axelrod 2004). Some characteristics manifest at birth, indicating that certain populations of autonomic and sensory neurons/axons either fail to develop or are already affected, but axonal/neuronal loss progresses even after birth. Although initial deficits such as dysautonomic crises appear to stem from the loss of small fibers, large myelinated fibers are progressively affected. Loss of sensation renders patients prone to self-injury. At least two syndromic neuropathies, cold-induced sweating and Stüve-Wiedemann/ Schwartz-Jampel type 2 syndrome have features in common with HSN-3 (Tab. 2). HSN-4 is a syndromic disease, characterized by congenital insensitivity to pain with anhydrosis (hence the alternative name, CIPA syndrome), with the associated features of small fiber sensory loss, autonomic failure, mental retardation, and acromutilation. CIPA syndrome is caused by mutations in NTRKA, which encodes a receptor tyrosine kinase for nerve growth factor (Indo 2001).

Syndromic Inherited Neuropathies and Pain

Demyelinating neuropathies are part of several recessive neurological syndromes, but are typically overshadowed by other manifestations (Tab. 2). Neuropathic pain is uncommon except in metachromatic leukodystrophy. An axonal neuropathy is a part of many syndromes, and most appear to be neuron-autonomous. Discussed below are some of the inherited syndromic axonal neuropathies that have pronounced effects on pain.

Familial amyloid polyneuropathy (FAP) 1 and 2 is caused by dominant mutations in the transthyretin (*TTR*) gene – almost all are caused by a single nucleotide change that results in an amino acid substitution (Benson 2000). In the United States, the majority of mutations are found in families of European ancestry, and, in many cases, the mutations have been traced to the country of origin. Adults develop dysesthesias in the lower extremities, with or without small fiber findings such as decreased temperature sensation, and/or autonomic dysfunction-constipation and diarrhea or impotence. The progressive loss of large myelinated (sensory and motor) fibers leads to progressive sensory loss and motor impairment. Amyloidosis results from the transformation of a protein into β-structured fibrils that are deposited in various organs, causing dysfunction by their presence and magnitude. FAP 3, caused by mutations in *Apoliproprotein A1*, also causes neuropathy and neuropathic pain.

Recurrent episodes of painful brachial plexus lesions are the hallmark of hereditary neuralgic amyotrophy – a dominantly inherited disorder (Windebank 1993). Individual episodes are similar to those in idiopathic neuralgic amyotrophy; both kinds are heralded by severe pain, followed by weakness within days, and recovery over weeks to months. Episodes may be triggered by immunization and childbirth, and perivascular inflammation and Wallerian degeneration are characteristic lesions (Klein et al. 2002). Subtle dismorphic features in affected patients with the inherited form indicate that this is a syndromic disorder. Neuralgic amyotrophy is caused by mutation in *SEPT9*, but another locus is possible.

Porphyrias are caused by mutations in the genes involved in heme biosynthesis. Dominant mutations in porphobilinogen deaminase, coproporphyrinogen 3 oxidase, protoporphyrinogen oxidase, ferrochelatase may produce different syndromes (photosensitivity, psychosis, and/or liver disease), but all can cause acute attacks of abdominal pain followed by neuropathy (Windebank and Bonkovsky 1993). High levels of porphyrins are found during attacks, and may be toxic to motor axons/neurons, but why those innervating certain muscle groups are mainly affected remains to be determined. The somatic neuropathy itself is usually not painful, but it is conceivable that the abdominal pain is related to damaged visceral afferent axons. Hereditary tyrosinemia type 1 causes crises that resemble the porphyrias, including elevated urinary δ-aminolevulinic acid, except for limb pain that may be neuropathic.

Fabry disease is caused by deficiency of an X-linked lysosomal hydrolase, α-galactosidase, leading to accumulation of glycosphingolipids in many cell types, including sensory neurons. The loss of sensory axons and sensory neurons is presumed to cause neuropathic pain, which is the most common and the earliest symptom (MacDermot et al. 2001). Patients had a mean pain score of five (1–10 scale) in spite of pharmacological therapy. In addition to constant pain, patients can have severe attacks of pain, often triggered by heat, fever, alcohol, or exercise.

Concluding Thoughts

Inherited neuropathies are common, and their genetic causes are rapidly being determined. A lack of pain in certain inherited neuropathies can be related to the loss of the relevant sensory axons/neurons, particularly for HSN-1, HSN-3, and HSN-4/CIPA syndrome. Discovering the molecular causes of even rarer kinds of inherited insensibility to pain should lead to a better understanding of the neurobiology of pain. Why pain is a characteristic of some neuropathies and not others is far less clear. It seems that neuropathies that mainly affect small myelinated and unmyelinated (nociceptive and other kinds of sensory) axons are more likely to cause pain than those that chiefly affect large myelinated (mo-

Hereditary Neuropathies, Table 2 Selected syndromic inherited neuropathies For references; see the following websites: http://www.ncbi.nlm.nih.gov/Omim/; http://molgen-www.uia.ac.be/ CMTMutations/DataSource/MutByGene.cfm; and http://www.neuro.wustl.edu/neuromuscular/. Bolded diseases have pronounced affects on pain. For abbreviations; see text

Disease (MIM)	Mutated gene/linkage	Clinical features
Dominantly inherited; syndromic demyelinating neuropathies		
Wardeenburg type IV (602229)	*SOX10*	CNS and PNS dysmyelination; Hirschsprung disease
Recessively inherited; syndromic demyelinating neuropathies		
Metachromatic leuko-dystrophy (250100)	*Arylsulfatase A*	Demyelinating neuropathy; optic atrophy; mental retardation; hypotonia; phase of neuropathic pain
Globoid cell leuko-dystrophy (245200)	*Galactosylceramide β-galactosidase*	Demyelinating neuropathy; spasticity; optic atrophy; mental retardation
Dominantly inherited; syndromic axonal neuropathies		
Hereditary Neuralgic Amyotrophy (162100)	*SEPT9*	Episodes of painful neuropathies of the brachial plexus; hypotelorism; small palpebral fissures; small mouth
FAP 1 and 2 (176300)	*TTR* (Transthyretin)	Painful axonal neuropathy with prominent involvement of small axons; other organs involved; FAP 2 also has carpal tunnel syndrome
FAP 3/"Iowa" type (107680)	*Apolipoprotein A-1*	Painful axonal neuropathy; renal and hepatic disease
FAP 4/"Finnish" type (105120)	*Gelsolin* (137350)	Corneal lattice dystrophy; cranial neuropathies; peripheral neuropathy not typically painful
Acute intermittent porphyria (176000)	*Porphobilinogen deaminase*	Acute neuropathy follows crises of abdominal pain; psychosis; depression; dementia; seizures
Coproporphyria (121300)	*Coproporphyrinogen 3 oxidase*	Skin photosensitivity; psychosis; crises of acute neuropathy (and abdominal pain) are rare
Variegate porphyria(176200)	*Protoporphyrinogen oxidase*	South Africa: founder effect; symptoms similar to those in acute intermittent porphyria
Erythopoietic proto-porphyria (17000)	*Ferrochelatase*	Dermatitis; photosensitivity; liver disease; acute neuropathy rare
Fabry disease (301500)	*α-galactosidase*	X-linked; painful neuropathy even painful crises; cardiomyopathy; renal failure; angiokeratoma
Recessively inherited; syndromic axonal neuropathies		
Giant axonal neuropathy (256850)	*Gigaxonin*	Mental retardation; spasticity; kinky/curly hair
Hereditary tyrosinemia type 1 (276700)	*Fumarylacetoacetase*	Hepatic and renal disease; cardiomyopathy; crises of acute neuropathy and abdominal pain similar to those in porphyrias (but in infancy/childhood)
Tangier Disease (205400)	*ABCA1* (60046)	Atherosclerosis and/or peripheral neuropathy; syringomyelia-like loss of pain sensation can result in painless ulcerations and acromutilation
Congenital sensory and autonomic neuropathy and neurotrophic keratitis (256810)	unknown	Affects Navajo infants/children; encephalopathy; myelopathy; neuropathy resulting in painless ulcerations and acromutilation; fatal liver disease
Cold-induced sweating (272430)	*CRLF1*	Poor sucking in infancy; cold-induced sweating; diminished pain caused by cold/hot/mechanical stimuli
Stüve-Wiedemann/ Schwartz-Jampel type 2 syndrome	*LIFR*	Osteodysplasia with similar findings to HSN-3/familial dysautonomia: lack of corneal reflex, lack of fungiform papillae, tongue ulceration; also cold-induced sweating

tor and non-nociceptive sensory) axons. This reasoning does not account for why it is that neuropathic pain is more common in CMT2 than in CMT1 (Gemignani et al. 2004), and so prominent CMT2-P_0 (see above). Further, it remains to be explained why pain was much more commonly reported in a patient survey (Carter et al. 1998) than described in typical reports. Part of this discrepancy may owe to the failure to discriminate between neuropathic pain from other causes (Carter et al. 1998) as discussed by Gemignani et al. (2004).

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Hereditary Neuropathy with Liability to Pressure Palsies

▶ Hereditary Neuropathies

Hereditary Sensory and Autonomic Neuropathy Type IV, HSAN IV, HSAN 4

▶ Congenital Insensitivity to Pain with Anhidrosis

Hereditary Sensory Neuropathy

Definition

Hereditary Sensory Neuropathy is an inherited neuropathy that mainly affects sensory axons and/or sensory neurons.

▶ Hereditary Neuropathies

Heritability of Inflammatory Nociception

JEFFREY S. MOGIL

Department of Psychology and Centre for Research on Pain, McGill University, Montreal, QC, Canada
jeffrey.mogil@mcgill.ca

Synonyms

Inflammatory Nociception, Heritability; Inflammatory Nociception, Genotypic Influences; Inflammatory Nociception, Genetic Factors

Definition

Humans and laboratory animals display widely variable responses to inflammatory stimuli. Even when the amount of inflammation is held constant, robust individual differences in the pain accompanying that inflammation are observed. Some proportion of this variability can be attributed to inherited genetic factors, and progress is being made in identifying the relevant genes using ▶ inbred strains of mice. Genes contributing to variability in inflammatory nociception are probably distinct from genes contributing to variability in the development of inflammation itself.

Characteristics

Susceptibility to developing inflammatory pathologies like rheumatoid arthritis is considerably ▶ heritable, with one recent meta-analysis of ▶ twin studies suggesting that inherited genetic factors account for approximately 60% of the variation in disease liability (MacGregor et al. 2000). A number of animal models of autoimmune and/or inflammatory disorders have been developed, and scores of "modifier" genetic loci (i.e. non–major histocompatibility complex genes) influencing disease susceptibility or severity have been detected using ▶ quantitative trait locus (QTL) mapping (Griffiths et al. 1999). These loci show considerable overlap with the results of human genome-wide scans for ▶ genetic linkage in pedigrees of autoimmune/inflammatory disease sufferers (Becker et al. 1998). In a few cases, the precise genes and DNA variants responsible for the modified susceptibility or severity have been unambiguously identified, including ▶ single nucleotide polymorphisms (SNPs) in the human *SLC22A4* gene encoding an organic cation

transporter (Tokuhiro et al. 2003) and the rat *Ncf1* gene encoding a cytosolic factor in the NADPH oxidase complex (Olofsson et al. 2003).

However, the heritability of inflammatory *pain* remains poorly understood; none of the genes described above are necessarily relevant to variable pain responses given a particular degree of inflammation. A large number of ▶ transgenic knockout mice have been developed that display altered sensitivity to inflammatory nociception (see Mogil and Grisel 1998), thus providing evidence for the crucial roles of the targeted genes in the processing of inflammatory pain. Knockout mice represent a poor model to study inherited variability though, because their genetic "lesion" is far more dramatic than the subtle changes in function and expression that more generally characterize genetic variation in a population. The contrasting responses of different inbred strains of rats and mice have clearly demonstrated that assays of inflammatory nociception featuring standardized stimuli are robustly heritable. For example, recuperative licking behavior on the "tonic" or "late" phase of the ▶ formalin test – thought by many to reflect ongoing inflammatory nociception – ranges by up to 10–fold among 14 strains tested (Mogil et al. 1998) (Fig. 1). We have extensively characterized the extreme–responding strains, A/J and C57BL/6, and observed differences in formalin potency and efficacy and alterations in the timing of licking behavior in the tonic phase. However, these strains do not differ in edema produced by formalin injection, whether assessed *via* hind-paw thickness, *via* hind-paw weight, or histologically.

To provide evidence that the behavioral strain difference in licking time truly reflects a difference related to pain processing rather than non-specific factors (e.g., emotionality, locomotor activity, propensity to lick injured tissue), we conducted a study evaluating the ▶ genetic correlation between formalin-induced licking and ▶ c-fos immediate-early gene expression in the spinal cord dorsal horn. We found an extremely high correlation (r=0.94) between tonic-phase licking and Fos-protein immunoreactivity in the deep (laminae V/VI) but not superficial (laminae I/II) dorsal horn among eight mouse strains (Bon et al. 2002). This high correlation suggests that the strain-dependent behavioral differences are reflected in the processing of the noxious stimulus in appropriate pain–relevant ascending pathways.

As a first step to identifying the genes responsible for the robust differences between A/J and C57BL/6J mice on the formalin test, we performed a QTL mapping study in an ▶ F2 intercross of these strains (Wilson et al. 2002). Two statistically significant QTLs were identified; one of these (called *Nociq2*), on distal mouse chromosome 10, was associated with the tonic phase and accounted for 15% of the overall trait variance. In this F_2 population, the ≈25% of mice inheriting two copies of the A/J ▶ allele at a gene very near the end of chromosome 10 displayed 200 seconds *less* licking in the tonic phase

than mice with one or two C57BL/6J alleles. We have now provided confirmatory evidence for the existence of this formalin test-relevant gene using more advanced mapping populations (e.g. recombinant inbred strains, recombinant congenic strains) (Darvasi 1998), and have pinpointed its exact location to less than 3 cM (i.e. <3 million nucleotides; unpublished data), a genomic region containing only 14 known genes.

When genes associated with variable inflammatory pain sensitivity are identified, what will their relevance be to other pain states? Using genetic correlation analysis applied to over 22 different nociceptive assays in 12 mouse strains, we have determined that at least five fundamental 'types' of nociception exist. The defining feature of these pain types is noxious stimulus modality; that is, sensitivity to thermal stimuli is inherited similarly, but sensitivity to noxious chemical stimuli depends on a different set of genes (Lariviere et al. 2002). Generally speaking, the same mouse strains that are sensitive on the formalin test are also sensitive to injection of acetic acid, capsaicin or bee venom; such strains might not, however, be sensitive in the hot-plate test. It is interesting that the presence or absence of inflammation does *not* appear to be the defining feature, but rather the use of a noxious chemical substance producing spontaneously emitted pain behaviors. Some inflammatory mediators produce very little behavioral evidence of spontaneous pain (e.g. carrageenan), instead yielding long-lasting thermal and mechanical hypersensitivity. In these cases, what appears to be inherited in mice is not sensitivity to the mediator itself, but rather sensitivity to the evoking stimulus. That is, mouse strains sensitive to the development of thermal hypersensitivity after carrageenan injection are not the same strains that are sensitive to the development of mechanical hypersensitivity (Lariviere et al. 2002), implying the existence of modality-selective genes. Another finding from this analysis is that the same set of genes appear to be relevant to hypersensitivity states, whether they were induced by inflammation or nerve damage, possibly suggesting an important inflammatory component in the development of neuropathic pain.

The predictions described above will require the identification of many more pain variability-related genes for their evaluation. It is interesting, however, that none of the existing murine QTLs for thermal nociception (see Mogil 2004) are located on distal chromosome 10. Furthermore, an unpublished study (H.S. Hain and J.K. Belknap, personal communication) using the chemical/inflammatory acetic acid writhing test has also detected a statistically significant QTL on distal chromosome 10.

Once genes associated with variable sensitivity to inflammatory nociception are identified, the demonstration of the relevance of those genes and their common variants to humans might be important in a number
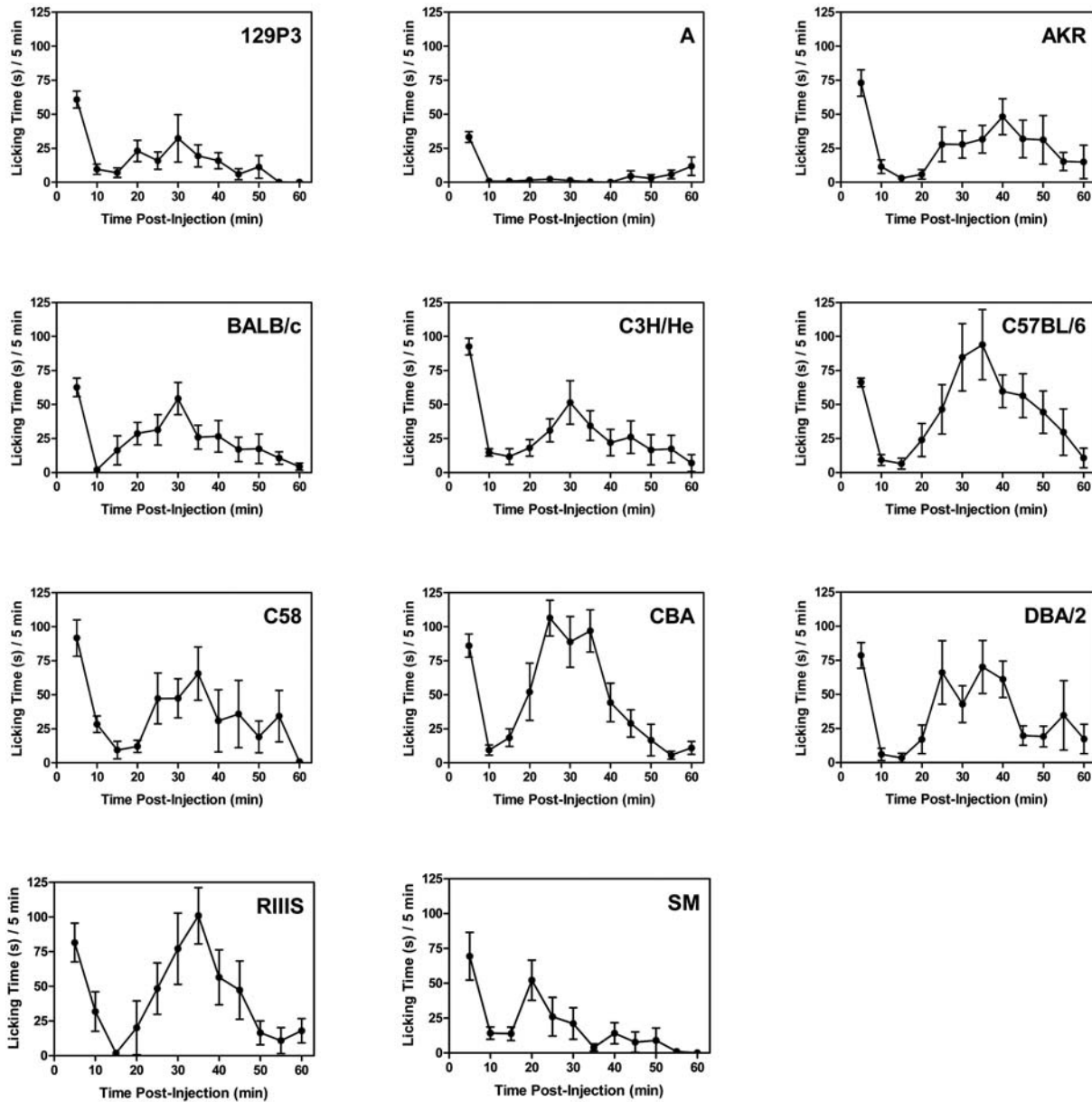
Heritability of Inflammatory Nociception, Figure 1 Strain-dependent responses to formalin injection in 11 inbred mouse strains. Naïve adult male mice were habituated to Plexiglas observation cylinders for at least 30 min. Then, 25 µl of 5% formalin was injected subcutaneously into the plantar surface of the right hind paw using a 50 µl microsyringe with a 30-gauge needle. Mice were then returned to the cylinders, and behavioral observations were begun immediately. The total time spent licking/biting the right hind paw over the next 60 min was measured with a stopwatch. Symbols represent mean ± S.E.M. time spent licking the affected hind paw in each 5-min period. These data were published in Mogil et al. (1998) in a different form.

of ways. For example, it is well appreciated that the amount of pain experienced by sufferers of osteoarthritis can not be easily predicted by the extent of their joint degeneration (e.g. Link et al. 2003). ▶ Genotyping of arthritis sufferers and others at relevant genes might allow better prediction and management of inflammatory pain. Finally, it should be noted that responses to analgesics used in the management of inflammatory pain are also highly variable (e.g. Walker et al. 1994) and that the ▶ pharmacogenetics of analgesia is also being studied (Wilson et al. 2003).

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Heritable

Definition

A heritable trait is one which is passed on through generations (i.e. „runs in families"), such that offspring tend to resemble their parents. The strong implication is that inherited genetic factors are responsible, although non-genomic transmission has been demonstrated. Heritability is best established in humans using *twin studies*, in which the similarity of pairs of monozygotic and dizygotic twins is compared. In animals, heritability is best established by successful selective breeding for the trait.
► Heritability of Inflammatory Nociception
► Opioid Analgesia, Strain Differences
► Twin Studies

Herpes Simplex Virus Vectors

Definition

Herpes simplex virus (HSV) is a human pathogen that causes the common cold sore and infections of the conjunctiva, and is a double-stranded DNA virus with a capsid and surrounding tegument and envelope. The 152 kB genome can potentially accommodate up to approximately 44 kB of foreign DNA. The propagation of replication-incompetent HSV vectors in cultured cells is accomplished using cell lines that complement essential gene products that have been removed from the vector genome. HSV vector genomes do not integrate, but remain as episomes in the nucleus of transduced cells. HSV vectors, like the parental virus, efficiently target to sensory neurons from the skin and can establish a life-long latent state in those neurons.
► Opioids and Gene Therapy

Herpes Virus

Definition

Herpes virus can infect nerve roots, including nerve roots of the sciatic nerve. In the case of shingles (Herpes zoster), a rash is usually present along the course of the infected nerve root.
► Sciatica

Herpes Zoster

Definition

Herpes zoster is an infection of the nervous system caused by the varicella zoster virus (VZV), the same virus that causes chickenpox. VZV can remain dormant in the sensory ganglia for decades after an infection. Herpes zoster results when the dormant virus in these nerves is reactivated, often as a result of decline in cellular immunity to VZV with aging or immunosuppression.
► Cancer Pain, Assessment in the Cognitively Impaired
► Postherpetic Neuralgia
► Postherpetic Neuralgia, Pharmacological and Non-Pharmacological Treatment Options

Herpes Zoster Pain

► Postherpetic Neuralgia, Etiology, Pathogenesis and Management

Heteromeric Channels

Definition

Heteromeric channels are protein complexes that form pores in the cell membrane. Typically, channels are made up of several subunits, which may be identical, result-

ing in homomeric channels, or different, resulting in heterometic channels.
▶ Purine Receptor Targets in the Treatment of Neuropathic Pain

Heterotopic Ossification

Definition

Heterotopic Ossification is the appearance of bony tissue elements in what are normally soft tissue structures.
▶ Spinal Cord Injury Pain

Heterozygosity

Definition

Heterozygosity is a state in which the maternal and paternal allele of a gene are not the same. In this common situation, the expression of that gene will depend on dominance of the alleles. In inbred strains, all heterozygosity is lost, and every gene is fixed in a homozygous state.
▶ Alleles
▶ Inbred Strains
▶ Opioid Analgesia, Strain Differences

Heterozygous Carriers

Definition

Heterozygous carriers refer to the state of possessing two different alleles of a particular gene, one inherited from each parent.
▶ NSAIDs, Pharmacogenetics

Hidden Triggers

Definition

Hidden Triggers are internal precipitating mechanisms.
▶ Sunct Syndrome

High Dependency or Intensive Care Units

Definition

High dependency or intensive care units are specialized wards where one or two highly trained nurses take care of each patient
▶ Postoperative Pain, Acute Pain Team

High Thoracic Epidural Anesthesia

Definition

High thoracic epidural anesthesia leads to a reversible cardiac sympathectomy blocking the segments T^1-T5. The epidural catheters are inserted at levels C7 -T1 or at level T^1-T2 by the median approach and with hanging drop technique.
▶ Postoperative Pain, Thoracic and Cardiac Surgery

High Threshold Mechanoreceptor

▶ Mechanonociceptors
▶ Nociceptors in the Orofacial Region (Skin/Mucosa)

High-Threshold Mechanosensitive Muscle Receptors

Definition

In experiments employing recordings from single muscle receptors with unmyelinated or thin myelinated afferent fibers, many units exhibit a high mechanical threshold when tested with local pressure stimuli (e.g. using a forceps with broadened tips on the exposed muscle). These receptors do not respond to passively stretching the muscle or aerobic active contractions, but require pressure stimulation of tissue-threatening and subjectively painful intensity for activation. The receptors are also typically responsive to stimulation with algesic substances. The general interpretation is that these receptors are nociceptors and induce muscle pain when activated.
▶ Muscle Pain Model, Ischemia-Induced and Hypertonic Saline-Induced

High Threshold Neurons

Synonym

HT neurons

Definition

HT neurons respond fairly selectively to noxious mechanical stimuli. They may have a minimal response to innocuous mechanical stimuli, but they are essentially tuned for strong stimuli. They may also respond to noxious thermal and chemical stimuli. Sometimes HT cells are referred to as nociceptive-specific neurons.
▶ Functional Changes in Sensory Neurons Following Spinal Cord Injury in Central Pain
▶ Nick Model of Cutaneous Pain and Hyperalgesia
▶ Spinothalamic Input, Cells of Origin (Monkey)
▶ Thalamus, Nociceptive Cells in VPI, Cat and Rat

High-Threshold VDCCs

▶ Calcium Channels in the Spinal Processing of Nociceptive Input

High Velocity Thrust Manipulation

▶ Spinal Manipulation, Characteristics

High-Voltage Calcium Channels

▶ Calcium Channels in the Spinal Processing of Nociceptive Input

Hindlimb Flexor Reflex

▶ Opioids and Reflexes

Hippocampal Formation or Hippocampal Region

Definition

The hippocampus (dentate gyrus and pyramidal cell fields CA1-3) and the subiculum are together referred to as the hippocampal formation, s. Hippocampus for details. Perhaps the most extensively studied structure in the brain, the hippocampal region has most often been implicated in memory processing.
▶ Hippocampus
▶ Hippocampus and Entorhinal Complex, Functional Imaging

Hippocampus

Definition

Brain structure comprising the dentate gyrus and the pyramidal cell fields of the hippocampus. There are three different pyramidal cell fields: CA1, CA2 and CA3. These subregions differ in their cellular organization and connectivity. The hippocampus is primarily organized as a unidirectional circuit. Information from the entorhinal cortex converges on the dentate gyrus, which in turn projects to field CA3, which sends projections to field CA1. The circuit is completed as CA1 projects to the subiculum, the major output region of the hippocampus. Strictly speaking, the subiculum does not form part of the hippocampus, but together the two structures make up the hippocampal formation.

Hippocampus and Entorhinal Complex, Functional Imaging

Siri Leknes[1, 2], Irene Tracey[1, 2]
[1]Pain Imaging Neuroscience (PaIN) Group, Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK
[2]Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, UK
irene.tracey@anat.ox.ac.uk

Synonyms

Entorhinal Cortex and Hippocampus, Functional Imaging; Parahippocampal Region, Neuroimaging

Definition

The ▶ hippocampus is comprised of the dentate gyrus and the CA1, CA2 and CA3 pyramidal cell fields. The ▶ hippocampal formation consists of the hippocampus and the subiculum. The adjacent entorhinal, perirhinal, and parahippocampal cortices comprise the ▶ parahippocampal region (Fig. 1). These limbic subregions differ in their cellular organization and connectivity, but are commonly implicated in memory and emotion processing.

The hippocampus lies at the end of a cortical processing hierarchy, and the entorhinal cortex is the major source of its cortical projections. Much of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive widespread projections from sensory and association areas in the frontal, temporal and parietal lobes (Squire et al. 2004).

