H

5-HT

► Serotonin

5-Hydroxytryptamine

► Serotonin

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.

Cross-References

► Infant Pain Mechanisms
► Migraine Without Aura
► Psychology of Pain, Sensitization, 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.

Cross-References

► Sciatica

Handicap

► Disability in Fibromyalgia Patients

Hansen's Disease

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Synonyms

Leprosy

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Definition

Hansen's disease is a chronic granulomatous infection of the skin and peripheral nerves caused by the obligate intracellular organism ▶ 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 low-resource 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). In the twenty-first century, significant progression has been made in controlling leprosy. Globally, the annual detection of new cases has been steadily declining, from 620,638 cases in 2002 to 249,007 in 2008. At the beginning of 2009, the registered prevalence of Hansen's disease globally was 213,036. The registered prevalence at the start of 2009 was highest in the following six countries: India, Brazil, Indonesia, Nigeria, Democratic Republic of the Congo, Ethiopia, and Bangladesh (WHO 2009).

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 reactions. 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. Three cardinal diagnostic features include (1) the presence of skin lesions with definite sensory loss, (2) the presence of thickened peripheral nerves, and (3) demonstration of acid-fast bacilli on slit skin smears or tissue biopsy (Walker and Lockwood 2007). 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). For assignment to treatment regimes, WHO is using a simplified operational classification based on the number of skin lesions. Leprosy is called paucibacillary if the number of skin lesions in a patient is between 1 and 5 and multibacillary if the number of skin lesions exceeds 5 (Walker and Lockwood 2007). 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). Early case finding and prompt treatment with the above-mentioned multidrug therapy (MDT) are the cornerstone of leprosy control programs.

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. Anesthesia of the extremities predisposes the patient to chronic ulcers and severe secondary deformities, and therefore, leprosy remains a significant cause of neurologic disability worldwide. Besides sensory nerve involvement, leprosy affects also motor and autonomic nerves. Peripheral motor nerve palsies usually occur during type 1 reactions. The most common manifestation of autonomic nerve dysfunction in leprosy patients is hypohidrosis. Sometimes deterioration of sensory and motor functions can occur insidiously without signs or symptoms of inflammation. This phenomenon is called silent neuropathy (van Brakel and Khawas 1994).

Since Hansen's disease causes severe sensory loss, it is assumed that pain is uncommon in leprosy. However, peripheral nerve pain, dysesthesias, and paresthesias 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 edematous 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 immobilization 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 center, 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), four 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 two patients, the course of femoral cutaneous nerve in one patient, and was located in both legs below mid-thigh in one patient. Allodynia, pain due to a stimulus that does not normally provoke pain, was noticed in two 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 fibers 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 fibers due to mycobacterial

invasion can cause dysfunction and damage leading to paresthesia and pain (Lund et al. 2007). 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 (Haanpaa 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 sensitization, which may manifest as chronic neuropathic pain. In a study of 17 leprosy patients, who had completed MDT and were suffering from chronic neuropathic pain, intraneural acid-fast bacilli were detected in 5 nerve biopsies (Lund et al. 2007). It is possible that, despite adequate therapy, in some leprosy patients, bacteria are persisting in the nerve, and this chronic infection may give cause to nerve pathology and neuropathic pain.

To date, there are no controlled studies on the efficacy of any drug in leprosy-related neuropathic pain.

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Hargreaves Test

▶ Thermal Nociception Test

Harm Principle

▶ Ethics of Pain Control in Infants and Children

Head Pain

▶ Headache

Headache

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Synonyms

Cephalalgia; Head pain

Definition

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. Similarly, 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
- Intensity
- Quality
- 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 hemorrhage, 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 hemorrhage, 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 3 or 4 days, interspersed with periods free of pain, are 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 hemorrhage, 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 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 hemorrhage 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.

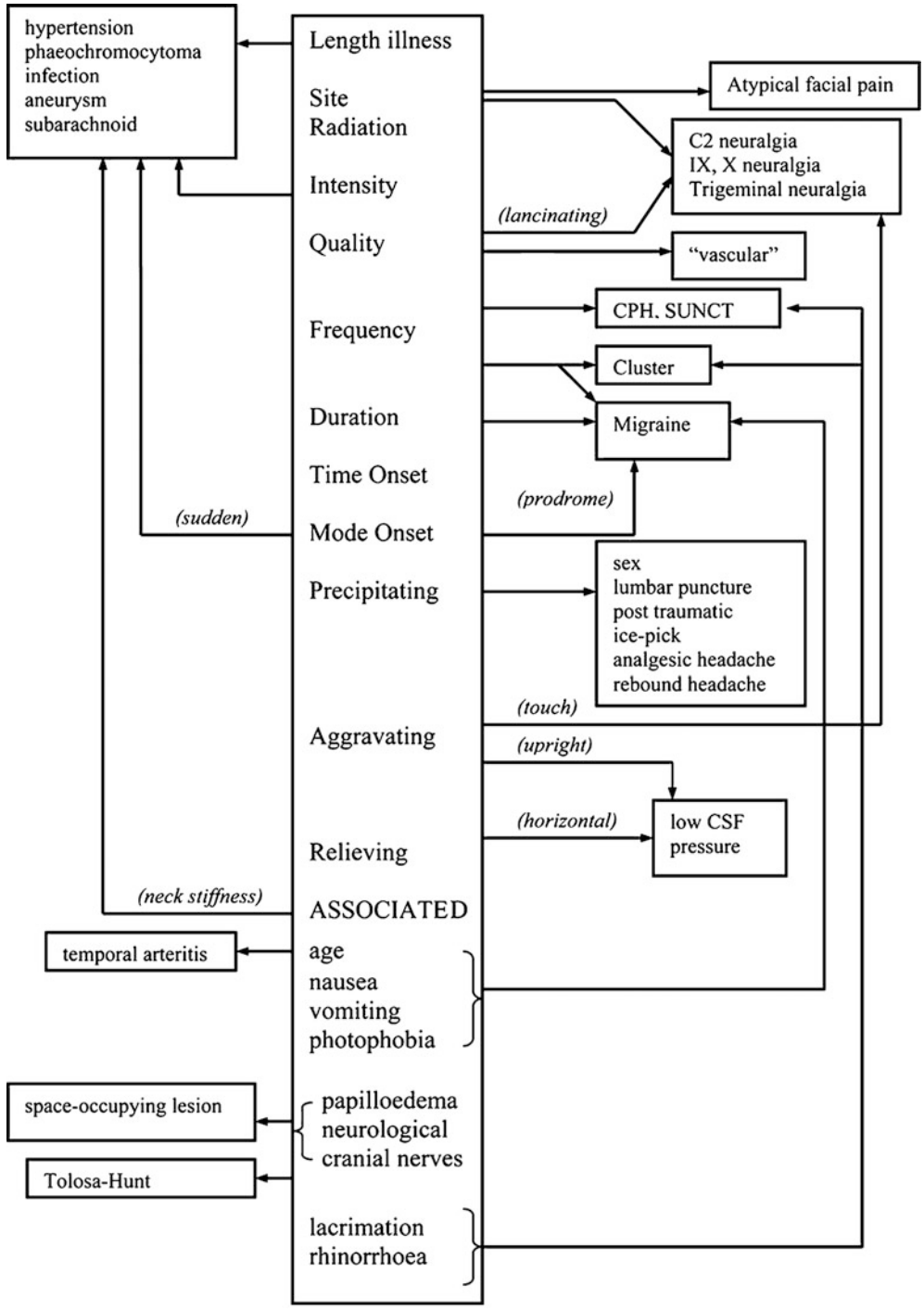
The diagnosis of acute herpes zoster can be made immediately once the eruption of vesicles occurs, but the pain may precede the eruption by up to 3 days.

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 center 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.



Headache, Fig. 1 The differential diagnosis of headache by clinical history and examination

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.

Cross-References

► Chronic Daily Headache in Children

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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 Somatization Disorder

► Headache Due to Somatoform Disorder

Headache Attributed to a Substance or Its Withdrawal

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Synonyms

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

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 ICHD-2 and new ICHD-3 classification (Headache Classification Committee 2003, 2013) now calls these headaches "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 preexisting primary headache is made worse in close temporal relation to substance exposure, the patient is given the diagnosis of both the preexisting primary or secondary headache and the diagnosis of headache attributed to the substance (Headache Classification Committee 2013).

Headache Attributed to Acute Substance Use or Exposure (Headache Classification Committee 2013)

Headache attributed to acute substance use or exposure may start instantly or within hours or days. This group of headache disorders can be caused by (1) an unwanted effect of a toxic substance, (2) an unwanted effect of a substance in normal therapeutic use, and (3) a substance used in an experimental study. Headache as a side effect has been recorded with many drugs, often as just a reflection of the very high prevalence of headache.

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. Nonsteroidal anti-inflammatory drugs 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

1. Coincidental
2. Reverse causality
3. Interaction headache
4. Causal

Acute: Primary effect and 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).

Vasodilators

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 a well-known 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 NO donor absorption 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 ▶ nucleotides (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 TTH, 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). Phenylethylamine, 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 in the third (Silberstein 1998).

Tyramine

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

Phenylethylamine

Chocolate contains large amounts of β-phenylethylamine, 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 ▶ congeners (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 day following 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-β, 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

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Synonyms

Angiitis of the CNS; Vasculitis

Definition

Headache is the most common complaint in cranial or ▶ 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 or primary ▶ angiitis of the central nervous system – PACNS).

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 in Europe is 18/100,000 per year; there is a frequent association with HLA-DRB1. 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 exudate 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 nonpulsating 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 (Kraemer et al. 2010). The superficial temporal artery may be thickened and tender without pulsation – "cord-sign." Ultrasound examinations of the temporal artery reveal the halo-sign; the inflammation of the vessel wall may be demonstrated by contrast enhanced MRI.

Diagnostic Criteria of Temporal Arteritis

- Age 50 years or more
- Newly developed headache

Headache Due to Arteritis, Table 1 Frequency of signs and symptoms with temporal arteritis (Adapted from Caselli and Hunder 1993)

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

- 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 (Table 1).

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 to 5 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). In order to avoid side effects of the treatment pantoprazole, aspirin, vitamin D, and calcium are recommended. If necessary, ▶ methotrexate may be used as steroid sparing agent.

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 and tension-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 is a typical symptom 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 and 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 (Sfikakis et al. 1998). In SLE patients with tension-type headache, there was an association with personality changes, emotional conflicts, and depression (Omdal et al. 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). ▶ Flunarizine may be helpful for prophylaxis in rheumatologic patients with migraine (Mazagri and Shuaib 1992).

Granulomatosis with Polyangiitis (GPA)

GPA ▶ Wegener's granulomatosis is a rare autoimmune disease (1 per 100,000) associated with antineutrophil 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 GPA, headaches are frequent and often caused by sinusitis, nonseptic 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 GPA. Alternatively, Rituximab may be given in the acute phase; once the patient is in remission Methotrexate or Azathioprine are less toxic drugs. Headaches are treated symptomatically with paracetamol or nonsteroidal antiphlogistics.

Behçet's Disease

▶ Behçet's disease presents with the triad 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 % (neuro-Behçet), either as ▶ meningoencephalitis of the brain stem and cerebellum (80 %) or as a ▶ sinus thrombosis, which presents often as pseudotumor cerebri (20 %; Akman-Demir et al. 1999). Headaches are the most common complaint in ▶ neuro-Behçet (87 % of patients). 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.

Primary Angiitis of the Central Nervous System (PACNS) (Isolated Arteritis of the Nervous System: IAN)

Primary angiitis of the central nervous system (PACNS) is an idiopathic medium and small vessel vasculitis affecting exclusively CNS vessels of the brain or spinal cord. About 500 cases have been documented worldwide (Berlit 2009, 2010). The major symptoms of PACNS 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 PACNS 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 % (Schmidley 2000). For definitive diagnosis of PACNS, a combined leptomeningeal and parenchymal biopsy is necessary, especially in order to exclude infections (endocarditis; Berlit 2009) 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. 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 secondary's (e.g., cancers of the lung and breast as well as melanoma), some only infrequently (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.

Cross-References

► Cancer Pain

Headache Due to Dissection

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Synonyms

Carotidynia; Horner's syndrome; Tolosa-Hunt syndrome (painful ophthalmoplegia)

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 produces headache.

Pathogenesis

We have however to keep in mind that pain is usually a symptom of arterial dissections anywhere in the body, e.g., also of the aorta and 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 artery (ICA) or vertebral artery (VA) dissections and their branches. We do not have data regarding dissection of external

carotid arteries 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? To detect ICAD as a cause, the MRI with special sequences must be performed of the neck region – and not (only) of the head!

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 performing Doppler- or Duplex examinations, MRA and/or conventional MRI. In the VA, it is well known that for various reasons MRI, as well as Doppler/duplex examination, is 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 of cervico-cerebral arteries 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. Fifty to eighty percent of patients with a dissection of the cervico-cerebral 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, 1995).

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).

Raeder's paratrigeminal syndrome (combination of pain, ipsilateral oculosympathetic defect and ipsilateral trigeminal dysfunction) may be due to spontaneous internal carotid artery dissection (ICAD) (Selky 1995). According to several studies, ICAD presents in 15 to 25 % as a painful Horner's syndrome (Sturzenegger 1995; Biousse 1994).

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).

The clinical features of Tolosa-Hunt syndrome ("painful ophthalmoplegia"; variable combination of periorbital pain, ipsilateral oculomotor nerve palsies, oculosympathetic palsy and trigeminal sensory loss) localise 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).

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 as follows: 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 (nontraumatic) 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 simply 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 at the same time. 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 Asia (Japan).

Spontaneous Internal Carotid Artery Dissection (sICAD)

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 (seICAD)

Headache is reported in 55–95 % of seICAD and was the first symptom in 47–68 % (Biousse et al. 1994; Fisher 1982; Schievink 2001; Silbert et al. 1995; Sturzenegger 1995). Headache and facial or orbital pain may be the sole symptom of dissection, probably more frequently than reported so far (5 %) and poses a diagnostic challenge (Maruyama et al. 2012). 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 periorbital (~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), or 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/she 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 assuming 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 (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; tearing and stuffed or running ipsilateral nose in cluster).

Spontaneous Dissection of the Intracranial Internal Carotid Artery (siICAD)

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. Thus the real incidence may be underestimated. 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 (sVAD)

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 pseudoaneurysms, 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 and was of sharp quality and severe intensity and 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 1–3 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 vertebrobasilar ischemic strokes, with frequently severe neurologic deficits. 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 therapy might be fatal.

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Headache Due to Hypertension

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Synonyms

Hypertensive encephalopathy; Hypertensive headaches; Reversible posterior leukoencephalopathy 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 ▶ leukoencephalopathy 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 preeclampsia 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 nonspecific 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 leukoencephalopathy" (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 mmHg 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 Subcommittee 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 clears 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 1 h of normalization of BP. For a headache to be attributed to preeclampsia or eclampsia, the IHS requires that the headache occurs during pregnancy (or the puerperium), that there be clinical features of preeclampsia or eclampsia (hypertension at least 140/90 and proteinuria), that appropriate investigation rules out other causes of hypertensive headaches such as medications, 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 preeclampsia/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

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Synonyms

Blood clot in brain; Epidural hematoma: acute traumatic epidural hematoma; Hemorrhagic stroke; Intracerebral hematoma: apoplexy: Subdural hematoma: posttraumatic subdural hemorrhage

Definition

Intracerebral Hematoma

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

Subdural Hematoma

Hemorrhage between the brain and the dura mater, 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 hemispheres and the cerebellar lobes. If the hematoma is in the cerebellar hemisphere, 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, small unequal pupils, and finally decerebrate posture, coma, and death. Computerized tomography will allow almost immediate visualization of the blood. Prompt surgical evacuation of the cerebellar hematoma is often lifesaving 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).

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 lifesaving 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

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Synonyms

Hypotension of spinal fluid; Low-intracranial-pressure headache; Post-lumbar puncture headache; Spontaneous aliquorrhea; Spontaneous intracranial hypotension; Symptomatic intracranial hypotension; Ventricular collapse

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 etiology is different for the 3 types. See Table 1 for compared classification criteria (Headache Classification Committee of the International Headache Society 2004).

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 (pachymeningeal enhancement)	
	Conventional or CT myelography, cisternography	
	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

Characteristics

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

1. "Liquorrhea" involving headache and ► papilledema, which later became known as pseudotumor cerebri.
2. "Spontaneous aliquorrhea," 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 1,500 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 and 210 ml; this means that the total volume is renewed 2–3 times per day. CSF volume is smaller in women, younger persons, 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 localization. The headache typically has orthostatic features in the beginning (e.g., onset within 30 min after standing up); however, these features may blur with 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 colorless, 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 hyperemia. 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 extra-arachnoidal 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 classified 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 papilledema in the neurological examination.

Management and 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 relief 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 20 ml/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 Somatoform Disorder

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Synonyms

Headache associated with psychotic disorder; Headache associated with somatization disorder

Definition

Headaches of no typical characterization (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 and cluster headaches) 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 complaint 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 somatization 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 somatization 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 and or the underlying psychiatric disorder. A causal relationship in any direction is under debate. Association of headaches with other psychiatric disturbances such as depression and phobias are classified separately. Headaches associated with somatization disorder are rare, and headaches associated with somatoform disorder are more frequent. So far only single cases and a few small series of cases have been published.

Headache Due to Venous Sinus Thrombosis

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Synonyms

Central venous thrombosis; Cerebral venous thrombosis; Intracranial venous thrombosis; Sinus-venous thrombosis (SVT); Venous sinus thrombosis

Definition

Cerebral venous sinus thrombosis (CVST) is a rare but challenging condition and is therefore often unrecognized. 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, or other disorders such as idiopathic intracranial hypertension (pseudotumor cerebri). Along with headache, additional symptoms typical to increasing intracranial pressure such as papilledema, nausea, vomiting, and cognitive decline may be present. Further symptoms are focal deficit and seizures. The headache does not typically respond to classical antiheadache drugs, which should be taken as an important sign that further evaluation is necessary. Typical patients with CVST are young females with risk factors such as oral contraceptive pill use, 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. Preexisting 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 collateralization 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. Hemorrhagic 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 noninfective 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. Among the noninfective 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 hemorrhage
- Space-occupying lesions
- Neurosurgery

Systemic Causes
- Severe dehydration
- Hormonal and endocrine causes
- Cardiac disease
- Red blood cell disorders
- Thrombocythemia
- Coagulation disorders (acquired or hereditary)
- Infusions via central venous catheter
- Surgery with immobilization
- 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 (Uzar et al. 2012; Bousser and Ferro 2007). Other important symptoms are focal deficits such as hemiparesis and hemisensory disturbance, seizures, impairment of level of consciousness, and papilledema (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 characterized 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, papilledema, 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) has largely replaced invasive cerebral angiography and conventional computed tomography (CT). Modern subsecond spiral CT and multidetector-row CT (MDCT) scanners, 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 visualizing 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 1997). 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, and 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 randomized and placebo-controlled trial, demonstrated the benefits of heparin in a series of 20 patients. There was a significant difference in favor 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 hemorrhage 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 et al. 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 catheterization 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 catheterization and thrombolysis with urokinase recovered well, and only a few patients suffered from an additional cerebral hemorrhage. 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 catheterization 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 lifelong requirement. No agreement has been reached regarding the question whether

patients who present with seizures should undergo antiepileptic 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 5,000 U and to continue according to the apTT elevation, which mostly requires dosages between 1,000 and 1,600 U/h for adults. Heparin is the first-line treatment, even in the presence of hemorrhagic infarction (Bousser 1999). In case of clinical deterioration despite adequate heparinization, selective local thrombolysis should be considered, in spite of the increased hemorrhagic risk.