▶ Functional imaging is a general term used to describe methodologies that allow function to be located either spatially or temporally within the brain (and other organs). The methods are generally non-invasive and used for human studies; the term neuroimaging is often used when applied specifically to brain studies. Methods include functional magnetic resonance imaging (FMRI), positron emission tomography (PET), magneto-encephalography (MEG) and electro-encephalography (EEG). Unless otherwise stated, the studies discussed in this article are FMRI or PET studies of the brain.

Characteristics

Melzack and Casey (1968) proposed that the hippocampus and associated cortices participate in mediating the aversive drives and affective characteristics of pain perception. A wide range of animal studies support the notion that pain processing is a primary function of the hip-
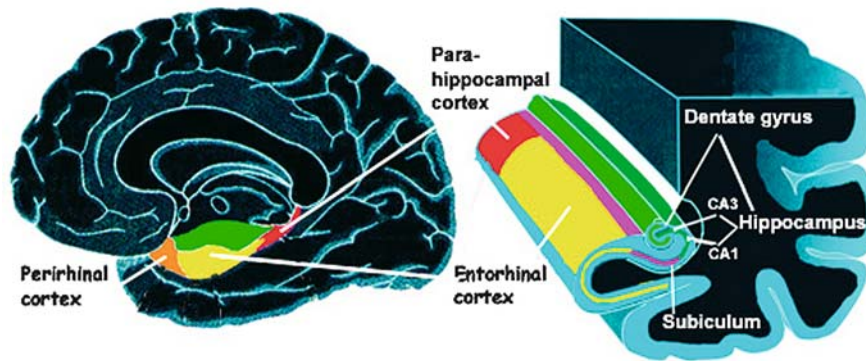
Hippocampus and Entorhinal Complex, Functional Imaging, Figure 1   (left) Medial view of the human brain outlining the perirhinal cortex (orange); parahippocampal cortex (red); and entorhinal cortex (yellow). (right) Section of the temporal lobe showing the components of the hippocampal/entorhinal complex in some detail: the dentate gyrus (pale green); the CA1 and CA3 hippocampal fields (green) that make up the hippocampus proper; the subiculum (pink); the perirhinal cortex (orange); parahippocampal cortex (red); and entorhinal cortex (yellow).

pocampal complex. Importantly, Dutar and colleagues (1985) demonstrated that septo-hippocampal neurons in rats respond directly to noxious peripheral stimulation. Similarly, functional imaging studies of pain perception have repeatedly reported a direct implication of areas within the hippocampus in the processing of nociceptive stimuli. Since nociceptive information is typically novel and of high priority, a direct role for the hippocampus in nociceptive processing is consistent with comparator theories of hippocampal function (e.g. McNaughton and Gray 2000). Comparator theory maintains that the hippocampus is involved in novelty detection and that its function is to compare actual and expected stimuli (i.e. stimuli registered in memory).

In an early PET study, Derbyshire and colleagues (1997) found hippocampal activation in response to mildly and moderately painful heat stimuli, when contrasted with warm, non-painful stimulation. Using very specific nociceptive stimuli (laser stimulation of A-δ fibers only) to subjects' left and right hands, Bingel and colleagues (2002) found bilateral activation of the amygdala and hippocampal complex. The receptive fields of hippocampal neurons are predominantly large and bilateral (Dutar et al. 1985). As other pain-related activation was lateralized, the authors suggested that the hippocampal activity reflected direct nociceptive projections to the hippocampus, perhaps revealing novelty detection (Bingel et al. 2002). Further, Ploghaus and colleagues (2001) found that pain modulation by drying stimulus temperature caused activation of a region of the hippocampus proper, consistent with a role of the hippocampus in pain intensity encoding (Fig. 2a).

Nevertheless, the large majority of human functional imaging studies of pain do not report activation of regions within the hippocampus / entorhinal complex. There are several possible explanations for this discrepancy. The first concerns the signal to noise ratio. As the complex is a relatively small structure, the spatial resolution of conventional whole-brain imaging paradigms means that partial volume effects might occur and decrease signal to noise in this region. One caveat specific to functional imaging of this region is the implication of the hippocampus in the ▶ resting state network (Greicius and Menon 2004). PET and FMRI studies have suggested that the resting brain has a default mode of internal processing in which the hippocampus is a central component. In the neuroimaging of pain perception, nociceptive processing is commonly compared with baseline (rest) conditions. The hippocampus' involvement in resting state / baseline processing may mask out the activation of this region in such task-baseline comparisons if increased baseline activity reduces subsequent stimulation evoked responses and therefore could yield a false negative result. Another factor that may mask out activation of regions within the medial temporal lobe is the registration of individual brains onto a standard template for group comparison. Traditional techniques that optimize whole-brain alignment (e.g. aligning to the atlas of Talairach & Tournoux) do not adequately account for variations in location and shape of medial temporal lobe structures (see Squire et al. 2004 for review).

Regions within the hippocampus / parahippocampal complex have been more consistently activated in studies where pain perception has been modulated by expectation and / or anxiety. It is clear that memory (which influences expectation) modulates pain perception. While certain expectation is associated with fear, uncertain expectation is associated with anxiety. For instance, a rat experiences fear when it must enter a space where a cat is present. Anxiety, on the other hand, corresponds to the state a rat is in when it must enter a space where a cat may or may not be present. While fear facilitates rapid reactions (fight or flight) and causes distraction and analgesia from the pain, anxiety is characterized by risk assessment behavior or behavioral inhibition (the rat hesitates to enter the space where a cat might be). This behavior is associated with
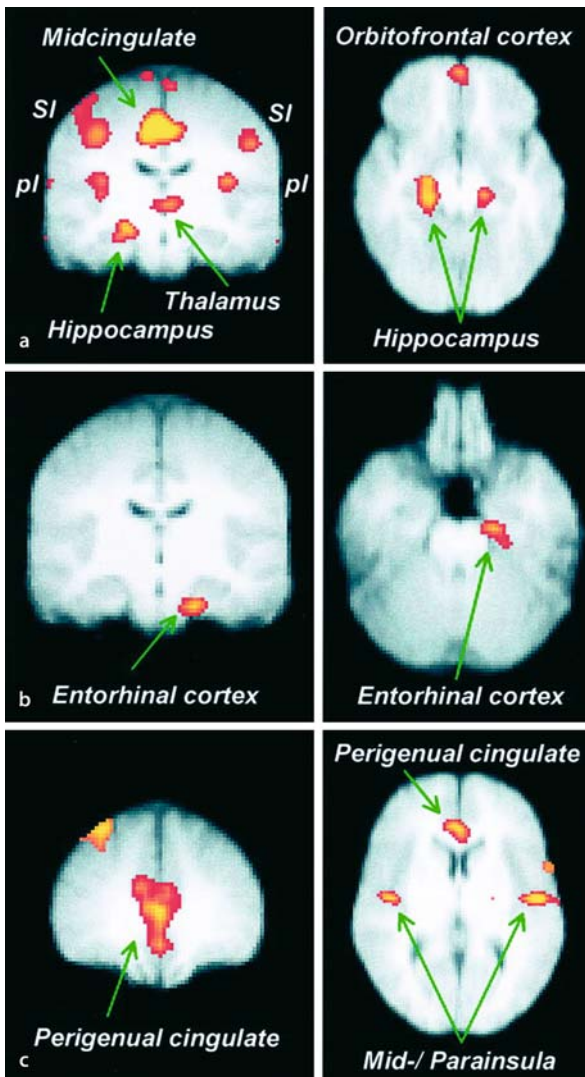
Hippocampus and Entorhinal Complex, Functional Imaging, Figure 2 (a) Temperature-related activation increases in perceived pain: Bilateral S1, dorsal margin of posterior insula, thalamus, midcingulate and right hippocampus. (b) Anxiety-related activation increases in perceived pain associated with significant activation in left entorhinal cortex. (c) Activity in the perigenual cingulated and the mid- / para insula was significantly correlated with entorhinal FMRI signal during pain modulation by anxiety. Reproduced with permission from Ploghaus et al. 2001.

increased somatic and environmental attention, which can lead to anxiety-driven hyperalgesia (McNaughton and Gray 2000).

Using FMRI to investigate the effects of expectation on pain perception, Ploghaus and colleagues (2000) found that areas in the hippocampal complex were activated during mismatches between expected and actual pain. Consistent with comparator theory, the same ▶ hippocampal regions were implicated in three different types of mismatch: when no pain was expected (novelty); when the nociceptive stimulus differed from expectation; and when the painful stimulus was unexpectedly omitted. In a subsequent study, Ploghaus

and colleagues (2001) manipulated the certainty of expectation about impending nociceptive stimulation, to investigate its modulation on pain perception. This study examined the neural mechanism by which anxiety (uncertain expectation) causes increased pain perception (hyperalgesia), and contrasted it with the process by which a heightened nociceptive stimulation causes increased pain perception. The Gray-McNaughton theory proposes that the hippocampal formation responds to aversive events such as pain whenever they form part of a behavioral conflict, e.g. a conflict caused by uncertain expectation of pain. This conflict induces anxiety. Output from the comparator has two effects that underpin anxiety and behavioral inhibition. First, it tends to suppress both of the currently conflicting responses. Second, it increases the valence of the affectively negative associations of each of the conflicting goals (McNaughton and Gray 2000).

As predicted from theory, Ploghaus and colleagues reported activation of the entorhinal cortex during anxiety-driven hyperalgesia, but not during increased pain perception caused by augmented nociceptive input (Fig. 2b; Ploghaus et al. 2001). Studies of other (not anxiety-related) types of hyperalgesia typically report no significant activation of the hippocampus / parahippocampal region (e.g. Zambreanu et al. 2005). One exception is a recent FMRI study of drug modulation during pain (Borras et al. 2004). Naloxone, a predominantly μ opioid antagonist, was administered to naïve subjects in low doses. During rest (baseline) conditions where no stimulation was applied, regions in the hippocampal / entorhinal complex were activated more in the drug condition than during placebo. According to the Gray-McNaughton theory, the entorhinal cortex primes responses that are adaptive to an aversive input, such as the motor response necessary for escape from a threatening environment. Enhanced activation in this region after naloxone infusion indicates a change in basal activity, potentially lowering the threshold for activation of adaptive responses.

In line with this argument, differences between naloxone and placebo conditions during nociceptive processing were found in several areas within the hippocampus / parahippocampal region. When pain ratings were matched across conditions, an area within the posterior parahippocampal gyrus was significantly more activated in the naloxone condition. Activation of the hippocampus proper to nociceptive stimulation in the drug condition compared to the placebo condition was found only when subjects rated the pain intensity higher in the naloxone condition (nociceptive stimuli were of equal intensity across conditions). This result adds further support for the role of the hippocampus proper in pain intensity encoding. In their study of anxiety-driven hyperalgesia, Ploghaus and colleagues (2001) found that the entorhinal cortex activation was predictive of activity in the perigenual cingulate and

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Hippocampus and Entorhinal Complex, Functional Imaging, Table 1 Summary of functional imaging studies outlined here, listing stimulus type, neuroimaging technique and activations/deactivations in hippocampal/parahippocampal regions

Authors	Stimulus type		Hippocampus proper	Parahippocampal region
Derbyshire et al. 1997	Laser (heat nociception or warm)	PET	Nociceptive encoding	-
Ploghaus et al. 2000	Thermal (heat nociception or warm)	FMRI	Expectation related	Expectation related
Ploghaus et al. 2001	Thermal (heat nociception)	FMRI	Nociceptive encoding	Expectation related
Bingel et al. 2002	A-δ-specific laser	FMRI	Nociceptive encoding	-
Wilder-Smith et al. 2004	Rectal balloon distension and thermal (cold nociception)	FMRI	Patients more than controls	Patients more than controls
Borras et al. 2004	Thermal (heat nociception)	FMRI	Nociceptive encoding	May be related to shift in threshold for adaptive response
Greicius and Menon 2004	Visual (resting state examined)	FMRI	Resting state network	Resting state network
Napadow et al. 2005	Acupuncture in pain-free controls	FMRI	Deactivation	-

mid-insula (Fig. 2c). Corresponding regions of the cingulate and insular cortices were also implicated in naloxone-induced increases in pain perception (Borras et al. 2004). The authors concluded that the regions where activation by noxious heat was modulated by naloxone were the sites of action of endogenous opioid pathways involved in regulating the central nervous system response to aversive stimuli.

Some support for the involvement of the hippocampus / parahippocampal region in opioid regulation of the brain's response to nociceptive input comes from functional imaging studies of acupuncture. Several studies investigating brain responses to acupuncture in healthy, pain-free volunteers have reported ► deactivation of regions within the hippocampus / entorhinal complex (e.g. Napadow et al. 2005). A recent study examining the effects of acupuncture in chronic pain patients does not report involvement of the hippocampus or parahippocampal areas (Pariente et al. 2005), but this study did not include a contrast for deactivation of specific brain regions.

There can be little doubt that the role of the hippocampus / entorhinal complex in nociceptive processing and the generation of pain perception demands further investigation in both healthy volunteers and in clinical pain patients. So far, the functional imaging studies of pain reporting hippocampus / entorhinal complex activation have been whole-brain studies examining the effects of nociceptive stimulation on all regions of the brain. This contrasts with the neuroimaging literature on the role of the hippocampal complex in memory, where researchers have been able to focus solely on this narrow region of cortex, improving spatial resolution and avoiding registration caveats e.g. by employing partial-coverage imaging techniques (Fig. 3) (see also Squire et al. 2004). To disentangle the roles of the sub-regions within the hippocampus / entorhinal complex in nociceptive processing and pain perception, high-

resolution studies of this region during pain, employing similar measures, are needed. Care must also be taken to optimize study design in order to avoid the masking out of nociceptive-related hippocampal activations by processing of the resting state network.

The role of hippocampus / entorhinal complex in clinical pain is still largely unknown. A study of patients suffering from irritable bowel syndrome (IBS) has recently shown involvement of hippocampus in pain processing in patients compared to healthy controls (Wilder-Smith et al. 2004). Given the known involvement of anxiety
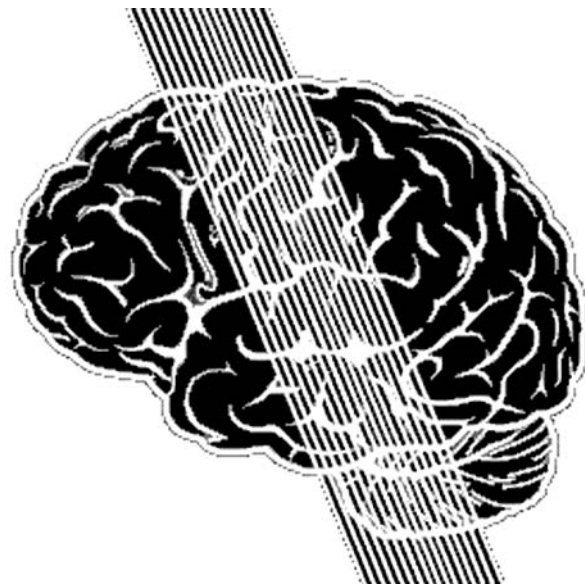
Hippocampus and Entorhinal Complex, Functional Imaging, Figure 3 Visualization of slice positioning in a high-resolution, partial-coverage study of hippocampus / entorhinal complex function. By only covering a section of the brain, resolution can be improved significantly, and it may be possible to begin disentangling the function of small subregions within the hippocampus/parahippocampal complex for nociceptive processing and pain perception.

in irritable bowel syndrome, this result lends further support to the postulated involvement of the hippocampus / entorhinal complex in anxiety-driven increases of pain perception. Further, the hippocampus may form part of a system of central involvement that drives the visceral hypersensitivity of these patients. More studies of anxiety and hippocampus / entorhinal complex function in clinical pain should shed light on the importance of centrally generated pain and hyperalgesia.

In conclusion, converging evidence from human neuroimaging and animal studies points to a direct role for the hippocampus in the processing of nociceptive information such as pain intensity encoding. Areas within the hippocampus / entorhinal complex are involved in the comparison between actual and expected nociceptive stimuli, and play a role in anxiety-driven hyperalgesia. The increases in pain perception caused by uncertain expectation may be due to a modulation of the opiate system, as hinted at by a study investigating the effects of the μ opioid antagonist naloxone (Borras et al. 2004).

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Histamine

Definition

Histamine is a naturally occurring compound that is endogenous in mammalian tissue. It is synthesized by the decarboxylation of the amino acid histidine. It is a hydrophilic vasoactive amine and is involved in many central nervous system functions, such as arousal, the physiologic response to anxiety and stress, water retention and the suppression of eating. It has been suggested that the neuronal histamine system functions as a danger response mechanism. In skin it is intensely pruritic and painful in higher concentrations.

▶ Cancer Pain Management, Gastrointestinal Dysfunction as Opioid Side Effects
▶ Nociceptor, Categorization

H

Histopathological

Definition

The method of microscopical examination to derive the diagnosis from typical changes in the normal structure of tissues.

▶ Facet Joint Pain

History of Analgesics

KAY BRUNE, BURKHARD HINZ
Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany
brune@pharmakologie.uni-erlangen.de,
hinz@pharmakologie.uni-erlangen.de

Synonym

Analgesics, History

Definition

Attempts to relieve pain are probably as old as mankind. Dioscourides, a Greek physician, prescribed extracts of willow bark against joint pain, whilst Hildegard von Bingen and the Reverend Stone, in his famous letter to the Royal Society of Medicine in London, suggested the same therapy (Brune 1997; Rainsford 1984). Local inflammation often goes along with "general inflammation" manifested by fever and malaise. The reasons for this were recently uncovered: the release of pyrogenic cytokines such as TNFα and IL–1. Fever along with malaise was treated on the basis of the Hippocratic concept by purgation, sweating and blood-letting (Brune 1984). Such practices were continued until the 19th century (Williams 1975) – probably without success.

It was only recently that the inhibition of the cytokine effect has become feasible (Smolen et al. 2000).

Characteristics

A scientific approach to pain therapy became possible in the 19th century, with substances isolated from plants including the willow tree (salic acid esters), and then the description of the complete synthesis by Kolbe (Marburg), (Brune 1997; Rainsford 1984). To provide sufficient amounts, the first "scale up" of a synthetic process was invented and the first drug factory built (Salicylic Acid Works founded by von Heyden, 1874; 6). Salicylic acid was found to be active against fever (Buss, Switzerland) and rheumatoid arthritis (Stricker, Berlin; Mac Lagan, Dundee) (Brune 1997; Rainsford 1984; Sneader 1985).

Earlier (1806), a pharmacist in Einbeck, Sertürner, had isolated morphine, the main analgesic ingredient of the opium resin. He checked extracts from opium for sedative activity in his pack of dogs and ended up with a pure substance (morphine) (Sertürner 1806; Sneader 1985). With morphine, for the first time, a pure (crystalline) drug was available. Death due to overdose or lack of effect could now be avoided by exact dosing (Bender 1966).

New Chemicals

The next step was taken by chemists who tried to compensate for an impaired supply of opium, chinea bark (quinine) and others by chemical synthesis. It was made possible by E. Fischer's discovery of phenylhydrazine, which allowed the synthesis of nitrogen-containing ring systems. His scholar, L. Knorr, tried to synthesize quinine, but produced phenazone (Fig. 1) (Brune 1997),

which proved to be active against fever. The patent for this compound (Antipyrine® was bought by a dye factory in Hoechst. This was the start of the pharmaceutical company Hoechst (Brune 1997). Another chemist (F. Hoffmann) esterified salicylic acid with acetate and (re-)discovered Aspirin. This synthesis was done in another dye factory, namely Bayer (Rinsema 1999). The new science of chemistry helped to transform the dye-industry by providing both synthetic dyes and new synthetic drugs.

Pain therapy was aided by another accidental discovery. In Strasbourg, two physicians, Cahn and Hepp, attempted to eradicate intestinal worms. The worms survived, but the fever resolved (Cahn and Hepp 1886). An analysis revealed that the pharmacy had provided acetanilide rather than naphthalene. This led to the discovery of acetanilide, which was marketed by another dye factory (Kalle) under the name Antifebrin® (Brune 1997; Sneader 1986). Bayer further investigated acetanilide and found that a by-product of aniline dye production, namely "acetophenitidine", was equally effective. It was marketed as Phenacetin® (Sneader 1986). These discoveries constituted, as Tainter phrased it (Tainter 1948), "[. . .] the beginning of the famous German drug industry and ushered in Germany's forty-year dominance of the synthetic drug and chemical field." Thus, by the end of the 19th century, 4 prototype substances were available for the treatment of pain: Morphine, salicylic acid, phenazone and phenacetin.

Chemical Modifications of Analgesics

Salicylic acid, phenazone and phenacetin were widely used, and physicians soon recognized the disadvantages of these drugs. They were of low potency, and had to
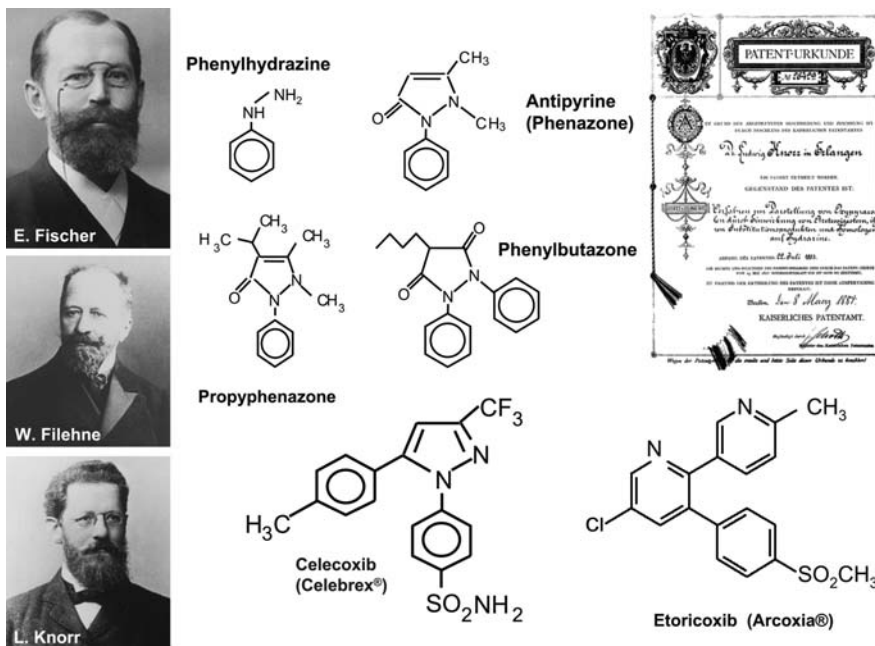
History of Analgesics, Figure 1 Synthesis of Phenazone, the first synthetic drug ever, in Erlangen 1882.

Adolf Kolbe

Felix Hoffmann   **Heinrich Dreser**

1899 Implementation of Acetylsalicylic Acid (Aspirin®)

History of Analgesics, Figure 2 Synthesis of acetylsalicyl acid in 1897.

be taken in gram quantities (spoon-wise). Sodium salicylate had an unpleasant taste. Taking several grams of phenacetin led to methaemoglobinaemia, while phenazone often caused allergic reactions. Consequently, the expanding drug industry set their chemists into action to produce improved derivatives.

F. Hoffman, a young chemist at the Bayer Company, attempted to improve the taste of salicylic acid to please his father who suffered from rheumatoid arthritis (Brune 1997; Sneader 1986). On a suggestion of v. Eichengrün (Bayer), Hoffmann produced acetylsalicylic acid, which his father preferred (Brune 1997; Sneader 1986). Acetylsalicylic acid proved difficult to handle due to its instability. Bayer, therefore, took a patent on the water-free production process invented by Hoffmann and secured the name Aspirin® (derived from acetyl and the plant spirea ulmaria). H. Dreser, the first pharmacologist at Bayer, tried to demonstrate the reduced toxicity of aspirin as compared to salicylic acid. He employed a goldfish model, believing that the "mucosa" of their fins comprised an analogue of human intestinal mucosa. Dipping the fins of goldfish into solutions of either salicylic acid or aspirin, he observed that higher concentrations of aspirin were necessary to "cloudy" the fins (Fig. 2). He concluded that this was proof of better gastrointestinal tolerability (Dreser 1899). Later, Heinrich Dreser himself recognised that he didn't measure a "gastrotoxic effect", but rather "acidity", and salicylic acid is more acidic than aspirin (Dreser 1907).

To further improve the tolerability of phenacetin, Bayer investigated a metabolite of phenacetin, acetaminophen (paracetamol). It appeared that (their) acetaminophen (due to impurities?) also caused methaemoglobinaemia. In contrast, Sterling (UK) found acetaminophen free of methaemoglobinaemia and marketed it as Panadol® (Sneader 1985).

At Hoechst, the structure of phenazone was modified. The resulting compounds amidopyrin, melubrin and dipyrone proved to be somewhat more active (Brune 1997). Roche substituted an amino group of phenazone with isopropyl. The resulting propyphenazone is still in use. It is relatively free of toxicity, i.e. it lacks kidney, GI- and bone marrow toxicity (Kaufman et al. 1991). Finally, several companies combined two active principles, e.g. by producing salts of aspirin with amidopyrine or esters between acetaminophen and salicylic acid (Benorylate®). Moreover, the three basic ingredients were mixed and supplemented, e.g. with caffeine (APC-powder); with vitamins, minerals and other partly obscure ingredients. This diversity of "drugs" pleased the consumer, but was without major medical benefit – it may rather have led to abuse and kidney toxicity (Dubach et al. 1983).

New Compounds: Pharmacology Comes into Play

In 1949, an unexpected observation once again paved the way for new analgesics. Hoping to reduce toxicity and increase effectiveness of aminophenazone, Geigy (Basel) produced an injection containing the salt of the basic aminophenazone with an acidic derivative – later named phenylbutazone (Fig. 3). This salt was found to be very active, particularly in rheumatoid pain (Brune

Gerhard Wilhelmi

Aminophenazone
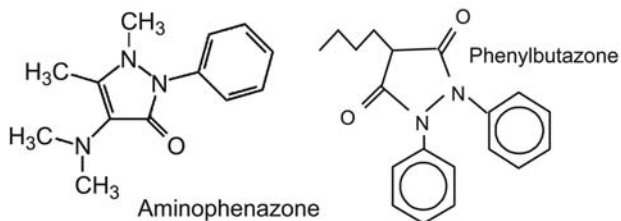
Phenylbutazone

Erythema of the depilated
back of a guinea pig

1997; Sneader 1985). Burns and Brodie related this effect to phenylbutazone, which was present for much longer periods of time than aminophenazone (Domejoz 1960). The conclusion was that the "salt forming" partner of aminophenazone was the dominant active ingredient. To further investigate this clinical observation, G. Wilhelmi (Geigy) developed novel models of inflammation (Wilhelmi 1949). Phenylbutazone turned out to be particularly active in reducing the UV erythema elicited in the skin of guinea pigs (Fig. 3) (Wilhelmi 1949). It was one of the first pharmacological models of inflammation, with which several phenylbutazone analogues were found.

 In the USA, C. Winter, at Merck (MSD) and later at Parke Davis, developed his models of inflammatory pain. He introduced the cotton string granuloma and the carrageenin-induced rat paw model (Shen 1984). These assays turned out to be especially useful for measuring anti-inflammatory activity (Winter et al. 1962) (Fig. 4). A similar model was employed by Randall and Selitto for detecting analgesic activity (Randall and Selitto 1957). Using these models led to the discovery of several chemical classes of analgesics. Merck identified indols (including indomethacin and sulindac, T.Y. Shen) (Shen 1984), Boots found propionic acid derivatives (ibuprofen and flurbiprofen, S. Adams; (Adams 1992), Parke Davis developed fenamates (e.g. mefenamic acid) (Shen 1984), Geigy was successful with new aryl-acetic acids, e.g. diclofenac (Shen 1984) and Rhone Poulenc with Bayer introduced ketoprofen (Shen 1984), and finally, Lombardino at Pfizer rediscovered the ketoenolic acids (phenylbutazone). The advantage of these compounds is that all pharmacokinetic parameters can be tailored by minor changes in the molecular structure (Lombardino 1974). Pfizer's piroxicam (Otterness et al. 1982) was soon followed by tenoxicam (Roche) and meloxicam (Boehringer). All of these differ in their potency and in pharmacokinetic parameters including their metabolism and drug interactions, although their mode of action is basically the same. Most were identified using animal models before the mode of action of "aspirin-like" drugs – as these substances were formerly named – was determined. It was 70 years after the synthesis of aspirin when John

Charles Winter

Carrageenan-induced rat paw edema

Dr. T.Y. Shen
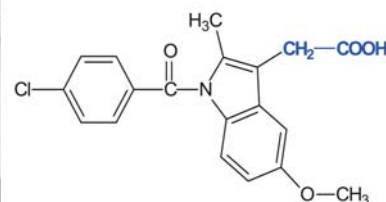
Indomethacin

History of Analgesics, Figure 4 Carrageenin-induced rat paw model.

Vane's group could demonstrate that these compounds were inhibitors of prostaglandin synthesis (Vane 1971). This discovery, however, did not answer the question of why many of the old compounds (found by serendipity – such as phenazone, propyphenazone, phenacetin, paracetamol) were non-acidic chemicals that barely inhibited cyclooxygenases, whilst all the compounds developed in animal models of inflammation and pain were acidic and potent inhibitors (Brune 1974)? All pharmacological models inflict an acute inflammation elicited by local prostaglandin production. Consequently, drugs that work by blocking cyclooxygenases in the inflamed tissue excel in these models. Acidic compounds (comprising pKa values of around 4, ~99% protein binding and amphiphilic structures) reach long lasting high concentrations in inflamed tissue, but also relatively high concentrations in liver, kidney and the stomach wall (Brune and Lanz 1985). This skewed distribution causes complete inhibition of prostaglandin synthesis in these locations resulting in superior anti-inflammatory activity, but also liver, kidney and stomach toxicity (Brune and Lanz 1985). This distributional selectivity may have reduced some of the side-effects including CNS toxicity and increased the anti-inflammatory effects. Non-acidic compounds such as phenazone or paracetamol distribute homogeneously throughout the body. Their inhibition of prostaglandin production in inflamed tissue is small. Consequently, they are used to curb mild pain, but not inflammation. The discovery of the existence of two cyclooxygenases, COX–1 and COX–2 (Flower 2003), has changed the landscape again. It provided a new dimension of selectivity, not limited to differences of tissue distribution, but based on enzyme selectivity.

Analgesics in the Age of Molecular Pharmacology

The discovery of prostaglandins and the inhibition of prostaglandin production by aspirin-like drugs caused the investigation of the effects of anti-inflammatory steroids on prostaglandin production. Many researchers observed that steroids can reduce prostaglandin production along with anti-inflammatory activity, but do not block it completely (e.g. Brune and Wagner 1979). Only P. Needleman came up with a molecular explanation that proposed 2 different enzymes, one being regulated by steroids (Fu et al. 1990; Masferrer et al. 1990). They were soon characterized (Kujubu et al.1991). For the first time in the history of pharmacology, 2 molecular drug targets, cyclooxygenase–1 and cyclooxygenase–2 (the expression in the inflamed tissue is blocked by steroids), were identified before the biological role of the enzymes was fully known.

It was soon clear that it might be advantageous to have drugs that block only cyclooxygenase–2, because this enzyme appeared not to be involved in the production of GI-protective prostaglandins. Diclofenac and meloxicam were found to exert some, but not sufficient selectivity to warrant GI-tolerance (Tegeder et al. 1999). This situation changed with the discovery of the highly selective sulfonomides, celecoxib and valdecoxib, and methylsulfones, rofecoxib and etoricoxib. These compounds are relatives of old compounds like phenazone (Fig. 1). They extend the paracetamol/phenazone group of non-acidic compounds which are devoid of gastrointestinal toxicity (Brune and Lanz 1985). However, these new analgesics are not free of other side effects. Inhibition of cyclooxygenase–2 affects kidney function, blood pressure and maybe more (for review, see e.g. Brune and Hinz 2004a; Hinz and Brune 2002). Another type of COX–2 selective inhibitor is Lumiracoxib. It is a relative of diclofenac and, like diclofenac, is sequestered into inflamed tissue. It combines COX–2 selectivity with selective tissue distribution (Feret 2003). The clinical success of this compound will tell us if this approach offers advantages.

Conclusion

After 120 years of development of pure analgesics, we have made some progress. Serendipity, as well as targeted research, has provided clinicians with many useful drugs that differ in many pharmacological and clinical aspects. Knowing a little of the history of their discovery and development may provide a perspective to better understand their effects and side-effects. A humble acknowledgment of the role of serendipity may change our attitude towards research and marketing claims. But then serendipity is not all, as E. Kästner, a German poet, phrased it:

Irrtümer sind ganz gut, Jedoch nur hier und da.
Nicht jeder, der nach Indien fährt, entdeckt AMERIKA.
Errors are fine, but only sometime(s).
Not everyone heading for India discovers AMERICA.

Acknowledgements

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Hit Rate or Sensitivity

Definition

Hit rate or sensitivity is the probability of response „A" when event A has occurred.
► Statistical Decision Theory Application in Pain Assessment

HIV and Pain

► Cancer Pain and Pain in HIV / AIDS
► Pain in Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

HMSN

Definition

The acronym for Hereditary Motor and Sensory Neuropathy.
► Hereditary Neuropathies

HNPP

► Hereditary Neuropathy with Liability to Pressure Palsies

Hoffman-Tinel Sign

► Tinel Sign

Holistic Medicine

► Alternative Medicine in Neuropathic Pain

Homeopathy

Definition

Homeopathy is a system of medicine developed by Samuel Hahnemann in the 19th century based on a concept of vital energy inherent in all matter, which increases in potency with repeated dilution; and on the idea that substances can be used to treat conditions that mimic their toxicity
► Alternative Medicine in Neuropathic Pain

Homeostasis

Definition

Homeostasis is a basic biological function associated with the maintenance of an internal environment that guarantees survival through adjusting important biological parameters (water, salt, glucose, temperature, acidity etc.).
► Clinical Migraine with Aura
► Functional Imaging of Cutaneous Pain

Homeostatic Adaptations

Definition

Physiological responses or behavioral actions which maintain or restore normal levels of biological function (e.g., maintain or restore normal body temperature).
► Opioids, Effects of Systemic Morphine on Evoked Pain

Homework

Definition

Activities that a patient is asked to complete or practice, usually outside of the hospital or clinic is referred to as homework.
► Multidisciplinary Pain Centers, Rehabilitation

Homologous Gene

Definition

An homologues gene has a similar, though often far from identical, sequence to another gene.
► Species Differences in Skin Nociception

Homomeric Channels

Definition

Channels are protein complexes, which form pores in the cell membrane. Typically, channels are made up of several subunits, which may be identical, resulting in homomeric channels, or different, resulting in heterometic channels.
► Purine Receptor Targets in the Treatment of Neuropathic Pain

Homozygous Carriers

Definition

Homozygous carriers refer to the state of possessing two identical alleles of a particular gene, one inherited from each parent.
► NSAIDs, Pharmacogenetics

Horsley-Clarck Apparatus or Stereotaxic Frame

Definition

Horsley-Clarck Apparatus or Stereotaxic Frame is a solid metallic frame made of two horizontal graduated bars fixed peripendicularly to a metal plate, holding a device for the fixation of the head of the animal through its upper jaw and orbits. The horizontal bars hold at mid-distance a device to fix two bars introduced into the ears (external auditory meatus).
► Post-Stroke Pain Model, Thalamic Pain (Lesion)

Hospice Care

Definition

Hospice care is a form of palliative or supportive care offered when the disease is at an advanced stage. The term hospice can refer to the philosophy of care, but is also used to describe the institution or site of care.
► Cancer Pain Management, Interface Between Cancer Pain Management and Palliative Care

Hostility

Definition

Hostility refers to "A set of negative attitudes, beliefs and appraisals concerning other". Can be inwardly di-

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rected towards oneself ("intrapunitiveness") or directed towards others ("extrapunitiveness"), Smith TW (1992).

► Chronic Gynecological Pain, Doctor-Patient Interaction
► Anger and Pain

Reference

Smith TW (1992) Hostility and Health: Current Status of a Psychosomatic Hypothesis. Health Psychology 11: 215-225.

Hot Plate Test (Assay)

Definition

Placement of the rat (or mouse) on a heated metal pad (temperature $\geq 50^{\circ}$C), with the time for paw licking or jumping corresponding to the latency of the test. This method is used to assess the threshold for thermonociception.

► Thalamotomy, Pain Behavior in Animals

Hot Tooth Syndrome

Definition

A tooth is sometimes described as 'hot' when it is very painful and difficult to anesthetize even with regional block anesthesia. The tooth is usually spontaneously painful, tender to touch and difficult to treat.

► Dental Pain, Etiology, Pathogenesis and Management

Household Income and Chronicity

► Pain in the Workplace, Risk Factors for Chronicity, Demographics

HPA Axis

Definition

The hypothalamus-pituitary-adrenal axis forms the basic response triad regulating endogenous glucocorticoid concentrations in the circulation.

► Fibromyalgia, Mechanisms and Treatment

HT Neurons

► High Threshold Neurons

Human Factors Engineering

► Ergonomics Essay

Human Infant Pain Neurophysiology

► Infant Pain Mechanisms

Human Models of Inflammatory Pain

LOUISE HARDING
Hospitals NHS Foundation Trust, University College London, London, UK
louise.harding@uclh.org

Synonym

Inflammatory Pain, Human Models

Definition

Research tools used to investigate the mechanisms and pharmacology of inflammatory pain and neuronal sensitisation.

Characteristics

Inflammation is a response of the body tissues to injury or irritation. Its most prominent features are pain, swelling, redness and heat. Through activation and sensitisation of nociceptors, inflammatory mediators also cause peripheral and central sensitisation of the somatosensory system, altering the way we perceive mechanical and thermal stimuli in and around inflamed skin. Studying these changes can provide information on the underlying mechanisms and, when combined with drug studies, on the pharmacology of inflammation and neuronal sensitisation. A number of experimental models have been developed for this purpose. In each model, inflammation is evoked by a different insult or injury and different models have specific characteristics. Table 1 compares the key features of the most common models which are summarised below.

The Capsaicin Model

► Capsaicin is the chemical component of chilli peppers that gives them their 'hot' quality. It directly activates ► TRPV1, a heat sensitive cationic ion channel expressed on cutaneous nociceptors, resulting in pain and inflammation. Capsaicin can either be applied topically, typically at 1 %, or injected intradermally (doses of 25–250 μg). Intradermal injection is associated with a quick hit of intense pain lasting 1–2 minutes, compared to the mild-moderate pain of topical application that develops slowly over 10–30 minutes. Both methods pro-

Human Models of Inflammatory Pain, Table 1 Comparison of somatosensory changes produced by different human models of inflammatory pain

	Capsaicin	Burn	Heat/Capsaicin	Mustard oil	Electrical	UVB	Freeze
1° heat pain[1]	yes	yes	yes	yes	yes	yes	yes
2° punctate[2]	yes	yes	yes	yes	yes	yes	yes
2° dynamic[3]	yes	yes	yes	yes	yes	no	no
dynamic duration[4]	< 1hr	<1 hr	4 hrs	< 1 hr	> 2 hrs	-	-
2° punctate onset[5]	< 1 hr	< 1 hr	< 1 hr	< 1 hr	< 1 hr	> 4 hrs	> 4 hrs

[1]decreased heat pain threshold in the inflamed site, [2]area of secondary punctate hyperalgesia, [3]area of secondary dynamic mechanical allodynia, [4]duration of dynamic mechanical allodynia, [5]time to onset of secondary punctate hyperalgesia. See text on individual models for data references

duce neurogenic inflammation and similar changes in somatosensory function (LaMotte et al. 1991). At the primary zone, i.e. the area of inflammation, heat pain thresholds are reduced in the capsaicin model due to sensitisation of TRPV1. Very high concentrations of capsaicin desensitise the heat responsive ion channel. This is sometimes evident following intradermal delivery, and is characterised by an increase in heat pain thresholds in a 1–3 mm area around the injection site. Surrounding the primary zone, two discrete areas of ▶ secondary hyperalgesia develop; an area of dynamic ▶ mechanical allodynia and an area of ▶ punctate hyperalgesia. These two areas differ in development time, size, pharmacological sensitivity and duration. The area of dynamic mechanical allodynia is maintained by ongoing afferent input from excited nociceptors and fades within an hour of capsaicin delivery as its concentration in the skin fades. In contrast, the area of punctate hyperalgesia, once established, appears independent of afferent input and may remain for 24 hours.

The Burn Model

In this model, heat is used to produce a first degree burn on the skin. CO_2 lasers and electronically coupled thermodes are typically used to induce the burn, by heating the skin to approximately 47°C for 7 minutes (Pedersen et al. 1998). The burn stimulus is moderately painful during its application; however, the pain quickly subsides once the heat stimulus is stopped. The injury produces a flare response similar to the capsaicin model. Evoked somatosensory changes in the primary zone are heat pain sensitisation (reduced heat pain threshold), together with a mild hypoesthesia (loss of sensation) to warming and cooling. A secondary area of punctate hyperalgesia develops around the primary zone and ▶ dynamic mechanical allodynia can also develop, but this depends on experimental conditions. Thermode size, location of skin stimulated, temperature and duration of burn stimulus shape the intensity of the burn. If the burn is very mild, insufficient afferent drive is sustained to maintain dynamic mechanical allodynia once the burn stimulus is removed.

The Heat/Capsaicin Model

This model, as it suggests, uses both heat and capsaicin to produces inflammatory pain and hyperalgesia. A heat stimulus of 45°C is applied to the skin for 5 min. followed by a 30 min. application of low dose (0.075 %) topical capsaicin (Petersen and Rowbotham 1999). This produces areas of primary and secondary hyperalgesia comparable to the capsaicin model. Like the capsaicin model, the area of dynamic mechanical allodynia starts to fade after approximately 20 minutes, but in this model the area can be rekindled by re-stimulating the treated site with a heat stimulus of 40°C for 5 minutes. This rekindling can be repeated every 20 minutes for up to four hours, providing a much longer opportunity to study the mechanisms of dynamic mechanical allodynia than the capsaicin and heat models alone.

The Mustard Oil Model

The irritant mustard oil, allyl isothiocyanate, produces characteristics of inflammation and somatosensory changes comparable to the capsaicin model, i.e. sensitisation to heat in the primary zone and secondary areas of dynamic mechanical allodynia and punctate hyperalgesia (Koltzenburg et al. 1992). Applied topically for 5 minutes, either at 100 % or diluted for a lesser effect, mustard oil produces moderate to severe pain and neurogenic inflammation. It's mechanism of action is essentially unknown. Allyl isothiocyanate has recently been shown to be an agonist of the ▶ TRPA1 receptor (previously known as ANKTM1) expressed in nociceptors (Jord et al. 2004), and this receptor may be key to its inflammatory effects. Prolonged application of mustard oil however causes blistering, which suggests the inflammation process in this model may also involve tissue damage pathways.

The Electrical Stimulation Model

As discussed, in experimental models of pain, dynamic mechanical allodynia is maintained by ongoing afferent input from excited c nociceptors. The electrical stimulation model uses continuous electrical activation of ▶ C-fibres to evoke and maintain a stable area of dynamic allodynia throughout the experimental period. Current is

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injected at a frequency of 5 Hz and adjusted until the subject reports a pain intensity of 5/10 on a numerical pain intensity rating scale (mean current: 67 mA) (Koppert et al. 2001). This method produces an inflammatory pain response with stable dynamic allodynia for study periods of up to 2 hours. Other characteristics of this model are the reduced heat pain thresholds in the primary zone, and secondary area of punctate hyperalgesia common to most established models of inflammation.

The UVB/Sunburn Model

This model has two essential differences to those discussed so far. Firstly, there is a prolonged delay period of 6–12 hours between the inflammatory stimulus and the development of erythema and hyperalgesia. Secondly, the stimulus event used to create inflammation is not in itself painful (Bickel at al 1998). This model is particularly interesting, therefore, as the mechanisms of inflammation and hyperalgesia may differ somewhat to those evoked by direct activation of nociceptors. In this model, inflammation is produced by irradiating the skin with ultraviolet light in the UVB wavelength range (290–320 nm), typically over an area of approximately 5 cm diameter. There is considerable intersubject variability in the dose of radiation required to produce inflammation, consequently, subjects are assessed prior to the experimental period to establish the minimum dose of UVB required. For studies of ► primary and secondary hyperalgesia, three times the minimum dose required to produce ► erythema is used for experimentation. The UV model produces primary hyperalgesia to heat and secondary hyperalgesia to punctate mechanical stimuli, but not dynamic mechanical allodynia. Both primary and secondary events have a delayed onset, and are typically studied 20 hours after irradiation. This model is therefore relatively demanding, compared to other models, as subjects are required on 3 consecutive days. An advantage of this model however, is that the sensory changes are stable for 10 hours, giving a long window for detailed study.

The Freeze Lesion Model

Delayed onset hyperalgesia is also a characteristic of the freeze lesion model. Freeze lesions can be created using a 1.5 cm diameter copper rod cooled to -28°C and held perpendicularly against the skin for 10 seconds (Kilo et al. 1994). This produces mild to moderate sharp prickling pain, vasodilation of the stimulated and surrounding area and a local oedema. Pain, oedema and flushing outside the contact area subside within 2 hours; however, a discrete erythmia at the contact area remains for a number of days. No primary or secondary hyperalgesia can be detected in the first hours following the injury, but both are developed by the subsequent day. This model does not produce dynamic mechanical allodynia, and the area of punctate hyperalgesia produced by the freeze lesion

model is typically much smaller than that produced by other models.

In addition to the models described above, inflammatory pain and hyperalgesia have been reported following administration of a number of other inflammatory stimuli. This is not an exhaustive list, but for reference includes Melatin from bee venom (Sumikura et al. 2003), acidic phosphate buffered solution (Steen and Reeh 1993) complete Freunds adjuvant (Gould 2000) and bradykinin (Manning et al. 1991).

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Human Thalamic Nociceptive Neurons

KAREN D. DAVIS, JONATHAN O. DOSTROVSKY
University of Toronto and the Toronto Western Research Institute, University Health Network, Toronto, ON, Canada
kdavis@uhnres.utoronto.ca, j.dostrovsky@utoronto.ca

Synonyms

Thalamic Nociceptive Neurons; Diencephalic Nociceptive Neurons in the Human; Wide dynamic range (WDR) neurons and nociceptive specific (NS) neurons in human thalamus

Definition

Central nervous system neurons whose cell bodies are located within the human thalamus (diencephalon) and that have a preferential or exclusive response to ► noxious stimuli.

The human thalamus, which is very similar to the monkey thalamus, includes several regions where neurons responding specifically or preferentially to nociceptive stimuli are found. However, in view of the very limited opportunities available to search for such neurons in the human and perform extensive testing on them, our knowledge concerning their properties and locations is extremely limited.

Characteristics

It is possible to directly study human thalamic nociceptive neurons during the electrophysiological mapping used by some neurosurgical teams as part of functional neurosurgical procedures for treating chronic pain, Parkinson's disease or other movement disorders (Lenz et al. 1988; Tasker and Kiss 1995). During these mapping procedures, microelectrodes are inserted into the thalamus to record the electrophysiological properties of individual thalamic neurons.

The unique opportunity afforded by functional stereotactic surgery to record and stimulate in the thalamus of awake patients, has provided some interesting findings and validation of subhuman primate studies related to thalamic function in pain. Unfortunately, the inherent limitations of these studies (time constraints, ethical considerations and lack of histological confirmation) limit the interpretation of the findings. The studies have attempted to address the following questions:

1. Where can one record nociceptive and thermoreceptive neurons?
2. What are the properties of nociceptive and thermoreceptive neurons?
3. What are the perceptual consequences of microstimulation in the regions containing nociceptive and thermoreceptive neurons?
4. Where can one evoke painful and temperature sensations by stimulating in the thalamus and what are the qualities of the sensations?
5. Are there any alterations in neuronal firing characteristics, receptive fields or stimulation-evoked sensations in chronic pain patients?

This section briefly summarizes the findings pertaining to these questions.

Nociceptive Neurons in Lateral Thalamus

The existence of nociceptive neurons in ► Vc (ventrocaudal nucleus often termed VP or ventroposterior nucleus) and adjacent regions has been reported by Lenz and colleagues (for review see Lenz and Dougherty 1997). The vast majority of Vc neurons are classified as non-nociceptive tactile neurons, since they respond to light touch of a distinct area of skin (i.e. the neuron's receptive field). However, there have been a few reports of some nociceptive neurons in Vc. Approximately 5–10% of Vc neurons have been classified as nociceptive, based on their responses to noxious thermal stimuli (Lenz et al. 1993a; Lenz et al. 1994). A larger proportion of Vc neurons, up to 25%, were found to respond selectively or preferentially to noxious mechanical stimuli (Lee et al. 1999; Lenz et al. 1994). These neurons were primarily located in the posterior-inferior portion of Vc. Interestingly, in the adjoining posterior-inferior area, which includes ► VMpo (Blomqvist et al. 2000), they identified NS neurons that responded to noxious heat, and none of the neurons in this area responded to innocuous tactile stimuli (Lenz et al. 1993a). The true proportion of thalamic nociceptive neurons may be underestimated in these studies for a variety of technical, physiological and ethical reasons. First, there are very few opportunities to test for nociceptive responses in awake human subjects, and the small body of data that has been obtained derives from patients with either movement disorders or a chronic pain condition. Second, extensive testing for nociceptive responses (both in terms of the number of neurons tested and the skin area tested) is limited due to the painful nature of the stimulus. Third, it is not clear whether there is any selection bias in the ability of microelectrodes to record from nociceptive versus tactile neurons (e.g. based on cell size, spontaneous activity, etc.).

Medial Thalamus

Much less is known regarding the role of the medial thalamus compared to the lateral thalamus in human pain, largely due to the fact that there are few opportunities to record and stimulate in this region during functional stereotactic surgery. There are some discrepancies in the incidence of medial thalamic nociceptive responses across the few published studies. One group (Ishijima et al. 1975) reported a similar proportion of mechanical- and thermally-responsive nociceptive neurons in the CM-Pf region, as compared to the findings of Lenz and colleagues in lateral thalamus. However, another group found only 2 of 318 medial thalamic neurons that responded to noxious stimuli (Jeanmonod et al. 1993). It is, however, difficult to evaluate these findings as few details were provided by the authors, and more recent studies have failed to replicate the findings (see Lenz and Dougherty 1997 for references).

Stimulation-Induced Pain

One of the unique aspects of electrophysiological studies in human patients is the ability to question the patient about sensations evoked by electrical stimulation within the brain. Electrical stimulation within Vc and adjacent regions of the thalamus usually evokes innocuous parasthesia. However, several early studies documented that stimulation in the area posterior-inferior to

Vc elicited reports of painful sensations in some patients (Halliday and Logue 1972; Hassler and Riechert 1959; Tasker 1984). Recent studies have examined the effects of stimulation in much greater detail (Davis et al. 1996; Dostrovsky et al. 2000; Lenz et al. 1993b), and these show that pain and innocuous thermal sensations can be evoked from a region at the posterior-inferior border of Vc and extending several millimeters posterior, inferior and medial. Microstimulation applied at the Vc sites of confirmed nociceptive neuronal responses rarely evokes pain, but rather produces a non-painful tingling sensation (Lee et al. 1999; Lenz et al. 1993a, b, 1994). A greater incidence of stimulation-evoked pain in Vc and the ventroposterior region has been reported in patients with a history of visceral pain, phantom pain or post-stroke pain (Davis et al. 1995; Davis et al. 1996; Davis et al. 1998; Lenz et al. 1995)

The incidence of evoked pain/thermal sensations is much higher in the posterior-inferior area than within Vc proper. Unlike the pareasthetic (tingling and 'electric shock') sensations evoked in Vc, the pain/thermal sensations are usually reported as quite natural. They are always perceived on the contralateral side of the body, and the projected fields can be quite small. The painful sensations are frequently described as burning pain. In a few cases, sensations of pain referred to deep and visceral sites have been elicited (Lenz et al. 1994; Davis et al. 1995). Lenz and colleagues have reported that microstimulation within Vc (at sites where WDR neurons responding to noxious mechanical stimuli were found) rarely results in pain, whereas at the sites in the region posterior-inferior to Vc where microstimulation evoked pain there was a high likelihood of finding nociceptive neurons (Lenz and Dougherty 1997). Histological confirmation of these stimulation and recording sites has of course not been obtained in such patients, but it seems likely that the physiologically localized region posterior-inferior to Vc corresponds anatomically to VMpo.

A few studies have reported that stimulation in the posterior aspect of medial thalamus can evoke pain (Jeanmonod et al. 1993; Sano 1979), but in most cases large tipped electrodes and high intensities were used for stimulation, so current spread is an issue. More recent studies have failed to replicate these findings.

Innocuous Cool Neurons and Sensations

Cells responding to innocuous thermal stimuli are also of great interest and highly relevant, due to the well-known association of the pain and temperature pathways. Cooling-specific neurons are only found in lamina I of the spinal and trigeminal dorsal horns, and have been shown to project to VMpo in the monkey (Dostrovsky and Craig 1996). In animal studies, cooling neurons in the thalamus have only been reported in VMpo (monkey) and medial VPM (cat). Cooling-specific neurons in human thalamus were located in

the region medial and posterior-inferior to Vc that likely corresponds to the human VMpo (Davis et al. 1999). Of particular interest was the finding that stimulation at such sites evoked cooling sensations that were graded with stimulus intensity, and that were referred to the same cutaneous region as the receptive fields of the cooling-specific neurons recorded at the site. Stimulation in this posterior-inferior region can also elicit pain (see above) and, as shown by Lenz and colleagues (1993a; 1993b), this region also contains nociceptive-specific neurons.

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Human Thalamic Response to Experimental Pain (Neuroimaging)

ALEXANDRE F. M. DASILVA,
NOUCHINE HADJIKHANI
Martinos Center for Biomedical Imaging,
Massachusetts General Hospital, Harvard Medical
School, Charlestown, MA, USA
alexandr@nmr.mgh.harvard.edu,
nouchine@nmr.mgh.harvard.edu

Synonyms

Thalamic Response to Experimental Pain in Humans

Definition

The thalamus is the major relay structure in the forebrain for noxious and non-noxious sensory inputs. In the case of ▶ noxious stimuli, the thalamus distributes the incoming information to other specific cortical areas for proper processing of their discriminative, cognitive and affective components. Recent neuroimaging techniques can effectively detect transient thalamic neuronal activation following the application of experimental stimuli that artificially replicate painful conditions in humans.

Characteristics

Thalamic neuronal activation is frequently observed in functional neuroimaging studies following ▶ experimental pain. Through the use of neuroimaging techniques, the role of the thalamus has been gradually dissected in the nociceptive CNS network. Under those studies, experimental pain resultant of different noxious stimuli has revealed a pattern of thalamic activation that depends on the type of stimuli (e.g. thermal), area of application, and conditions inherent to the subject or patient, such as attention, or the presence of a chronic pain disorder.

Techniques

Of the neuroimaging technologies available, ▶ functional magnetic resonance imaging (fMRI) and ▶ positron emission tomography (PET) have greatly expanded our knowledge of human thalamic response to pain. Both indirectly measure the neuronal activity based on changes in the metabolism during a particular transient task (e.g. experimental pain) compared to a baseline state (e.g. no-pain state). The specific contrast for fMRI is the blood oxygenation level-dependant (BOLD) contrast, which does not require any tracer agent but relies on blood volume and blood flow, whereas radioactive labeled tracers are used to measure changes in cerebral blood flow and metabolism in PET.

Thalamic Nuclear Function

There are 14 major thalamic nuclei identified, but this number diverges depending on the histological technique applied. Some of them, or subdivisions, have specific roles in the thalamic nuclear configuration for pain processing. Activations of the ventroposterior nuclei of the ventrobasal complex (lateral), and other more medial nuclei of the thalamus, have being consistently described in neuroimaging studies. These studies confirm previous animal experiments that noxious and innocuous discriminative input from cranial and the body parts are respectively processed by the ventroposterior medial nucleus (VPM) and the ▶ ventroposterior lateral nucleus (VPL), and afterward projected to the somatosensory cortex. The lateral nuclear activation has a clear somatotopic configuration for different kinds of sensory input, while the medial thalamus, such as the ▶ dorsomedial nucleus (DM), has particular thermoceptive functions. Noxious thermal stimulation to the facial skin of each trigeminal division in healthy human volunteers activates the contralateral VPM, while the same noxious stimulation applied to the palmar surface of the thumb activates the VPL (DaSilva et al. 2002). In both cases, during trigeminal and thumb noxious thermal stimulation, the contralateral DM nucleus of the thalamus shows activation (Fig. 1).