Prognosis

Mortality in untreated cases of venous thrombosis has been reported to range from 13.8 % to 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. Buccino et al. (2003) found a good overall outcome in a series of 34 patients with CSVT. Still, ten patients (30 %) suffered from episodic headaches, three patients (8.8 %) from seizures, four patients (11.7 %) from pyramidal signs, two patients (5.9 %) from visual deficits, and six patients (17.6 %) from working memory deficit and depression. In a series of 100 patients (Gameiro et al. 2012), the outcome of cerebral venous thrombosis with isolated headache diagnosed early or late was favorable. 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 from Cranial Bone

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Synonyms

Facial pain associated with disorders of the cranium; Headache associated with disorders of the cranium

Definition

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

Characteristics

Most disorders of the skull (e.g., congenital abnormalities, fractures, tumors, metastases) are not usually accompanied by headache (Göbel and Edmeads 2000; International Headache Society Classification Subcommittee 2004). Exceptions of importance are osteomyelitis, multiple myeloma, and Paget's disease (Georgalas et al. 2011; Göbel 2012; Kazan et al. 2012; Lu and Yao 2011; Voorhies and Sundaresan 1985). 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

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Synonyms

Abacterial meningitis; Aseptic meningitis; Serous meningitis; Viral 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 cerebrospinal fluid (CSF).

Historically, the word "aseptic" was introduced to denote the nonbacterial etiology 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,

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

Infectious etiologies	Noninfectious 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	Noninfectious 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	
Coccidioides immitis	
Blasto. dermatitides	
Parasites	
Toxoplasma gondii	
Taenia solium	

rickettsial, or mycoplasmal origin; noninfective causes (Table 2) include tumors of the central nervous system, carcinomas, leukemias, sarcoidosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, certain drugs, vaccines, immunoglobulins, intrathecal agents, and rarely some disorders of unproven etiology like Behcet's syndrome and 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 treated. Worldwide 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 (Lamonte 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 hemorrhage and other acute headaches.

The cell count in aseptic meningitis is usually less than 1,000 per cu. mm, and there may be an early predominance of polymorphonuclear leukocytes. Repeated lumbar puncture in 8–12 h 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 hematogenous 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 68–71, 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, spirochetal, 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.

Conjunctival 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 spirochetal cause of aseptic meningitis and meningoencephalitis. The spirochete is tick borne, common in northeastern United States from May to July (Eppes et al. 1999).

Leukemias 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, Behcet's 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 nonsteroidal 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-sulfamethoxazole, 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 recognize. 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 inquire about a past history of infectious disease, immunizations, contact with animals, insect bites, recent respiratory or gastrointestinal 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 Mollaret's 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 etiology 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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Headache, Acute Posttraumatic

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Synonyms

Posttraumatic headache; PTHA

Definition

Posttraumatic headache (PTHA) is usually one of the several symptoms of the "posttraumatic 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 posttraumatic 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. Posttraumatic 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 (GCS) score, 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 posttraumatic 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 preexisting 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 posttraumatic 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 Posttraumatic Headache

Acute Posttraumatic Headache with Moderate or Severe Head Injury

Diagnostic Criteria

1. Headache, no typical characteristics known, fulfilling criteria C and D.
2. Head trauma with at least one of the following:
   1. Loss of consciousness for >30 min
   2. Glasgow Coma Scale (GCS) <13
   3. Posttraumatic amnesia for >48 h
   4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracerebral and/or subarachnoid hemorrhage, brain contusion, and/or skull fracture)
3. Headache develops within 7 days after head trauma or after regaining consciousness following head trauma.
4. 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.

Acute Posttraumatic Headache with Mild Head Injury

Diagnostic Criteria

1. Headache, no typical characteristics known, fulfilling criteria C and D.
2. Head trauma with all of the following:
   1. Either no loss of consciousness or loss of consciousness of <30 min duration
   2. Glasgow Coma Scale (GCS) >13
   3. Symptoms and/or signs diagnostic of concussion
3. Headache develops within 7 days after head trauma.
4. 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 Posttraumatic Headache

Chronic Posttraumatic Headache with Moderate or Severe Head Injury

Diagnostic Criteria

1. Headache, no typical characteristics known, fulfilling criteria C and D.
2. Head trauma with at least one of the following:
   1. Loss of consciousness >30 min
   2. Glasgow Coma Scale (GCS) <13
   3. Posttraumatic amnesia >48 h

4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracerebral and/or subarachnoid hemorrhage, brain contusion, and/or skull fracture)
3. Headache develops within 7 days after head trauma or after regaining consciousness following head trauma.
4. Headache persists for >3 months after head trauma.

Chronic Posttraumatic Headache with Mild Head Injury

Diagnostic Criteria

1. Headache, no typical characteristics known, fulfilling criteria C and D.
2. Head trauma with all of the following:
   1. Either no loss of consciousness or loss of consciousness of <30 min duration
   2. Glasgow Coma Scale (GCS) >13
   3. Symptoms and/or signs diagnostic of concussion
3. Headache develops within 7 days after head trauma.
4. Headache persists 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; and 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 posttraumatic 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 to moderate head injury.

Age; gender; certain mechanical factors; a low intellectual, educational, and socioeconomic 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 Coma 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, medicolegal issues should be solved as soon as possible.

Pathophysiology of PTHA

Pathophysiology of posttraumatic 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 post-concussive 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 (biofeedback), 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 posttraumatic 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, Episodic Tension-Type

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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, 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 on 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

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 2004).

Characteristics

With a lifetime prevalence of 30–78 % in general population, tension-type headache is the most common primary headache and has a high socioeconomic impact. The male to female ratio is 1:1.5. The prevalence in childhood ranges from 0.5 to 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 sensitization 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 nonspecific analgesics and can lead to further problems, including chronification of the headache.

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 min 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 suggests migraine (certainly when both are present). There is no blurred vision and no focal neurological disturbance. Patients may complain of a feeling of giddiness or lightheadedness, 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 increase 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 to 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 favor of tension-type headache is a highly variable temporal profile and pain improvement with exercise. Unsuccessful treatment with ergotamines or triptans for acute attacks, or with beta-blockers or flunarizine for prevention, also suggests 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 neurological 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, nonpsychological 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 recognized. 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 nonspecific 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! (Cave: balance!)
3. Drugs should not be taken on more than 2 days a week!(Cave: balance!)
4. The use of compound analgesics (codeine, caffeine, etc.) should be avoided, or at least limited and carefully monitored!

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 behavioral 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, unphysiological working conditions, and disturbed sleep patterns. Physiotherapy, physical treatment (hot and cold packs), ultrasound, 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).

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

List of effective acute drugs			
Paracetamol/ acetaminophen	1,000 mg		
Aspirin	1,000 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 (2003)
Metamizol	1,000 mg	Martinez et al.	Cephalalgia (2001)
Medications for children			
Ibuprofen	10 mg/Kg		
Paracetamol	15 mg/Kg		

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Headaches Associated with Substances or their Withdrawal

▶ Headache Attributed to a Substance or Its Withdrawal

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.

Cross-References

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

Heat Lesion

▶ Radiofrequency Neurotomy, Electrophysiological Principles

Heat Sensor

▶ Capsaicin Receptor

Heightened Attention

► Hypervigilance and Attention to Pain

Helical CT

► CT Scanning

Helicobacter Pylori

Definition

Helicobacter pylori are bacteria that cause inflammation and ulcers in the stomach.

Cross-References

► NSAIDs, Adverse Effects

Heliotherapy

Definition

Heliotherapy is the exposure to sunrays and ultraviolet rays.

Cross-References

► 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 one's circumstances, symptoms, and life.

Cross-References

► Catastrophizing
► Cognitive-Behavioral Perspective of Pain

Hemianesthesia

Definition

Hemianesthesia is the sensory loss in the left or right side of the body.

Cross-References

► 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.

Cross-References

► Adjuvant Analgesics in Management of Cancer-Related Bone Pain

Hemicrania Continua

Definition

Hemicrania continua is a continuous (always present) but fluctuating unilateral headache,

often accompanied by cranial autonomic symptoms, such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, or eyelid edema. It is completely responsive to indomethacin.

Cross-References

- ▶ Chronic Daily Headache in Children
- ▶ New Daily Persistent Headache
- ▶ Paroxysmal Hemicrania

Hemicrania Continua (HC)

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Synonyms

Cranial autonomic symptoms; SUNCT syndrome; Unilateral headache

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, occur 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 to 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, 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 min 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

1. Headache for >3 months fulfilling criteria B-D
2. All of the following characteristics:
   (a) Unilateral pain without side-shift
   (b) Daily and continuous, without pain-free periods
   (c) Moderate intensity but with exacerbations of severe pain

1. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
   (a) Conjunctival injection and/or ▶ lacrimation
   (b) Nasal congestion and/or ▶ rhinorrhea
   (c) Ptosis and/or miosis

1. Complete response to therapeutic doses of indomethacin
2. 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), and 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 and 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 to 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 reported to occur within 2 h 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 rofecoxib (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 Simplex

▶ Migraine Without Aura

Hemipain

Definition

Hemipain is pain that is situated in one half of the body.

Cross-References

▶ Diagnosis and Assessment of Clinical Characteristics of Central Pain

Hemisphere

Definition

The hemisphere is either half of the cerebrum or brain; the human brain has a left and a right hemisphere.

Cross-References

► 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.

Cross-References

► Hereditary Neuropathies

Hereditary Motor and Sensory Neuropathy (HMSN)

► Hereditary Neuropathies

Hereditary Neuropathies

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Synonyms

Charcot-Marie-Tooth disease (CMT); Dejerine-Sottas Neuropathy (DSN); Familial Amyloid Polyneuropathy (FAP); Hereditary Motor and Sensory Neuropathy (HMSN); Hereditary Neuropathy with liability to Pressure Palsies (HNPP); Hereditary Sensory and Autonomic Neuropathy (HSAN); Hereditary Sensory Neuropathy (HSN)

Definition

Hereditary neuropathies are inherited diseases that injure axons in peripheral nerves.

Characteristics

The Biology of Myelinated Axons

Axons are the longest cells in the body and are vulnerable to defects in axonal transport; this is the basis for the long-standing doctrine that neuropathies are length dependent. Genetic evidence strongly supports this doctrine, as mutations in the genes that encode several axonal cytoskeleton and motor proteins cause axonal neuropathies. Neurofilaments are the main components of the axonal cytoskeleton, and 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), and recessive mutations of *NEFL* also cause a neuropathy in which axons lack neurofilaments (Table 1). Microtubules are the tracks for axonal transport, and are comprised of a polymer comprised of

Hereditary Neuropathies, Table 1 Non-syndromic inherited neuropathies with a genetically identified cause

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
Dominant Intermediate CMT (DI-CMT; autosomal dominant)		
DI-CMTA (606483)	10q24.1-25.1	Onset of weakness in before 10 years, and median nerve motor conduction velocities range from 25 to 45 m/s
DI-CMTB (696482)	*DNM2*	Progressive, distal weakness and sensory loss; some families have associated neutropenia
DI-CMTC (608323)	*YARS*	Progressive distal weakness and sensory loss. Median motor responses range between 30 and 40 m/s
Autosomal dominant axonal neuropathies		
CMT2A (609260)	*MFN2*	Most have childhood onset with progression to severe proximal and distal weakness
CMT2B (600882)	*RAB7*	Onset 1st–3rd decade; severe sensory loss with distal ulcerations; also length-dependent weakness
CMT2C (606071)	*TRPV4*	Variable weakness, can be severe and proximal, with vocal cord and diaphragmatic weakness
CMT2D (601472)	*GARS*	Arm more than leg weakness; onset of weakness 2nd–3rd decade; motor axons more affected than sensory axons
CMT2E (162280)	*NEFL*	Variable onset and severity; ranging from DSS-like to CMT2 phenotype; pain sensation may be diminished
CMT2F (606595) allelic to HMN-II	*HSPB1*	Onset weakness 2nd–4th decade, followed by weakness in the distal muscles of arms
CMT2G (608591)		Late onset (average 30 years), progressing to mild, sensory, and motor neuropathy
CMT2I, CMT2J, CMT2-P_0 (118200)	*MPZ*	Late onset (30y or older); but progressive neuropathy; pain; hearing loss; abnormally reactive pupils
CMT2K (607831)	*GDAP1*	Onset ranges from infancy to childhood, and weakness and sensory loss worsen with time but typically milder than recessive *GDAP1* mutations
CMT2L (608673) allelic to HMN-II	*HSPB8*	Onset of weakness ranged from 15 to 33 years; distal legs are affected before the distal arms
CMT2N (613287)	*AARS*	Variable onset (10–54 years)
CMT2O (614228)	*DYNC1H1*	Childhood onset of motor > sensory axonal neuropathy
CMT2P (604484)		Adult onset proximal weakness with cramping and distal sensory loss
CFEOM3 (600638)	*TUBB3*	Patients with D417N and E410K can develop lower extremity weakness and sensory loss in the second to third decade, in the absence of congenital contractures

(*continued*)

Hereditary Neuropathies, Table 1 (continued)

Disease (MIM)	Mutated gene/linkage	Clinical features
Hereditary neuralgic amyotrophy (162100)	*SEPT9*	Attacks of severe pain in the neck, arm(s), and/or shoulder(s), followed by weakness and sensory loss in the distribution of the affected part of the brachial plexus
Hereditary thermosensitive neuropathy (602107)		Reversible episodes of ascending weakness, paresthesiae, and areflexia triggered by elevated body temperature
Severe demyelinating neuropathies (autosomal dominant or recessive; "CMT3 or HMSN III")		
Dejerine-Sottas neuropathy (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 modalities subserved by large myelinated axons; motor NCVs less than 10 m/s; dysmyelination on nerve biopsies
Congenital hypomyelinating neuropathy (605253)	dominant (*EGR2*; *PMP22*; *MPZ*) & recessive *(EGR2)* mutations	Clinical picture often similar to that of Dejerine-Sottas neuropathy 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)	*SH3TC2*/*KIAA1985*	Childhood onset typical; often progressing to wheelchair-dependency; scoliosis; severe to moderate NCV slowing
CMT4D (601455)	*NDRG1*	Childhood onset; progression to severe disability by 50 y; hearing loss and dysmorphic features
CMT4E (605253)	*EGR2*	Infantile onset; progressing to wheelchair-dependency
CMT4F (605260)	*PRX*	Childhood onset; usually progression to severe disability; prominent sensory loss
CMT4G (605285)	*HK1*	Also called HMSN Russe. Childhood onset of severe motor and sensory axonal neuropathy.
CMT4H (609311)	*FDG4*	Onset infancy to 1st decade, with severe distal weakness and sensory loss; slow progression
CMT4J (611228)	*FIG4*	Abrupt declines of strength; electrophysiologically a motor neuronopathy; minimal sensory involvement
Autosomal recessive axonal neuropathies ("AR-CMT2" or "CMT 2B")		
AR-CMT2A (605588)	*LMNA*	Onset of neuropathy in 2nd decade; progresses to severe weakness and atrophy in distal muscles
AR-CMT2B (605589)	*MED25*	Onset 28–42 y, weakness and atrophy in the distal muscles of the arms and legs, as well as distal sensory loss
AR-CMT2 (608340)	*GDAP1*	Onset typically by age 2, progressive neuropathy that results in severe proximal and distal weakness, and may cause inability to walk and vocal cord paresis
AR-CMT2 (no OMIM)	*MFN2*	The clinical onset is by age 3, and the neuropathy progresses to cause profound distal weakness, atrophy, and sensory loss
AR-CMT2 (no OMIM)	*NEFL*	Onset before age 2, with hypotonia and delayed motor milestones; progressive motor and sensory loss progress lead to severe distal and even proximal weakness

(*continued*)

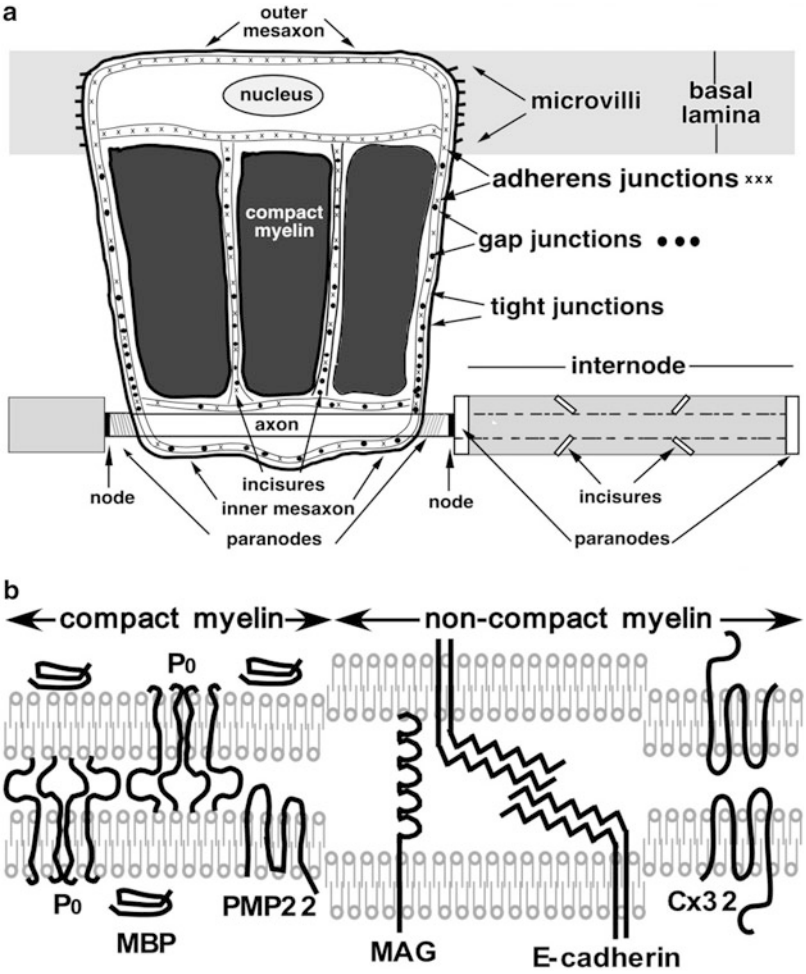
Hereditary Neuropathies, Table 1 (continued)

Disease (MIM)	Mutated gene/linkage	Clinical features
AR-CMT2 (no OMIM)	*LRSAM1*	Early adult onset of weakness and sensory loss
Hereditary Sensory (and Autonomic) Neuropathies (HSN or HSAN)		
HSAN1A (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.
HSN1B (608088)	Dominant; 3p22-p24	Adult onset cough and sensory neuropathy; with sensory loss; painless injuries; and/or lacinating pains
HSN1C (616640)	Dominant *SPTLC2* mutations	Progressive distal sensory loss and distal muscle weakness in the lower limbs beginning in the 30s
HSN1D (613708)	Dominant *ATL1* mutations	Early adult onset of what becomes severe sensory > motor axonal neuropathy. Some patients also have a myelopathy.
HSN1E (126375)	Dominant *DNMT1* mutations	Sensorineural deafness and sensory neuropathy by the age of 20–35 years; cognitive and behavioral declines in fourth decade
HSN2A (201300)	Recessive *WNK1* mutations	Childhood onset of progressive loss of sensation, including pain, may culminate in ulcers, osteomyelitis, and amputation; no overt autonomic dysfunction
HSN2B (613115)	Recessive *FAM134B* mutations	Impaired sensation, mutilating ulcers, and arthropathy begins in childhood
HSN2C (614213)	Recessive *KIF1A* mutations	Clinical onset of an ulcero-mutilative neuropathy by the age of 10 years, leading to distal amputations.
HSN3 (Riley-Day syndrome; 223900)	Recessive *IKBKAP* mutations	Congenital onset; dysautonomic crises; decreased pain sensation; absent fungiform papilla; overflow tears
HSAN4 (CIPA; 256800)	Recessive *NTRKA* mutations	Congenital onset of dysautonomia, loss of pain sensation, no sweating; unheeded pain leads to development of Charcot joints; deceased sensation to multiple modalities
HSAN5 (608654)	Recessive *NGFB* mutations	Congenital onset of dysautonomia, loss of pain sensation, no sweating; unheeded pain leads to development of Charcot joints; deceased sensation to multiple modalities

The neuropathies are classified by OMIM (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

α- and β-tubulin heterodimers. Dominant mutations in *TUBB3*, which encodes β3-tubulin, cause an axonal neuropathy, usually as part of a syndrome. Kinesins are the molecular motors that move cargo from the cell body to distal terminals. Recessive mutations in *KIF1A*, the gene encoding one of these kinesins, cause an axonal neuropathy (HSN2C). Conversely, mutations that affect components of the retrograde motor, a complex of dynactin and dynein, also cause neuropathies: A dominant mutation in *DYNC1H1*, which encodes a subunit of dynein, causes an axonal neuropathy (CMT2O), and a dominant mutation in the p150 subunit of dynactin causes a hereditary motor neuropathy (HMN7B). Defective axonal transport has been implicated in a host of other inherited neurological diseases, including the inherited spastic paraplegias, many of which can be regarded as length-dependent axonopathies of CNS neurons (Blackstone et al. 2011).

The structure and function of myelinating Schwann cells is the basis for understanding how mutations cause demyelinating neuropathies (Arroyo and Scherer 2000). The myelin sheath itself can be divided into two domains, compact



Hereditary Neuropathies, Fig. 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

and non-compact myelin, each of which contains a nonoverlapping set of proteins (Fig. 1). Compact myelin forms the bulk of the myelin sheath. It is largely composed of lipids, mainly cholesterol and sphingolipids, including galactocerebroside and sulfatide, and three proteins – MPZ/P_0, PMP22, and myelin basic protein (MBP). Non-compact myelin is found in the paranodes and incisures, and 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. Gap junctions formed by connexin32 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 300-fold) than a circumferential route. Homozygous mutations that cause loss-of-function in genes encoding proteins that play an essential function in myelinating Schwann cells would be expected to cause demyelination. Similarly, mutations of genes that are expressed by myelinating Schwann cells, that cause a toxic gain-of-function, would also be expected to cause demyelination (Scherer and Wrabetz 2008). Although Schwann cells are quite adept at remyelinating axons, if the remyelinating Schwann cells also express the causative mutation, then this does not result in long-lasting remyelination.

Classification of Inherited 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 (Table 1) are called CMT or HMSN. Different kinds are recognized clinically, aided by electrophysiological testing of peripheral nerves If the forearm motor nerve conduction velocities 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 (Barisic et al. 2008; Shy et al. 2005; Wrabetz et al. 2004). Because some non-syndromic inherited neuropathies distinctive phenotypes, they have been given different names, including HSAN and HSN. What makes things even more confusing is that mutations in different genes cause similar phenotypes, and different mutations in the same gene can cause different phenotypes (Table 1). In some cases, such as *PMP22* and *MPZ*, the evidence favors the idea that the more severe phenotypes are caused by gain-of-function alleles, and that (heterozygous) loss-of-function alleles cause milder phenotypes (Scherer and Wrabetz 2008).

In addition to non-syndromic neuropathies, there are more than 200 genetic diseases in which peripheral neuropathy has been noted. In Table 2, I have listed only those in which pain sensation has been lost to an extreme degree, and those with pronounced neuropathic pain.

Inherited Neuropathies Associated with Decreased Nociception

With the exception of some of the hereditary motor neuropathies, patients who have a hereditary neuropathy have diminished nociception. For hereditary axonal neuropathies – CMT2, AR-CMT2, HSAN, and HSN (Table 1) – this is expected, as these neuropathies affect unmyelinated axons, albeit to varying degrees. The diminished pinprick sensation that one finds in patients with inherited demyelinating neuropathies is probably due to the involvement of A-delta sensory axons, which are thinly myelinated. In some inherited neuropathies, however, the appreciation of pain can become so diminished that patients develop Charcot joints, ulcers, and infections, to the point where amputations are required. This distinct ("ulcero-mutilating") phenotype is the reason that these patients are usually classified as having a distinct for HSAN and HSN, but patients with CMT2B also fit this description (Auer-Grumbach et al. 2006). HSAN/HSN is the rarest kind of hereditary neuropathy – only ~20 % of affected patients have been found to mutations in these genes – so many causes remain to be discovered (Rotthier et al. 2009). Three recessively inherited syndromic neuropathies are associated with an ulcero-mutilating phenotype (Table 2). Recessive mutations in *CCT5* cause a severe sensory, ulcero-mutilating neuropathy, but also a prominent spastic paraplegia. Tangier disease causes a severe sensory neuropathy in syringomyelia-like pattern, and can result in painless ulcerations and acromutilation. Mitochondrial DNA depletion syndrome 6, which is found in Navajo children owing to a founder effect, causes an ulcero-mutilating neuropathy, but also encephalopathy, myelopathy, and fatal liver disease.

I have highlighted several important advances into the causes of HSAN/HSN below.

HSAN1A and 1C. Missense mutations in either serine palmitoyltransferase, long chain base subunit-1 (*SPTLC1*) or *SPTLC2* – which encode two of the three subunits of the enzyme serine palmitoyltransferase – cause HSAN1A and HSAN1C, respectively. Serine palmitoyltransferase catalyzes the condensation of serine and palmitoyl-CoA, which is the first and rate-limiting step in the de novo synthesis of ceramide, a signaling molecule itself, and a precursor for complex sphingolipids. In addition to reducing enzymatic activity, the dominant *SPTLC1* and *SPTLC2* mutations associated with HSAN1 reduce the substrate specificity of serine palmitoyltransferase, allowing the incorporation of L-alanine and L-glycine, and subsequently the formation of two atypical deoxysphingolipids (Gable et al. 2010; Penno et al. 2010). Because they can neither be converted into complex sphingolipids nor degraded by the classical catabolic pathways, deoxysphingolipids accumulate in cells. Supplementation with L-serine reverses the accumulation of these abnormal lipids, making this a possible therapy for these diseases (Garofalo et al. 2011).

Hereditary Neuropathies, Table 2 Selected syndromic inherited neuropathies that prominently affect pain

Disease (MIM)	Mutated gene/ linkage	Clinical features
Recessively inherited, syndromic demyelinating neuropathies that prominently affect pain		
Metachromatic leuko-dystrophy (250100)	*ARSA*	Demyelinating neuropathy; optic atrophy; mental retardation; hypotonia; phase of neuropathic pain
Dominantly inherited, syndromic axonal neuropathies that prominently affect pain		
FAP 1 and 2 (176300)	*TTR*	Painful axonal neuropathy with prominent involvement of small axons; other organs involved; FAP 2 also has carpal tunnel syndrome
FAP 3/"Iowa" type (107680)	*APOA1*	Painful axonal neuropathy; renal and hepatic disease
Fabry disease (301500)	*GLA*	X-linked; painful neuropathy even painful crises; cardiomyopathy; renal failure; angiokeratoma
Acute intermittent porphyria (176000)	*HMBS*	Acute neuropathy follows crises of abdominal pain; psychosis; depression; dementia; seizures
Coproporphyria (121300)	*CPOX*	Skin photosensitivity; psychosis; crises of acute neuropathy (and abdominal pain) are rare
Variegate porphyria (176200)	*PPOX*	South Africa: founder effect; symptoms similar to those in acute intermittent porphyria
Erythropoietic proto-porphyria (177000)	*FECH*	Dermatitis; photosensitivity; liver disease; acute neuropathy rare
Recessively inherited; syndromic conditions that cause neuropathy and prominently affect pain		
Tangier disease (205400)	*ABCA1*	Atherosclerosis and/or peripheral neuropathy; syringomyelia-like loss of pain sensation can result in painless ulcerations and acromutilation
HSN with spastic paraplegia (256840)	*CCT5*	Infantile onset of spasticity, followed by severe sensory > motor axonal neuropathy
Hereditary tyrosinemia type 1 (276700)	*FAH*	Hepatic and renal disease; cardiomyopathy; crises of acute neuropathy and abdominal pain similar to those in porphyrias (but in infancy/childhood)
Mitochondrial DNA depletion syndrome 6 (256810)	*MPV17*	Affects Navajo infants/children; encephalopathy; myelopathy; neuropathy resulting in painless ulcerations and acromutilation; fatal liver disease
Recessively inherited conditions that prominently affect pain in which neuropathy is not documented		
Cold-induced sweating 1 (272430)	*CRLF1*	Poor sucking in infancy; cold-induced sweating; diminished pain caused by cold/hot/mechanical stimuli
Cold-induced sweating 2 (610313)	*CLCF1*	Poor sucking in infancy; unexplained fevers; cold-induced sweating; diminished pain caused by cold/hot/mechanical stimuli
Stüve-Wiedemann/Schwartz-Jampel type 2 syndrome (601559)	*LIFR*	Osteodysplasia with similar findings to HSN-3/familial dysautonomia: lack of corneal reflex, lack of fungiform papillae, tongue ulceration; also cold-induced sweating
Congenital indifference to pain (253000)	*SCN9A*	Congenital onset of inability to feel any kind of pain.
Dominantly inherited conditions that prominently affect pain in which neuropathy is not documented		
Familial episodic pain syndrome (no OMIM)	*TRPA1*	Debilitating upper body pain starting in infancy; skin biopsies and quantitative sensory testing is normal
Primary erythromelagia (133020)	*SCN9A*	Onset in childhood or adolescence of recurrent attacks of red, warm, and painful hands and/or feet
Paroxysmal extreme pain disorder (167400)	*SCN9A*	Neonatal or infantile onset of attacks of pain accompanied by autonomic signs, often triggered by defecation; skin biopsies show no consistent abnormalities

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/

HSAN2A and HSN2C. Recessive mutations in *WNK1* cause HSAN2. *WNK1* is a member of the family of With No Lysine Kinases, and regulates the function of ion channels and transporters in a variety of cell types, and presumably in neurons/axons, too. Although a global loss of *WNK1* function is probably lethal (Zambrowicz et al. 2003), the mutations that cause HSAN2A reside in exon 11, which is mainly expressed by PNS neurons (Shekarabi et al. 2008). The sequence that is encoded by exon 11 interacts with the portion of KIF1A (one on the main orthograde motors in axons) that is encoded by exon 25b, which is highly expressed in sensory neurons. Remarkably, a homozygous frameshift mutation in exon 25b causes an axonal neuropathy, providing strong support for the functional importance of this interaction (Riviere et al. 2011).

HSAN3/Familial Dysautonomia/Riley-Day Syndrome. Recessive mutations in *IKBKAP* cause HSAN3. Most patients are homozygous for a mutation in a donor splice site; this causes a cell type–specific reduction in the levels of IKBKAP protein (Cuajungco et al. 2003). IKBKAP is a component of the elongator complex, which has diverse cellular functions, including the acetylation of microtubules (which increases their stability) and neuronal maturation (Creppe et al. 2009).

HSAN4/CIPA syndrome and HSAN5. Recessive mutations in *NTRK1* and *NGFB* cause HSAN4 and HSAN5, respectively. *NGFB* and *NTRK1* encode nerve growth factor (NGF), and its receptor, TrkA, respectively. Based on the neurobiology of *Ngfb*- and *Ntrk1*-null mice, autonomic and small sensory neurons likely die in utero, so that HSAN4 and HSAN5 are likely to be congenital neuronopathies (Bibel and Barde 1999). HSAN4 is much more common than HSAN5, but has a similar phenotype (Carvalho et al. 2011; Indo 2001). As predicted from the knockout mouse model, myelinated axons (C-fibers) and thinly myelinated axons (A-delta fibers) that subserve nociception are globally and congenitally absent in HSAN4, whereas larger myelinated afferent axons (A-alpha and A-beta), which subserve several kinds of mechanoreceptors (associated with Merkel cells, hair follicles, Pacinian corpuscles, Meissner corpuscles, Golgi tendon organs, and muscle spindles) appear to be spared. Biopsies of skin and sweat glands are largely devoid of axons (Nolano et al. 2000).

Inherited Neuropathies Associated with Prominent Neuropathic Pain

Neuropathic pain is seldom a prominent feature of CMT. It is typical of patients who have CMT2-P_0 (Gemignani et al. 2004), 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, however, is not a prominent symptom in most patients with *MPZ* mutations; they have a demyelinating neuropathy (CMT1B or DSN).

Recurrent episodes of painful brachial plexus lesions are the hallmark of hereditary neuralgic amyotrophy (Windebank 1993). This is a dominantly inherited disorder caused by mutations in *SEPT9*. 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.

Pain is a prominent feature of most of the syndromic neuropathies listed in Table 2. FAP types 1, 2, and 3 are caused by dominant mutations in transthyretin or apolipoprotein A1 that result in amyloid deposition in peripheral nerves and other tissues. Fabry disease is an X-linked disease caused by the lack of α-galactosidase, and is associated with a painful peripheral neuropathy and even painful crises. Several of the porphyrias, especially acute intermittent porphyria, as well as hereditary tyrosinemia, are associated with acute, painful, axonal neuropathies. Finally, abnormal pain is a feature of several conditions in which neuropathy has not been well documented – familial episodic

pain syndrome, primary erythromelagia, paroxysmal extreme pain disorder, cold-induced sweating 1 and 2, and Stüve-Wiedemann/Schwartz-Jampel type 2 syndrome.

Summary

Almost all neuropathies result in diminished nociception; when this is profound, an ulcero-mutilating neuropathy is the result. The *Ntrka-* and *Ngfb*-null mice show how animal models can illuminate the clinical problem; other, genetically authentic animal models of these diseases are needed for further study. Finding the genes that are essential for nociception will potentially lead to novel targets for treating neuropathic pain, as exemplified by the search for compounds that selective block Nav1.7 (the Nav channel encoded by SCN9A). Except for the dominant mutations of *SCN9A* and *TRPA1*, both of which encode ion channels, how mutations result in enhanced neuropathic pain remains unexplained at a molecular level.

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Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

► Hereditary Neuropathies

Hereditary Sensory and Autonomic Neuropathy (HSAN)

► 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.

Cross-References

► Hereditary Neuropathies

Hereditary Sensory Neuropathy (HSN)

► Hereditary Neuropathies

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.

Cross-References

- ▶ 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 lifelong latent state in those neurons.

Cross-References

- ▶ Opioids and Gene Therapy

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 sensory ganglia for decades after an infection. Herpes zoster results when the dormant virus in these nerve cell bodies is reactivated, often as a result of decline in cellular immunity to VZV with aging or immunosuppression.

Cross-References

- ▶ Cancer Pain, Assessment in the Cognitively Impaired
- ▶ Postherpetic Neuralgia
- ▶ Postherpetic Neuralgia, Pharmacological and Nonpharmacological Treatment Options

Herpes Zoster Pain

- ▶ Postherpetic Neuralgia, Etiology, Pathogenesis, and Management

Heterocyclic Antidepressants

- ▶ Antidepressant Analgesics in Pain 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, resulting in homomeric channels, or different, resulting in heteromeric channels.

Cross-References

- ▶ GABAA Receptors
- ▶ Nicotinic Receptors
- ▶ 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.

Cross-References

► Spinal Cord Injury Pain

Heterozygosity

Definition

Heterozygosity is a state in which the maternal and paternal alleles 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.

Cross-References

► 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.

Cross-References

► NSAIDs, Pharmacogenetics

Hidden Triggers

Definition

Hidden triggers are internal precipitating mechanisms.

Cross-References

► 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.

Cross-References

► Postoperative Pain, Acute Pain Team

High Thoracic Epidural Anesthesia

Definition

High thoracic epidural anesthesia leads to a reversible cardiac sympathectomy blocking the segments T1–T5. The epidural catheters are inserted at levels C7–T1 or at levels T1–T2 by the median approach and with hanging drop technique.

Cross-References

► Postoperative Pain, Thoracic and Cardiac Surgery

High Threshold Neurons

Synonyms

HT neurons

Definition

HT neurons respond fairly selectively to noxious mechanical stimuli. They may have a minimal response (a few action potentials) 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.

Cross-References

- ▶ 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 Calcium Channels

▶ Calcium Channels in the Spinal Processing of Nociceptive Input

High-Threshold Mechanoreceptor

▶ Nociceptors in the Orofacial Region (Skin/Mucosa)

High-Threshold Mechanoreceptors

▶ Mechanonociceptors

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 (e.g., bradykinin). The general interpretation is that these receptors are nociceptors and induce muscle pain when activated.

Cross-References

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

High-Threshold Neurons

▶ Thalamus, Nociceptive Cells in VPI, Cat and Rat

High-threshold VDCCs

▶ Calcium Channels in the Spinal Processing of Nociceptive Input

High-Velocity Thrust Manipulation (HVTM)

▶ Spinal Manipulation, Pain Management

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 formations. Perhaps the most extensively studied structure in the brain, the hippocampal region has most often been implicated in memory processing.

Cross-References

► 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.

Cross-References

► Hippocampus and Entorhinal Complex: Functional Imaging

Hippocampus and Entorhinal Complex: Functional Imaging

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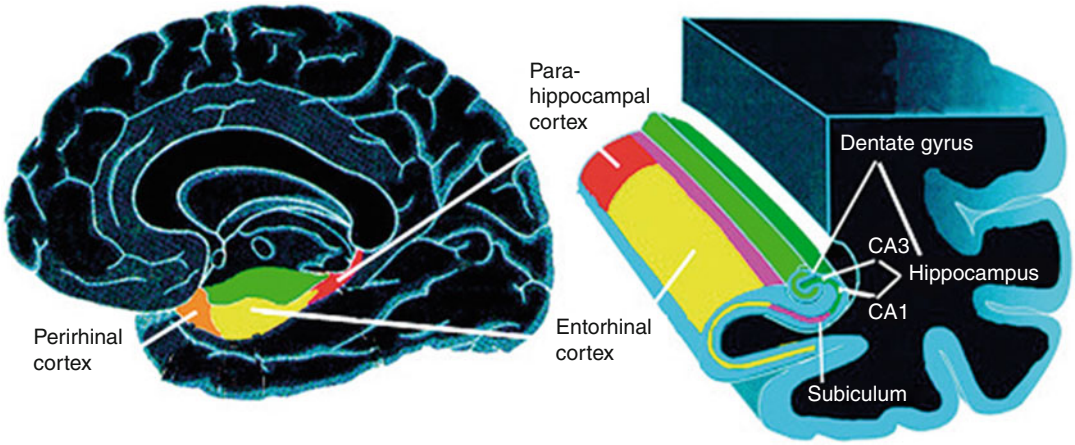
Synonyms

Entorhinal cortex and hippocampus; Functional imaging; Neuroimaging; Parahippocampal region

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



Hippocampus and Entorhinal Complex: Functional Imaging, Fig. 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*)

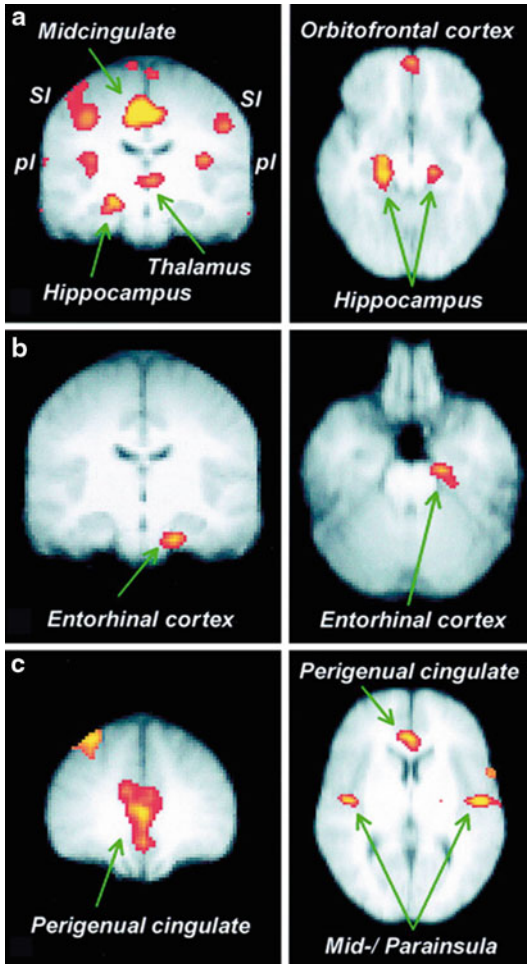
parahippocampal cortices, which in turn receive widespread projections from sensory and association areas in the frontal, temporal, and parietal lobes (Squire et al. 2004).