A specific thalamic nuclear pathway is involved in interoceptive mechanism of homeostasis: the basal part of the ventromedial nucleus (VMb) and the ▶ posterior part of the ventromedial nucleus (VMpo) play an important role in thermal nociceptive inflow through main direct projections to the insular cortex (Craig 2002). With the future improvement of the spatial resolution (2 mm for PET and <1 mm for fMRI) and signal noise rate in the neuroimaging studies, as well as the superposition of structural ▶ diffusion tensor imaging (DTI) maps to delineate nuclear architecture under the activations (Fig. 2), we will be able to precisely define the pattern of thalamic activation following painful stimulus in human (DaSilva et al. 2003; Wiegell et al. 2003).

Experimental Noxious Stimuli

Most of the noxious stimuli used in neuroimaging studies are thermal in nature, applying temperatures higher than 45C for heat pain, and usually lower than 6C for cold pain, enough to activate nociceptive fibers (C and A-delta). The noxious thermal stimuli are delivered by non-magnetic contact probes, water immersion, and laser (heat) to a particular part of the body in an alternating fashion with a non-noxious state (e.g. neutral 32C x noxious 46C). Similar noxious sensations have also been produced by interlaced application of non-noxious
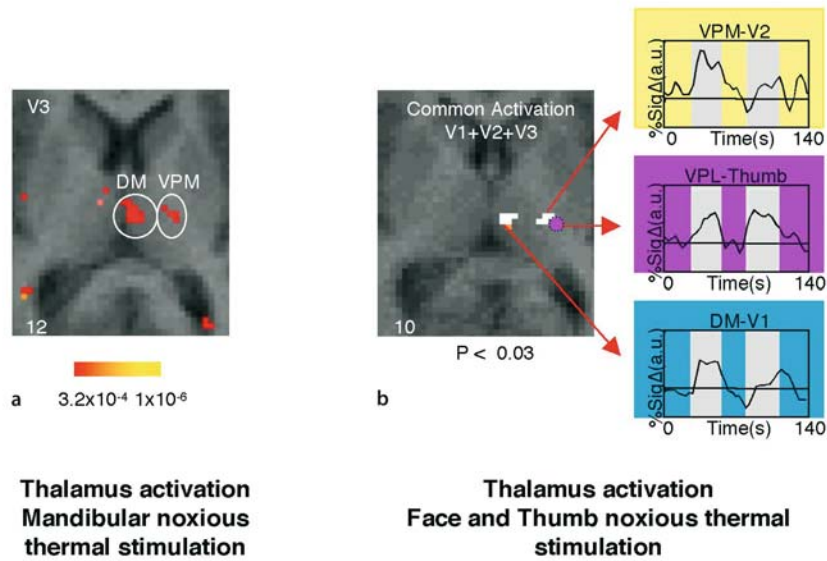
Human Thalamic Response to Experimental Pain (Neuroimaging), Figure 1 Activation in Thalamus. (a) Activation in the thalamus contralateral to a noxious thermal stimulus to the V3 (mandibular trigeminal branch) region of the face. (b) Activation in the thalamus following contralateral stimulation to the face and hand. The white areas show regions of common activation following noxious thermal stimulation to the V1 (ophtalmic), V2 (maxillary) and V3 (mandibular) distributions of the face, in regions defined as the dorsomedial (DM) and ventroposteromedial (VPM) nuclei. Activation of the thumb is mapped onto the same anatomical section (purple circle) and corresponds to the ventroposterolateral (VPL) nucleus. The regions are defined anatomically using the Talairach Atlas. Time courses of activation for each area are shown in inserts. Percent signal change is shown in arbitrary units (a.u.); numbers in bottom corners indicate the Talairach coordinate in the rostro-caudal (z) axis. (Da Silva et al. 2002).xxx
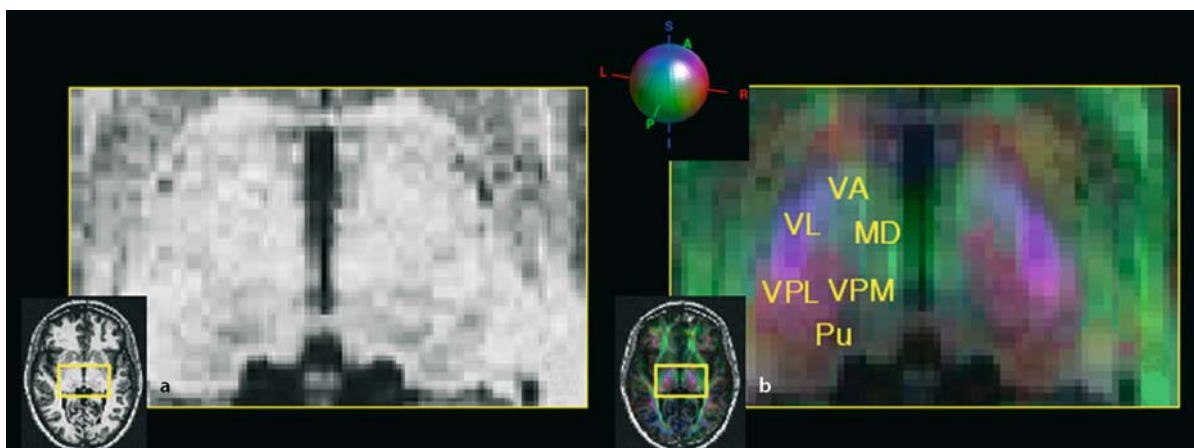
Human Thalamic Response to Experimental Pain (Neuroimaging), Figure 2 Color-coded DTI map superimposed on high-resolution anatomical image. Comparison of an axial (a) MPRAGE structural image and the corresponding (b) color-coded DTI map. The ROI is taken from the yellow box shown in the whole slice image at bottom-left. On the MPRAGE, the thalamus appears homogeneous, whereas the DTI map shows significant substructure. The thalamic nuclei have been labeled according to their anatomical position and fiber orientation. The color-coding depicts the local fiber orientation (i.e. the principal eigenvector of the diffusion tensor) with red indicating mediolateral, green anteroposterior, and blue superoinferior. The color-coding is also indicated by the red-green-blue sphere shown at top-center. Abbreviations: VA, ventral anterior; VL, ventrolateral; MD, mediodorsal; VPL, ventral posterior lateral; VPM, ventral posterior medial; Pu, pulvinar. (Da Silva et al. 2003).

warm and cold temperatures, which is known as the thermal-grill illusion of pain. Other noxious stimuli that have been used in pain studies are mechanical (e.g. tonic pressure), electrical (e.g. intramuscular electrical stimulation) and chemical (e.g. subcutaneous injection of ► capsaicin or ascorbic acid).

Neuroimaging studies applying experimental stimuli produce thalamic activation. Noxious and innocuous thermal stimuli (cold and heat) activate the medial and lateral thalamic nuclei, with predominant contralateral activation, while innocuous mechanical stimuli mostly activate the lateral thalamus. Noxious mechanical stimuli (tonic pressure) elicit inconsistent contralateral thalamic activation (Creac'h et al. 2000), as tonic pain (long duration) elicits less thalamic activation than phasic pain (short duration). In addition, the amount

of thalamic activation observed depends on the size of the somatotopical representation of the body part being stimulated (the face has, for example, a much bigger cortical representation than the foot).

If the experimental noxious stimulus is applied to the same region but in different tissues, the thalamic activation pattern can also be distinct, as in the case of experimental skin and muscular pain (Svensson et al. 1997). Although noxious intramuscular electrical stimulation and cutaneous pain, elicited by CO_2 laser in the left brachioradialis area produce equal positive correlation between increases in regional cerebral flow (rCBF) in thalamus and anterior insula, only the cutaneous noxious stimulation shows a negative relationship in rCBF changes between thalamus and contralateral primary sensorimotor cortex, indicating a possible inhibitory mechanism between both structures.

Chemical experimental pain using capsaicin has been used in neuroimaging studies in two different ways: to induce acute and/or allodynic pain. Capsaicin is a hot pepper-derived derived substance that induces consistent ongoing pain, with a response including midline thalamic nuclei such as the DM nucleus (Iadarola et al. 1998). The cutaneous area treated with capsaicin, injected or topically applied, also develops secondary ▶ allodynia. Allodynia is a reversible state of painful sensitivity to non-noxious stimuli, such as brush and warm stimuli that replicates a clinical phenomenon common in ▶ neuropathic pain, burn lesions and ▶ migraine patients. Capsaicin-allodynia to non-noxious heat activates the medial thalamus simultaneously with the frontal cortex, orbital and dorsolateral prefrontal (DLPFC), suggesting a greater affective and cognitive response, which correlates with the higher unpleasantness rating compared to normal heat pain rating (Lorenz et al. 2003).

Conditions inherent to the subjects also affect the thalamic response to experimental pain. There is an indication that gender differences in pain perception influence thalamus function. For the same thermal noxious pain, females show a higher rating for pain intensity than males, translated into higher activation in the contralateral thalamus, as well as in the prefrontal cortex and anterior insula (Paulson et al. 1998). Male subjects demonstrate higher μ-opioid system activation than female subjects in the anterior thalamus, ventral basal ganglia and amygdala during sustained deep muscular pain (Zubieta et al. 2002). Pain perception is also altered by attention, hypnosis or pharmacologic effect through a modulation of the pain system involving mainly the thalamus and cingulated cortex. Distraction tasks presented to subjects during thermal pain correlate with decreased perception of pain, and consequently lower medial thalamic activation (Bantick et al. 2002). In a hypnotic state, the patient's reduced pain perception correlates with high functional modulation between the midcingulate cortex, the thalamus and the midbrain (Faymonville et al. 2003). Under the influence of fentanyl, a μ-opioid receptor agonist, there is a strong attenuation of responses to noxious cold stimulation in the contralateral thalamus and primary somatosensory cortex (Casey et al. 2000).

Acute and chronic pain can alter the pattern of thalamic and cortical activation. Patients suffering acute post-dental extraction show increased response to heat pain applied to the ipsilateral hand in the somatosensory pathway, including thalamus and S1 (Derbyshire et al. 1999). This increased level of rCBF does not occur when the same noxious stimulus is applied to the hand contralateral to the dental extraction. This fact can be explained by the ongoing post-surgical inflammatory process, and its repercussions in the CNS awareness, amplifying any further sensory input from the ipsilateral areas, surrounding or distant (for safeguard) from the injury. Chronic pain disorders have shown a central distinct neuroplastic mechanism in response to the persistent pain input overflow. Instead of thalamic increase activation to painful stimulation, there is attenuation of the response and even a decrease of the rCBF in the thalamus. This is the case for ▶ fibromyalgia and neuropathic patients, where chronic thalamic activation following their persistent evoked and ongoing clinical pain, attenuates or decreases its response after time (Gracely et al. 2002; Hsieh et al. 1995; Kwiatek et al. 2000). Patients suffering from ▶ cluster headache, a primary headache disorder, also show similar results, with significantly lower rCBF changes during the headache-free period compared to control subjects in the contralateral thalamus and S1 after ipsilateral tonic cold pain stimulation (Di Piero et al. 1997).

Conclusion

Although it is clear that neuroimaging research can contribute to the understanding of the thalamic neuronal activation regarding experimental and clinical pain, its nuclear specificity is yet to be completely defined. Technical improvement of imaging tools will provide better anatomical and functional nuclear maps of the thalamus, and consequently, of its correlation with each intrinsic aspect of a noxious event.

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Hunner's Ulcer

Definition

Hunner's ulcer is a focal inflammatory lesion of the bladder wall in chronic interstitial cystitis; its surface may crack and bleed with bladder distension.

► Interstitial Cystitis and Chronic Pelvic Pain

HVTM

► High Velocity Thrust Manipulation

Hyaline Cartilage

Definition

Hyaline cartilage is translucent cartilage that is common in joints and the respiratory passages.

► Sacroiliac Joint Pain

Hyaluronan

BRIAN MCGUIRK

Occupational (Musculoskeletal) Medicine, Hunter Area Health Service, Newcastle, NSW, Australia
mgillam@mail.newcastle.edu.au

Synonyms

Hyaluronic acid; Viscosupplementation

Definition

Hyaluronic acid is a naturally occurring glycosamino-glycan, consisting of a repeating dimer of glucuronic acid and N-acetyl-glucosamine (Weissman and Meyer 1954). The proprietary form is known as hyaluronan. This agent is administered by intra-articular injection, as a treatment for osteoarthritis.

Characteristics

Hyaluronic acid is a widely distributed polysaccharide, which plays an important role in all mammalian connective tissues, due to its peculiar physico-chemical and biological properties. By nature of its propensity to form highly hydrated and viscous matrices, hyaluronic acid imparts stiffness, resilience and lubrication to various tissues. The unique biophysical properties of hyaluronic acid are manifested in its mechanical function in the synovial fluid, the vitreous humour of the eye, and the ability of connective tissues to resist compressive forces (Laurent 1998).

In normal human synovial fluid, hyaluronic acid has a high molecular weight and acts in a visco-elastic manner. Due to its hyaluronic acid content, joint fluid acts as a viscous lubricant during slow movement of the joint, as in walking, and as an elastic shock absorber during rapid movement, as in running.

In osteoarthritis, both the concentration and molecular weight of hyaluronic acid in the synovial fluid are reduced (Marshall 1998; George 1998), which impacts on its biophysical properties. It was this finding that gave rise to the concept of *viscosupplementation,* in which injection of exogenous hyaluronic acid into the joint space is presumed to augment the functions of endogenous hyaluronic acid.

Mechanism

The mechanism by which intra-articular hyaluronic acid works in patients with osteoarthritis remains unknown. Although restoration of the elasto-viscous properties of synovial fluid seems to be the most logical explanation, other mechanisms must exist. The actual period that the injected hyaluronic acid product stays within the joint space is in the order of hours to days, but the time of clinical efficacy is often in the order of months (Cohen 1998; Balazs and Denlinger 1993). Possible explanations include stimulation of endogenous production of

hyaluronic acid; inhibition of inflammatory mediators such as cytokines and prostaglandins; stimulation of cartilage matrix synthesis as well as inhibition of cartilage degradation; and a direct protective action on nociceptive nerve endings.

Technique

Hyaluronan is injected into the joint to be treated using a strict, no-touch, aseptic technique. If an effusion is present, aspiration of the joint is recommended before the injection, in order to prevent dilution of the injectate. Excessive weight-bearing physical activity should be avoided for 1–2 days.

Applications

The US Food & Drug Administration has approved the use of hyaluronan for patients with osteoarthritis of the knee, whose joint pain has not responded to non-medicinal measures and analgesic drugs. The guidelines for osteoarthritis from the American College of Rheumatology (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines 2000) state that it may be "especially advantageous in patients in whom non-selective ▶ NSAIDs and Cox-2 specific inhibitors are contra-indicated, or in whom they have been associated either with a lack of efficacy or with adverse events". Intra-articular hyaluronic acid is generally used after non-pharmacologic treatments, analgesics and a trial of several NSAIDs.

Efficacy

Since the 1970s many studies have been carried out to evaluate the efficacy of hyaluronan. Despite a number of randomised, controlled trials having been carried out, the results and their interpretation, remain conflicting. Whereas the earliest studies suggested benefits, more recent double-blind placebo-controlled trials did not show any benefit over placebo. In other studies, hyaluronan has been suggested to have an overall benefit over placebo.

An extensive review on intra-articular administration of hyaluronan, published by Brandt et al. (2000), concludes that "although several clinical trials indicate that intraarticular injection of [hyaluronan] results in relief of joint pain in patients with knee [osteoarthritis], and that this effect may last for months, similar results are seen with placebo, and it is not clear that the difference between [hyaluronan] and placebo, even if statistically significant, is clinically significant."

In response, Miller, in correspondence to the Journal of American Academy of Orthopaedic Surgeons (Miller 2001), argued that the decrease in the total number of knee replacements performed in the USA has occurred as a direct result of the use of viscosupplementation, citing a number of studies that formed the basis of the presentation to the FDA for its approval of hyaluronan as a treatment for osteoarthritis.

Side Effects

Transient localised pain and/or effusion is the most commonly reported side effect, albeit occurring in a low (0–3) percentage of patients, based on the majority of clinical trials conducted to date (Puttick et al. 1995). These resolve spontaneously within a short period. Several cases of pseudogout have been confirmed (Luzar and Altawil 1998). Long-term side-effects have not been identified.

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Hyaluronic Acid (HA)

Definition

Investigational drug for the treatment of IC; appears to temporarily replace defective mucosa.

▶ Hyaluronan
▶ Interstitial Cystitis and Chronic Pelvic Pain

Hydrodistention

Definition

Hydrodistention is the filling of bladder under anesthesia, to assess for mucosal tears, glomerulations, and bladder capacity; part of diagnostic workup as well as therapy for IC.

▶ Interstitial Cystitis and Chronic Pelvic Pain

Hydroperoxides

Definition

Hydroperoxides such as PGG_2 are required to initiate the conversion of arachidonic acid into prostaglandins.
▶ Cyclooxygenases in Biology and Disease

Hydrotherapy

Definition

Hydrotherapy is the external application of water, e.g. the immersion of the body in thermal water.
▶ Chronic Pain in Children, Physical Medicine and Rehabilitation
▶ Spa Treatment

Hydroxy–7.8–Dihydrocodeinone

▶ Oxycodone

Hypalgesia

▶ Hypoalgesia
▶ Hypoalgesia, Assessment

Hypalgia

▶ Hypoalgesia, Assessment

Hyperaesthesia

▶ Hyperalgesia

Hyperaesthesia, Assessment

KRISTINA B. SVENDSEN[1], TROELS S. JENSEN[2], F. W. BACH[2]
[1]Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark
[2]Danish Pain Research Center and Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
kristina@akhphd.au.dk, tsj@akhphd.au.dk

Definition

Hyperaesthesia is increased sensitivity to stimulation, excluding the special senses (Merskey and Bogduk 1994). ▶ Allodynia and ▶ hyperalgesia are included in the definition.

Characteristics

Hyperaesthesia refers to both the finding of a lowered threshold to a non-noxious or a noxious stimulus, and to an increased response to suprathreshold stimuli (Merskey and Bogduk 1994). It can best be described as a leftward shift of the stimulus-response curve, which relates the response to the stimulus intensity (Fig. 1). Hyperaesthesia has to be distinguished from hyperpathia, which is a classical feature of neuropathic pain and easily demonstrated in skin territories innervated by damaged nerve fibres (Jensen et al. 2001),(Jensen and Baron 2003).

Hyperaesthesia may occur after traumatic or inflammatory injury to the skin (Treede et al. 1992) or in the undamaged skin in neuropathic pain conditions (Boivie 1999, Woolf and Mannion 1999). Hyperaesthesia may also be found in the skin area of referred muscle (Svensson et al. 1998) and visceral pain (Hardy 1950, Stawowy et al. 2002). In tissue injury, increased sensibility to stimuli may be found in both the injured area (normally called primary hyperalgesia) and in surrounding non-injured skin area (secondary hyperalgesia) (Treede and Magerl 2000).

Induction and Assessment

Hyperaesthesia may be induced by different stimulus modalities including mechanical, thermal, and chemical stimuli (Treede et al. 1992, Jensen et al. 2001, Woolf and Mannion 1999).

Hyperaesthesia can be assessed by determining ▶ detection thresholds for a given stimulus. In the case of noxious stimuli, pain detection and pain tolerance thresholds can be used. Assessment of hyperalgesia includes stimulus-response curves, where noxious stimuli of different intensities (e.g. thermal stimuli or
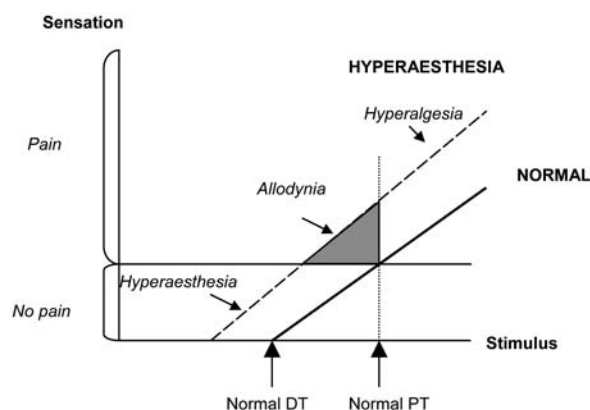
Hyperaesthesia, Assessment, Figure 1 Hyperaesthesia refers to both lowered thresholds and to increased response to suprathreshold stimuli. Decreased pain threshold is called allodynia. Increased response to normally painful stimulus is called allodynia. DT, detection threshold. PT, pain threshold.

pressure) are applied in a random order and the pain sensation/intensity is assessed for each stimulus.
Hyperaesthesia is present when the detection and/or ▶ pain threshold for a given stimulus is decreased (Fig. 1), or the response to suprathreshold stimuli is increased. In the case where pain is induced by a normally non-painful stimulus, the term allodynia is used. Increased response to normally painful stimuli, e.g. evaluated by the stimulus-response curve, is termed hyperalgesia.

Clinical Examination/Studies

Bedside sensory screening may be useful in the evaluation of the anatomical distribution and the qualitative characterisation of sensory abnormalities of the skin (Hansson and Lindblom 1992). Bedside examination includes mechanical stimuli (cotton wool, paintbrush, pressure with fingertip, pinprick), thermal stimuli (thermal rollers kept at 20° and 40°C, acetone drop) and vibration sense (tuning fork) (Table 1).
Sensory examination is normally done in the area with maximal pain and compared with the contralateral site of the body (Andersen et al. 1995, Jensen et al. 2001) or the adjacent body area not involved in disease. Hyperaesthesia is present in the case of increased sensation/pain to a non-painful (hyperaesthesia/allodynia) or a painful stimulus (hyperalgesia).
Quantitative assessment of hyperaesthesia is performed using quantitative sensory testing (QST). QST includes mechanical (▶ Von Frey hair, pressure algometry) and thermal stimuli (Thermotest) (Table 1). The results of QST from the affected site of the body are normally compared with results from an unaffected contralateral body site. However, when the contralateral site is also affected by disease, values from healthy subjects/general population may be used (Kemler et al. 2000). For standard-

ized regions such as feet, hands and face several laboratories have established normative data for thermal and mechanical stimuli. Hyperaesthesia is present in the case of lowered detection and/or pain thresholds. Pain Detection and Pain Tolerance Thresholds (see ▶ Pain Detection and Pain Tolerance Thresholds) indicates hyperalgesia.
The qualitative aspect of pain can be assessed by various questionnaires such as McGill Pain Questionnaire (Melzack 1975), verbal rating scales, visual analogue scales, numerical rating scales etc. (Turk and Melzack 1992).

Patient Example

A 54 year old man with peripheral neuropathic pain following a trauma located to the right antebrachium. The sensory function of the right hand was assessed by QST, and the results were compared with the healthy contralateral site. The patient had signs of hyperaesthesia with decreased tactile detection threshold, allodynia with decreased tactile pain threshold; decreased pressure pain threshold, decreased heat and cold pain thresholds and hyperalgesia with decreased pressure tolerance threshold (see Fig. 2). In addition he had cold allodynia evoked by acetone drop.

Experimental Studies

Human

Hyperaesthesia is found in various human pain models: Burn injury of the skin (a model of cutaneous injury) is followed by heat and mechanical allodynia in both injured and the adjacent non-injured surrounding skin (Pedersen and Kehlet 1998).
Capsaicin application of the skin produces allodynia with decreased heat pain threshold at the site of injection, and pain induced by a light normally non-painful

Hyperaesthesia, Assessment, Table 1 Sensory testing

	Stimulus	Method	Sensation
Bedside examination	Mechanical stimuli -Dynamic Touch -Static Touch -Punctate stimuli	Stroking the skin with a paintbrush / cotton swab Gentle pressure with fingertip Pinprick	Increased sensation/pain = hyperaesthesia
	Thermal stimuli -Cold -Warm	Metallic thermal roller kept at 20°C Acetone / menthol Metallic thermal roller kept at 40°C	
Quantitative sensory testing	Mechanical stimuli -Tactile detection threshold -Tactile pain threshold -Pressure pain threshold -Pressure pain tolerance threshold	Von Frey Hair Pressure Alogometry	Decreased threshold = hyperaesthesia
	Thermal stimuli -Cold detection threshold -Warm detection threshold -Cold pain threshold -Heat pain threshold -Heat tolerance threshold	Thermotest	
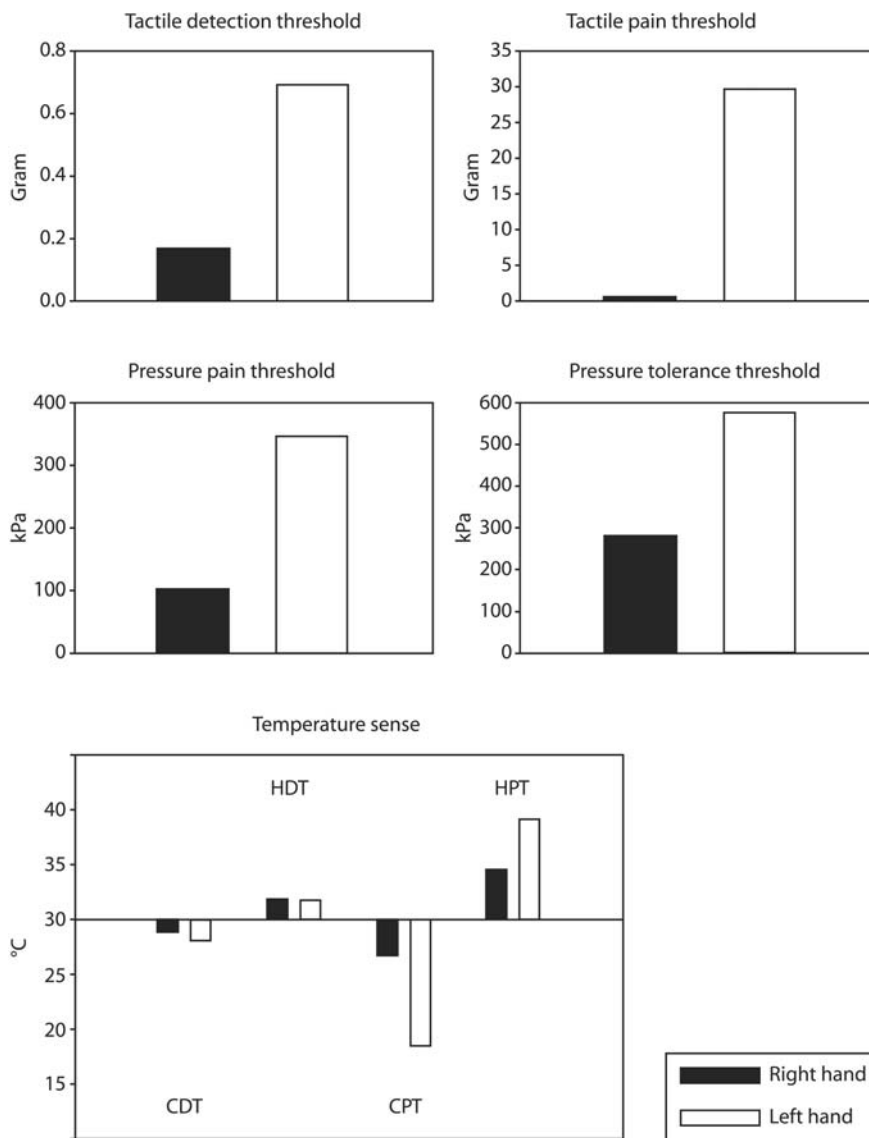
Hyperaesthesia, Assessment, Figure 2 Quantitative sensory testing in a patient with nerve lesion of the right antebrachium. CDT, cold detection threshold; HDT, heat detection threshold; CPT, cold pain threshold; HPT, heat pain threshold.

mechanical stimulus in an area surrounding the injection site (Treede et al. 1992). Burn injury has also been combined with capsaicin in a heat-capsaicin sensitisation model (Petersen et al. 2001).

Intramuscular injections of hypertonic saline, capsaicin, glutamate and other excitatory or algogenic substances have been used as a model of localised and referred muscular pain (Graven-Nielsen and Arendt-Nielsen 2003). In these muscle pain models decreased pressure pain thresholds have been found. Hypertonic saline may induce mechanical hyperaesthesia located to the overlying or adjacent skin (Svensson et al. 1998).

Animal

Strictly speaking, hyperaesthesia including allodynia and hyperalgesia with increased sensitivity to specific sensory stimulation cannot be determined in experimental animal models. Nevertheless, it is generally accepted that increased motor responses to mechanical (Von Frey hair), thermal (cold bath, hot plate, acetone, focal heat) and chemical (capsaicin) stimuli in animal models of nerve injury, inflammation or diabetes reflects a hypersensitivity of the animal to the pertinent stimulus (Scholz and Woolf 2002).

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Hyperalgesia, Table 1 Types of hyperalgesia and their likely mechanisms

| Test stimulus	Occurrence	Afferents	Sensitization
heat	primary zone	type I &II AMH, CMH	peripheral
blunt pressure	primary zone	MIA, (type I AMH?)	peripheral
impact	primary zone	MIA, (type I AMH?)	peripheral
punctate	neuropathic secondary zone primary zone	type I AMH type I AMH type I AMH, MIA	central central peripheral/central?
stroking	neuropathic secondary zone primary zone	Aβ-LTM Aβ-LTM Aβ-LTM	central central central
cold	neuropathic pain secondary zone?	? ?	central? central?
chemical	inflammation	type II AMH, CMH, MIA ?	peripheral ?

Abbreviations: Aβ-LTM Aβ-fiber low-threshold mechanoreceptor ("touch receptor"), probably rapidly adapting subtype (Meissner corpuscle); type I AMH A-fiber nociceptor with slow high-threshold heat response (no TRPV1), probably equivalent to A-fiber high-threshold mechanoreceptor; type II AMH A-fiber nociceptor with rapid low-threshold heat response (TRPV1); CMH C-fiber mechano-heat nociceptor (TRPV1); MIA mechanically insensitive (silent) nociceptive afferent (From Treede et al. 2004).
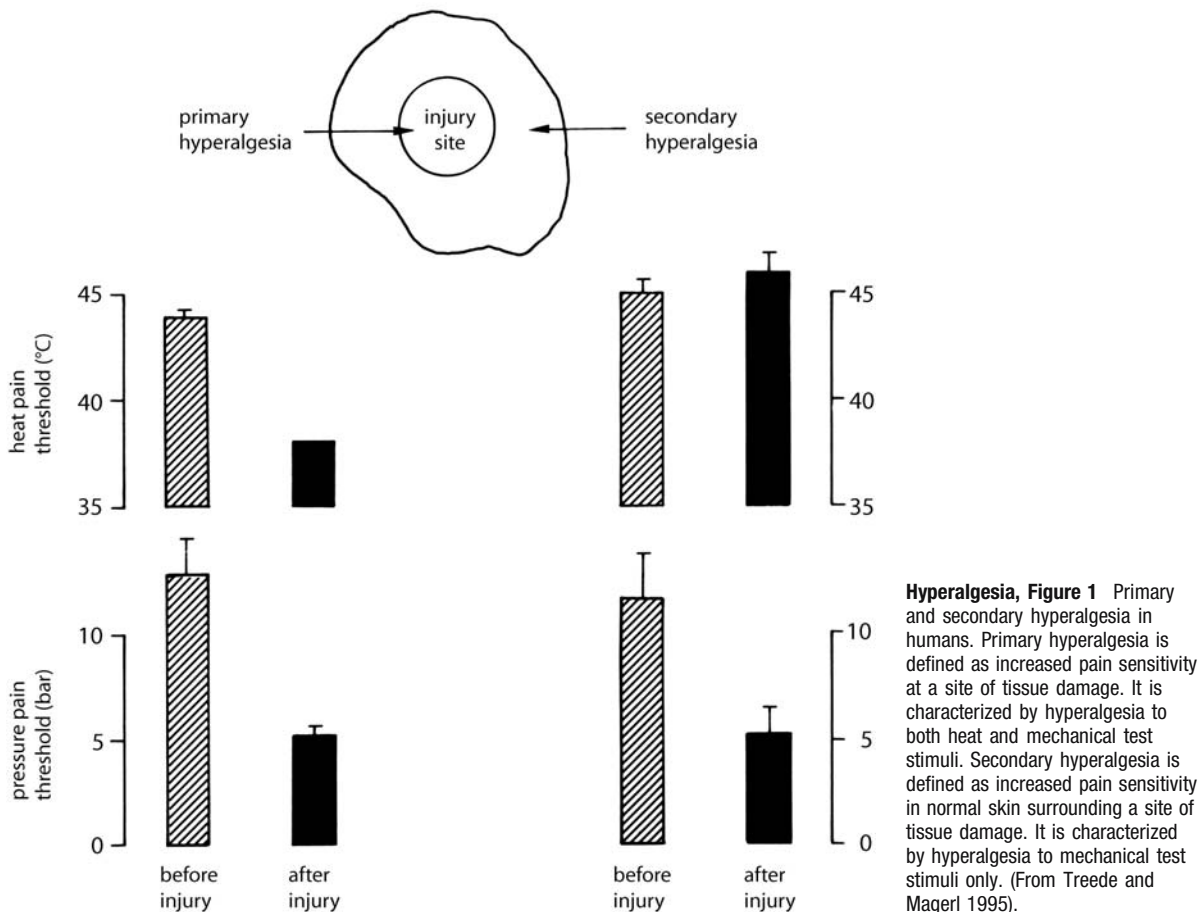
Hyperalgesia, Figure 1 Primary and secondary hyperalgesia in humans. Primary hyperalgesia is defined as increased pain sensitivity at a site of tissue damage. It is characterized by hyperalgesia to both heat and mechanical test stimuli. Secondary hyperalgesia is defined as increased pain sensitivity in normal skin surrounding a site of tissue damage. It is characterized by hyperalgesia to mechanical test stimuli only. (From Treede and Magerl 1995).

an increase in suprathreshold responses (Simone et al. 1991). In addition, expansion of the ▶ receptive field is a prominent feature of central sensitization. The molecular mechanisms of central sensitization resemble those of long-term potentiation of synaptic efficacy (LTP). LTP has been demonstrated for neurons in isolated spinal cord slices, in intact animals and on a perceptual level in human subjects (Klein 2004; Sandkühler 2000;
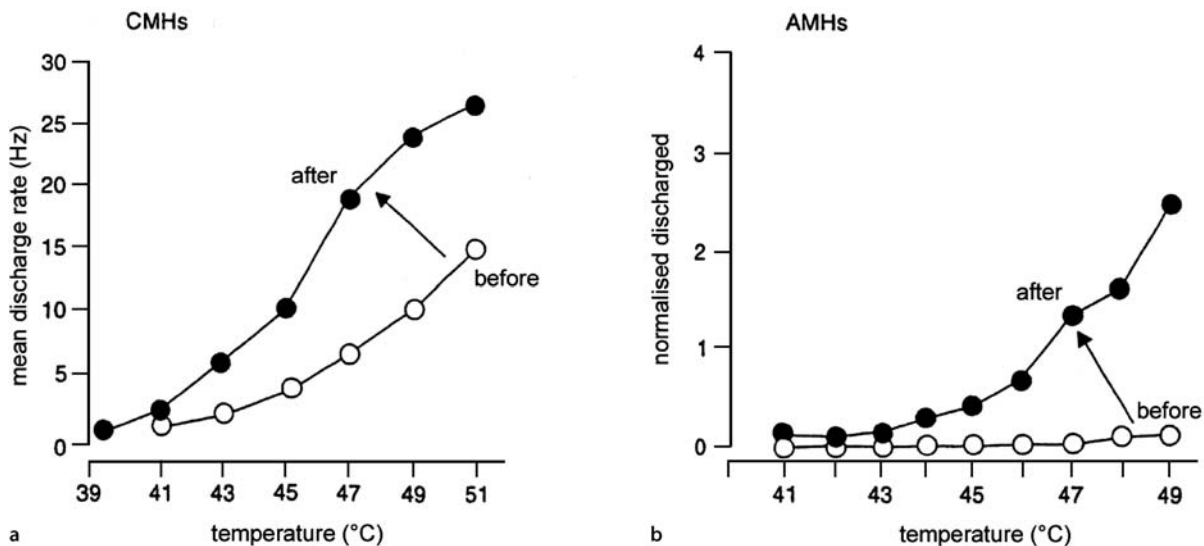
Hyperalgesia, Figure 2 Peripheral sensitization of nociceptive afferents by a burn injury in monkey. The stimulus response function relating the discharge rate of nociceptive C- (a) and A-fiber nociceptors (b) is shifted to the left following injury to the receptive field. This shift is characterized by a drop in threshold, increased responses to suprathreshold stimuli, and by spontaneous activity. Spontaneous discharges occur when the heat threshold is below body temperature. Peripheral sensitization is restricted to the injured part of the receptive field. (From Treede et al. 1992).

Treede and Magerl 1995). As a cellular correlate of learning and memory, LTP in the nociceptive system is a phylogenetically old mechanism, present even in invertebrates (Woolf and Walters 1991).

Although not characterized in as much detail, descending supraspinal mechanisms may contribute to both primary and secondary hyperalgesia, *via* reduced descending inhibition or *via* enhanced descending facilitation (Millan 2002; Porreca et al. 2002). Moreover, central sensitization may also occur at the thalamic or cortical level.

The mechanisms of cold hyperalgesia, which is a frequent finding in some ▶ neuropathic pain states, are still enigmatic (Wasner et al. 2004). Peripheral sensitization of nociceptive afferents cannot be ruled out, because the peripheral encoding of noxious cold stimuli has not been investigated sufficiently (Raja et al. 1999). Some evidence supports the concept of central disinhibition by selective loss of a sensory channel specific for non-noxious cold that exerts a tonic inhibition on nociceptive channels (Craig and Bushnell 1994). Central sensitization, similar to mechanical hyperalgesia, is another possibility.

Clinical Implications

Primary and secondary hyperalgesia occur transiently after each injury, and are hence part of the normal clinical picture of postoperative pain. Chronic inflammatory hyperalgesia resembles primary hyperalgesia. Hyperalgesia in neuropathic pain and referred hyperalgesia in visceral pain resemble secondary hyperalgesia (Treede et al. 1992). Cancer pain and musculo-skeletal pain states including low-back pain may also be accompanied by hyperalgesia. Parallel to the definition of sensi-

tization, hyperalgesia is characterized by a decrease in pain threshold, increased pain to suprathreshold stimuli and spontaneous pain.

Hyperalgesia Versus Allodynia

The current IASP taxonomy has restricted the term "hyperalgesia" to increases in pain to suprathreshold stimuli (Merskey and Bogduk 1994). But are threshold changes and suprathreshold changes two independent phenomena needing two separate terms? This question can be addressed in a clinical example, the increased pain sensitivity to punctate mechanical stimuli in patients suffering from neuropathic pain (Baumgärtner et al. 2002). Figure 3 illustrates that hyperalgesia to calibrated pinpricks in these patients is characterized by both an increase in pain to suprathreshold stimuli and a decrease in pain threshold. According to the IASP taxonomy the threshold decrease would be labeled 'allodynia', whereas the increase in pain to suprathreshold stimuli would be labeled 'hyperalgesia' (Fig. 3). Consistent use of the IASP taxonomy is obviously awkward in this case, because these observations reflect two aspects of the same phenomenon and the same data, i.e. a dramatic leftward shift of the psychometric function and upward shift of the stimulus response function of pain to the same set of test stimuli. The traditional usage of the term 'hyperalgesia' as an umbrella term for all phenomena of increased pain sensitivity describes hyperalgesia to punctate mechanical stimuli more adequately (Treede et al. 2004).

▶ Allodynia and Alloknesis
▶ Allodynia (Clinical, Experimental)
▶ Amygdala, Pain Processing and Behavior in Animals
▶ Cancer Pain

reduced threshold

increased response
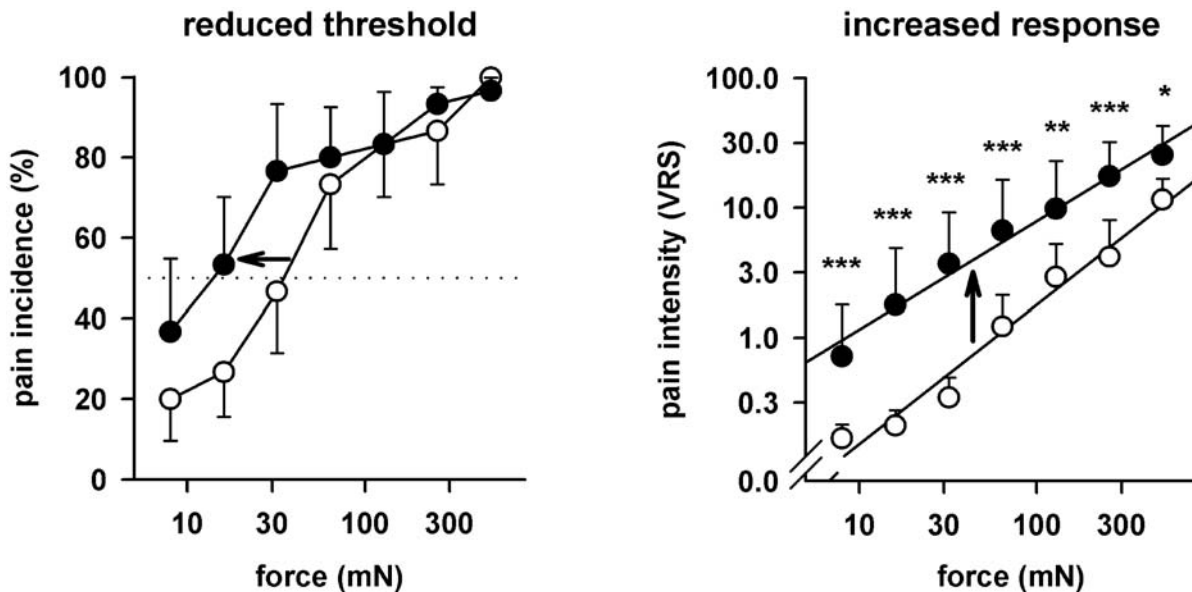
Hyperalgesia, Figure 3 Hyperalgesia to punctate mechanical stimuli in neuropathic pain. Averaged data from a group of six patients with neuropathic pain were plotted in two different ways: as incidence (left) and as intensity (right) of pain sensation in neuropathic pain skin areas (filled circles) compared to normal skin (open circles). Stimuli were graded punctate probes (diameter 0,2 mm) of seven intensities (8–512 mN). Left panel: reduced threshold (intersection with dotted line at 50%) implies pain due to a stimulus, which does not normally evoke pain ("allodynia?"). Right panel: Increased pain response to a stimulus, which is normally painful ("hyperalgesia?"). Note that both graphs are different aspects (pain incidence and pain intensity) plotted from the same data set. Arrows: leftward shift of pain incidence and upward shift of pain intensity. VRS = verbal rating scale. Mean $\pm$ SEM across subjects. Post hoc least significant differences tests: ** $p < 0.01$; *** $p < 0.001$. (From Treede et al. 2004).

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Hyperalgesia, Primary and Secondary

Definition

Primary Hyperalgesia is increased pain sensitivity at a site of tissue damage. Secondary hyperalgesia is increased pain sensitivity in normal skin surrounding a site of tissue damage. It is characterized by hyperalgesia to mechanical test stimuli.
▶ Allodynia (Clinical, Experimental)
▶ Hyperalgesia

Hyperemia

Definition

Increased blood flow or an excess of blood in a body parties known as hyperemia.
▶ Clinical Migraine with Aura

Hyperesthesia

▶ Hyperalgesia

Hyperexcitability

Definition

Large diameter sensory neurones with myelinated A-fiber axons that lie in dorsal root ganglia that project into a damaged peripheral nerve are often more easily discharged than the same type of neurone in ganglia from uninjured animals. The neurones fire from a greatly reduced current threshold. In some cases, a small depolarization produced by the local action of, e.g. a humoral substance, or by modifications in the extracellular environment (e.g. ischemia) may be enough to discharge these cells.
▶ Sympathetic and Sensory Neurons after Nerve Lesions, Structural Basis for Interactions

H

Hyperglycemic Neuropathy

▶ Diabetic Neuropathies

Hyperhidrosis

Definition

Hyperhidrosis means increased sweating.
▶ CRPS, Evidence-Based Treatment

Hyperknesis

Definition

Hyperknesis is 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.
▶ Allodynia and Alloknesis

Hyperpathia

JOHN W. SCADDING

The National Hospital for Neurology and Neurosurgery, London, UK

jwscadding@hotmail.com

Definition

The IASP, in its Classification of Chronic Pain (1994), defines hyperpathia thus:

"Hyperpathia is a painful syndrome characterized by an abnormally painful reaction to a stimulus, as well as an increased threshold."

The following note is added:

"It may occur with ► allodynia, ► hyperesthesia, ► hyperalgesia, or ► dysesthesia. Faulty identification and localization of the stimulus, delay, radiating sensation and after-sensation may be present, and the pain is often explosive in character."

Characteristics

Introduction

Use of the term hyperpathia varies in the current scientific literature, and many avoid it. For example, in the fourth edition of The Textbook of Pain (1999), hyperpathia is mentioned by name in only 4 of 68 chapters, and possible explanations for the symptom complex are discussed in depth in only one of these. Likewise, several recent influential studies and reviews, tackling the difficult and elusive problem of linking individual symptoms and signs to underlying pathophysiological mechanisms, avoid use of the word hyperpathia altogether, or make only passing reference to it (Woolf et al. 1998; Woolf and Mannion 1999; Otto et al. 2003; Jensen and Baron 2003).

The reason is that hyperpathia describes a complex sensory experience occurring in the context of ► neuropathic pain. This complex can be broken down into component parts, each of which may be experienced by patients independent from the other constituent properties of hyperpathia; however, there is a tendency for the whole complex to occur in many patients suffering from neuropathic pain.

Historical Aspects

A brief historical examination reveals the variable usage of the term hyperpathia. Foerster (1927) suggested a lengthy and all-inclusive definition and description of hyperpathia, which most would agree comprehensively encapsulates the properties of stimulus-evoked painful sensations in patients suffering from neuropathic pain. He proposed the term hyperpathia be used when the following symptoms could be elicited from a regenerating area:

"a relative elevation of threshold, when the duration of the stimulus or summation of stimuli become important,

a latent period, an intensive explosive outbreak of pain of pain of abnormal unpleasant character accompanied by strong withdrawal movements, vasomotor and vegetative reactions, lack of or insufficient relationship between the strength of the stimulus and the strength of the sensation, a long after-reaction of the pain when the stimulus has ceased, irradiation, faulty localisation, and the inability to identify the nature of the stimulus which causes the pain."

Livingston (1943) equated hyperpathia with hyperalgesia:

"Any injury that directly or indirectly involves the sensory nerves may lead to the development of an abnormal sensitiveness of the skin. All sensory experiences derived from the skin may be altered in this condition, so that it is frequently called a "hyperesthesia" or a "hyperpathia". However, since the principal alteration in sensibility is an intensification of pain sensation it is more commonly referred to as a "hyperalgesia." In this state the tissues are unduly sensitive and they tend to react to the most innocuous stimuli with explosive sensations of pain accompanied by withdrawal reflexes."

Finally, Noordenbos (1959) suggests:

"Hyperpathia is present when the response to noxious or non-noxious stimuli presents the following features: delay, overshooting and after-reaction."

Definition or Description

This brief historical survey serves to emphasise two important points. The first, is the general point that a definition should include those characteristics that are the minimum necessary to categorise a condition, item or state as separate and identifiably distinct; in relation to the definition of diseases and clinical syndromes/states, a definition must have clinical relevance and usefulness. The second point, with reference specifically to the definition of hyperpathia, is that the definition is based on a collection of symptoms and signs. As is evident throughout this Encyclopaedic Reference, the last few decades have witnessed enormous progress in the basic neuroscience of pain. However, it is still not yet possible to define conditions and terms such as neuropathic pain, hyperalgesia, hyperesthesia, allodynia and hyperpathia on the basis of pathophysiological mechanisms, though there are, of course, numerous candidate mechanisms. It seems likely that each of the symptoms and signs of painful states may be produced by more than one underlying pathophysiology.

For the moment, however, we are stuck with frustratingly imprecise clinical syndromal definitions.

Symptoms and Signs Comprising Hyperpathia

It is notable that the current IASP definition of hyperpathia, quoted above, includes little detail, and it is left to the accompanying note to elaborate the symptoms. Most would agree that there are four main clinical features to hyperpathia:

1. An increased threshold to stimulation.
2. An abnormal delay in perception of a stimulus.
3. Summation, by which is meant increasingly painful sensation to a repetitive stimulus of steady intensity. Summation may take the form of an explosive, unbearable increase in pain, and it leads to brisk withdrawal from the provoking stimulus.
4. After-sensation. This is a perception by the sufferer that the stimulus evoking the pain continues after the stimulus has in fact ceased. Painful after-sensations may persist for seconds, minutes, or even hours, following brief periods of stimulation lasting only a few seconds.

Conditions in Which Hyperpathia Occurs

It is clear from numerous published accounts that hyperpathia may accompany (or, perhaps more accurately, be a part of) neuropathic pain, due to lesions at any level in the peripheral or central nervous system sensory pathways. This includes painful cutaneous scars, peripheral sensory or mixed peripheral neuropathies, brachial or lumbar plexopathies, spinal sensory radiculopathies, myelopathies, and brain stem, thalamic, sub-cortical and, very occasionally, cortical lesions. In other words, all of the many causes of neuropathic pain may be associated with hyperpathia, and multiple aetiologies are involved (Scadding 2003).

Noordenbos (1959) described in detail six patients with peripheral and central lesions, all of whom had severe hyperpathia, specifically to illustrate the occurrence of hyperpathia. Other classical accounts are to be found in Weir Mitchell et al. (1864), Riddoch (1938) and Livingston (1943).

Is Hyperpathia a Clinically Relevant and Useful Term?

Hyperpathia is very common and troublesome to patients, despite the impression one might get from perusal of the recent basic and clinical scientific literature on pain, which, as discussed above, tends to consider the component properties of hyperpathia rather than addressing hyperpathia as a whole. It is certainly highly relevant to patients. For example, a patient suffering from post-herpetic neuralgia (PHN) in a mid-thoracic dermatome, with an accompanying hyperpathic response to normally innocuous stimulation, may find the gentle rubbing of clothes on the affected area of skin quite intolerable. Indeed, for patients with PHN, it is often hyperpathia, much more than ongoing pain, which is the major component of their suffering and immobilization. Hyperpathia at other sites has the same devastating effect on the lives of numerous patients.

Although tremendous advances have been made in the measurement of pain, and particularly in the various attributes of neuropathic pain, hyperpathia is difficult to quantify, and so has tended to be underestimated in published studies (routine quantitative sensory testing does not accurately assess this).

Hyperpathia, Table 1   Possible Pathophysiological Substrates for Hyperpathia

Symptom	Mechanism
1. Increased threshold lesion	Reduced input due to sensory lesion
2. Delay in perception	Reduced large fibre input
3. Summation	Crossed after-discharge in lesionEphaptic transmission in lesion?Central sensitization
4. After-sensation	Crossed after-dischargeDRG ectopic firingCentral disinhibition

DRG, dorsal root ganglion
Woolf and Mannion (1999), Devor and Seltzer (1999), Jensen and Baron (2003)

Pathophysiology

Table 1 lists some possible pathophysiological substrates for the development of hyperpathia.

▶ Cancer Pain
▶ Causalgia, Assessment
▶ Deafferentation Pain
▶ Peripheral Neuropathic Pain
▶ Hypoesthesia, Assessment

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Hyperpathia, Assessment

ASTRID J. TERKELSEN, TROELS S. JENSEN
Danish Pain Research Center and Department of
Neurology, Aarhus University Hospital, Aarhus,
Denmark
astrid@akhphd.au.dk, tsj@akhphd.au.dk

Definition

Hyperpathia is a painful syndrome characterized by an
abnormally painful reaction to a stimulus, especially a
repetitive stimulus, as well as an increased threshold for
sensory detection (Merskey and Bogduk 1994).

Characteristics

Hyperpathia includes increased ▶ detection threshold,
steeper stimulus-response function than normal and of-
ten a time lag between stimulus and sensation, abnormal
summation, after-sensations, pain radiating phenomena,
faulty identification and faulty localization of the stim-
ulus (Noordenbos 1979; Lindblom 1979; Merskey and
Bogduk 1994; Bennett 1994).

Induction and assessment

Thermal-, mechanical-, and chemical- hyperpathia may
exist singly or in any combination. Therefore, multiple
different noxious and innocuous stimulus modalities
have to be used to document or to exclude hyperpathia
(Lindblom 1994) (Table 1).

Hyperpathia is assessed by performing stimulus-
response curves, repetitive suprathreshold stimulation,
and by asking the patient to report after-sensations, pain
radiation, and coexistent phenomena.
Hyperpathia is present at increased detection threshold,
decreased ▶ pain threshold, and ▶ allodynia (Fig. 1A
and B, and Fig. 2B). At increased detection threshold
without allodynia (Fig. 1, example 1C and 1D, and
Fig. 2A), hyperpathia is present at steeper stimulus-
response curve than normal (Fig. 3) or at exaggerated
response (increased intensity and duration of pain) fol-
lowing single or repetitive suprathreshold stimulation
(Table 1 and Fig. 1E).
In unilateral involvement, the contralateral mirror im-
age area is used as control. In bilateral involvement, data
should preferably be compared with normal values from
sex- and age-matched controls.

Stimulus-Response

An increased sensory detection threshold (Fig. 1 and
Fig. 2) characterizes hyperpathia. There can be poor
localization of the stimulus and faulty identification
where the patient feels pain, but not the specific modal-
ity of the stimulus (Fig. 2B) or the patient's misnaming
of the stimulus modality (Fig. 3). The pain is often
felt by a remarkable delay characterized by a time lag
between the stimulus and the report of any sensory
perception. The time lag can extend from two to three
seconds to more than ten seconds .