► 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 noninvasive 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), magnetoencephalography (MEG), and electroencephalography (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 hippocampal 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



Hippocampus and Entorhinal Complex: Functional Imaging, Fig. 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))

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

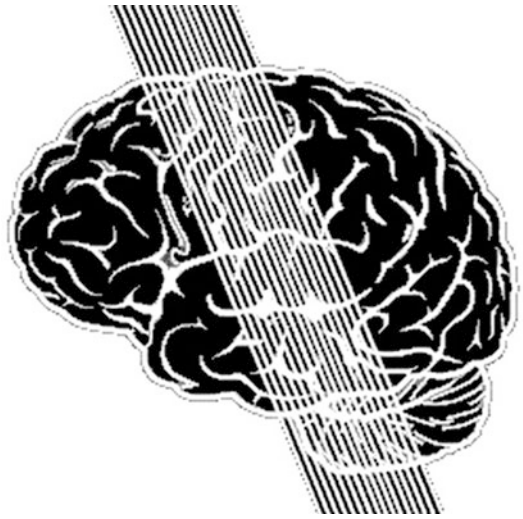
and analgesia from the pain, anxiety is characterized by risk assessment behavior or behavioral inhibition (the rat hesitates to enter the space where a cat might be). This behavior is associated with increased somatic and environmental attention, which can lead to anxiety-driven hyperalgesia (McNaughton 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 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



Hippocampus and Entorhinal Complex: Functional Imaging, Fig. 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

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 subregions 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 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) (Table 1).

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	–

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Histamine

Definition

Histamine (2-(4-imidazolyl)-ethylamine), a biogenic amine, is synthesized by decarboxylation

of the amino acid histidine mostly in mast cells. It is a hydrophilic vasoactive amine, a potent vasodilator, and also a neuromodulator in the central nervous system. As a strongly vasodilating substance, histamine plays a key role in many allergic reactions. In the superficial layers of the skin, histamine released from mast cells is strongly pruritogenic, by binding to H1 receptors in the terminal membranes of a special subgroup of C-afferent fibers.

Cross-References

► Nociceptor, Categorization

Histology of Nociceptors

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Synonyms

Chemo-nociceptors; Mechano-nociceptors; Polymodal nociceptors; Silent nociceptors

Characteristics

Extremes of stress and damage to most tissues of the body elicit a very salient unpleasant or aversive sensation, broadly termed "pain." Pain serves an essential survival component to all species, and the loss of pain perception often results in dysfunction and untimely death of the organism. Sensory neurons located among the dorsal root and cranial nerve ganglia with thin, slowly conducting axons innervate all tissues from which a sensory perception of pain can be elicited, and the generation of pain sensations has been attributed to activation of these "small-caliber" primary sensory neuron terminals, defined as ► nociceptors (Latin "nocere" meaning "to injure"). Axons supplying nociceptors are either thin, unmyelinated C axons or slightly thicker, lightly myelinated Aδ axons; the latter thought to account for the initial "fast, pricking pain" associated with noxious insults, while C axons account for the subsequent "slow, burning pain" following acute injury and particularly inflammation (Albrecht and Rice 2010; Rice and Albrecht 2008).

Electrophysiologic recording techniques have defined subsets of small-caliber axons that preferentially respond to specific modalities of painful stimuli such as noxious substances (*chemo-nociceptors*), extreme temperatures (*thermo-nociceptors*), intense mechanical stimuli (*mechano-nociceptors*), as well as various modality combinations (*polymodal nociceptors*). Most small-caliber axons are generally unresponsive to the broad variety of test stimuli used to elicit electrophysiological responses, but often, these same neurons can become responsive to noxious or even non-noxious stimuli under experimentally induced, prolonged pain conditions such as inflammation and nerve injury and, thus, have been inferred as *silent nociceptors*. However, it is more likely that the molecular signals involved in driving these small-caliber axons are more subtle and complex than the rather simplistic combinations of standard stimulus paradigms (Albrecht and Rice 2010; Rice and Albrecht 2008).

Most tissues, including skin, receive a rich variety of sensory innervation which includes large-caliber, myelinated Aβ axons that supply low-threshold mechanoreceptors, as well as small-caliber C and Aδ axons. Therefore, the identification of specific nociceptors was focused on tissues supplied principally by C and Aδ fibers where nearly any stimulation readily elicits a pain perception or withdrawal reflexes. Thus, most nociceptor histology was first elucidated in epithelial tissues such as cornea, inner tympanic membrane, tooth pulp, or highly vascularized connective tissues such as pericardium, testes, and joints (Kruger et al. 1981; Yeh and Kruger 1984). The nociceptive endings in such sites consistently lacked the distinctive

unique morphologies and encapsulations associated with low-threshold mechanoreceptive endings supplied by Aβ fibers (Kruger et al. 1981; Kruger 1988). These non-corpuscular nociceptive endings have been referred to as "free nerve endings" (FNE), and the electrophysiologically characterized and accurately mapped testicular nociceptive "spots" enabled fine-structural characterization based on serial reconstruction (Kruger et al. 2003a).

With the initial development of antibodies selective for neuropeptides, most of C and Aδ fibers first identified by immunohistochemistry contained substance P (SP) and calcitonin gene-related peptide (CGRP) (i.e., peptidergic). The endings of these peptidergic fibers in various tissues were more numerous and marked than previously known terminations of thin-caliber axons best seen at the time with reduced silver stains (Kruger et al. 1989). Importantly, many of these newly revealed endings were located in the epidermis, which was thought to lack innervation, and around blood vessels that were only thought to have sympathetic innervation. In dorsal root and cranial nerve ganglia, SP and CGRP were detected in many small neurons generally accepted as the source of the thin-caliber nociceptor axons. However, a large proportion of small-caliber neurons did not express peptides but were revealed by fluoride-resistant acid phosphatase (FRAP) histochemistry, which only labeled the cell bodies and, thus, did not reveal their axons (Zylka et al. 2005). Additionally, most of these non-peptidergic neurons and their axons, as well as some containing peptides, were found to bind the B_4 fragment of plant isolectins in rodents (Silverman and Kruger 1988).

Perhaps the densest thin-fiber peptidergic innervation accessible to external stimuli is in the dentinal tubules underlying the grinding surface of molar teeth (Silverman and Kruger 1987). This led to the concept of a "noceffector" system that would not subserve sensory detection but rather efferent maintenance of peripheral tissues. While damage inflicted to a tooth can result in severe pain, such a dense innervation of relatively protected dentinal tubules far exceeds that of the exposed superficial cornea from which pain can be elicited with stimuli that are innocuous elsewhere. As such, innervation density (axons/unit area) and pain do not appear to be linearly related. Similarly, thin-fiber innervation of glands, placodal epithelia (including the cochlear, vestibular, olfactory and vomeronasal, and gustatory organs), vascular and lymphoid tissue, as well as select secretory epithelia and most visceral organs is only more recently being explained in relation to nociception and pain. Examples of sheetlike distributions have enabled electron microscopic characterization of endings in the inner surface of the tympanic membrane (Yeh and Kruger 1984) and the tunica vasculosa of the testis, where 3-D reconstruction revealed clusters of "synaptic" vesicles at successive sites of a physiologically characterized nociceptive receptive field (Kruger et al. 2003a, b). Therefore, it is clearly evident that thin unmyelinated fibers are not invariably nociceptors, and it cannot be inferred from their distribution or simple histology that they respond to noxious stimuli with impulse production or that they are usually concerned with pain (Light and Perl 2003).

Importantly, not all thin-caliber neurons are nociceptors. In fact, a wide variety of non-nociceptive sensory perceptions including warmth, cold, tickle, itch, light touch, and stroking are associated with small to medium size C and/or Aδ axons which can be responsive innocuous thermal stimuli (thermoreceptors), molecules involved in normal tissue signaling (chemoreceptors), products of normal metabolism (metaboreceptors), and light mechanical stimuli (low-threshold mechanoreceptors) (Light and Perl 2003). Additionally, major sets of thin-caliber peptidergic C and Aδ fibers supply cutaneous blood vessels, where release of CGRP and SP has effector functions, including vasodilation and plasma extravasation, which are now known to mediate the process of "neurogenic inflammation" as described by Bayliss over 100 years ago (Bayliss 1901; Brain and Williams 1985, 1988; Brain et al. 1985). This innervation is likely involved in vasodilation normally related to thermal regulation and in meeting normal local tissue metabolic demands exacerbated by function, growth, or injury. Altogether, these lines of evidence raise questions about the functional identity of nociceptive sensory endings and evoked doubts about whether specific "nociceptors" even exist (Melzack and Wall 1962).

Subsequently, a major breakthrough occurred with the development of a specific antibody directed against protein gene product 9.5 (PGP9.5)/ubiquitin c-terminal hydrolase 1 (UCHL-1), a cytoplasmic enzyme important in protein regulation and enriched in neuroendocrine cells from all mammals and many nonmammalian species. Utilizing anti-PGP9.5 as an immunolabel distinctly and specifically marks peripheral nerves and was found to reveal far more extensive thin-caliber innervation and endings than were previously known. Under normal tissue and immunolabeling procedures, the PGP9.5 antibody consistently reveals the total innervation seen with all other antibodies against other neuronal antigens (Albrecht and Rice 2010; Rice and Albrecht 2008; Fundin et al. 1997).

Functional Characteristics of Nociceptors

Currently, a wide range of functional characteristics defined by molecular properties are implicated in the transduction and/or modulation of various types of nociceptive stimuli. The functions of a particular molecule are typically determined using a combination of in vitro and in vivo pharmacologic, electrophysiologic, and behavioral assessments involving specific agonists and antagonists, thermal and mechanical stimuli, and gain or loss of function mutations. The immunochemical and/or molecular identification of functional proteins expressed within presumptive small-caliber nociceptors includes specific neurotransmitters, cytokines, growth factors, amino acids, protons, ligand- and voltage-gated ion channels, and ligand-activated G-protein-coupled receptors (GPCR) (Albrecht and Rice 2010; Rice and Albrecht 2008) [see Stucky (2013) entry "Immunocytochemistry of Nociceptors" in this Encyclopedia].

In general, nociception is thought to be driven by direct activation of the nociceptor sensory potential by a specific noxious stimulus (i.e., thermal, chemical, mechanical) acting on an identified molecular receptor. More recently it has been demonstrated that nociceptor function may also be modulated indirectly via cells of the terminal tissue (i.e., keratinocytes, smooth muscle, endothelium, immune mediators). Furthermore, it is appreciated that the molecular signaling can lead to increased action potential generation (e.g., excitatory, pronociceptive, implicated in algesia) or decreased action potential generation (e.g., inhibitory, antinociceptive, implicated in analgesia) (Albrecht and Rice 2010; Rice and Albrecht 2008). For example, GPCR-activated second messenger signaling that opens sodium channels is implicated in pronociception, while signaling that activates inward-rectifying potassium channels (GIRKS) is usually implicated in anti-nociception.

Currently, there are several identified pronociceptive cellular signaling mechanisms which enhance small-fiber nociceptor activity either directly or indirectly, including, but not limited to:

1. *Neuropeptide signaling* (e.g., CGRP activation of RAMP1/CRLR complexes, substance P activation of NK1 receptors).
2. *Purinergic signaling* (e.g., ATP activation of multiple P2X receptors, ADP activation of multiple P2Y receptors) (Dussor et al. 2009).
3. *Endothelin-1 signaling* is mediated through two differentially expressed receptors (i.e., ETA, ETB); specific activation of ETA on nociceptors leads to painful responses (Balonov et al. 2006; Gokin et al. 2001).
4. *Biogenic amine signaling* (i.e., histamine activation of multiple H receptors) (Cannon et al. 2007).
5. *Cytokine signaling* (i.e., bradykinin activation of multiple B receptors).
6. *Proton activation* of multiple acid-sensing ion channels (ASICS), including even specificity for types of acids (i.e., lactic acid activation of ASIC3) (Molliver et al. 2005).
7. *MAS-related G-protein-coupled receptors* (*Mrgpr*) *activation*, particularly the epidermal fiber-targeted MrgprD, but which are also demonstrating genetic differentiation of non-noxious perceptions (i.e., itch, gentle stroking) (Zylka et al. 2005; Liu et al. 2008, 2009; Vrontou et al. 2013).
8. *Voltage-gated ion channel activation* directing largely sodium, calcium, and chloride movements, as exampled by the expression of Nav1.7 on nociceptors, for which a gain-of-function mutation results in hyperactivity of nociceptors and congenital painful

conditions (familial erythromelagia) (Estacion et al. 2008; Sheets et al. 2007; Dib-Hajj et al. 2005; Cho et al. 2012).

Additionally, of particular interest in pronociceptive mechanisms is the multimodal transient receptor potential (TRP) ligand-gated cation channel family, comprised of at least seven distinct subclasses, several of which are expressed robustly among small-caliber sensory neurons. The prototypical vanilloid family member (TRPV1) can be activated by noxious heat, protons, and exogenous chemicals (capsaicin) and is modulated by endogenous cannabinoid ligands (anandamide) (Caterina and Julius 2001). The prototypical ankyrin family member (TRPA1) is activated by multiple modalities including pungent exogenous chemicals (mustard oil) and endogenous (ankyrin) ligands but is also implicated in thermal perceptions of noxious cold and mechanical transduction (Kwan et al. 2009; Karashima et al. 2009). The prototypical melastatin-like family member (TRPM8) is also activated by noxious cold temperatures, exogenous chemicals (menthol, icilin), and endogenous ligands (lysophospholipids from PLA2 activity) (McCoy et al. 2011).

Conversely, there are some identified antinociceptive cellular signaling mechanisms which inhibit small-fiber nociceptor activity either directly or indirectly, including, but not limited to:

1. *Opioid signaling* mediated through several classes of opioid receptor (OR) and driven by numerous exogenous substances (e.g., morphine) and endogenous ligands (e.g., β-endorphin); particularly μOR activation leads to hyperpolarization of the nociceptors and inhibition of activity (Khodorova et al. 2003).
2. *Cannabinoid signaling* mediated through the cannabinoid receptors (CB1, CB2) driven by exogenous substances (THC) and endogenous phospholipid mediators (anandamide, 2-AG). Several lines of evidence suggest both indirect and direct modulation of nociceptor activity can be mediated through CB1 and/or CB2 activation, as well as CB ligand and receptor interactions with the TRP channels A1 and V1 (Ibrahim et al. 2005; Potenzieri et al. 2008; Akopian et al. 2008; Fioravanti et al. 2008).
3. *Voltage and ligand-gated ion channel activation* directing largely potassium movements, as exampled by activation of ATP-sensitive and various voltage-gated potassium channels in nociceptors, which directly inhibit activation and are modulated by a wide range of substances (Nicol et al. 1997; Rasband et al. 2001; Chi and Nicol 2007; Du et al. 2011; Tsantoulas et al. 2012; Passmore et al. 2012) and for which autoimmune-mediated loss of function leads to idiopathic pain conditions (Klein et al. 2012).
4. *Endothelin-1 signaling* is mediated through two differentially expressed receptors (i.e., ETA, ETB); specific activation of ETB leads to nociceptor inhibition directly or indirectly via keratinocyte-mediated opiate release and μOR activation (Khodorova et al. 2002, 2003). Importantly, ETB activation can have analgesic or algesic effects depending on the site where it is expressed and the timing of its activation following injury (Raffa et al. 1996; Werner et al. 2010).

The continued development of specific antibodies directed against many of these molecules, and the use of conditional promoter gene expression of fluorescent reporter molecules, has enabled the microscopic visualization (histology) of neurons that express these functional molecules, including neuronal cell bodies, axons, peripheral sensory endings, and central terminations. Structurally, the small-caliber sensory endings most often terminate with FNE morphology, although the location of the endings that express a particular immunochemical property may be specific to a particular target or multiple targets. For example, endings that express MrgprD only terminate in the epidermis, whereas endings that express CGRP terminate in numerous tissues, including the skin, where they can be located in the epidermis, and dermis around blood vessels, hair follicles, and sweat glands (Albrecht and Rice 2010; Zylka et al. 2005). Such CGRP expressing endings presumably serve different functions in these disparate locations (Rice and Albrecht 2008). The fine structure of physiologically marked FNE reveals nearly complete Schwann cell process envelopment and sequential

zones of clustered vesicles (Kruger et al. 2003a), and the dense-core vesicles have been labeled with colloidal gold, revealing peptide localization within the dense core.

The multi-molecular profiles of sensory endings with particular morphologies and tissue locations have been elucidated through the use of multiple combinations of immunolabels and reporter gene expressions applied to alternating sections from the same and similar tissue specimens, as well as on sensory ganglia where mRNA expression can also be assessed by in situ hybridization. The combined molecular properties can then be used to infer the potential functional properties of a particular sensory ending. Continued small-caliber axon research, particularly with the sensory neuron-specific Mrgpr receptor family, is beginning to uncover molecular expression signatures that are consistent with the functional varieties of nociceptors defined by electrophysiology. Indeed, the use of multi-molecular morphological strategies has confirmed that sensory ending expression of certain molecules (i.e., TrpV1) correlates with electrophysiological properties (i.e., thermal nociception).

Critically, these comprehensive immunolabeling studies demonstrate that all sensory axon endings, including those which are likely nociceptors, express complex molecular properties responsible for integrating multiple stimulus modalities. Therefore, molecularly, all sensory axons appear to be capable of polymodal functioning. Certain structural and enzymatic properties of sensory neuron axons are consistently co-expressed. For example, co-expression of the pan-neuronal enzyme PGP (which reveals all innervation), the 200 kD neurofilament protein (NF), and the myelin basic protein (MBP) has been consistently revealed in species ranging from mice, mole rats, manatees, monkeys, to humans. Utilizing that preparation, the PGP-positive thin-caliber fibers which lack NF or MBP immunolabeling represent the C fiber populations, whereas the NF/MBP-positive population represents Aδ fiber populations. Further immunolabel combinations have revealed additional detailed classification breakouts, including that CGRP is expressed in subsets of C fibers and Aδ fibers, while the P2X3 receptor is exclusively expressed in C fibers that nearly all lack CGRP. Thus, thin-caliber expression of P2X3 and CGRP appears to be mutually exclusive. Moreover, the μOR receptor is almost exclusively expressed by C fibers that express CGRP, but not C fibers that express P2X3, and rarely on Aδ fibers that express CGRP. Therefore, it can be inferred that peripheral opiate analgesia involving the μOR is likely acting on CGRP expressing C fibers. By contrast, TrpV1 expression appears in C fibers that express CGRP or P2X3 and can be found with varying proportions in different species. The myriad permutations of multi-molecular characteristics among the small-caliber sensory neuron populations are gradually being elucidated, and the functional implications of these markers revealed. Currently, several important observations can be highlighted from these comprehensive multi-molecular immunochemical assessments of small-caliber (nociceptor) peripheral innervation histology:

1. Dense concentrations of molecularly complex C and Aδ fiber-free nerve endings with nociceptive immunochemical labeling properties are located at sites which rarely receive nociceptive inputs (e.g., dental pulp, bone marrow) but which may be responsible for sensing increased stress of these hard structures prior to overt damage.
2. Thin-caliber C fibers endings with nociceptive immunochemical labeling properties terminate individually in some anatomical sites (i.e., epidermis, dermal vasculature) and also terminate in close association with certain types of Aβ low-threshold mechanoreceptors in dermal papilla of glabrous skin (i.e., Meissner corpuscles) and surrounding hair follicles (i.e., piloneural complexes). The Aβ fibers in both locations are purportedly rapidly adapting low-threshold mechanoreceptors that contribute to detecting vibration across glabrous skin and hairs. Some of the C fibers contain CGRP and SP, while the Aβ endings express neuropeptide receptors, allowing for stimulus integration at the site of sensory transduction. Moreover, the Aβ fiber endings in these locations can also express various molecular properties implicated in nociception, suggesting that these

low-threshold mechanoreceptors may impart functional signals as part of the pain perception (Pare et al. 2001). Indeed, patients suffering from complex regional pain syndrome type 1 (CRPS I) with severe hairy skin allodynia have profound neuropathology associated with the organization of both large- and small-caliber hair follicle endings (Albrecht et al. 2006).