Hyperpathia, Assessment, Table 1 Assessment of hyperpathia with Quantitative Sensory Testing (QST)

Stimuli to evoke hyperpathia	Assessment of detection threshold (DT) and pain threshold (PT)	Stimulus response function following graded innocuous and / or noxious stimuli	Repetitive suprathreshold stimulation
Thermal stimuli:			
Screening with metallic cold and heat thermorollers			
Quantitative thermal Sensory Testing with Peltier device:-Heat: -Cold:	DT, PTDT, PT	Ass. of thermal allodynia / hyperalgesia++	Repetitive heat or cold pulses++
Mechanical stimuli:			
Light touch:-Wisp of cotton:-Camel-hair brush:	–	–	Brushing with a velocity > 0.3 Hz++
Punctuate stimuli: Screening with safety pin -Von Frey hair:	DT, PT	Ass. of ▶ punctuate allodynia / hyperalgesia +	Multiple > 0.3 Hz pinprick stimuli +
Static stimuli: -Pressure: -Skin fold:	PTPT	Ass. of ▶ static allodynia / hyperalgesia++	++
Electrical stimulation:	DT, PT	+	+
Vibrametry:	DT, (PT)	+	+
Chemical stimuli:			
Topical capsaicin:	Time before detection (DT) and pain (PT)	Pain increase as a function of time	-
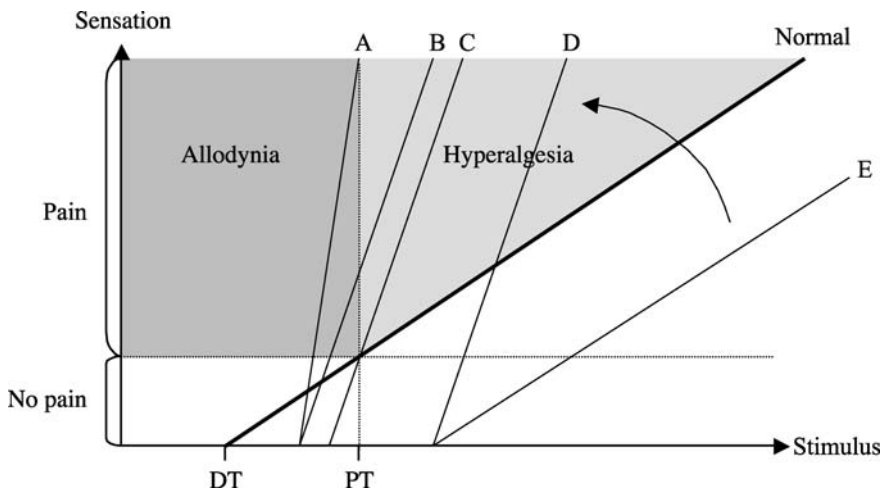
Hyperpathia, Assessment, Figure 1 Schematic description of different stimulus-response curves occurring at hyperpathia. Normal response (Normal) with normal detection threshold (DT) and normal pain threshold (PT). (A) Hyperpathia with increased DT, decreased PT, allodynia, and steeper stimulus-response curve as compared to normal. (B) Hyperpathia with increased DT, decreased PT, allodynia, hyperalgesia, and steeper stimulus-response curve as compared to normal. (C) Hyperpathia with increased DT, normal PT, hyperalgesia, and steeper stimulus-response curve. (D) Hyperpathia with increased DT, increased PT, hyperalgesia, and steeper stimulus-response curve. (E) At repetitive stimulation, pain threshold decreases and the slope of the stimulus-response curve increases thereby unmasking hyperpathia.
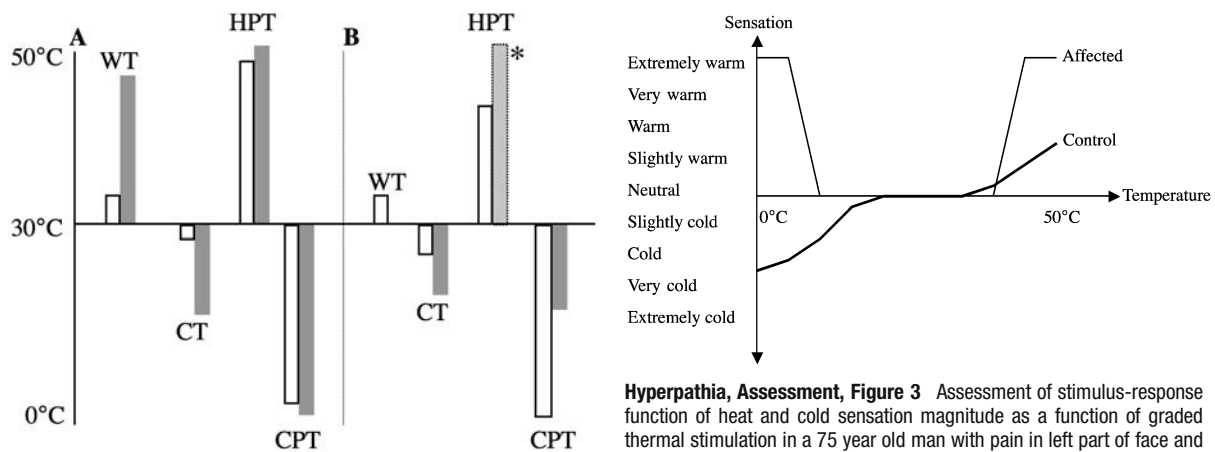
Hyperpathia, Assessment, Figure 2 Assessment of stimulus-response function of heat and cold sensation magnitude as a function of graded thermal stimulation in a 75 year old man with pain in left part of face and right leg and arm following brain stem infarct. Stimulus-response curve at right affected forearm (Affected) shows hyperpathia with steeper stimulus-response curve than at control side (Control) and faulty identification of stimulus modality with cold stimulation misnamed as heat stimulation. Control stimulus-response curve is assessed at contralateral mirror image area. Modified from Vestergaard and co-workers .

Hyperpathia, Assessment, Figure 3 Assessment of stimulus-response function of heat and cold sensation magnitude as a function of graded thermal stimulation in a 75 year old man with pain in left part of face and right leg and arm following brain stem infarct. Stimulus-response curve at right affected forearm (Affected) shows hyperpathia with steeper stimulus-response curve than at control side (Control) and faulty identification of stimulus modality with cold stimulation misnamed as heat stimulation. Control stimulus-response curve is assessed at contralateral mirror image area. Modified from Vestergaard and co-workers .

There is a steeper stimulus-response function than normal (Fig. 1 and Fig. 3) (Hansson and Lindblom 1992) with an intense, exaggerated, and explosive pain response to suprathreshold stimuli. Stimulus and response modality may be the same (▶ hyperalgesia) and/or different (allodynia) (Fig. 1) (Merskey and Bogduk 1994).

Temporal Summation

Hyperpathia is most likely elicited by increasing stimulus duration or by repetitive stimulation (Nordenbos 1959). Temporal summation refers to an abnormally increasing painful sensation to repetitive stimulation, although the actual stimulus remains constant and is the clinical equivalent to ▶ wind-up (Mendell and Wall 1965; Price et al. 1992). At repetitive stimulation above sensory detection threshold, hyperpathic subjects can report a gradual change from a faint sensation to a mildly unpleasant sensation and then a sudden exaggerated response with unbearable pain (Lourie and King 1966). During this repetitive stimulation, pain threshold decreases and the slope of the stimulus-response curve increases (Fig. 1E). This exaggerated response can be provoked by both noxious and innocuous stimuli (Table 1).

After-Sensations

After-sensations refer to abnormal persistence of pain seconds to minutes after termination of stimulation (Gottrup et al. 2003).

Pain Radiation

There may be a radiating sensation out from the point of stimulation to the cutaneous area around the stimulus or to wide adjacent areas (Bennett 1994).

Coexistent Phenomena

Hyperpathia is often accompanied by a general alerting response with strong withdrawal movements, vasomotor and vegetative reactions. It may occur with allodynia, ► hyperesthesia, hyperalgesia, or ► dysesthesia (Merskey and Bogduk 1994).

Clinical Examination/Studies

Pain history evaluates symptoms evoked by stimulation of the affected extremity like after-sensations, pain radiating phenomena, and allodynia induced by movement, non-painful cold or heat, wind touching the extremity, contact with clothing or bedlinen etc.

A bedside screening for hyperpathia is performed with heated and cold thermorollers kept at 20°C and 40°C, respectively, a wisp of cotton, and pinprick (Von Frey hair or safety pin), moving from the normal towards the painful area (Jensen et al. 2001). This screening may detect areas with possible increased sensory detection and exaggerated pain responses.

Usually the site of maximal pain reported by the patient is chosen as the test area. In this area, Quantitative Sensory Testing is performed (Fruhstorfer et al. 1976; Hansson and Lindblom 1992; Backonja and Galer 1998) to estimate detection- and pain thresholds (Table 1 and Fig. 2). At increased detection threshold, stimulus-response curves (Fig. 3) and repetitive stimulation with suprathreshold stimuli (Table 1) are performed in the test area. During examination, patient's behavioral responses are observed, such as facial expression or withdrawal from stimulus.

Experimental Studies

Hyperpathia is a clinical phenomenon and cannot be induced in human or animal experimental conditions.
► Allodynia (Clinical, Experimental)
► Amygdala, Pain Processing and Behavior in Animals
► Cordotomy Effects on Humans and Animal Models
► Nerve Growth Factor Overexpressing Mice as Models of Inflammatory Pain
► Opioids, Effects of Systemic Morphine on Evoked Pain

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Hyperpolarization

Definition

Hyperpolarization is an increase in inside negativity of the transmembrane resting potential of an excitable cell, such as a neuron that can make a neuron less excitable and, if of sufficient magnitude, can prevent the occurrence of action potentials.
► Chronic Pain
► Descending Circuitry, Opioids
► Drugs with Mixed Action and Combinations, Emphasis on Tramadol
► Thalamic Bursting Activity

Hyperresponsiveness

Definition

Increased responsivity and improper frequency control of classes of sensory neurons in the central nervous system originated by anomalous inputs.
► Deafferentation Pain

Hypersensitivity

Definition

Hypersensitivity is an increased sensation of stimuli or increased scores of symptoms in response to standard stimuli.
- ▶ Chronic Pelvic Pain, Musculoskeletal Syndromes
- ▶ Deafferentation Pain
- ▶ Psychology of Pain, Sensitisation, Habituation and Pain
- ▶ Recurrent Abdominal Pain in Children
- ▶ Sensitization of Visceral Nociceptors

Hypersensitivity Maintained Pain

Synonyms

Central sensitization

Definition

A phenomenon developing in the central nervous system after peripheral injury by which mechanoreceptors acquire the ability to evoke pain. Clinically, it is characterized by secondary hyperalgesia, i.e. an increased painfulness of stimuli applied to a region outside the area of injury.
- ▶ Alpha(α) 2-Adrenergic Agonists in Pain Treatment

Hyperstimulation Analgesia

Definition

Hyperstimulation Analgesia is a short but very painful stimulation that reduces (short-term) pain.
- ▶ Acupuncture Mechanisms

Hypertensive Encephalopathy

Definition

Hypertensive encephalopathy is a change in the brain caused by failure of auto regulation of the cerebral circulation in the presence of severe hypertension, characterized pathologically by vasogenic cerebral edema and, sometimes, microhemorrhages and microinfarcts, and characterized clinically by headache, obtundation, seizures, visual changes, and/or focal deficits.
- ▶ Headache Due to Hypertension

Hypertensive Headaches

- ▶ Headache Due to Hypertension

Hypertonic Saline

Definition

Hypertonic saline is a solution of greater that 155 mM sodium chloride. Sodium chloride solutions of 1.0 M can be injected into muscle tissue and produce pain, presumably due to their osmotic strength.
- ▶ Nociceptors in the Orofacial Region (Temporomandibular Joint and Masseter Muscle)

Hypervigilance

Definition

Hypervigilance is the excessive predisposition to attend to a certain class of events, or the excessive readiness to select and respond to a certain kind of stimulus from the external or internal environment. In the context of fear of movement, hypervigilance concerns the increased attention to pain, potential signals of pain and other possible somatosensory signals. General hypervigilance is the tendency of highly anxious individuals to pay attention to other irrelevant (neutral) stimuli.
- ▶ Disability, Fear of Movement
- ▶ Dyspareunia and Vaginismus
- ▶ Fear and Pain
- ▶ Hypervigilance and Attention to Pain
- ▶ Muscle Pain, Fear-Avoidance Model

Hypervigilance and Attention to Pain

GEERT CROMBEZ[1], STEFAAN VAN DAMME[1], CHRISTOPHER ECCLESTON[2]
[1]Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium
[2]Pain Management Unit, University of Bath, Bath, UK
geert.crombez@ugent.be,
stefaan.vandamme@ugent.be, c.eccleston@bath.ac.uk

Synonyms

Heightened Vigilance; Overalertness; Heightened Attention

Definition

▶ Hypervigilance to pain or somatic sensations is the excessive tendency to attend to pain/somatic sensations, or the excessive readiness to select pain-related information over other information from the environment. In the context of pain, hypervigilance is assumed to be initiated and maintained by its immediate threat value. ▶ Pain-related fear and ▶ Catastrophic Thinking have often been found to be strong predictors of hypervigilance to pain.

H

Characteristics

Chapman (1978) was one of the first to apply the construct of (hyper)vigilance to somatic sensations and pain. He referred to hypervigilance as a perceptual habit of scanning of the body for somatic sensations. Hypervigilance was thought to be an emergent property of the threat value of pain. People who appraise bodily sensations as dangerous were thought to be more likely to develop a habit of scanning the body for threatening sensations. His view is similar to the view expressed by Watson and Pennebaker (1989), who explored diverse explanations for the robust relationship between ▶ negative affectivity (NA) and somatic complaints. Indeed, an impressive number of studies has revealed that NA is strongly associated with symptom reporting and a heightened self-report of all types of physical sensations and symptoms, even in the absence of medical markers of disease. Watson and Pennebaker argued that this relationship is best explained by a hypervigilance to somatic information in persons with high levels of NA: "First, [individuals with] high NA may be more likely to notice and attend to normal body sensations and minor aches and pains. Second, because their scanning is fraught with anxiety and uncertainty, [individuals with] high NAs may interpret normal symptoms as painful or pathological" (Watson and Pennebaker 1989, p 247).

Hypervigilance has become a key theoretical and clinical construct in explaining high symptom reporting, especially in situations of medically unexplained or ambiguous sensations (Barsky and Klerman 1983; Rollman and Lautenbacher 1993). We should, however, be careful in equating high symptom reporting with hypervigilance. Hypervigilance is only one possible explanation for high symptom reporting, and other explanations using central nervous processes are often not taken into account. It is also presumptuous to conclude that a low ▶ pain threshold and a low ▶ pain tolerance are sensitive and specific indicators of hypervigilance. Hypervigilance may only be invoked as an explanatory construct when attentional processes are involved. Hypervigilance may be assessed by using self-report, psychophysiological and behavioural measures (Van Damme et al. 2004b).

In understanding hypervigilance, it is important to consider "normal" attention to pain. Eccleston and Crombez (1999) were among the first to systematically investigate the "normal" attentional processes to pain. In their cognitive-affective model of the interruptive function of pain, they argued that pain imposes an overriding priority for attentional engagement by activating a primitive defensive system that urges escape from somatic threat. Whether pain will demand attention, is the result of both pain-related characteristics (i.e. intensity, novelty, catastrophizing about pain, pain-related fear) and characteristics of other demands in the environment (monotonous environment, attention absorption in other activities). In their model, it is difficult to draw a sharp delineation between vigilance and hypervigilance. Hypervigilance to pain does not seem to result from an abnormal characteristic of the individual, such as negative affectivity. Available evidence suggests that hypervigilance to pain emerges as the working of normal attentional mechanisms in abnormal situations. Such situations are: (1) the chronic presence of high-intensity pain, (2) monotonous environments, or environments that lack external stimulation, and (3) most importantly, the high threat value of pain. Indeed, Goubert et al. (2004) found that the key mediating variable in explaining hypervigilance to pain was not an abnormally high level of negative affectivity, but the immediate threat value of pain, measured by pain-related fear and catastrophic thinking about pain (Fig. 1). Negative affectivity was best conceived as a vulnerability factor: It lowers the threshold at which pain is perceived as threatening, and at which catastrophic thoughts about pain emerge.

The idea that one is hypervigilant for threatening information is well-known in the clinical literature on fear and anxiety (Eysenck 1992; Pincus and Morley 2001). In contrast with the view of Chapman (1978), hypervigilance to threat is not restricted to one particular attentional mechanism, i.e. scanning. It is therefore reasonable to assume that hypervigilance to pain and somatic sensations may also become manifest in a variety of ways. The following example may clarify these different components: Imagine a person, afraid of back pain and (re)injury during movements, who has to resume a backstraining job after a period of pain-related work absence. The thought of going back to work will be sufficient to make him fearful. This thought may make him distracted by several irrelevant stimuli in the environment (▶ distractibility). From the moment he starts with some backstraining activities at work, he may begin to scan his body for pain or for other potential signals of bodily harm (▶ scanning). This may result in the rapid detection of any bodily sensation in his back. Attention will be drawn automatically to any change in back sensations (▶ attentional bias), and once it is detected, the person may experience difficulties disengaging attention from these somatic sensations and to re-engage attention towards his work (difficulty disengaging attention).

There are a number of promising paradigms that allow these various components of hypervigilance to pain to be disentangled (Van Damme et al. 2002; Spence et al. 2002). Studies have begun to investigate the critical role of these components in hypervigilance to pain. Results suggest that the rapid detection of pain or signals of pain is not critically dependent upon the presence of pain (attentional bias). The introduction of any somatosensory stimulus – painful or non-painful – introduces a rapid shift of attention towards that stimulus.
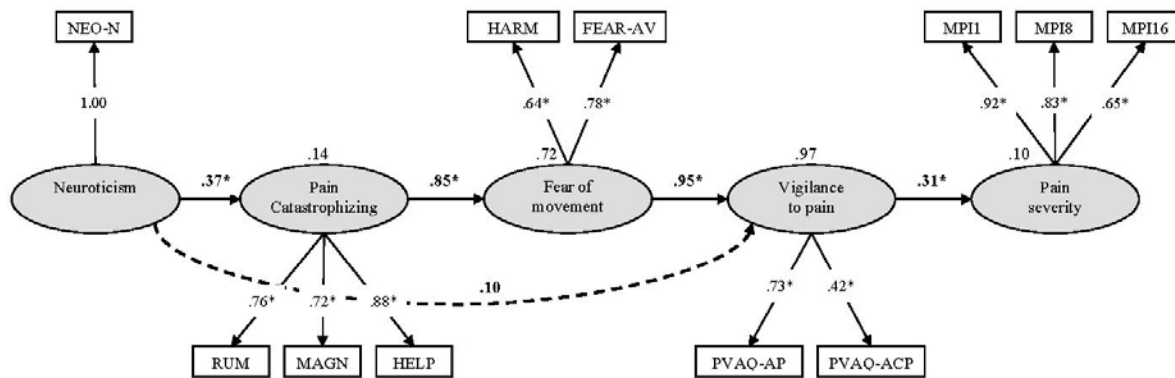
Hypervigilance and Attention to Pain, Figure 1 Psychology of Pain, hypervigilance and attention to pain.

Of more importance seems to be the effect of threat upon the difficulty disengaging from pain. Once pain or signals for pain have been detected, there is a difficulty disengaging from that threatening information. The difficulty is even more pronounced for those who catastrophize about pain (Van Damme et al. 2004a). Our understanding of hypervigilance has a number of implications. First, hypervigilance may be one mechanism by which pain-related fear may fuel avoidance. Patients with ► kinesiophobia are also hypervigilant for pain and possible signals of impending pain. Their attention dwells more on somatic sensations and will easily promote ► avoidance behaviour (Vlaeyen and Linton 2000). Second, hypervigilance to pain and somatic sensations will result in the more frequent reporting of symptoms. Third, as research shows that a high threat value of pain results in difficulty disengaging from pain and pain signals, cognitive interference will occur. Fourth, as hypervigilance seems to be mediated by the threat value of pain, distraction is probably not an effective treatment technique in patients with a high level of catastrophic thinking about pain. This was confirmed in the study by Hadjistavropoulos et al. (2000), who found that distraction was not effective in chronic pain patients with a high level of health anxiety.

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Hypesthesia

Definition

Hypesthesia is a decreased sensation to stimuli.
► Hypoesthesia, Assessment
► Viral Neuropathies

Hypnic Alarm Clock Headache Syndrome

► Hypnic Headache

Hypnic Headache

James W. Lance
Institute of Neurological Sciences, Prince of Wales
Hospital and University of New South Wales, Sydney,
NSW, Australia
jimlance@bigpond.com

Synonym

Hypnic Alarm Clock Headache Syndrome

Definition

Headache awakening the subject from sleep, not occurring during waking hours, usually lasting less than 180 min and not associated with autonomic features.

Characteristics

The headache is unilateral in about 40% of patients but is bilateral in the remainder. It usually develops after the age of 50 years, recurs more than fifteen times a month and is not severe but persists for more than 15 min after waking. It may be accompanied by nausea, photophobia or phonophobia, but not all three of these migrainous features. The bilateral site, mild intensity and the lack of autonomic features distinguish it from cluster headache. It usually responds to the administration of caffeine or lithium taken on retiring to bed.

Clinical Reports and Pathophysiology

Raskin (1988) first drew attention to this uncommon syndrome. He reported six patients, five of whom were male, all aged 60 years or more who were waking up consistently with generalised headaches that persisted for 30–60 min. Two volunteered that they were always woken from a dream by these headaches. Three patients reported accompanying nausea. The headaches were not alleviated by amitriptyline or propranolol but responded to lithium 300 mg or propranolol 600 mg at night. Raskin attributed the condition to a disorder of the brain's "▶ biological clock" in the hypothalamus, pointing out that cluster headache, cyclical migraine and manic-depression disorder were also tied to bodily rhythms and responded to lithium.

Ten of the nineteen patients described by Dodick et al. (1998) were awakened by headache at a consistent time, usually between 1.00 am and 3.00 am, giving rise to the term "alarm clock" headache. Three patients had infrequent but identical headaches during daytime naps. One described the headaches as developing during vivid dreams. Three patients mentioned infrequent nausea. It is not clear why one patient who had a severe unilateral headache with ipsilateral lacrimation and rhinorrhea was included in this series and not classified as cluster headache. An additional link with dreaming was provided by one of the three patients described by Morales-Asin at al. (1998).

In attempts to clarify this question, ▶ polysomnography has been carried out successfully in recording the onset of hypnic headache in six patients. Dodick (2000) found that an episode started during ▶ rapid eye movement (REM) sleep at a time of severe oxygen desaturation. Evers et al. (2003) reported two patients with onset during REM sleep, one of whom had periodic limb movements throughout the night. Oxygen desaturation did not exceed 85% at any time. Pinessi et al. (2003) recorded four hypnic headaches in two patients, all emerging from the REM phase of sleep without any oxygen desaturation. These authors pointed out that a patient reported by Arjona et al (2000) as being aroused by hypnic headache in stage 3 slow wave sleep, was being treated with venlafaxine, which may have altered her sleep pattern.

Cells that switch REM sleep cells off are found in the locus coeruleus and dorsal raphe nucleus and discharge regularly during waking hours, ceasing during REM sleep. Their action depends on noradrenergic and serotonergic transmission respectively. Since pathways from these areas form part of the body's endogenous pain control system their switching off could account for the onset of pain with REM sleep. (Dodick et al. 2003; Pinessi et al. 2003) The sleep-wake cycle is controlled by the suprachiasmatic nucleus of the hypothalamus and reduced ▶ melatonin secretion is thought to play a part in the initiation of hypnic headache.

Martins and Gouveia (2001) reported the case of a patient in remission for 10 months after lithium therapy who flew from Portugal to Brazil over three time zones. Her hypnic headaches recurred each night for 10 days while away but ceased on her return.

Summary

Evers and Goadsby (2003) have reviewed the seventy-one cases of hypnic headache reported in the literature to date. There were twenty-four men and forty-one women ranging in age from 26 to 83 years. The headache was bilateral in 61% and unilateral in 39%. It varied in frequency from one each week to six per night. It usually started 2–4 h after falling asleep, was moderate in intensity and persisted for 15 min to 3 h.

Nausea was reported by 19.4%. Mild photophobia, phonophobia or both were experienced by 6.8%. Some autonomic features such as lacrimation were recorded in six patients, two of whom developed ptosis. No relevant abnormality was found on CT, MRI, EEG or carotid Doppler ultrasound studies.

Evers and Goadsby (2003) summarised the response to treatment in reported cases. Good results were achieved by lithium in 26 / 35 patients; caffeine in 6 / 16, indomethacin in 7 / 18, flunarizine in 4 / 5, melatonin in 3 / 7 and prednisone in the only two patients in whom it had been tried (Relja et al. 2002).

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Hypnosis

Definition

A process of focusing attention that typically produces deep relaxation and openness to verbal suggestions; it can be performed on oneself or by others by using a combination of relaxation and intensive guided imagery techniques. The resulting altered state of consciousness is known as a trance. Hypnosis is widely used in both adults and children, and is broadly effective in the management of chronic and acute pain, especially cancer pain.

▶ Complex Chronic Pain in Children, Interdisciplinary Treatment
▶ Coping and Pain
▶ Hypnotic Analgesia
▶ Psychological Treatment in Acute Pain
▶ Relaxation in the Treatment of Pain

Hypnotherapy

▶ Therapy of Pain, Hypnosis

Hypnotic Analgesia

DONALD D. PRICE[1], PIERRE RAINVILLE[2]
[1]Oral Surgery and Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL, USA
[2]Department of Stomatology, University of Montreal, Montreal, QC, Canada
dprice@dental.ufl.edu, pierre.rainville@umontreal.ca

Definition

Psychological factors and interventions can sometimes powerfully modulate pain, and there is an emerging neurobiology of pain-modulatory mechanisms. Central neural mechanisms associated with such phenomena as placebo/nocebo, hypnotic suggestion (see ▶ Post-Hypnotic Suggestion), attention, distraction and even ongoing emotions are now thought to modulate pain by decreasing or increasing neural activity within many of the brain structures shown in Figure 1 (Rainville 2002). This modulation includes endogenous pain-inhibitory and pain-facilitation pathways that descend to spinal dorsal horn, the origin of ascending spinal pathways for pain as well as modulation, which takes place within cortico-limbic circuits once nociceptive information has reached cortical levels (De Pascalis 2001; Fields and Price; Hofbauer 2001; Porro et al. 2002; Rainville 2002). Hypnotically induced reduction in pain is based on changes in pain induced by suggestions and facilitated by an alteration of consciousness (Hilgard and Hilgard 1983; Price and Barrell 1990; Rainville and Price 2003). This alteration is accompanied by changes in brain activity involved in the regulation of consciousness (Rainville and Price 2003). Hypnotic changes in pain experience can consist of selective changes in the ▶ affective dimension (component) of pain, or reductions in both sensory and affective dimensions depending on the nature of the suggestions. Changes in affective and sensory components of pain are associated with corresponding changes in anterior cingulate cortical activity and somatosensory cortical activity respectively (Rainville and Price 2003; Rainville 2002). Different hypnotic analgesic approaches are clinically useful.

Characteristics

What are the Types of Hypnotic Suggestions for Analgesia

The suggestions for alteration of the experience of pain in studies of hypnotic analgesia, relate closely to the dimensions of pain and to the psychological stages of pain processing. Thus, there are suggestions that specifically target the affective-motivational dimension of pain, as distinguished from the ▶ sensory-discriminative dimension (Rainville et al. 1999). These would include suggestions for reinterpreting sensations as neutral or pleasant rather than unpleasant, as well as suggestions for reducing or eliminating the implications of threat or harm from the sensations. Then there are suggestions designed for specifically altering the quality and/or intensity of painful sensations so that they become less intense or absent altogether. There are three very different types of hypnotic suggestions for altering pain sensation in-
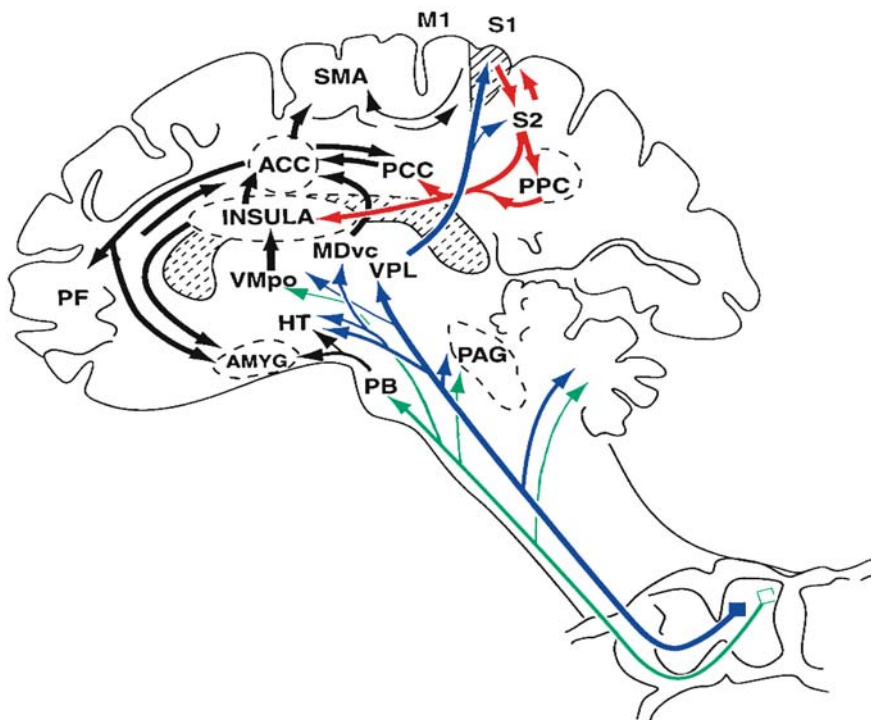
Hypnotic Analgesia, Figure 1 Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing pain. PAG, periaqueductal grey; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of the posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; HY, hypothalamus; S-1 and S-2, first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex (Figure from Price, Science (2001)).

tensity (De Pascalis et al. 1999; De Pascalis 2001). One type provides ▶ dissociative imagery by suggesting experiences that are disconnected from the felt sense of the body. An example would be a suggestion to imagine oneself "floating out of the body and up in the air" combined with the implicit or explicit suggestion that the pain belongs to the body and not to the one who experiences being somewhere else. Common to suggestions for dissociation, is the intention of having subjects not feel parts of their bodies that would otherwise be painful, and/or experience themselves in another location and context altogether. Another type is ▶ focused analgesia, which is intended to replace sensations of pain with others, such as numbness or warmth or with the complete absence of sensation. In complete contrast to dissociative analgesia, focused analgesia requires increased attention to the body area wherein pain is present, combined with a replaced sensation in that body area. For example, focused analgesia might include suggestions to focus on sensations in the hand, and to experience all sensations of the hand *as* if it were in a large glove. A third type of suggestion involves the reinterpretation of the meaning of the sensory experience. In this case, the significance of the experience for the integrity of the body is reduced or completely abolished, so that pain sensations are no longer associated with feelings of threat. Just as studies are needed to assess the role of hypnotic depth and individual components of hypnosis on pain, so there also need to be studies of differential effects of various types of suggestion on sensory and affective dimensions of pain experience. For example, what are the effects on pain of suggestions exclusively designed to reinterpret the meanings of the sensations so that they are less threatening or unpleasant?