3. Dense concentrations of C and Aδ fibers with nociceptive immunochemical labeling properties terminate within the adventitia of cutaneous and visceral arteries, arterioles, and arteriole-venule shunts. Subsets of these visceral fibers express the lactic acid receptor ASIC3, while others express the TrpV1 receptor, even though that vascular anatomical location would be unlikely challenged by noxious heat stimuli. Most of this vascular sensory innervation expresses CGRP and substance P, which are potent vasodilators, and implicated in inflammatory pain. As such, these thin-caliber sensory fibers presumably function in monitoring peripheral vascular status while contributing an essential effector role in vasodilatation.
4. Numerous studies have now demonstrated significant and essential interactions of thin-caliber axons and mediators derived from target tissues (i.e., epidermal keratinocytes and immune cells, vascular smooth muscle and endothelium). For example, a variety of neural signaling molecules are expressed in differentially stratified distributions across the deep to superficial layers of keratinocytes, involving mediators implicated in both analgesic (ETB, CB2) and algesic (Nav, CGRP, ATP/P2X, TrpV1) mechanisms (Albrecht and Rice 2010; Rice and Albrecht 2008; Ibrahim et al. 2005; Khodorova et al. 2002; Hou et al. 2011; Lumpkin and Caterina 2007; Zhao et al. 2008).

Importantly, protein immunocytochemistry has ushered in an era of labeling for antigens that have physiological properties implicated in eliciting or modulating nociception. These include neuropeptides, neurotransmitters, immune neuromodulators, G-protein-coupled receptors, endothelin and purinergic receptors, and a variety of ion channels. Concomitant molecular advances continue to indicate that specific molecular expressions can be linked to specific functional varieties of thin-axon nociceptors but importantly also to thin-caliber non-nociceptive neurons, such as those now implicated in itch (Liu et al. 2009) and even pleasurable perceptions such as gentle skin stroking (Vrontou et al. 2013), potentially demonstrating the existence of a small-caliber "volupticeptor" population.

Distinctive morphological patterns (Zylka et al. 2005), complex protein immunochemistry (Rice and Albrecht 2008), and microneurographic electrophysiological evidence (Campero et al. 2009; Obreja et al. 2010; Orstavik et al. 2006) are mounting to suggest that many thin-caliber sensory axon and associated small sensory neurons have an inherent capacity to be polymodal at the molecular/protein expression level (e.g., immunolabeling). However, these same classes remain somewhat singularly definable in electrophysiologic functionality testing (e.g., the nociceptor, or pruritic specific, or as noted above, the idea of a pleasure specific population) based from experimental stimuli. Thus, most (if not all) thin-caliber sensory neurons may have a spectrum of functional capabilities, potentially related to nociception, but that most likely also subserve homeostatic tissue maintenance mechanisms. Since peptide release may constitute a principal constitutive function of peptidergic sensory neurons, the afferent/efferent functional duality led to the term "noceffector" (Kruger 1988, 1996; Kruger et al. 1989) for those thin-caliber neurons whose peptides and target receptor-binding sites had been identified. This definition also serves as a compromise with the potentially misleading and erroneous nociceptor designation when evidence for nociception cannot be invoked or is exceedingly rare, as in teeth, testis, ducts, sphincters, etc. Certainly, the specific sensory neuron molecular identities and histologic characterizations subserving various nociceptive/pain perceptions are far from resolved.

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History

▶ History of Analgesics

History of Analgesics

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Synonyms

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, while 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 bloodletting (Brune 1984). Such practices were continued until the nineteenth century (Williams 1975) – probably without success. It was only recently that the inhibition of the cytokine effect has become feasible (Smolen et al. 2000).

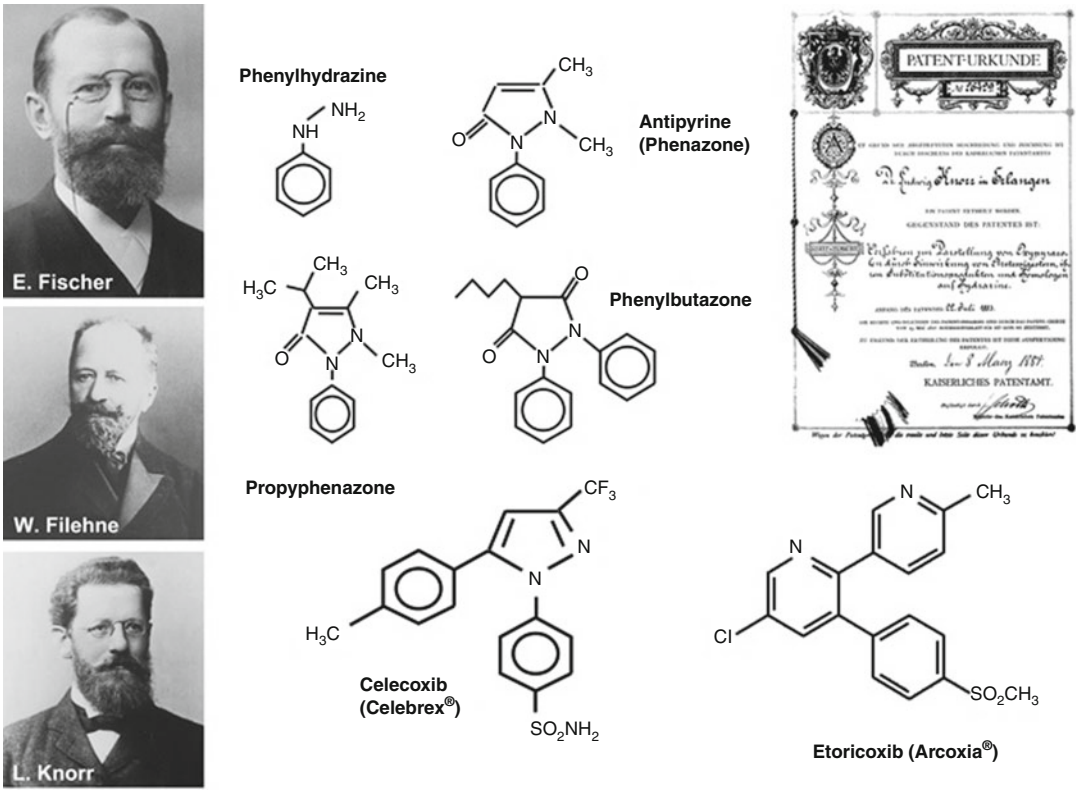
Characteristics

A scientific approach to pain therapy became possible in the nineteenth century, with substances isolated from plants including the willow tree (salicylic 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 in 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, china 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)



History of Analgesics, Fig. 1 Synthesis of phenazone, the first synthetic drug ever, in Erlangen 1882

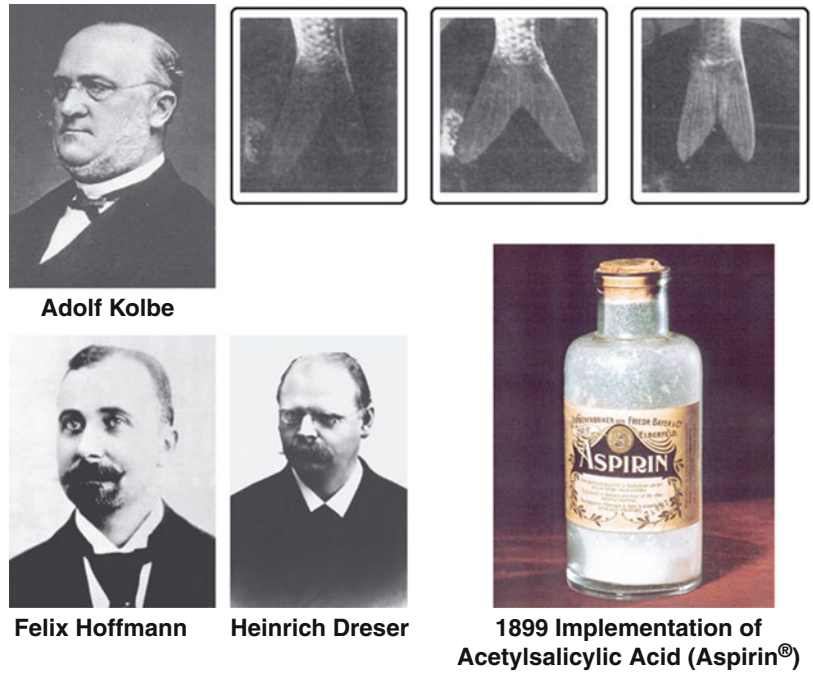
esterified salicylic acid with acetate and (re-)discovered Aspirin. This synthesis was done in another dye factory, namely, Bayer (Rinsema 1999). The new science of chemistry helped to transform the dye industry by providing both synthetic dyes and new synthetic drugs.

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 1985). Bayer further investigated acetanilide and found that a by-product of aniline dye production, namely, "acetophenetidin," was equally effective. It was marketed as Phenacetin® (Sneader 1985). These discoveries constituted, as Tainter phrased it (Tainter 1948), "[. . .] the beginning of the famous German drug industry and ushered in Germany's 40-year dominance of the synthetic drug and chemical field." Thus, by the end of the nineteenth century, four 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 be taken in gram quantities (spoon-wise). Sodium salicylate had an unpleasant taste. Taking several grams of phenacetin led to methemoglobinemia, 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

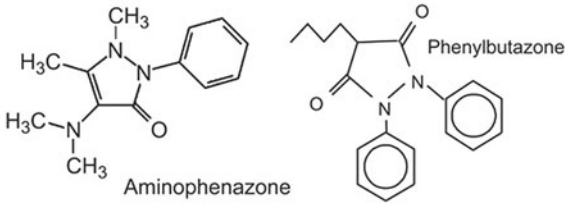


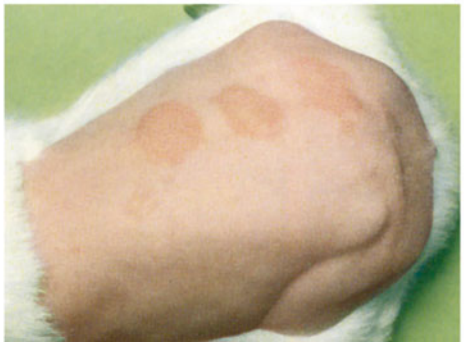
History of Analgesics, Fig. 2 Synthesis of acetylsalicylic acid in 1897

acid to please his father who suffered from rheumatoid arthritis (Brune 1997; Sneader 1985). On a suggestion of v. Eichengrün (Bayer), Hoffmann produced acetylsalicylic acid, which his father preferred (Brune 1997; Sneader 1985). 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 Spiraea 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 recognized that he did not 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 methemoglobinemia. In contrast, Sterling (UK) found acetaminophen free of methemoglobinemia and marketed it as Panadol® (Sneader 1985).

At Hoechst, the structure of phenazone was modified. The resulting compounds amidopyrine, 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, gastrointestinal, 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, analgesics were mixed and supplemented, e.g., with caffeine (APC powder) and 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).



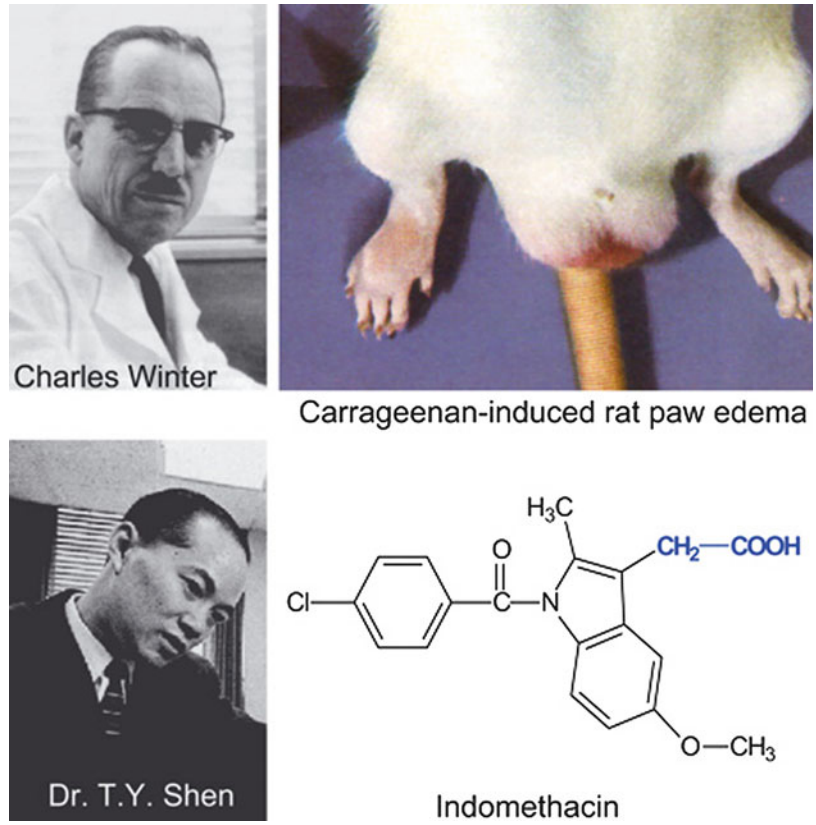


History of Analgesics, Fig. 3 Synthesis of phenylbutazone in 1949

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 1997; Sneader 1985). Burns and Brodie related this effect to phenylbutazone, which was present for much longer periods of time than aminophenazone (Domenjoz 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



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

formerly named – was determined. It was 70 years after the synthesis of aspirin when John 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 nonacidic chemicals that barely inhibited cyclooxygenases, while 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. Nonacidic 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 two 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, two molecular drug targets, COX-1 and COX-2 (the expression of COX-2 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 COX-2, because this enzyme appeared not to be involved in the production of gastrointestinal-protective prostaglandins (for a review, see, e.g., Brune and Hinz 2004; Hinz and Brune 2002). Diclofenac and meloxicam were found to exert some but not sufficient selectivity to warrant gastrointestinal tolerance (Tegeder et al. 1999). Selective COX-2 inhibitors currently used for the treatment of osteoarthrosis and rheumatoid arthritis are the sulfonamide celecoxib and the methylsulfone etoricoxib. Others were withdrawn due to cardiovascular (rofecoxib) or cardiovascular and cutaneous (valdecoxib) side effects. However, comparable rates of thrombotic cardiovascular events have been subsequently reported for etoricoxib and diclofenac (Cannon et al. 2006), suggesting that there is presently no rationale for a differentiation of selective COX-2 inhibitors and nonselective COX inhibitors in terms of cardiovascular safety (for a review, see, e.g., Hinz et al. 2007; Brune et al. 2010). Another selective COX-2 inhibitor, lumiracoxib, is a relative of diclofenac and, like diclofenac, is sequestered into inflamed tissue. It combines COX-2 selectivity with selective tissue distribution (Feret 2003). However, the compound was withdrawn due to hepatotoxic effects.

Conclusion

After more than 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.

Acknowledgement The helpful discussion with many scientists, in particular I. Otterness, A. Sallmann, T.Y. Shen (†), and G. Wilhelmi, is gratefully acknowledged.

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Hit Rate or Sensitivity

Definition

Hit rate or sensitivity is the probability of response "A" when event A has occurred.

HIV and Pain

► Pain in Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

HIV/AIDS-related Pain

► Cancer Pain and Pain in HIV/AIDS

HIV-associated Neuropathy

► Pain in Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

HMSN

Definition

The acronym for hereditary motor and sensory neuropathy.

Cross-References

► Hereditary Neuropathies

Hoffmann-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 nineteenth 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.

Cross-References

► 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.).

Cross-References

► 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).

Cross-References

► 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, are referred to as homework.

Cross-References

► Multidisciplinary Pain Centers, Rehabilitation

Homologous Gene

Definition

A homologous gene has a similar, though often far from identical, sequence to another gene.

Cross-References

► 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 heteromeric channels.

Cross-References

► 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.

Cross-References

► NSAIDs, Pharmacogenetics

Horner's Syndrome

► Headache Due to Dissection

Horsley-Clarke Apparatus or Stereotaxic Frame

Definition

Horsley-Clarke apparatus or stereotaxic frame is a solid metallic frame made of two horizontal graduated bars fixed perpendicularly 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).

Cross-References

► Poststroke Pain Model, Thalamic Pain (Lesion)

Hospice Care

Definition

The term "hospice care" can refer to the care provided in a special health-care system (as in the USA) or it can be used to denote end-of-life care or palliative care generally (in countries other than the USA). In the USA, hospice is a government-supported health-care system established more than 25 years ago to provide specialist palliative care for patients with far advanced illness. The core of this system is a home care program offering a range of services to the patient and family.

Cross-References

► 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 others." Can be inwardly directed toward oneself ("intrapunitiveness") or directed toward others ("extrapunitiveness"), Smith (1992).

Cross-References

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

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Hot Plate Test (Assay)

Definition

The hot plate test involves placement of a rat or mouse on a heated surface (usually $\geq$50 °C) and measuring the latency (in seconds) to licking of a hindpaw or jumping. The hot plate test, which employs a fixed temperature, has largely been supplanted by what is termed the "Hargreaves Test" in which a rat or mouse is placed on a glass surface and the animal's hindpaw is heated from below by a radiant heat source. Latency from stimulus to withdrawal of the paw is measured in this test.

Cross-References

► 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.

Cross-References

► Dental Pain, Etiology, Pathogenesis, and Management

Household Income and Chronicity

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

HPA Axis

Definition

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

Cross-References

▶ Fibromyalgia, Mechanisms, and Treatment

HT Neurons

▶ High Threshold Neurons

Human Factors Engineering

▶ Ergonomics Essay

Human Models

▶ Human Models of Inflammatory Pain

Human Models of Inflammatory Pain

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Synonyms

Human models; Inflammatory pain

Definition

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

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 sensitization of nociceptors, inflammatory mediators also cause peripheral and central sensitization 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 sensitization. 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 summarized below.

The Capsaicin Model

▶ Capsaicin is the chemical component of chili 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 min compared to the mild-moderate pain of topical application that develops slowly over 10–30 min. Both methods produce 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 sensitization of TRPV1. Very high concentrations of capsaicin desensitize the heat responsive ion channel. This is sometimes evident following

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[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2° Punctate[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2° Dynamic[c]	Yes	Yes	Yes	Yes	Yes	No	No
Dynamic duration[d]	<1 h	<1 h	~ 4 h	<1 h	>2 h	–	–
2° Punctate onset[e]	<1 h	<1 h	<1 h	<1 h	<1 h	>~4 h	>~4 h

[a]Decreased heat pain threshold in the inflamed site
[b]Area of secondary punctate hyperalgesia
[c]Area of secondary dynamic mechanical allodynia
[d]Duration of dynamic mechanical allodynia
[e]Time to onset of secondary punctate hyperalgesia. See text on individual models for data references

intradermal delivery and is characterized 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 h.

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 min (Pedersen and Kehlet 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 sensitization (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 produce 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 min, but in this model the area can be rekindled by restimulating the treated site with a heat stimulus of 40 °C for 5 min. This rekindling can be repeated every 20 min for up to 4 h, 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., sensitization to heat in the primary zone and secondary areas of dynamic mechanical allodynia and punctate hyperalgesia

(Koltzenburg et al. 1992). Applied topically for 5 min, either at 100 % or diluted for a lesser effect, mustard oil produces moderate to severe pain and neurogenic inflammation. Its 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 (Jordt 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 fibers to evoke and maintain a stable area of dynamic allodynia throughout the experimental period. Current is 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 h. 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 h 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 et 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 h after irradiation. This model is therefore relatively demanding, compared to other models, as subjects are required on three consecutive days. An advantage of this model, however, is that the sensory changes are stable for 10 h, 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 s (Kilo et al. 1994). This produces mild to moderate sharp prickling pain, vasodilation of the stimulated and surrounding area, and a local edema. Pain, edema, and flushing outside the contact area subside within 2 h; however, a discrete erythema 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 melatonin 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 Rights

► Ethics of Pain Control in Infants and Children

Human Thalamic Nociceptive Neurons

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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. Such neurons are generally classified as ► wide dynamic range (WDR) and ► nociceptive specific (NS).

Introduction

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 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. See also ► Lateral Thalamic Pain-Related Cells in Humans and ► Central Pain, Human Studies of Physiology.

Characteristics

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, 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). In a more recent study by Lenz and colleagues (Kobayashi et al. 2009), a painful laser stimulus was used and evoked responses in 1/3 of the neurons tested; many responded with early and/or late latency peaks of activity, consistent with activity arising from Aδ and C fibers. Many of the activated neurons were located posterior and inferior to Vc.

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, the regions explored are limited in extent and location and are determined by the target location for the surgery. Fourth, 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).

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 mechanically 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 paresthesia. 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 poststroke pain (Davis et al. 1995, 1996, 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 paresthetic (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, b), this region also contains nociceptive-specific neurons.

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Human Thalamic Response to Experimental Pain (Neuroimaging)

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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-dependent (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.

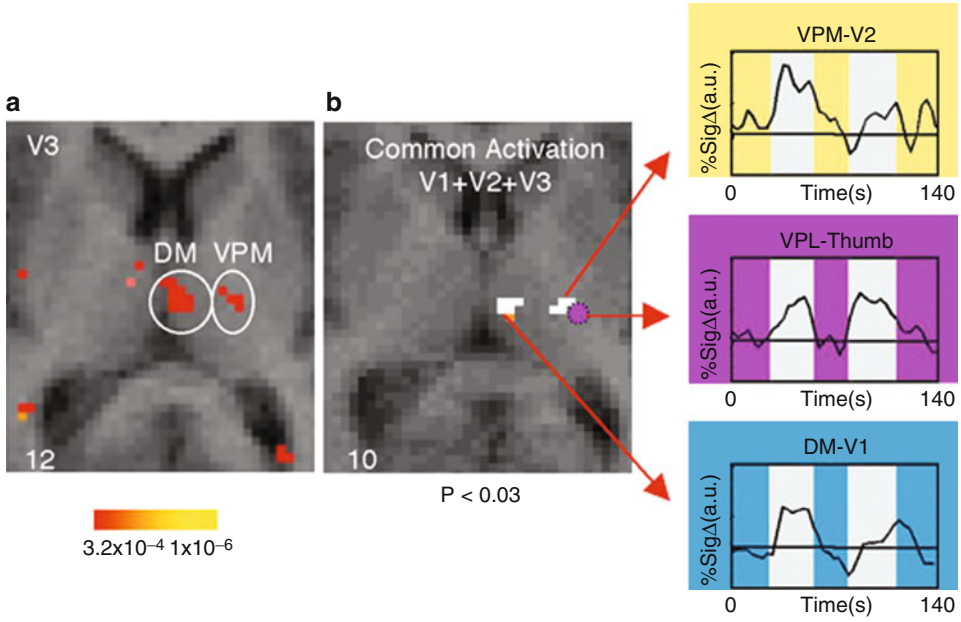
Thalamic Nuclear Function

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 been consistently described in neuroimaging studies. These studies confirm previous animal experiments that noxious and innocuous discriminative input from cranial and the body parts is 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 thermoreceptive 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 45 °C for heat pain and usually lower than 6 °C for cold pain, enough to activate nociceptive fibers (*C*- and *A*-delta). The noxious thermal stimuli are delivered by nonmagnetic contact probes, water immersion, and laser

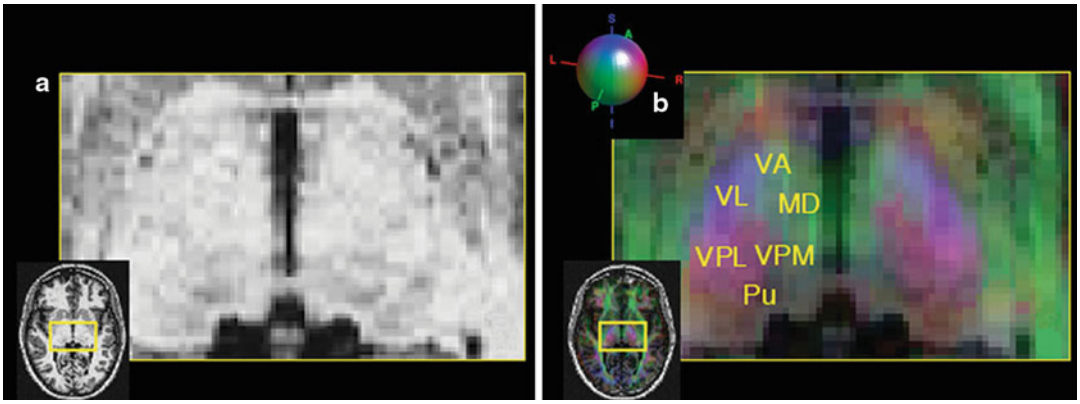


Human Thalamic Response to Experimental Pain (Neuroimaging), Fig. 1 Activation in the thalamus. (**a**) Activation in the thalamus contralateral to a noxious thermal stimulus to the V3 (mandibular trigeminal branch) region of the face. (**b**) Activation in the thalamus following contralateral stimulation to the face and hand. The *white areas* show regions of common activation following noxious thermal stimulation to the V1 (ophthalmic), 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 rostrocaudal (z) axis (Da Silva et al. 2002)

(heat) to a particular part of the body in an alternating fashion with a non-noxious state (e.g., neutral 32 °C x noxious 46 °C). Similar noxious sensations have also been produced by interlaced application of non-noxious 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, e.g., 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



Human Thalamic Response to Experimental Pain (Neuroimaging), Fig. 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)

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 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 postsurgical 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).

Can We Modulate the Thalamic Response to Pain?

The motor cortex is a reliable target to modulate the sensory and motor subthalamic activity associated with pain, independent of the type of stimulation applied (Garcia-Larrea et al. 1997, 1999; Strafella et al. 2004), which also affects other pain-matrix structures. This occurs directly and indirectly, because of the multiple connections between the corticospinal tract and thalamus. Using a forward modeling analysis for primary motor cortex (M1) modulation with transcranial direct current stimulation (tDCS), researchers predicted current flow in multiple areas of cortex, as well as several subcortical regions implicated in pain perception and modulation, especially the thalamus (DaSilva et al. 2012). In fact, M1-tDCS protocol can decrease pain in chronic migraine patients following repetitive sessions (DaSilva et al. 2011). There is an immediate reduction in μ-opioid receptor binding in response to an acute M1 neuromodulation. Levels of μ-opioid receptor-binding potential in a chronic trigeminal pain patient (post-herpetic neuralgia) during a single M1-tDCS application induced significant decrease in μ-opioid receptor binding in the thalamus (– below) and other pain-matrix structures, including nucleus accumbens (NAcc), ACC, and insula. Hence, analgesic effect of tDCS is possibly due to acute increase of endogenous opioids release, by direct and indirect effect of M1 stimulation on the thalamus and pain-matrix (DosSantos et al. 2012). Recently, it was reported that acute tDCS modulates functional connectivity depending on its polarity (Polania et al. 2012). Anodal stimulation over M1 with contralateral supracortical (SO) cathode placement (our protocol) immediately increases functional coupling between ipsilateral M1 and thalamus. On the contrary, cathodal tDCS over M1 decreases functional coupling between ipsilateral M1 and contralateral putamen.

Summary

Although it is clear that neuroimaging research can contribute to the understanding of the thalamic neuronal activation and its modulation 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.

Cross-References

► Interstitial Cystitis and Chronic Pelvic Pain

HVCCs

► Calcium Channels in the Spinal Processing of Nociceptive Input

Hyaline Cartilage

Definition

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

Cross-References

► Sacroiliac Joint Pain

Hyaluronan

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Synonyms

Hyaluronic acid; Viscosupplementation

Definition

Hyaluronic acid is a naturally occurring glycosaminoglycan, 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 physicochemical 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 humor 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 viscoelastic 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 nonselective ▶ 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 randomized, 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 localized 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

▶ Hyaluronan

Hyaluronic Acid (HA)

Definition

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

Cross-References

▶ 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 work-up as well as therapy for IC.

Cross-References

▶ Interstitial Cystitis and Chronic Pelvic Pain

Hydrogen Magnetic Resonance Spectroscopy

▶ MRS

Hydromorphone

▶ Postoperative Pain, Hydromorphone

Hydroperoxides

Definition

Hydroperoxides such as PGG_2 are required to initiate the conversion of arachidonic acid into prostaglandins.

Cross-References

▶ Cyclooxygenases in Biology and Disease

Hydrotherapy

Definition

Hydrotherapy is the external application of water, e.g., the immersion of the body in thermal water.

Cross-References

▶ Chronic Pain in Children, Physical Medicine and Rehabilitation
▶ Spa Treatment

Hydroxy-7.8-Dihydrocodeinone

▶ Oxycodone

Hypalgia

► Hypoalgesia, Assessment

Hyperaesthesia, Assessment

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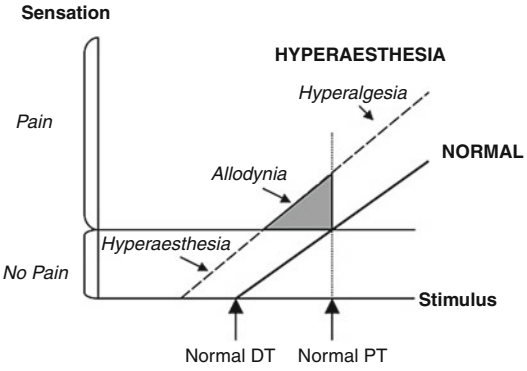
Definition

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 nonnoxious 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 fibers (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 et al. 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 noninjured skin area (secondary hyperalgesia) (Treede and Magerl 2000).



Hyperaesthesia, Assessment, Fig. 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 stimuli is called allodynia. *DT* detection threshold, *PT* pain threshold

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 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 nonpainful stimulus, the term allodynia is used. Increased response to normally painful stimuli, e.g., evaluated by the stimulus-response curve, is termed hyperalgesia.

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	Increased sensation/ pain = hyperaesthesia
		Gentle pressure with fingertip	
		Pinprick	
	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 threshold	von Frey hair	Decreased threshold = hyperaesthesia
		Pressure algometry	
	Thermal stimuli – Cold detection threshold – Warm detection threshold – Cold pain threshold – Heat pain threshold – Heat tolerance threshold	Thermotest	

Clinical Examination/Studies

Bedside sensory screening may be useful in the evaluation of the anatomical distribution and the qualitative characterization 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 °C and 40 °C, acetone drop), and vibration sense (tuning fork) (Table 1).

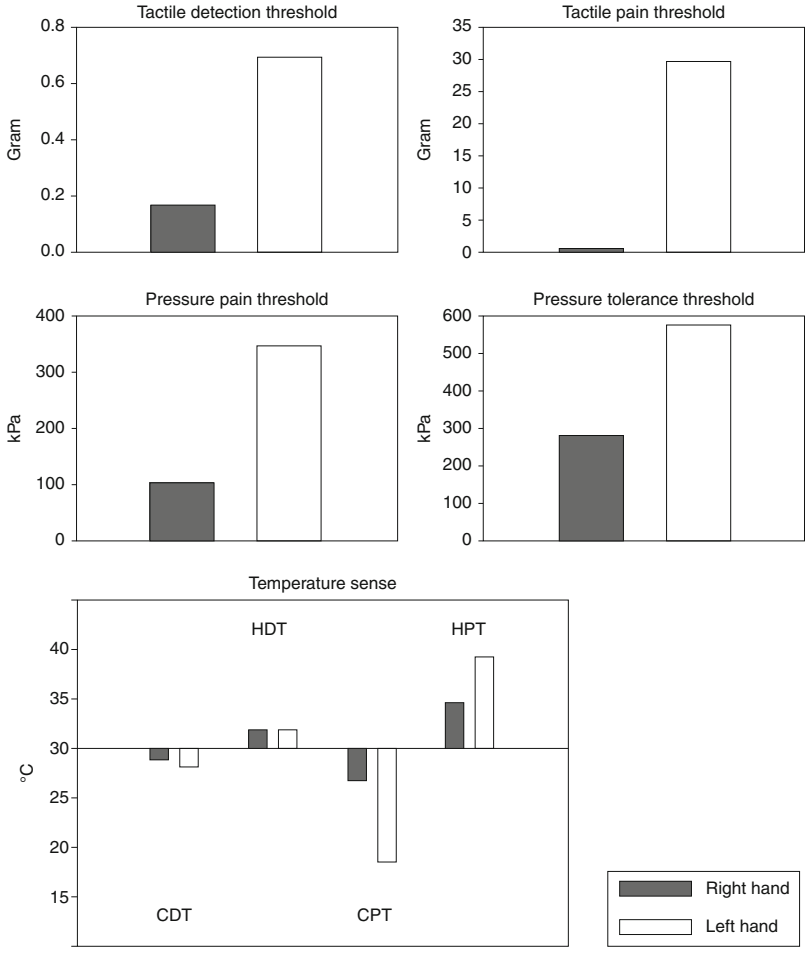
Sensory examination is normally done in the area with maximal pain and compared with the contralateral site of the body (Andersen et al. 1995; Jensen et al. 2001) or the adjacent body area not involved in disease. Hyperaesthesia is present in the case of increased sensation/pain to a nonpainful (hyperaesthesia/allodynia) 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 standardized 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) indicate 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, and numerical rating scales (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.



Hyperaesthesia, Assessment, Fig. 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

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 noninjured 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 nonpainful 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 sensitization 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 localized 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 reflect a hypersensitivity of the animal to the pertinent stimulus (Scholz and Woolf 2002).

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Hyperalgesia

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Synonyms

Algesia; Hyperesthesia; Primary hyperalgesia; Secondary hyperalgesia

Definition

Increased pain sensitivity. Antonym: ▶ hypoalgesia (decreased pain sensitivity). Increased pain sensitivity at a site of tissue damage is called primary hyperalgesia. Increased pain sensitivity in normal skin surrounding a site of tissue damage is called secondary hyperalgesia.

Hyperalgesia was traditionally defined as the psychophysical correlate of ▶ sensitization (either peripheral or central) of the nociceptive system. As such, it is characterized by a decreased pain threshold and increased pain to suprathreshold

Hyperalgesia, Table 1 Types of hyperalgesia and their likely mechanisms

Test stimulus	Occurrence	Afferents	Sensitization
Heat	Primary zone	Type I and II AMH, CMH	Peripheral
Blunt pressure	Primary zone	MIA, (type I AMH?)	Peripheral
Impact	Primary zone	MIA, (type I AMH?)	Peripheral
Punctate	Neuropathic	Type I AMH	Central
	Secondary zone	Type I AMH	Central
	Primary zone	Type I AMH, MIA	Peripheral/central?
Stroking	Neuropathic	Aβ-LTM	Central
	Secondary zone	Aβ-LTM	Central
	Primary zone	Aβ-LTM	Central
Cold	Neuropathic pain	?	Central?
	Secondary zone?	?	Central?
Chemical	Inflammation	Type II AMH, CMH, MIA?	Peripheral?

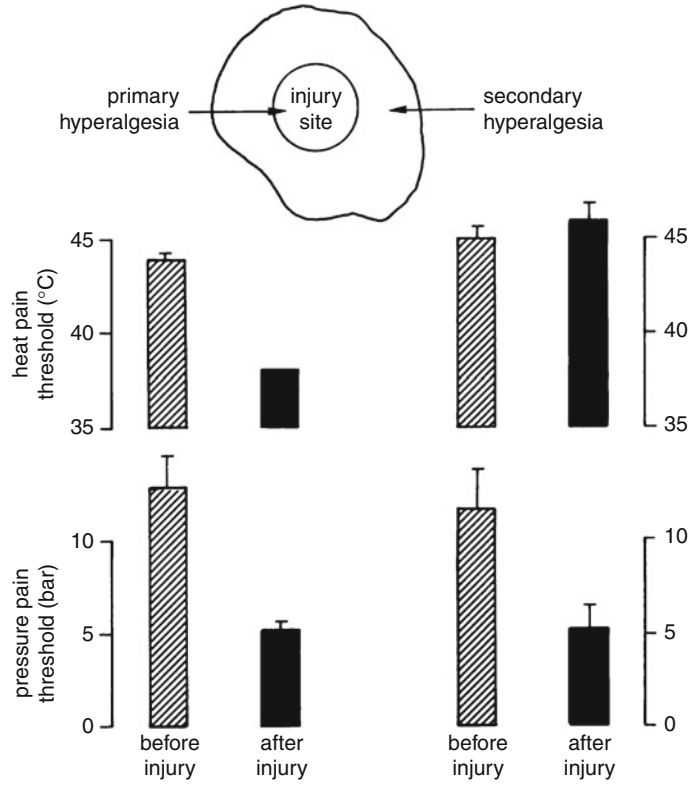
Abbreviations: Aβ-LTM Aβ-fiber low-threshold mechanoreceptor ("touch receptor"), probably rapidly adapting subtype (Meissner corpuscle); type I AMH A-fiber nociceptor with slow high-threshold heat response (no TRPV1), probably equivalent to A-fiber high-threshold mechanoreceptor; type II AMH A-fiber 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))

stimuli. The current definition by the International Association for the Study of Pain (IASP) refers only to the latter phenomenon ("increased pain to a stimulus that is normally painful"). A decreased pain threshold would operationally fulfill the IASP definition of ▶ allodynia ("pain induced by stimuli that are not normally painful"). This narrow definition has proved to be counterproductive for two reasons: (1) all known mechanisms of sensitization lead to changes in both threshold and suprathreshold response and (2) the extended use of the term allodynia has distracted from its initial clinical meaning and has hampered the transfer of knowledge from animal research to the clinic. Therefore, this essay uses the traditional definition of hyperalgesia as the psychophysical correlate of sensitization, which will probably be adopted by IASP in the near future.