Which Types of Hypnotic Suggestions are Most Effective in Producing Analgesia

Very few hypnotic analgesia studies have directly compared effects from the different types of hypnotic suggestions described above. However, De Pascalis et al. conducted studies that compared analgesic effects produced by experimental conditions of Deep Relaxation, Dissociated Imagery, Focused Analgesia, and Placebo in comparison to a Waking Control condition (De Pascalis et al. 1999; De Pascalis 2001). They compared these conditions across groups of high, medium, and low hypnotizable participants, and utilized several dependent pain-related measures. These included pain and distress ratings, pain threshold determinations, somatosensory event-related potentials (SERP), heart rate, and skin conductance responses (SCR). The experimental stimuli consisted of non-painful and painful levels of electrical pulses delivered to the right wrist.

Of the four experimental conditions, Deep Relaxation, Dissociated Imagery, and Focused Analgesia produced statistically significant reductions on all pain-related measures among all three groups of participants (i.e. low, mid-, high). However, these analgesic effects interacted with ▶ hypnotizability, as shown in Figure 2. During Focused Analgesia, highly hypnotizable participants had larger reductions in pain ratings in comparison to low and medium hypnotizable participants. Further-
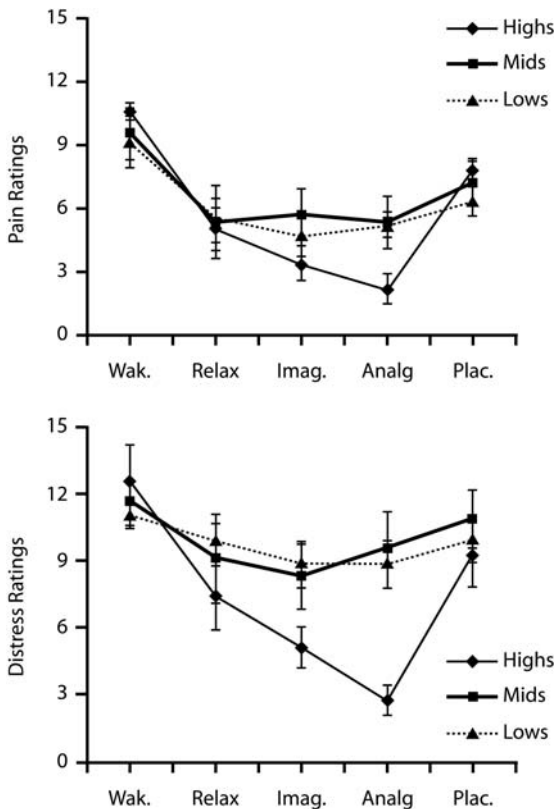
Hypnotic Analgesia, Figure 2 Pain sensory and distress ratings in response to noxious electrical stimulation delivered to the wrist in normal subjects with high (Highs), moderate (Mids), or low (Lows) hypnotic susceptibility. Both pain sensory and distress ratings decrease significantly in response to hypnotic suggestions for relaxation (Relax), dissociative imagery (Imag.), and focused analgesia (Analg), compared to the baseline wakefulness (Wak.) and placebo (Plac.) conditions. Larger pain reductions are observed in more susceptible subjects (Highs) and during focused analgesia. Also, note that there is no significant placebo analgesia observed for all three groups. (De Pascalis et al. 2001).

more, highly susceptible subjects had more pronounced reductions in distress ratings during Focused Analgesia and Dissociated Imagery, in comparison to the other two groups. Focused Analgesia produced the largest reductions in all dependent measures within highly hypnotizable participants. No significant placebo effects were obtained for any of the three groups. The combination of these results indicates several interesting features of hypnotic analgesia. First, hypnotic analgesia cannot simply be understood as a placebo effect and is more than just relaxation. Second, very different types of suggestions for analgesia are effective and are facilitated by hypnotizability. Third, hypnotic analgesia can affect physiological reflexive responses associated with pain (Hilgard and Hilgard 1983; Rainville 2002). Each of the types of hypnotic suggestion discussed so far can be given directly or indirectly. A ► direct suggestion for analgesia would be "You will notice that the pain is less intense. ..." whereas an ► indirect suggestion would be "I wonder if you will notice whether the

sensation you once experienced as painful will be experienced as just warmth or pressure or perhaps even numbness. ... " The latter is permissive, ambiguous, and refers to alternative experiences without the implication of a direct instruction. Resistance to hypnotic suggestions may be less in the case of permissive-indirect as compared to restrictive-direct suggestions, because one is not directly told what to experience. Furthermore, restrictive-direct suggestions may be perceived as unnecessarily authoritarian. One might expect that a larger proportion of people could benefit from a hypnotic approach that uses indirect suggestions and there is some, albeit limited, evidence that this is so (Price and Barber 1987; Price and Barrell 1990).

What are the Factors that Determine the Efficacy of Hypnotic Analgesia

The efficacy of hypnotic analgesia and its relationship to hypnotic susceptibility has been shown to depend on several factors (Price and Barber 1987). These include the pain dimension that is measured, baseline pain intensity, the maintained presence of the hypnotist or hypnotic suggestions, and finally hypnotic ability. Some of these factors are shown in Table 1. When suggestions were given for both reinterpreting the meaning of experimentally induced heat sensations and for experiencing them as less intense, pain sensation intensity was reduced by an average of about 50 percent, and pain unpleasantness was reduced by 87 percent in a group of sixteen subjects. Thus, pain affect was more powerfully attenuated in comparison to pain sensation. Although hypnotic suggestions exerted a more powerful reduction of pain affect than pain sensation, it was also quite apparent that both dimensions were reduced, as has been amply demonstrated in several experimental laboratories (Barber and Mayer 1977; De Pascalis et al. 1999; De Pascalis 2001; Rainville et al. 1999; Rainville 2002). Reduction in pain sensation was statistically associated with hypnotic susceptibility, albeit at modest levels (Tab. 1). Therefore, the component of the hypnotic intervention that relied on hypnotic ability and a hypnotic state was the one most influential on pain sensation intensity. Interestingly, the association became stronger with increasing levels of pain intensity (Tab. 1). It makes sense that the reduction

Hypnotic Analgesia, Table 1 Hypnotic Susceptibility and Analgesia

| Stimulus Temperature	Sensory Analgesia Spearman Correlation Coefficient	Affective Analgesia
44.5^o C	+0.04	-0.23
47.5^o C	+0.21	-0.11
49.5^o C	+0.43*	-0.08
51.5^o C	+0.56*	+0.10

*$P < 0.05$

in stronger pains requires more hypnotic ability than the reduction in weaker pains. A final factor was maintained contact between the hypnotist and the subject. Statistically significant analgesia developed in one group of subjects that had maintained contact with the hypnotist during the pain testing session, and did not develop in the group that did not have maintained contact. Thus, multiple factors are involved in analgesia that results from a hypnotic intervention. These may include those that are unrelated to hypnotic susceptibility and perhaps even to a hypnotic state. Such potential multiple factors are closely related to different proposed mechanisms of hypnotic analgesia.

Rainville et al. further clarified the relationship between different types of hypnotic suggestions for analgesia, and the dimensions of pain that are modulated by these suggestions (Rainville et al. 1999). This study conducted two types of experiments, one in which hypnotic suggestions were selectively targeted toward increasing or decreasing the sensory intensity of pain, and the other in which hypnotic suggestions were targeted toward decreasing or increasing the affective dimension of pain. In both types of experiments, normal subjects who were trained in hypnosis, rated pain intensity and pain unpleasantness produced by a tonic heat pain test (^{1}min immersion of the hand in 45.0–47.5° C water). The results of the two experiments are illustrated in Figure 3.

In the first experiment, suggestions to modulate pain sensation intensity resulted in significant changes in both pain sensation intensity ratings and pain unpleasantness ratings, that is, both dimensions were modulated in parallel. This was so, despite the fact that no suggestions were given about pain affect. In the second experiment, pain unpleasantness was significantly increased and decreased after suggestions were given for these changes, and these changes occurred without corresponding changes in pain sensation intensity. Hypnotic susceptibility (Stanford Hypnotic Susceptibility Scale Form A) was specifically associated with pain sensation intensity modulation in the first experiment (directed toward pain sensation; Spearman-r = 0.69), and with pain unpleasantness modulation in the second experiment (directed toward pain affect; Spearman-r = 0.43).

Thus, hypnotic changes in pain experience can consist of selective changes in the affective dimension of pain or reductions in both sensory and affective dimensions, depending on the nature of the suggestions. Selective changes in only affective components of pain are associated with corresponding changes in anterior cingulate cortical activity, and changes in sensory components are accompanied by corresponding changes in somatosensory cortical activity (Hofbauer 2001; Rainville 2002). Reinterpretation of meanings of pain, dissociation, and focused analgesia reflect different psychological mechanisms of hypnotic analgesia. These multiple mecha-
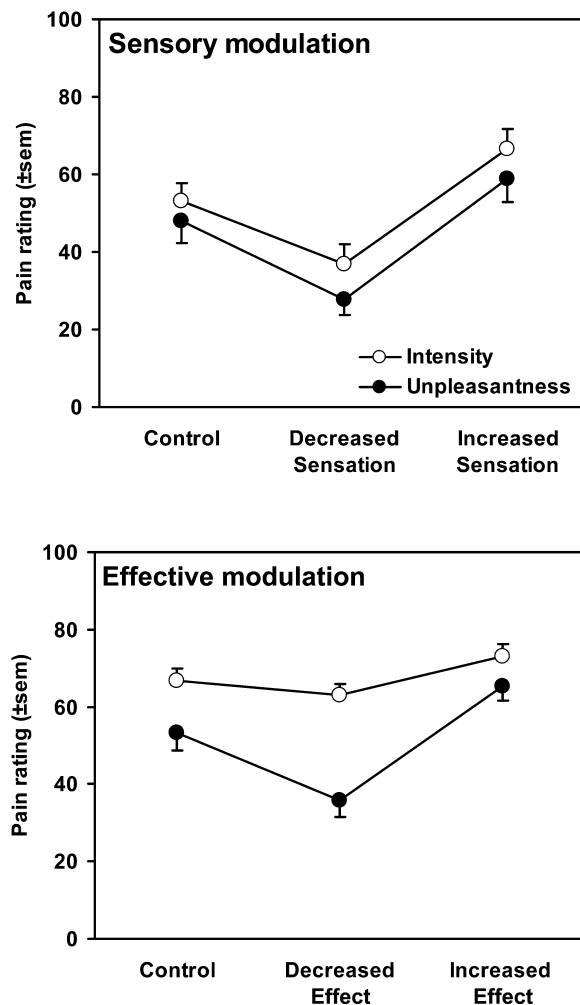
Hypnotic Analgesia, Figure 3 Self-reports of the pain experienced during the immersion of the hand in hot water following hypnotic suggestions directed at the sensory and affective dimension of pain. Suggestions directed at the sensory aspect of pain (Sensory modulation) produce parallel changes in self-reports of pain sensation intensity and unpleasantness. In contrast, suggestions for the reinterpretation of pain with decreased and increased sense of threat and discomfort (Affective modulation) produce specific changes in pain unpleasantness that largely exceed the changes in pain sensation intensity. (Rainville et al. 1999)

nisms are likely to be associated with intracortical and descending brain-to-spinal cord mechanisms, to varying extents. Although there is some evidence that hypnotic analgesia has demonstrable clinical efficacy, there is a strong need for improvements in methodologies of clinical studies. In particular, there is a need to compare the efficacy of different hypnotic approaches and provide rigorous standardized outcome measures.

It is useful to consider how results of experiments by De Pascalis et al. (De Pascalis et al. 1999; De Pascalis 2001) and Rainville et al. (Rainville et al. 1999; Rainville 2002), described above, help identify the necessary and sufficient psychological factors for hypnotic analgesia. Hypnotic analgesia cannot work only by means of dis-

traction, because suggestions for Focused Analgesia are among the most effective, particularly among highly hypnotizable participants. Focused Analgesia requires greater not lesser attention to the body area wherein analgesia develops. Hypnotically induced changes in pain affect can occur directly through suggestions that alter the meaning of the experience of the stimulus, or indirectly through suggestions that target the pain sensation. Hypnotic changes in the latter can also occur through suggestions for dissociation or through suggestions for changes in the way the sensory qualities are experienced (e. g. numbness versus burning). Hypnotic analgesia cannot only work by means of a placebo effect, because subjects are likely to experience placebo and hypnotic suggestions differently. Moreover, there is now good evidence that ▶ placebo analgesia, but not hypnotic analgesia, requires an endogenous opioid pain-inhibitory mechanism. Placebo analgesia is naloxone reversible in studies of experimental pain, whereas several studies have shown than hypnotic analgesia is not naloxone reversible (Barber and Mayer 1977; Goldstein and Hilgard 1975). Finally, placebo analgesia, unlike hypnotic analgesia, is not significantly associated with hypnotic susceptibility (Hilgard and Hilgard 1983).

Conclusions

The combination of anatomical, psychological, and neurophysiological approaches to understanding the brain mechanisms underlying sensory and affective dimensions of pain and its modulation by psychological interventions, such as hypnotic suggestions, has led to a vastly improved ability to answer questions that only 10 years ago were relatively impenetrable. In particular, studies that combine brain imaging with psychophysical methods and sophisticated experimental designs, have led to the possibility of understanding complex mechanisms by which sensory and affective dimensions of pain are interrelated, and how these dimensions can be modulated by cognitive factors. The brain networks for these mechanisms are extensive and involve both serial and parallel circuitry, which is itself under dynamic control from several brain regions.

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H

Hypnotic Relaxation

▶ Relaxation in the Treatment of Pain

Hypnotism

▶ Therapy of Pain, Hypnosis

Hypnotizability

Definition

Hypnotic susceptibility, hypnotic capacity or hypnotic responding delineates a variable that determines the extent to which an individual is able to respond to hypnotic suggestion. Research has shown that hypnotizability can be measured with good reliability and is a remarkably stable trait in adults. It correlates with dissociative experiences and with measures of absorption. Highly hypnotizable individuals tend to have a high imaginative capacity.

▶ Hypnotic Analgesia
▶ Therapy of Pain, Hypnosis

Hypoaesthesia

Definition

Hypoaesthesia is a decreased sensitivity to stimulation, excluding special senses.

Hypoalgesia, Assessment

MISHA-MIROSLAV BACKONJA
Department of Neurology; University of Wisconsin-Madison, Madison, WI, USA
backonja@neurology.wisc.edu

Synonyms

Hypalgia; Assessment of Hypoalgesia

Definition

IASP Taxonomy (Merskey and Bogduk 1994) defines hypoalgesia as "decreased perception of noxious stimuli." Hypoalgesia could be in response to a wide variety of mechanical stimuli such as pinch, strong pressure or punctuate and to thermal noxious stimuli of heat and cold, basically any physical force of sufficient intensity to disrupt or threaten the integrity or homeostasis of any tissue.

In other terms, hypoalgesia is diminished experience of pain in response to a normally painful stimulus. Hypoesthesia covers the case of diminished sensitivity to stimulation that is normally not painful.

Hypoalgesia is also defined as raised threshold to painful stimuli.

Characteristics

Hypoalgesia is a ► negative sensory phenomenon seen exclusively in patients with neurological disease or injury, including patients with ► neuropathic pain (Backonja and Galer 1998; Lindblom and Ochoa 1986; Backonja 2003). Hypoalgesia indicates a decrease or loss of function that comes as a result of neurological disease or injury affecting thermonociceptive pathways, anywhere from primary afferents to cerebral cortical structures. Distinction of hypoalgesia from hypoesthesia is based primarily on the type and intensity of the stimulus applied to the thermonociceptive sensory system.

Methods of Assessment and the Interpretation

Assessment of the sensory nervous system function is most commonly done at the bedside where testing is primarily qualitative in nature, while quantitative assessment, increasingly using computerized electronic equipment, is done in a quantitative sensory laboratory (Backonja and Galer 1998; Greenspan 2001). Either should be able to detect hypoalgesia, but the way these methods arrive to the conclusion about presence and severity of hypoalgesia is distinct, and that is also reflected in the

definition. Qualitative bedside exam relies on patient report. Quantitative sensory testing arrives at its conclusion about hypoalgesia on the basis of the raised thresholds to painful stimuli.

Qualitative assessment is based on the subject's ability to compare and report quality of sensation from standard methods of stimulation, from the ► symptom affected areas, when it is compared to normal unaffected areas. Qualitative method is very convenient for bedside evaluations. Frequently utilized bedside methods include standard neurological examination tools such as safety pin, monofilament, and various metal objects that could be conveniently warmed or cooled in the clinical setting. A degree of quantification is possible, and requires that the subject reports whether a decrease of pain from painful stimulation is mild, moderate, severe or completely absent, when compared to a normal unaffected area. Since a qualitative method requires psychophysical interaction, this method can be used only in humans who can linguistically communicate with the examiner, and as such it cannot be used in animal models of pain studies.

Quantitative assessment of sensory deficits requires a more sophisticated approach and frequently utilizes electronically controlled devices, although a number of psychophysical methods, especially mechanical stimuli, are used and all of them place much longer time demands on patients. Traditionally this method is known as quantitative sensory testing (QST). The primary outcome of QST is determination of thresholds for specific modalities which are then compared to the established norms (Greenspan 2001; Goetz et al. 2005). Increase in threshold to painful stimuli is then interpreted as hypoalgesia. QST methods could be used not only in human studies but also in animal models.

One of the main goals of neurological evaluation is to determine the site and level of ► neuraxis where pathological processes that produce symptoms, including pain, originate (Dyck and O'Brien 2003). In addition to establishing the nature of ► neurological deficit, such as hypoalgesia to a specific modality, it is important to establish a special pattern of these abnormalities, since the pattern serves as the basis for the determination whether the lesion that is causing symptoms, including pain, involve specific peripheral nerve structures, such as peripheral nerves, plexus or the nerve root, versus central nervous system structures such as spinal cord, brainstem, subcortical or cortical structures and pathways of the brain.

Caveats and Unresolved Issues

Difficulty of assessing hypoalgesia arises from the inherent difficulty of assessing negative sensory phenomenon. For example, conceptually it is easier to illustrate ► positive sensory phenomenon to subjects, such as pain with instruction that 0 = none, and 10 = worst imaginable. In contrast, it is much harder conceptually to illustrate and request a rating of spontaneous

loss of sensation because it is not possible to feel what one is not able to feel, in spite of the instruction that the patient is to imagine scaling between one end being a normal sensation and the other absence of sensation.

Another phenomenon that can result from painful stimulation and the one that is on the opposite end of the spectrum of sensory experience is ► hyperalgesia. The difficulty of assessing sensory abnormalities which are characterized by hypoalgesia to one sensory modality and hyperalgesia to another sensory modality in the same area frequently seen in patients with neuropathic pain leads to confusion not only for patients but also for inexperienced clinicians Depending on the way stimulation is conducted even when hypoalgesia is present, the outcome can be either hyperalgesia or hyperpathia. For example, in the case of partial hypoalgesia and when the stimulus is "strong enough" the outcome could be hyperalgesia, and in the case that stimulus is not "strong enough" with temporal and special summation that could result in increased pain, which would become hyperpathia. Consequently, from the pain mechanisms prospective, the relationship between hypoalgesia and hyperalgesia still far from clear. In summary, hypoalgesia is a ► clinical sign of neurological injury or disease, which in some patients can lead to neuropathic pain. Methods for determining the presence of hypoalgesia are qualitative, such as in bedside exam or quantitative, such as QST. Mechanisms of hypoalgesia for specific modalities, and in particular its relationship to hyperalgesia and hyperpathia, are poorly understood.

► Allodynia (Clinical, Experimental)
► Amygdala, Pain Processing and Behavior in Animals
► Cordotomy Effects on Humans and Animal Models
► Nerve Growth Factor Overexpressing Mice as Models of Inflammatory Pain
► Opioids, Effects of Systemic Morphine on Evoked Pain

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Hypochondriaca

Definition

Hypochondriaca refers to a persistent conviction that one is or is likely to become ill, when a patient complains of symptoms that have no organic basis. These symptoms persist despite reassurance and medical evidence to the contrary

► Psychiatric Aspects of Visceral Pain

Hypochondriasis

H

Definition

Hypochondriasis is a minimum six month preoccupation with fears of having a serious disease, based on misinterpretation of bodily symptoms (e.g. a sore throat is thought to be throat cancer), which persists in spite of medical evidence that the serious disease is not present.

► Somatization and Pain Disorders in Children

Hypochondriasis, Somatoform Disorders and Abnormal Illness Behaviour

ISSY PILOWSKY
Emeritus Professor of Psychiatry, University of Adelaide, Adelaide, SA, Australia
issyp@med.usyd.edu.au

Synonyms

Abnormal Illness Behaviour of the Unconsciously Motivated, Somatically Focussed Type; Discordant Illness Behaviour; Dysnosognosia; somatoform disorders

Definition

In the Fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (1994), Hypochondriasis is defined according to the following criteria:

- Because of misinterpreting bodily symptoms, the patient becomes preoccupied with ideas or fears of having a serious illness.
- Appropriate medical investigation and reassurance do not relieve these ideas.
- These ideas are not delusional (as in Delusional Disorder) and are not restricted to concern about appearance (as in Body Dysmorphic Disorder).
- They cause distress that is clinically important or impair work, social or personal functioning.
- They have lasted 6 months or longer.

- These ideas are better explained by Generalized Anxiety Disorder, Major Depressive Episode, Obsessive-Compulsive Disorder, Panic Disorder, Separation Anxiety or a different Somatoform Disorder.

Specify when with poor insight: During most of this episode, the patient does not realize that the preoccupation is excessive or unreasonable.

It is of interest to compare this development with the earlier criteria for the diagnosis of hypochondriasis as listed in DSM–IIIR (the revised edition of DSM–III).

They are as follows:

a) Preoccupation with the fear of having, or the belief that one has, a serious disease, based on the person's interpretation of physical signs or sensations as evidence of physical illness.
b) Appropriate physical evaluation does not support the diagnosis of any physical disorder that can account for the physical signs or the person's unwarranted interpretation of them, and the symptoms in 'A' are not just those of panic attacks.
c) The fear of having or belief that one has a disease persists despite medical reassurance.
d) Duration of the disturbance is at least six months.
e) The belief in A is not of delusional intensity, as in Delusional Disorder, Somatic Type (i.e. the person can acknowledge the possibility that the fear or the belief of having a serious illness is unfounded). [Comment: In which case the psychopathological phenomenon could be labelled an 'abnormal preoccupation' or an 'overvalued idea'.].

Characteristics

Hypochondriasis is regarded as one of the Somatoform Disorders in both the DSM IV, and the tenth edition of the WHO Classification of Mental and Behavioural Disorders: (ICD–10): Clinical descriptions and diagnostic guidelines.

The Somatoform disorders are defined in DSM IV as essentially the presence of physical symptoms for which there are no demonstrable organic findings or known physiological mechanisms'.

In both DSM–IV and ICD–10, a significant departure is made from the principle of classifying on the basis of phenomenological description only. Thus, in DSM–IV we find the inclusion of the statement that 'the symptoms are linked to psychological factors or conflicts'.

Illness, the Sick role, illness behaviour and abnormal illness behaviour. (Pilowsky 1969, 1978, 1997).

Illness is defined as any state of an organism which fulfils the requirements of a relevant reference group for admission to a sick role.

The Sick Role

As delineated by the sociologist Talcott Parsons (1964, 1978), the sick role is a partially and conditionally granted social role. The individual seeking this role is required to fulfil three obligations. These are: a) accept that the role is "undesirable"; one which should be relinquished a soon as possible; b) co-operate with others so as to achieve "health", and c) utilize the services of those regarded by society as competent to diagnose and treat the condition. (In technologically advanced societies, this person is usually a formally registered doctor who is granted the authority to sign 'sickness certificates')

If these obligations are met, the following privileges are granted: a) the person is regarded as not "responsible" for the condition (i.e. he cannot produce or terminate it by an act of will, and is not to be considered a malingerer); b) the person is regarded as someone requiring care, and c) is entitled to exemption from age appropriate normal obligations.

All of these definitions demonstrate how central the role of the doctor is (in Technologically advanced societies) when it comes to the allocation of healthcare resources. It also draws attention to the pressures on the Doctor-Patient relationship from without, and their inevitable interaction with interpersonal and intrapersonal forces.

Abnormal Illness Behaviour (AIB)

This is defined as: An inappropriate or maladaptive mode of experiencing, evaluating or acting in relation to one's own state of health, despite the fact that a doctor (or other recognized social agent) has offered accurate and reasonably lucid information concerning the person's health status and the appropriate course of management (if any), based on a thorough examination of all parameters of functioning (i.e. physical psychological and social) taking into account the individuals age, educational and socio-cultural background.

A detailed analysis of this definition is to be found in Pilowsky (1997).

Clinical Characteristics

Pain is a common feature of hypochondriacal disorders. Since the patient tends to reject the presence of psychological problems, such individuals are not encountered in psychiatric settings but rather in medical, surgical and, in the case of conversion disorders, in neurological clinics.

Another relevant somatoform disorder is 'conversion disorder', also known as 'Hysterical neurosis, conversion type' The difference between hypochondriasis and conversion, is that the latter is defined as manifesting 'a loss or alteration of physical functioning that suggests a physical disorder in the absence of physical signs on examination to support the presence of a physical disorder'. However 'psychological factors are judged to be aetiologically related, because of a temporal relationship between a psychosocial stressor that is apparently related to a psychological conflict or need, and initiation or exacerbation of the symptom.'

A feature often described in association with a conversion disorder is 'la belle indifference', which refers not simply to an absence of concern, but rather to a sort of positive serenity, clearly inappropriate to the apparent seriousness of the physical disability.

The condition named 'somatoform pain disorder' is described in virtually the same terms as conversion disorder, except for the statement that it is primarily characterised by: 'Pain which causes significant distress or impairment in functioning, which cannot be fully explained by a physician. It must be judged to be related to psychological factors and cannot be better explained by another disorder'.

Thus, the major difference between pain as a feature of hypochondriasis, and pain as a conversion symptom, is that in the former case there is concern and preoccupation as to what the pain may mean, in terms of specific illnesses such as cancer or heart disease; while in the latter the patient denies concern over any specific condition, but is rather troubled by the experience of pain as a cause of disability and suffering.

Management

The key to management is the establishment of an alliance with the patient. This issue is of particular salience, when the clinician is a psychologist or psychiatrist, has been discussed at length in Pilowsky (1997), because patients often consider a referral to such a person to mean that the referring doctor believes 'it is all in my mind'. By which is meant that they are being accused of malingering. Achieving an alliance is not possible unless the acceptance of the reality of the symptoms is clearly conveyed to the patient by the attention paid to the alleviation of discomfort, and prevention of further disability by appropriate supportive psychotherapeutic, physiotherapeutic and psychopharmacological (e.g. antidepressants in low doses), and if necessary by psychological methods such as cognitive-behavioural therapy. In theory, this should be easiest at the initial presentation to the first doctor who sees the patient, especially as this is usually a non-psychiatrist, and most often a family doctor who should, ideally, be well acquainted with the patient and his circumstances, as well as, hopefully, his family.

How this doctor might manage the situation has been described and researched by Goldberg et al. (1989). They have developed a methodology whereby the doctor can help the patient to reattribute the physical symptoms to psychological causes. Once this has been achieved, it is reasonable to proceed with a problem-solving approach to any of the difficulties the patient is invariably experiencing in his life (Rost and Smith 1990; Wilkinson and Mynors-Wallis 1994; Scicchitano 20000) .When a multi-modal approach is necessary, this is generally best provided by a multidisciplinary pain clinic, when it is available.

Some Pain Clinics have in-patient facilities with well trained experienced staff that are able to provide programmes for patients manifesting severe invalidism and perhaps dependence on drugs such as opiates.