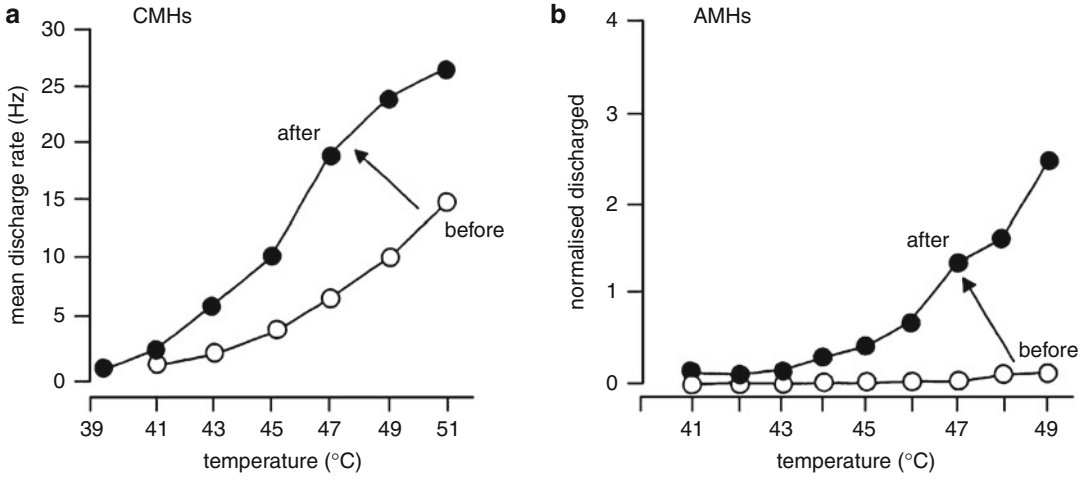
Characteristics

Increased pain sensitivity (hyperalgesia) can be differentiated according to the test stimulus that is perceived as more painful, mechanical hyperalgesia, heat hyperalgesia, cold hyperalgesia, and chemical hyperalgesia (Table 1). Mechanical hyperalgesia can be further differentiated according to the size of the object contacting the skin (punctate or blunt) and the temporal dynamics of its application (static or dynamic). The underlying mechanisms are sensitization either in the periphery or in the central nervous system or both. Hyperalgesia at a site of tissue damage is called primary hyperalgesia; hyperalgesia surrounding this site is called secondary hyperalgesia. The sensory characteristics of primary and secondary hyperalgesia differ considerably (Fig. 1). Whereas primary hyperalgesia encompasses increased sensitivity to both mechanical and heat stimuli, secondary hyperalgesia is relatively specific for mechanical stimuli (Treede et al. 1992).

Primary hyperalgesia to heat stimuli is fully accounted for by ▶ peripheral sensitization of the terminals of primary nociceptive afferents (Raja et al. 1999). Peripheral sensitization shifts the stimulus response function for heat stimuli to the left. This leftward shift is associated with a decreased threshold, increased responses to suprathreshold stimuli, and spontaneous activity (Fig. 2). Primary nociceptive afferents express the heat-sensitive ion channel TRPV1 (Caterina and Julius 2001). This channel can be sensitized by inflammatory mediators, and the ensuing



Hyperalgesia, Fig. 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))



Hyperalgesia, Fig. 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))

drop in heat threshold turns normal body temperature into a suprathreshold stimulus (Liang et al. 2001). Thus, primary hyperalgesia to heat can also explain ongoing pain of inflammatory origin.

Secondary hyperalgesia to mechanical stimuli is not associated with any change in peripheral coding (Baumann et al. 1991) but can be explained by enhanced synaptic responses of second-order neurons in the spinal cord to their normal afferent input (► central sensitization). These neurons also exhibit a drop in threshold and 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 et al. 2004; Sandkühler 2000; 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.

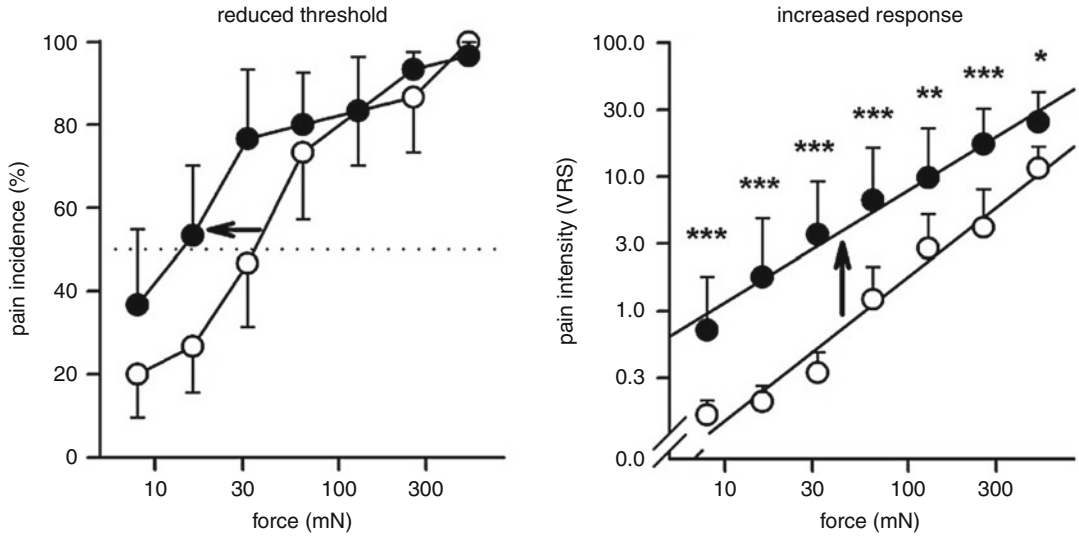
The mechanisms of cold hyperalgesia, which is a frequent finding in some ► neuropathic pain states, are still enigmatic (Wasner et al. 2004). Peripheral sensitization of nociceptive afferents cannot be ruled out because the peripheral encoding of noxious cold stimuli has not been investigated sufficiently (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 musculoskeletal pain states including low-back pain may also be accompanied by hyperalgesia. Parallel to the definition of sensitization, 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).



Hyperalgesia, Fig. 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 ± SEM across subjects. Post hoc least significant differences tests: ** $p < 0.01$; *** $p < 0.001$ (From Treede et al. (2004))

Cross-References

- ▶ Allodynia (Clinical, Experimental)
- ▶ Allodynia and Alloknesis
- ▶ Amygdala, Pain Processing and Behavior in Animals
- ▶ Calcium Channels in the Spinal Processing of Nociceptive Input
- ▶ Cancer Pain
- ▶ Cancer Pain, Animal Models
- ▶ Capsaicin Receptor
- ▶ CRPS, Evidence-Based Treatment
- ▶ Cytokine Modulation of Opioid Action
- ▶ Deafferentation Pain
- ▶ Diagnosis and Assessment of Clinical Characteristics of Central Pain
- ▶ Drugs Targeting Voltage-Gated Sodium and Calcium Channels
- ▶ Forebrain Modulation of the Periaqueductal Gray and Its Role in Pain
- ▶ Freezing Model of Cutaneous Hyperalgesia
- ▶ Hyperpathia
- ▶ Hyperpathia, Assessment
- ▶ Hypoesthesia, Assessment
- ▶ Inflammation, Modulation by Peripheral Cannabinoid Receptors
- ▶ Lateral Thalamic Lesions, Pain Behavior in Animals
- ▶ Metabotropic Glutamate Receptors in Spinal Nociceptive Processing
- ▶ Muscle Pain Model, Inflammatory Agents-Induced
- ▶ Nerve Growth Factor Overexpressing Mice as Models of Inflammatory Pain
- ▶ Neuropathic Pain Model, Tail Nerve Transection Model
- ▶ Nociceptive Circuitry in the Spinal Cord
- ▶ Nociceptive Processing in the Amygdala: Neurophysiology and Neuropharmacology
- ▶ Nocifensive Behaviors, Muscle and Joint
- ▶ NSAIDs, Mode of Action
- ▶ Opioid Receptor Trafficking in Pain States
- ▶ Pain-Modulatory Systems, History of Discovery

- ▶ Polymodal Nociceptors, Heat Transduction
- ▶ Postherpetic Neuralgia, Etiology, Pathogenesis, and Management
- ▶ Postherpetic Neuralgia, Pharmacological and Nonpharmacological Treatment Options
- ▶ Poststroke Pain Model, Thalamic Pain (Lesion)
- ▶ Psychiatric Aspects of Visceral Pain
- ▶ Psychology of Pain, Sensitization, Habituation, and Pain
- ▶ Sensitization of Visceral Nociceptors
- ▶ Spinal Cord Injury Pain Model, Contusion Injury Model
- ▶ Spinothalamic Tract Neurons, Central Sensitization
- ▶ Sympathetically Maintained Pain in CRPS II, Human Experimentation
- ▶ TENS, Mechanisms of Action
- ▶ Thalamotomy, Pain Behavior in Animals
- ▶ Thalamus, Clinical Pain, Human Imaging
- ▶ Thalamus, Dynamics of Nociception
- ▶ Transition from Acute to Chronic Pain
- ▶ Vagal Input and Descending Modulation
- ▶ Visceral Nociception and Pain
- ▶ Visceral Pain and Nociception

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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.

Cross-References

- ▶ Allodynia (Clinical, Experimental)
- ▶ Hyperalgesia

Hyperemia

Definition

Increased blood flow or an excess of blood in a body parties known as hyperemia.

Cross-References

► Clinical Migraine with Aura

Hyperesthesia

► Hyperalgesia

Hyperexcitability

Definition

From Greek/Latin: extremely excitable. Besides being an awkward mixed Greek/Latin word, the term is not well defined. Basically, it can label afferent nerve fibers or neurons which are more excitable than usual. In the case of peripheral afferents, this state is usually characterized as "sensitized". However, the label "hyperexcitable" is most often used not for sensitized nociceptors, but for fast conducting mechanoreceptors which have become spontaneously active, and apparently more excitable, as a consequence of a nerve lesion.

Cross-References

► Sympathetic and Sensory Neurons after Nerve Lesions, Structural Basis for Interactions

Hyperglycemic Neuropathy

► Diabetic Neuropathies

Hyperhidrosis

Definition

Hyperhidrosis means increased sweating.

Cross-References

► 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.

Cross-References

► Allodynia and Alloknesis

Hyperpathia

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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. The changes in this note [*from the previous edition of the IASP Taxonomy*] are the specification of allodynia and the inclusion of hyperalgesia explicitly.

Allodynia: Allodynia is pain due to a stimulus which does not normally provoke pain.

Hyperalgesia: Hyperalgesia is an increased response to a stimulus which is normally painful.

Hyperesthesia: Hyperesthesia is an increased sensitivity to stimulation, excluding the special senses.

Dysesthesia: Dysesthesia is an unpleasant abnormal sensation, whether spontaneous or evoked.

Neuropathic Pain: Neuropathic pain is arising as a direct consequence of a lesion affecting the somatosensory system.

Characteristics

Introduction

Use of the term hyperpathia varies in the current scientific literature, and it is avoided by many. For example, in Wall and Melzack's Textbook of Pain (McMahon and Koltzenburg 2005), hyperpathia receives a single listing in the index and is not discussed a specific and complete entity in any chapter in the book. Likewise, several influential studies and reviews, tackling the 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, with various components, 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, the delay in perception of a stimulus, the summation of pain with repetitive stimulation, and aftersensation characteristic of the hyperpathic response (see below) are usually seen in combination with allodynia and hyperalgesia, when hyperpathia occurs in patients with 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 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 localization, 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 emphasize three important points. The first is the general point that a definition should include those characteristics that are the minimum necessary to categorize a condition, item, or state as separate and identifiably distinct. Secondly, in relation to the definition of diseases and clinical syndromes/states, a definition must have clinical relevance and usefulness.

And thirdly, with reference specifically to the definition of hyperpathia, the definition is based on a collection of symptoms and signs. As is evident throughout this encyclopedic reference, the last few decades have witnessed enormous progress in the basic neuroscience of pain. However, it is still not yet possible to tightly 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, and it is likely that each of the symptoms and signs of painful states may be produced by more than one underlying pathophysiological property.

For the moment, however, we are forced to rely on 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. Aftersensation. This is a perception by the sufferer that the stimulus evoking the pain continues after the stimulus has in fact ceased. Painful aftersensations may persist for seconds, minutes, or even hours, following even 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, subcortical, and, very occasionally, cortical lesions. In other words, all of the many causes of neuropathic pain may be associated with hyperpathia, and multiple etiologies are involved (Scadding 2009).

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 postherpetic 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

Hyperpathia, Table. 1 Possible pathophysiological substrates for hyperpathia

Symptom	Mechanism
1. Increased threshold	Reduced input due to sensory lesion
2. Delay in perception	Reduced large fiber input
3. Summation	Afterdischarge in damaged sensory neurons
	Crossed afterdischarge in sensory neurons
	Ephaptic transmission in nerve lesion?
	Central sensitization
4. Aftersensation	Crossed afterdischarge in sensory neurons
	DRG ectopic firing
	Central disinhibition

DRG dorsal root ganglion
Sources: Woolf and Salter (2005), Devor (2005), Jensen and Baron (2003)

tended to be underestimated in published studies (routine quantitative sensory testing does not accurately assess this).

Pathophysiology

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

Cross-References

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

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Hyperpathia, Assessment

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Definition

The International Association for the Study of Pain (IASP) define hyperpathia as a painful

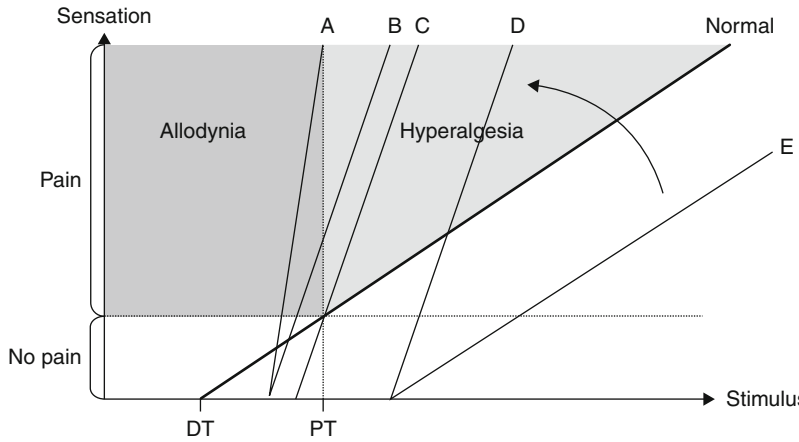
syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Characteristics

Hyperpathia includes increased ▶ detection threshold. There is a steeper stimulus-response

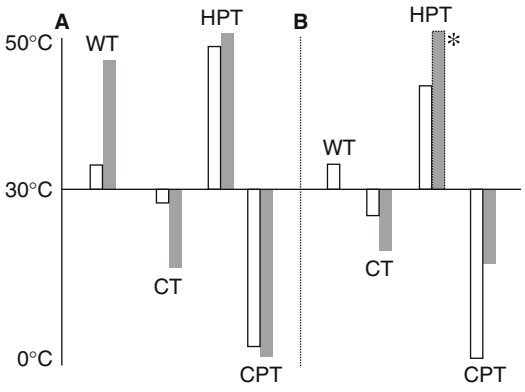
Hyperpathia, Assessment, Table 1 Assessment of hyperpathia

Stimulus	Assessment of detection (DT) and pain (PT) threshold	Stimulus-response function following graded innocuous and/or noxious stimuli	Repetitive suprathreshold stimulation
Thermal stimulation:			
Screening with metallic cold and heat thermo rollers	–	–	–
Thermal quantitative sensory testing	DT, PT	Ass. of thermal allodynia/ hyperalgesia	Repetitive heat or cold pulses
Mechanical stimulation:			
Light touch: wisp of cotton or camel-hair brush	–	–	Brushing with a velocity >0.3 Hz
Punctuate stimuli: screening with safety pin. Testing with von Frey hair	DT, PT	Ass. of ▶ punctuate allodynia/hyperalgesia	Multiple >0.3 Hz pinprick stimuli
Static stimuli: pressure or skin fold	PT	Ass. of ▶ static allodynia/ hyperalgesia	+
Electrical stimulation	DT, PT	+	+
Vibrametry	DT, (PT)	+	+
Chemical stimulation:			
Topical capsaicin	Time before detection (DT) and pain (PT)	Pain increase as a function of time	–



Hyperpathia, Assessment, Fig. 1 Schematic description of different stimulus-response curves occurring with 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

function than normal (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) (Merskey and Bogduk 1994). 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 2–3 s to more than 10 s. There may be abnormal summation, aftersensations, and pain-radiating phenomena. There can be poor localization of the stimulus and faulty identification where the patient feels pain but not the specific modality of the stimulus (Fig. 2b) or with misnaming of the stimulus modality (Fig. 3). (Noordenbos 1979; Lindblom 1979; Merskey and Bogduk 1994; Bennett 1994).



Hyperpathia, Assessment, Fig. 2 Quantitative sensory testing. Schematic presentation of thermal quantitative sensory testing at control side (*empty box*) and affected side (*grey box*) in two patients (**a** and **b**). Warm (WT) and cold (CT) detection threshold and heat (HPT) and cold (CPT) pain threshold are expressed as average temperature of five consecutive stimuli. (**a**) A 46-year-old woman with pain following abdominal surgery. There is increased detection but normal pain threshold to warm and cold. The patient report increased cold and heat pain at threshold in the painful area as compared to the unaffected homologous region. Hyperpathia is present if there is steeper stimulus-response curve than normal (Fig. 1) or at exaggerated response to repetitive suprathreshold stimulation. (**b**) A 50-year-old man with pain following arm amputation after an explosion accident. The patient does not feel heat but pain induced by heat (*). Heat pain threshold is increased. Heat hyperpathia is present if there is steeper stimulus-response curve than normal (Fig. 1) or at exaggerated response to repetitive suprathreshold stimulation. Cold hyperpathia is present, as there is increased cold detection, decreased cold pain threshold, and the patient report exaggeration of pain following innocuous cold stimuli

Induction and Assessment

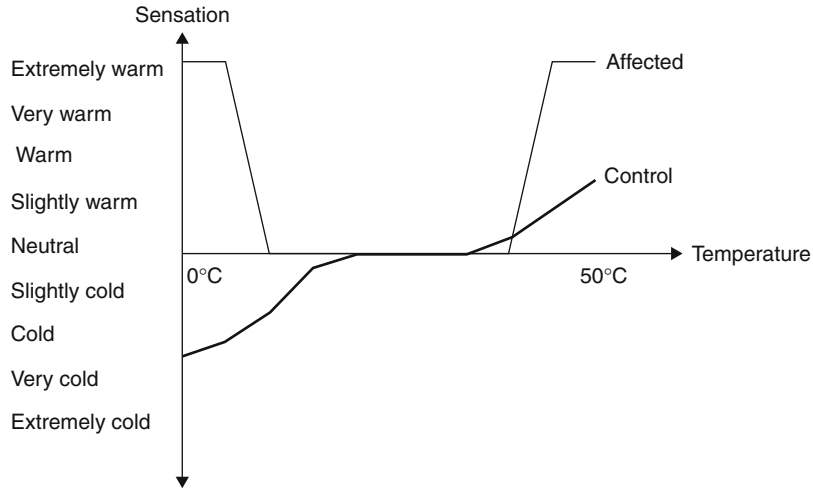
Thermal, mechanical, and chemical hyperpathia may exist singly or in any combination. Therefore, multiple different noxious and innocuous stimulus modalities have to be used to document or to exclude hyperpathia (Lindblom 1994) (Table 1). Hyperpathia is assessed by performing stimulus-response curves with assessment of detection- and pain thresholds, repetitive suprathreshold stimulation, and by asking the patient to report aftersensations, pain radiation, and coexistent phenomena (Table 1, Figs. 1, 2 and 3). Usually, the site of maximal pain reported by the patient is chosen as the test area. At unilateral involvement, the contralateral mirror image area is used as control. At bilateral involvement, data should preferably be compared with normal values from sex- and age-matched controls.

Temporal Summation

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). Hyperpathia is most likely elicited when stimulus duration is increased or at repetitive stimulation. 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. 1). This exaggerated response can be provoked by both noxious and innocuous stimuli (Table 1).

Aftersensations

Aftersensations refer to abnormal persistence of pain seconds to minutes after termination of the stimulation (Gottrup et al. 2003).



Hyperpathia, Assessment, Fig. 3 Stimulus-response function. Stimulus-response function for heat and cold sensation 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 coworkers (1995))

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 and vasomotor and vegetative reactions. It may occur with allodynia, ▶ hyperesthesia, hyperalgesia, or ▶ dysesthesia (Merskey and Bogduk 1994).

Clinical Examination

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

A bedside screening for hyperpathia is performed with heated and cold thermo rollers kept at 20°C and 40°C, respectively; a wisp of cotton; and pinprick (Von Frey hair or safety pin), moving from the normal toward the painful area (Jensen et al. 2001). This screening may detect areas with possible increased sensory detection and exaggerated pain responses. Hyperpathia is then assessed objectively as described in "induction and assesment".

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.

Cross-References

- ▶ 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.

Cross-References

- ▶ 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, e.g., originated by anomalous inputs.

Cross-References

- ▶ Deafferentation Pain

Hypersensitivity

Definition

Increased sensation of stimuli, or increased responsiveness of neuronal structures to stimuli.

Cross-References

- ▶ Chronic Pelvic Pain, Musculoskeletal Syndromes
- ▶ Deafferentation Pain
- ▶ Functional Abdominal Pain in Children
- ▶ Psychology of Pain, Sensitization, Habituation, and Pain
- ▶ Sensitization of Visceral Nociceptors

Hyperstimulation Analgesia

Definition

Hyperstimulation analgesia is mediated by a short but strong painful stimulation usually applied in the form of a train of electrical impulses which reduces another, background pain.

Cross-References

► Acupuncture Mechanisms

Hypertensive Encephalopathy

Definition

Hypertensive encephalopathy is a change in the brain caused by failure of autoregulation 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.

Cross-References

► Headache Due to Hypertension

Hypertensive Headaches

► Headache Due to Hypertension

Hypertonic Saline

Definition

Hypertonic saline is a solution of greater than 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.

Cross-References

► 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.

Cross-References

► 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

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Synonyms

Heightened attention; Overalertness; Selective attention

Definition

Attention is a key theoretical and clinical construct in explaining amplified pain perception, disability, and distress. Patients with chronic pain are often thought to be hypervigilant, i.e., excessively attentive, for pain and/or somatic sensations (Crombez et al. 2005). Hypervigilance is best defined as the readiness to select pain-related information over other information from the environment (Eccleston and Crombez 1999). It should be noted that hypervigilance is conceptually different from other constructs that have been associated with pain hypersensitivity in chronic pain patients, such as hyperalgesia (increased pain response to a noxious stimulus) and allodynia (painful response to a normally innocuous stimulus) typically resulting from abnormalities in central nociceptive pathways. Hypervigilance may only be inferred when the involvement of attentional processes can be demonstrated (Crombez et al. 2005).

Characteristics

Hypervigilance to pain and somatic sensations may become manifest in a variety of ways. The following example may clarify this: Imagine a man, suffering from chronic low back pain, who is resuming his job after a period of pain-related work absence. Increases in pain intensity during work frequently attract his attention. Afraid of (re) injury due to back-related movements, he begins to scan his body for pain or for other potential signals of bodily harm, which may result in the rapid detection of any bodily sensation in his back. Once such bodily sensation is detected, the person may experience difficulties disengaging attention from it and to concentrate on his work.

Theoretical views emphasize that hypervigilance emerges as the working of normal attentional mechanisms in an abnormal situation, i.e., the chronic presence of threatening, high-intensity pain. In understanding hypervigilance, it is therefore important to consider "normal" attention to pain. Eccleston and Crombez (1999) were among the first to systematically investigate "normal" attentional processes in the context of 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 bodily threat. In a more recent development of this model (Legrain et al. 2009), it has been argued that pain can be selected by the attentional system in two different ways: bottom-up and top-down.

First, bottom-up selection of pain is the unintentional, stimulus-driven capture of attention by pain because of its salience. The involuntary capture of attention by pain has been shown to be mediated by its sensory characteristics such as intensity and novelty (Eccleston and Crombez 1999; Legrain et al. 2009). Because chronic pain patients are characterized by sensitized nociceptive pathways and are continuously confronted with increases in pain intensity, there is frequent bottom-up selection of pain, leading to task interruptions, increased distractibility, and reduced cognitive performance (Moriarty et al. 2011).

Second, top-down selection of pain is an intentional and goal-directed process in which pain-related information is prioritized because of its relevance for current concerns or goals (Van Damme et al. 2010). It has been shown that the threat of bodily harm results in stronger interruption of attentional tasks by pain, makes one more rapidly aware of innocuous somatic sensations in the threatened body part, and results in more difficulty disengaging from that body part (Peters et al. 2000; Van Damme et al. 2007). Furthermore, the selection of pain-related information has been shown to be more pronounced when the goal to avoid or escape is strongly activated (Notebaert et al. 2011). In chronic pain patients, one may expect increased top-down selection of pain-related information because of the frequent presence of fear-avoidance beliefs, i.e., catastrophic misinterpretation of pain as a sign of serious injury or pathology over which one has little or no control (Vlaeyen and Linton 2000), and because the goal of pain relief or pain control is highly salient and often becomes chronically activated (Eccleston and Crombez 2007).

Implications

Our understanding of hypervigilance has a number of implications. First, it has often been assumed that hypervigilance is a maladaptive attentional mechanism resulting from abnormal personality characteristics such as negative affectivity (NA) or neuroticism. However, empirical evidence does not support the idea that hypervigilance in chronic pain patients emerges as a result of dysfunctional personality traits. For instance, Goubert et al. (2004) found that the key mediating variable in explaining hypervigilance to pain was not an abnormally high level of NA but the immediate threat value of pain. NA was rather conceived as a vulnerability factor, lowering the threshold at which pain is perceived as threatening.

Second, although hypervigilance primarily concerns attention to bodily sensations, the majority of studies in patients with chronic pain was conducted by means of visual attention paradigms using pain-related words (Van Damme et al. 2010). Such approach does, however, not allow firm conclusions about bodily hypervigilance. The development of experimental paradigms allowing the valid measurement of the attentional selection of pain and somatic sensations in clinical populations is therefore an important challenge for future research (Moore et al. 2012; Van Damme et al. 2010).

Third, 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. Other techniques may be more suitable in those patients, such as the cultivation of mindful attention and nonjudgmental body awareness (Mehling et al. 2009).

Fourth, we have recast hypervigilance within a motivational perspective on pain and disability. Attentional distraction may be optimized by making the distraction task motivationally relevant. For example, it has been shown that the selection of pain-related information can be substantially reduced by the activation of a competing personal goal (Schrooten et al. 2012). However, techniques merely directed at reducing attention to pain might have limited value in these chronic pain patients in which hypervigilance has become part of persistent attempts to control a largely uncontrollable problem (Eccleston and Crombez 2007) and are probably best integrated within a broader cognitive-behavioral approach aimed at coping with disability and optimizing goal regulation.

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Hypesthesia

Definition

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

Cross-References

- ▶ Hyperaesthesia, Assessment
- ▶ Hypoaesthesia
- ▶ Hypoesthesia, Assessment

Hypnic "Alarm Clock" Headache Syndrome

- ▶ Hypnic Headache

Hypnic Headache

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Synonyms

Hypnic "alarm clock" headache syndrome

Definition

Headache awakening the subject from sleep, not occurring during waking hours, and 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 15 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 (1998) 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 generalized 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 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 19 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 et 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 71 cases of hypnic headache reported in the literature to date. There were 24 men and 41 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) summarized 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.

Cross-References

- ▶ 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

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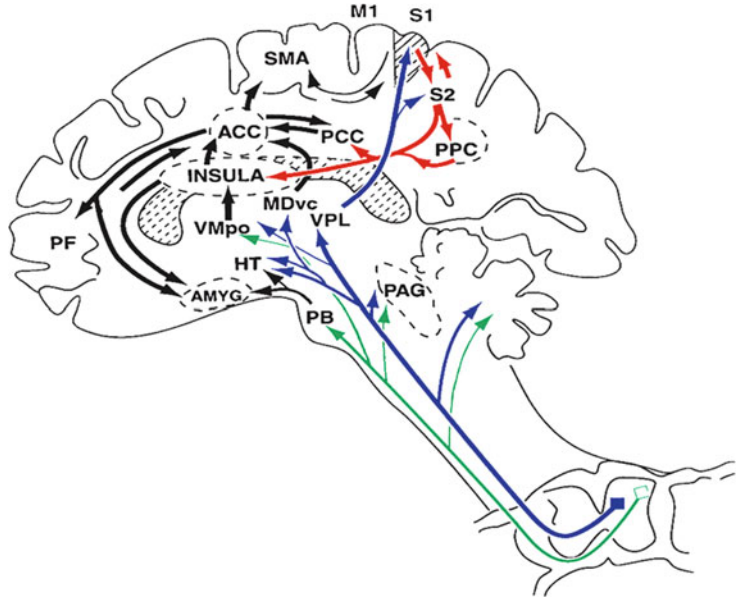
Definition

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 Fig. 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 corticolimbic circuits once nociceptive information has reached cortical levels (De Pascalis et al. 2001; Fields and Price 1997; Hofbauer et al. 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

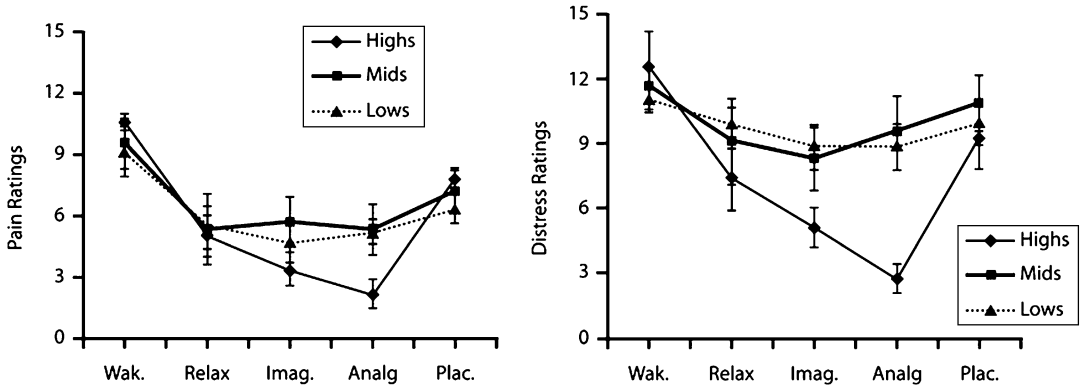
What Are the Types of Hypnotic Suggestions for Analgesia

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



Hypnotic Analgesia, Fig. 1 Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing pain. *PAG* periaqueductal gray, *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))

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 intensity (De Pascalis et al. 1999, 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



Hypnotic Analgesia, Fig. 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)

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, 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 Fig. 2. During focused analgesia, highly hypnotizable participants had larger reductions in pain ratings in comparison to low- and medium-hypnotizable participants. Furthermore, 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, 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 %, and pain unpleasantness was reduced by 87 % in a group of 16 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, 2001; Rainville et al. 1999, Rainville 2002). Reduction in pain sensation was statistically associated with hypnotic susceptibility, albeit at modest levels (Table 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

Hypnotic Analgesia, Table 1 Hypnotic susceptibility and analgesia

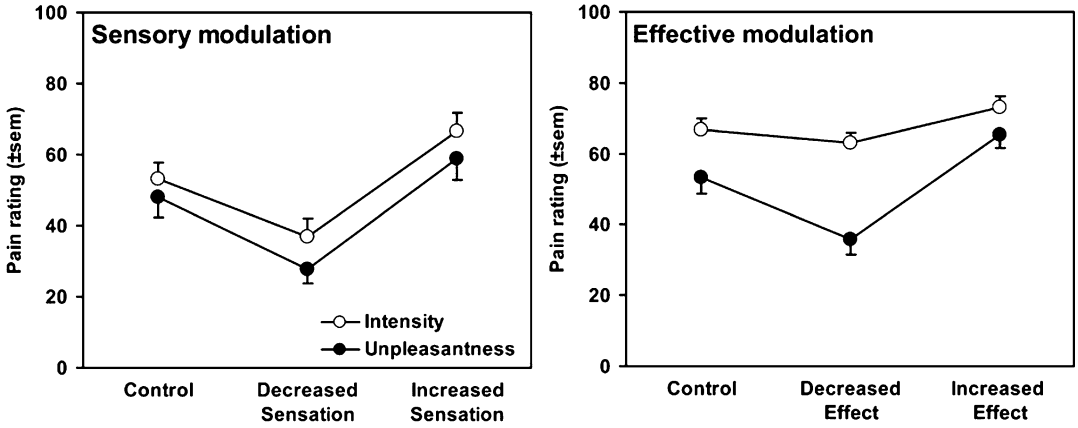
Stimulus temperature	Sensory analgesia	Affective analgesia
	Spearman correlation coefficient	
44.5 °C	+0.04	−0.23
47.5 °C	+0.21	−0.11
49.5 °C	+0.43*	−0.08
51.5 °C	+0.56*	+0.10

*$P < 0.05$

(Table 1). It makes sense that the reduction 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 Fig. 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



Hypnotic Analgesia, Fig. 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)

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 et al. 2001; Rainville 2002). Reinterpretation of meanings of pain, dissociation, and focused analgesia reflect different psychological mechanisms of hypnotic analgesia. These multiple mechanisms 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. (1999, 2001) and 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 distraction, 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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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.

Cross-References

▶ Hypnotic Analgesia
▶ Therapy of Pain, Hypnosis

Hypoaesthesia

▶ Hypoesthesia, Assessment

Hypoalgesia, Assessment

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Synonyms

Assessment of hypoalgesia; Hypalgia

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; Getz 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, involves specific peripheral nerve structures, such as peripheral nerves, plexus, or the nerve root, versus central nervous system structures, such as spinal cord, brain stem, or 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.

Cross-References

- ▶ 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.

Cross-References

- ▶ Psychiatric Aspects of Visceral Pain

Hypochondriasis

Definition

Hypochondriasis is a minimum 6-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.

Hypochondriasis, Somatoform Disorders, and Abnormal Illness Behavior

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Synonyms

Abnormal illness behavior of the unconsciously motivated, somatically focussed type; Discordant illness behavior; 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:

1. 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.
2. 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.
3. The fear of having or belief that one has a disease persists despite medical reassurance.
4. Duration of the disturbance is at least 6 months.
5. 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 as 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 Behavioral 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 behavior, and abnormal illness behavior (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 the following: (a) accept that the role is "undesirable," one which should be relinquished a soon as possible; (b) cooperate 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) the person 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 Behavior (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 sociocultural background.

A detailed analysis of this definition is 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, 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 characterized 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-behavioral 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 nonpsychiatrist 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 1990; Scicchitano 2000).

When a multimodal approach is necessary, this is generally best provided by a multidisciplinary pain clinic, when it is available.

Some pain clinics have inpatient facilities with well-trained experienced staff that are able to provide program for patients manifesting severe invalidism and perhaps dependence on drugs such as opiates.

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Hypoesthesia, Assessment

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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 sensation 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 (Kelly Getz et al. 2005). 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 and O'Brien 2003).

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, brain stem, 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 administered in the way to produce temporal and spatial summation, it 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 is 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.

Cross-References

▶ 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.

Cross-References

▶ Trigeminal Neuralgia: Diagnosis and Treatment

Hypophysectomy

Definition

Excision of the pituitary gland is known as hypophysectomy.

Cross-References

► 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.

Cross-References

► Fibromyalgia

Hypothalamic-Pituitary-Adrenal Axis Response

► Postoperative Pain, Pathophysiological Changes in Neuroendocrine Function in Response to Acute Pain

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 caudorostral levels (mammillary, posterior, intermediate, anterior, and preoptic). Its role includes the neuroendocrine regulations (arcuate, paraventricular, and supraoptic nuclei), autonomic regulations (cardiorespiratory, 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.

Cross-References

► Descending Circuitry, Transmitters and Receptors
► Parabrachial Hypothalamic and Amygdaloid Projections

Hypothalamus and Nociceptive Pathways

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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 mediolateral

zones, periventricular, medial, and lateral, and four caudo-rostral regions, mammillary, tuberal, anterior, and preoptic. Combination of zones and regions permitted the recognition of 12 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 hypophyseal 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, for example, hunger, the pleasures of eating and satiety, sexual desire, aggressiveness, fear, drowsiness, alertness, and numerous other fundamental motivations of life.

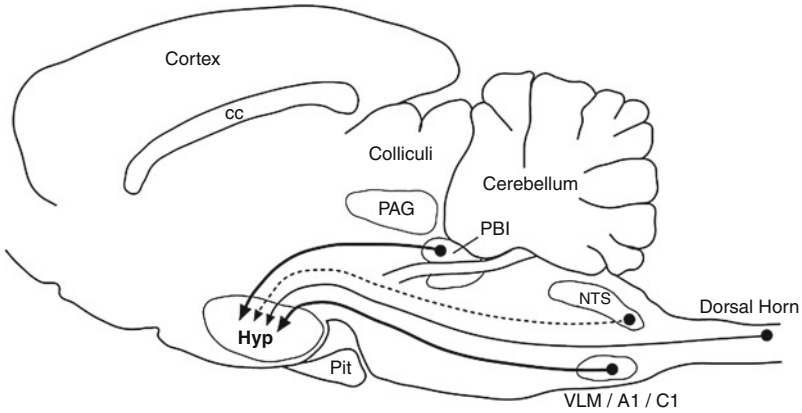
Considering these functions, it seems that the hypothalamus should play an important role in the autonomic and ▶ motivational components of pain. All the same, the precise role of hypothalamus in different components of pain remains unclear. The only clearly accepted function of the hypothalamus in pain 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, that is, 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



Hypothalamus and Nociceptive Pathways, Fig. 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

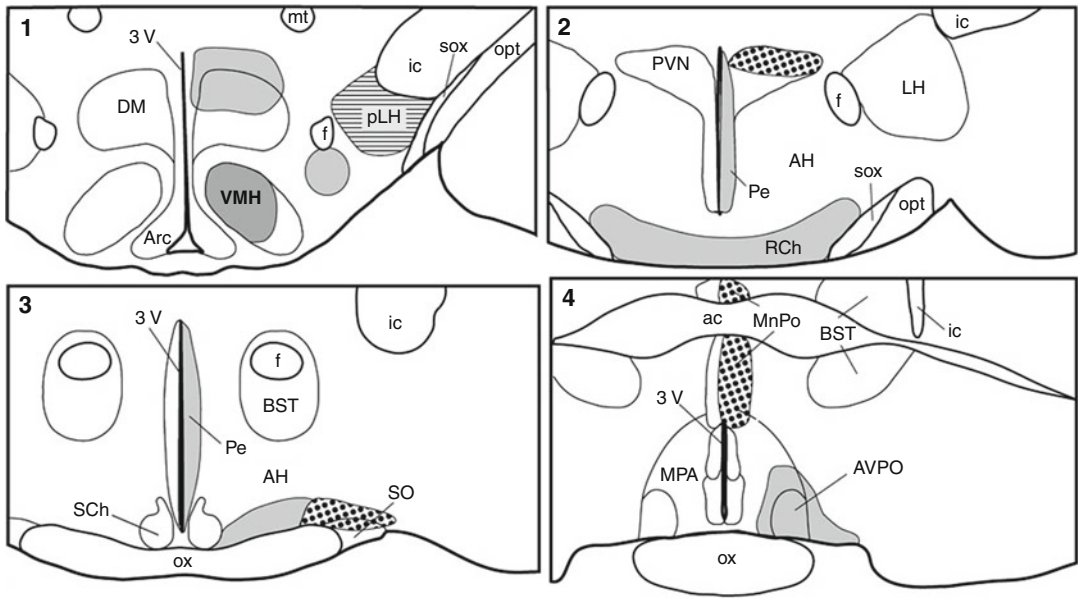
seems to point to at least a moderate but indisputable nociceptive projection, mainly to the lateral (Fig. 2) but also to the posterior and the paraventricular hypothalamic nuclei.

- 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.



Hypothalamus and Nociceptive Pathways, Fig. 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

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 (which contain vasopressin and oxytocin). Painful stimuli evoke specifically c-fos expression in neurons containing corticotropin releasing hormone, vasopressin, 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 anti-nociceptive 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 et al. 2001). One role of nociceptive inputs upon neurons of the posterior lateral hypothalamus could be to trigger awakening.

Summary

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.

Cross-References

▶ 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.

Cross-References

▶ NSAIDs and Cancer