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Hypoesthesia, Assessment

MISHA-MIROSLAV BACKONJA
Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA
backonja@neurology.wisc.edu

Synonyms

Hypesthesia; hypoaesthesia

Definition

Hypoesthesia refers to decreased perception of innocuous stimuli, a condition where the body is much less sensitive than normal to stimulation that by its nature and intensity does not produce pain. Special senses are excluded (Merskey and Bogduk 1994). Hypoesthesia refers to diminished perception of a large range of mechanical stimuli such as touch, brush, pressure and vibration and thermally innocuous stimuli of warm and cold. Stimulation and locus are specified. Hypoesthesia is also defined as a raised threshold to nonpainful stimuli and this definition is used as a criterion for hypoesthesia during quantitative sensory testing (QST). There are two phenomena that are the opposite of hypoesthesia, hyperesthesia and allodynia. Hyperesthesia is increased

but not painful sensation from innocuous stimulation and allodynia is pain from innocuous stimulation. If stimulation is of nature or intensity to produce tissue damage and the subject perceives it as harmless, then the phenomenon is defined as hypoalgesia.

Characteristics

Hypoesthesia is a ▶ negative sensory phenomenon seen primarily in patients with neurological disease or injury, including patients with ▶ neuropathic pain (Lindblom and Ochoa 1986; Backonja and Galer 1998; Backonja 2003). Hypoesthesia indicates decrease or loss of function that arises as a result of neurological disease or injury affecting somatic sensory and thermal pathways, anywhere from primary afferents to cerebral cortical structures. Hypoesthesia is demonstrated by means of sensory examination during which standard methods of mechanical and thermal stimulus are applied with the goal of activating specific classes of receptors. The specificity of somatic sensory pathways in conducting particular somatic sensations is significantly altered by disease and injury of the ▶ somatosensory nervous system and hypoesthesia is probably the most sensitive and reliable indication of such injury. In contrast, positive sensory phenomena, such as allodynia and ▶ hyperalgesia, are relatively frequent components of neuropathic pain; the complexity of underlying mechanisms makes them much more difficult to interpret. Understanding the relationship between injury of the somatosensory neural structures and its manifestations, such as hypoesthesia is relevant to pain mechanisms, because methods of testing and interpretations are based on the specificity of sensory modalities. Distinction of hypoesthesia from hypoalgesia is based primarily on the type and intensity of the stimulus applied to the thermonociceptive sensory system.

Methods of Assessment and Interpretation

Assessment of sensory nervous system function is most commonly done at the bedside and under these circumstances the testing is primarily qualitative in nature. Quantitative assessment increasingly utilizes computerized electronic equipment in the environment of a quantitative sensory laboratory (Backonja and Galer 1998; Greenspan 2001). Either approach should be able to detect hypoesthesia, but the ways in which these methods arrive at conclusions about the presence and severity of hypoesthesia are distinctly different and this distinction is also reflected in the definitions stated earlier. Qualitative bedside examination of the presence of hypoesthesia is based primarily on patient report that a stimulus is perceived as decreased. Quantitative sensory testing arrives at conclusions about hypoesthesia on the basis of raised thresholds to painful stimuli. Qualitative somatosensory assessment is based on the subject's ability to compare and report quality of sensa-

tion resulting from standard methods of stimulation of affected areas compared to normal unaffected areas. The qualitative method is very convenient for bedside evaluations. Frequently utilized bedside methods include standard neurological examination tools such as cotton tips, monofilaments, tuning forks for testing of vibration and various metal objects that can conveniently be warmed or cooled in the clinical setting. A degree of quantification is possible and requires that the subject report whether the decrease in perceived sensation from applied stimuli is mild, moderate, severe or completely absent when compared to a normal unaffected area. Since the qualitative method requires psychophysical interaction, this method can only be used in humans who can communicate linguistically with the examiner and hence cannot be used in infants or aphasic subjects or in animal models in somatosensory and pain research.

Quantitative assessment of sensory deficits requires a more sophisticated approach and frequently utilizes electronically controlled devices, though a number of psychophysical methods especially mechanical stimuli are used. Traditionally this method is known as quantitative sensory testing (QST). All of the quantitative methods require much longer times for completion. The primary outcome of QST is determination of thresholds for specific modalities, which are then compared, to the established norms (Greenspan 2001). Increases in the threshold to innocuous stimuli are interpreted as hypoesthesia. The QST method can be used not only in human studies but also in animal models.

A crucial step in the interpretation of QST is to obtain a pain rating at the threshold. In spite of the fact that the pain threshold is increased, the presence or absence of positive sensory phenomena, one of them being ▶ hyperpathia (increased threshold but even innocuous stimuli are perceived as painful) and consequently presence of a painful neuropathic disorder (Getz Kelly 2004). The advantage of testing with innocuous stimuli and detecting hypoesthesia, especially for cold detection, is that it is one of the most sensitive methods of detecting somatic sensory deficits, which characterize neurological disorders, including neuropathic pain disorders (Dyck 2000).

One of the main goals of neurological evaluation is to determine the site and level of ▶ neuraxis where pathological processes that produce symptoms, including pain, originate (Dyck and O'Brien 2003). In addition to establishing the nature of the ▶ neurological deficit, such as hypoesthesia, to a specific modality, it is important to establish the special pattern of these abnormalities, since the pattern serves as the basis for the determination as to whether the lesion that is causing symptoms including pain, involves specific peripheral nerve structures, such as peripheral nerves, plexuses or nerve roots, or central nervous system structures such as spinal cord, brainstem, subcortical or cortical structures and pathways of the brain.

Caveats and Unresolved Issues

The difficulty of assessing hypoesthesia arises from the inherent difficulty of assessing a negative sensory phenomenon. For example, it is easier conceptually to illustrate to the subjects a ▶ positive sensory phenomenon, such as pain, with instructions that 0=none and 10=worst imaginable. In contrast, it is much harder conceptually to illustrate and request a rating of spontaneous loss of sensation, because it is not possible to feel what one is not able to feel, in spite of the instruction that the patient is to imagine scaling between normal sensation and absence of sensation.

Other phenomena that can result from innocuous stimulation and are on the opposite end of the spectrum of sensory experience are hyperesthesia, allodynia or even hyperpathia. Confusion for the examiner as well as for the patient is caused by the difficulty of assessment that comes from the fact that pain disorders, most frequently neuropathic pain, are characterized by allodynia or hyperalgesia to one sensory testing modality but are also found to have evidence of hypoesthesia to another testing modality in the same area. Depending on the way stimulation is conducted, even when hypoesthesia is present, the outcome can be hyperpathia in case of repeated stimulation. For example, in the case of partial hypoesthesia when the stimulus is in the way to lead to temporal and special summation could result in increased threshold but what is perceived is painful, which is then interpreted as hyperpathia. Consequently, from the pain mechanisms perspective, the relationship of hypoesthesia and hyperpathia still far from clear.

In summary, hypoesthesia is a sensitive clinical sign of neurological injury or disease, which in some patients can lead to neuropathic pain. Methods for determining the presence of hypoesthesia are qualitative, as in bedside examination or quantitative, as with QST. Mechanisms of hypoesthesia for specific modalities and its relationship to hyperpathia are still not well understood.

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Hypogastric Neurectomy

Definition

Hypogastric Neurectomy is a surgical resection of the hypogastric nerves.
▶ Visceral Pain Models, Female Reproductive Organ Pain

Hyponatremia

Definition

Hyponatremia represents less than normal levels of sodium ions, or salt, in the blood, which may result in cognitive impairment.
▶ Trigeminal Neuralgia, Diagnosis and Treatment

Hypophysectomy

Definition

Excision of the pituitary gland is known as hypophysectomy.
▶ Cancer Pain Management, Neurosurgical Interventions

Hypotension of Spinal Fluid

▶ Headache Due to Low Cerebrospinal Fluid Pressure

Hypothalamic Pituitary Axis

Definition

These organs combine with the gonads to play a critical role in the development and regulation of a number of the body's systems, such as the reproductive and immune systems.
▶ Fibromyalgia

Hypothalamus

Definition

The hypothalamus is a very prominent group of neurons located below the thalamus at the base of the brain forming the ventral-most part of the diencephalon. It is divided into three lateral levels (medial, intermediate and lateral) and five caudo-rostral levels (mammillary, posterior, intermediate, anterior, and preoptic). Its role

includes the neuroendocrine regulations (arcuate, paraventricular and supraoptic nuclei), autonomic regulations (cardio-respiratory, thermoregulation, metabolic, digestive) and processing of motivational behaviors like sexual, feeding, drinking, waking/sleep state, aggressiveness and illness feeling. It is also involved in modulating nociception.

▶ Descending Circuitry, Transmitters and Receptors
▶ Parabrachial Hypothalamic and Amydaloid Projections

Hypothalamus and Nociceptive Pathways

Jean-François Bernard
Faculté de Médecine Pitié-Salpêtrière, Institut National de la Santé et de la Recherche Médicale, INSERM U-677, Paris, France
jfbernar@ext.jussieu.fr

Definition

The hypothalamus is a complex structure that occupies the ventral half of the diencephalon below the thalamus on either side of the third ventricle. It lies just above the ▶ pituitary gland responsible for neuroendocrine secretions.

The hypothalamus includes about 40 nuclei of very different shapes and sizes. For simplification, it is generally divided into three medio-lateral zones, periventricular, medial and lateral and four caudo-rostral regions, mammillary, tuberal, anterior and preoptic. Combination of zones and regions permitted the recognition of twelve hypothalamic areas (Simerly 1995).

Neurosecretory neurons are mainly located within the periventricular zone with a particularly high density in the paraventricular nucleus. In addition, another important group of neurosecretory neurons is located in the supraoptic nucleus, a well-individualized nucleus located in the lateral region, on the lateral border of the optic chiasm. The neurosecretory system is subdivided into two parts, 1) magnocellular neurosecretory neurons (oxytocin and vasopressin), which directly innervate the posterior pituitary gland and 2) parvocellular neurosecretory neurons (corticotropin, gonadotropin, growth hormone, thyrotropin releasing hormones, somatostatin, angiotensin II and dopamine), which innervate the median eminence, the hypothalamic hormones being transported to the anterior pituitary gland *via* the hypophysial portal system (Swanson 1987).

The medial and lateral zones of the hypothalamus are chiefly devoted to the control of ▶ autonomic functions (cardiovascular, respiratory, blood fluid balance, energy metabolism, thermoregulatory and digestive) and major basic instinctive behaviors (feeding, drinking, reproductive, flight, defensive and aggressive) including the wakefulness-sleep cycles (Swanson 1987).

Characteristics

The hypothalamus is a fascinating region of the brain, which is much more than a control center for neuroendocrine secretion. Indeed, the hypothalamus is the upper center for autonomic functions and basic behaviors that assure the survival of both the individual and the species. It is easy to understand the role of the hypothalamus when it guarantees an adequate level of homeostasis for autonomic functions needed for survival. It is not so obvious to appreciate the importance of the myriad basic behaviors it generates. Thus, it is basically responsible for most of the motivations that govern our life, such as for example, hunger, the pleasures of eating and satiety, sexual desire, aggressiveness, fear, drowsiness, alertness and numerous other fundamental motivations of life. Considering these functions, it seems that the hypothalamus should play an important role in the autonomic and ▶ motivational components of pain. All the same, the precise role of hypothalamus in different components of pain remains unclear. The only clearly accepted function of the hypothalamus in pain is the neuroendocrine corticotropin response.

In humans, imagery studies indicate that the acute traumatic pain comes with a noticeable activation of the hypothalamus (Hsieh et al. 1996). However, these studies provide neither information about the activation of different hypothalamic nuclei nor data about the role of hypothalamus in pain. In fact until now, most evidence for an involvement of the hypothalamus in nociceptive processing comes from anatomical and c-fos data. Cross-checking these data with the known functions of hypothalamic nuclei, it becomes possible to make hypotheses about the involvement of the hypothalamus in pain.

Nociceptive Afferent Inputs to the Hypothalamus

The hypothalamus has three well-documented sources of nociceptive inputs, the spinal and trigeminal dorsal horn, the parabrachial area and the ventrolateral medulla (Fig. 1).

- Spinal and trigeminal inputs – a number of spinal and trigeminal neurons are labeled after a large injection of retrograde axonal tracer within the hypothalamus. Labeled neurons are located in superficial and, above all, in deep laminae of the dorsal horn i.e. in regions known to be involved in nociceptive processing. Electrophysiological studies indicate that most spino / trigemino-hypothalamic neurons respond to a variety of noxious stimuli (Burstein 1996). These data, which seem to indicate a major nociceptive input to the hypothalamus, are challenged by anterograde axonal tracing studies that show much lower spinal and trigeminal projection upon the hypothalamus (Gauriau and Bernard 2004). Comparative examination of all the studies seems to point
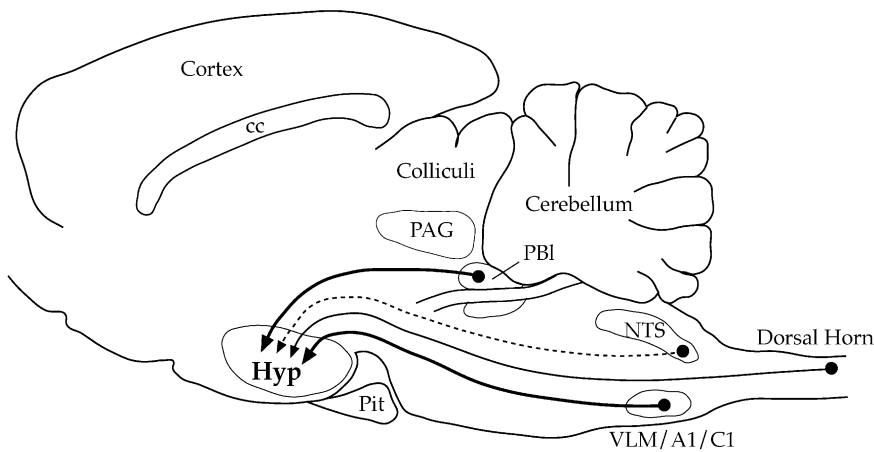
Hypothalamus and Nociceptive Pathways, Figure 1   Schematic representation, in sagittal sections, of the three main hypothalamic nociceptive inputs: the PBl, the VLM/A1/C1 region and the trigeminal and spinal dorsal horn (mainly the deep laminae). Thick line: extensive nociceptive projection; thin line: medium density nociceptive projection; dotted line: hypothetical nociceptive projection. Abbreviations: A1, A1 noradrenaline cells; C1, C1 adrenaline cells; cc, corpus callosum; Hyp, hypothalamus; NTS, nucleus tractus solitarii; PAG, periaqueductal gray matter; PBl, lateral division of the parabrachial nucleus; Pit, pituitary gland; VLM, ventrolateral medulla.

to at least a moderate but indisputable nociceptive projection, mainly to the lateral (Fig. 2) but also to the posterior and the paraventricular hypothalamic nuclei.

- Parabrachial inputs (see parabrachial hypothalamic and amygdaloid projections) – the lateral parabrachial area receives a heavy nociceptive input from spinal and trigeminal lamina I nociceptive neurons. The lateral parabrachial area projects heavily to the hypothalamic ventromedial nucleus and extensively to the retrochiasmatic, the median and the ventrolateral preoptic hypothalamus. Although less extensive, a notable projection reaches the dorsomedial, the periventricular, the paraventricular and the lateral nuclei (Fig. 2). Electrophysiological studies indicate that this strong afferent input to the hypothalamus from the parabrachial nucleus is primarily nociceptive (Bernard et al. 1996; Bester et al. 1997).
- Caudal ventrolateral medulla inputs – this reticular region includes the A1 / C1 catecholaminergic neurons and receives nociceptive inputs from both the superficial and the deep laminae of the dorsal horn. The caudal ventrolateral medulla projects extensively to the paraventricular nucleus and, to a lesser extent, to the periventricular, the supraoptic and the median preoptic hypothalamic nuclei (Fig. 2). Here again it was shown that this afferent input contains nociceptive neurons (Burstein 1996; Pan et al. 1999).

The nucleus of the solitary tract was also proposed as a nociceptive input for the hypothalamus. However, this nucleus is primarily a center for autonomic / visceral and gustatory information. The role and the importance of solitary tract neurons in conveying nociceptive messages from the spinal cord to the hypothalamus need to be confirmed.

To summarize, anatomical data indicate several hypothalamic subregions that appear to be more specifically involved in nociceptive processing:

1. The neuroendocrine group (the paraventricular nucleus and to a lesser extent the periventricular and supraoptic nuclei) that receives nociceptive messages from all the nociceptive sources described above.
2. The ventromedial nucleus, the perifornical and the retrochiasmatic areas that receive a very prominent nociceptive input from the parabrachial area.
3. The median and ventrolateral preoptic area, the dorsomedial, the lateral and the posterior hypothalamic region, which receive lower but yet substantial nociceptive inputs.

Corroborating the anatomical data closely, it was shown that various painful stimuli evoke c-fos expression in regions receiving nociceptive afferent projections. The strongest c-fos expression was observed in neuroendocrine neurons of the hypothalamus located in the paraventricular, the supraoptic and the periventricular / arcuate nuclei. A substantial c-fos expression is evoked in the posterior, the ventromedial and the dorsomedial nuclei and the retrochiasmatic, the lateral and the anterior regions of the hypothalamus (Rodella et al. 1998; Snowball et al. 2000).

Role of Hypothalamus in Visceromotor Responses to Painful Stimuli

The anatomical data indicate that both parabrachial and A1 / C1 projections to the paraventricular nucleus innervate more densely neurons containing corticotropin releasing hormone as well as ▶ magnocellular neurons (that contain vasopressin and oxytocin). Painful stimuli evoke specifically c-fos expression in neurons containing corticotropin releasing hormone, vasopressin
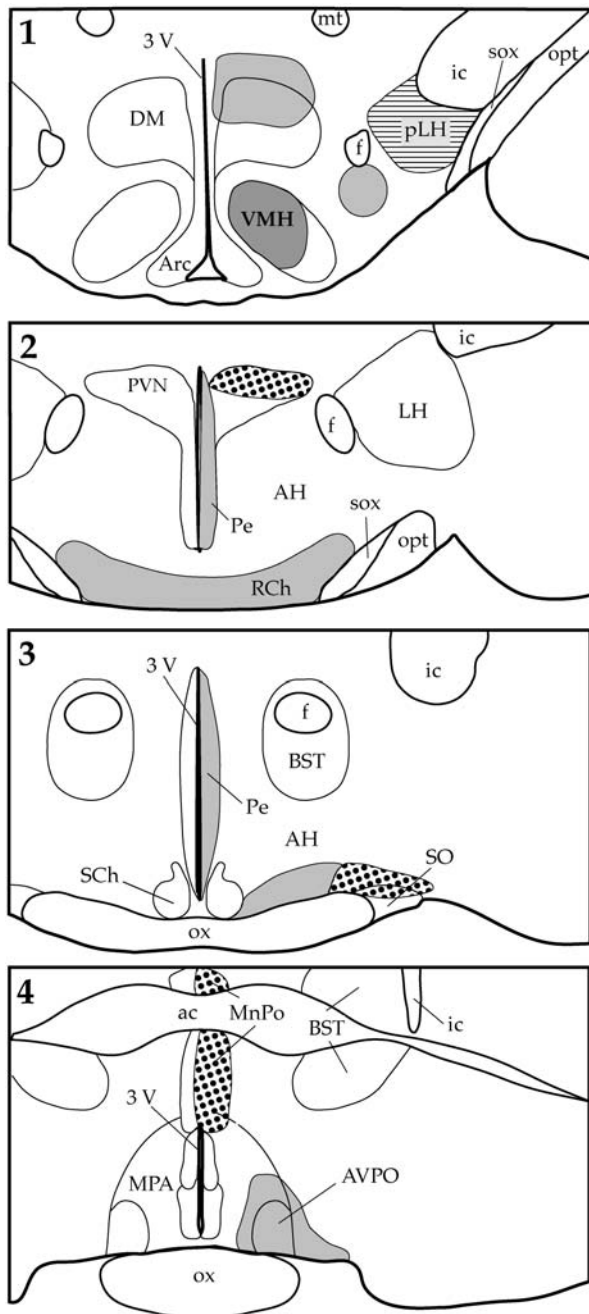
Hypothalamus and Nociceptive Pathways, Figure 2 Summary diagram illustrating, in coronal sections, the location of nociceptive projections within the hypothalamus (1–4, caudal to rostral). The parabrachial "nociceptive" area projects primarily upon the VMH (dark gray) and extensively upon the DM and the perifornical area (1), the RCh and the Pe (2), the rostral Pe and the ventral AH (3) and the AVPO (4) hypothalamic nuclei (gray). Both the parabrachial nucleus and the A1/C1 group within the ventrolateral medulla project to the PVN (2), the SO (3) and the MnPO (4) (black points). Both the parabrachial area and the spinal and trigeminal dorsal horn project to the pLH (1) (horizontal hatching). Abbreviations: 3V, third ventricle; A1/C1 A1, noradrenaline cells, C1, adrenaline cells; ac, anterior commissure; AH, anterior hypothalamic area; Arc, arcuate nucleus; AVPO, anteroventral preoptic nucleus; BST, bed nucleus of stria terminals; DM, dorsal medial nucleus; f, fornix; ic internal capsule; LH, lateral hypothalamus; MnPO, median preoptic nucleus; MPA, medial preoptic area; mt, mammillothalamic tract; opt, optic tract; ox optic chiasm; Pe, periventricular nucleus; pLH, posterior portion of lateral hypothalamus; PVN, paraventricular nucleus; RCh, retrochiasmatic area; SCh, suprachiasmatic nucleus; SO, supraoptic nucleus; sox, supraoptic decussation; VMH, ventromedial hypothalamic nucleus

and oxytocin at the levels of paraventricular, arcuate and supraoptic nuclei. This neuroendocrine response is specific for these neurohormones; it does not include gonadotropin, growth hormone, and thyrotropin releasing hormones (Pan et al. 1996).

The neuroendocrine component of pain is indisputably under hypothalamic control with well-identified pain pathways to drive it. The role of these neurohormones in pain is not completely understood. It is likely that an increase in the corticotropin hormone axis is important to cope with the dangerous or traumatic situation that comes with pain (mobilization of metabolism and mental energy). Nonetheless, in the case of chronic pain, the stimulation of the corticotropin axis might become deleterious (anxiety, depression, decrease of immunity, neuronal loss). Vasopressin may accompany corticotropin secretion to increase or maintain blood pressure. The role and amount of oxytocin secretion in cases of acute pain remain yet poorly understood.

Importantly, psychological stress (immobilization, anxiety, and fear) acts on the corticotropin axis of the hypothalamus *via* limbic projections (bed nucleus of the

stria terminalis, prefrontal cortex) different from those described for nociceptive stimuli (physical stress).

Numerous paraventricular neurons (chiefly in a dorsal position) are not neuroendocrine cells but provide descending projections to the brainstem and the spinal cord. Although the paraventricular nucleus provides the more extensive set of descending projections, other hypothalamic nuclei also receiving nociceptive messages send similar descending projections, namely the periventricular, the retrochiasmatic area, the dorsomedial, the dorsal, the perifornical and the lateral hypothalamic areas. These hypothalamic neurons project to the periaqueductal gray matter, the parabrachial area, the solitary tract, the motor vagus, the ambiguous nuclei and the ventrolateral medulla in the brainstem. In the spinal cord, they project chiefly to the sympathetic preganglionic column (Saper 1995). These hypothalamic neurons are adequately placed to drive both the sympathetic and the ▶ parasympathetic components of pain. They might, in connection with brainstem neurons, increase or decrease blood pressure and cardiac frequency and modify circulatory territory, according to the nature of the painful stimuli.

Role of Hypothalamus in Behavioral Response to Painful Stimuli

Several hypothalamic nuclei, which receive an extensive nociceptive input, play an important role in motivational components of pain.

The first group, including the ventromedial and the dorsomedial nuclei, the perifornical and the retrochiasmatic areas, is markedly involved in defensive-aggressive behavior. This group of nuclei projects extensively to the periaqueductal gray matter, each nucleus targeting a specific quadrant. The periaqueductal gray matter appears to be a major hypothalamic descending output to mediate aggressive-defensive behavior. Each nucleus of this hypothalamic group receives an extensive nociceptive input from the lateral parabrachial area, the ventromedial hypothalamic nucleus receiving the heaviest input. The ventromedial nucleus has been involved in aggressive-defensive behavior. Stimulation applied in this nucleus induces vocalization, attack, escape, piloerection, mydriasis and micturition that resemble the pseudo-affective reactions induced by noxious stimuli (Bester et al. 1997; Swanson 1987). Recently, the dorsomedial portion of the ventromedial nucleus has been shown to be responsible for the vocalization induced by painful electrical shock applied to the tail (Borszcz 2002). The ventromedial nucleus has also been involved in feeding behavior (it has long been considered as the "satiety center") and regulation of energy metabolism (Swanson 1987). Recently, the ventromedial hypothalamic nucleus has thus been proposed to be responsible for the anorexia induced by migraine (Malick et al. 2001). Pain should act on appetite *via* a parabrachio-ventromedial CCKergic link. Leptin receptors, which are abundant in this hypothalamic nucleus, might also participate in the loss of appetite. Finally, stimulation applied within the ventromedial nuclei produces an analgesia, which is also probably mediated *via* the periaqueductal output. Thus, it appears that the medial zone of the tuberal (posterior) and the anterior hypothalamus is responsible for the defensive-aggressive and feeding motivational component of pain.

The second group, including the median and the anteroventral preoptic hypothalamic nuclei, is involved in osmotic / blood fluids balance regulation and sleep promoting / thermoregulation functions. These nuclei also receive a substantial nociceptive input from the lateral parabrachial area. The influence of nociceptive input upon the neurons of this hypothalamic region is less clear. It might alter drinking behavior, vasopressin secretion, falling asleep and the thermoregulation set point according to the nature of the nociceptive aggression (Saper et al. 2001; Swanson 1987).

The posterior portion of the lateral hypothalamus receives a diffuse but substantial nociceptive input directly from the deep laminae of the dorsal horn and indirectly *via* the internal lateral parabrachial nucleus. The role of the lateral hypothalamus in nociceptive processing remains obscure because this hypothalamic region was involved in a myriad functions, such as feeding behavior (it has long been considered to be a "feeding center"), drinking behavior and cardiovascular and visceral regulation, as well as in wakefulness and antinociceptive and rewarding mechanisms. However, the recent discovery that ▶ narcolepsy can be induced by lack of orexin / hypocretin (a peptide located in the neurons of lateral hypothalamus), indicates that the lateral hypothalamus is probably markedly involved in the wakefulness mechanism (Saper 2001). One role of nociceptive inputs upon neurons of the posterior lateral hypothalamus could be to trigger awakening.

Conclusion

Bringing together anatomical and functional data, the hypothalamus appears as a key center for most visceromotor (neuroendocrine, autonomic response) and motivational (aggressive-defensive reactions, ingestive behaviors, wakefulness, antinociception) components of pain. It yet remains to check experimentally the actual role of hypothalamic subregions and / or neuromodulators in the genesis of different components of pain. Anatomical data also indicate that hypothalamic functions are probably strongly modulated by the upper limbic structures (notably the extended amygdala and the cingulate / prefrontal cortex), which are also involved in the emotional appreciation of pain.

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Hypothalamus-Anterior Pituitary-Gonadal Axis

Definition

The hypothalamus controls endocrine function by direct release of neuropeptides, or indirectly through the secretion of regulatory hormones to the anterior pituitary. These regulatory substances are secreted by the hypothalamus into the local portal plexus within the median eminence, which then drains into the blood vessels of the anterior pituitary. There are a wide number of substances released by the hypothalamus that either inhibit or stimulate the release of anterior pituitary hormones, including factors that affect the release of growth hormone, thyrotropin, and others. Related to sexual and reproductive function, the hypothalamus secretes prolactin-releasing factor (PRF), which stimulates the release of prolactin. Dopamine, also secreted by the hypothalamus, inhibits prolactin's release. Additionally, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) to the pituitary gland, which triggers the secretion of luteinizing hormone (LH) from the pituitary gland. Luteinizing hormone then stimulates the Leydig cells of the testes to produce testosterone or the ovaries to produce progesterone.

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

Hypoxia

Definition

Hypoxia is a pathological condition in which the whole organism (*generalized hypoxia*) or only a region of the organism (*tissue hypoxia*) is deprived of adequate oxygen supply.

▶ NSAIDs and Cancer