Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms

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Alldynia (pain due to a stimulus that does not usually provoke pain) and hyperalgesia (increased pain from a stimulus that usually provokes pain) are prominent symptoms in patients with neuropathic pain. Both are seen in various peripheral neuropathies and central pain disorders, and affect 15–50% of patients with neuropathic pain. Alldynia and hyperalgesia are classified according to the sensory modality (touch, pressure, pinprick, cold, and heat) that is used to elicit the sensation. Peripheral sensitisation and maladaptive central changes contribute to the generation and maintenance of these reactions, with separate mechanisms in different subtypes of alldynia and hyperalgesia. Pain intensity and relief are important measures in clinical pain studies, but might be insufficient to capture the complexity of the pain experience. Better understanding of alldynia and hyperalgesia might provide clues to the underlying pathophysiology of neuropathic pain and, as such, they represent new or additional endpoints in pain trials.

Introduction

Neuropathic pain is an umbrella term for a series of different conditions caused by a lesion or disease of the parts of the nervous system that usually signal somatosensory information. A range of disorders of the peripheral nervous system—such as postherpetic neuralgia, painful nerve lesions, trigeminal neuralgia, postamputation pain—and a series of neuropathies are included under the term. Additionally, CNS disorders such as stroke, spinal cord injury, and multiple sclerosis can have pain as an important symptom. Diseases causing neuropathic pain therefore vary substantially both in terms of anatomical location and cause. Despite this diversity, neuropathic pain disorders have common clinical characteristics, including some, but not necessarily all, of the following: pain in an area with partial or complete sensory loss; different types of evoked pain; specific descriptors such as burning pain; increased pain after repetitive stimulation; and pain persisting after stimulation. Two particularly bothersome and prominent symptoms in different types of neuropathic pain are alldynia (ie, pain elicited by a stimulus that normally does not cause pain) and hyperalgesia (ie, an increased pain response produced by a stimulus that normally causes pain; figure 1).3

In clinical pain trials, the intensity and degree of pain relief represent important outcome measures. However, these two measures might not capture all aspects of pain, particularly not with the development of new compounds targeting specific occurrences of pain. Current pain treatment is not satisfactory. An elaborate and detailed assessment of neuropathic pain might help to identify subsets of patients who respond to a particular pain treatment.6–11 Alldynia and hyperalgesia are symptoms and signs that might serve as readouts for pain and thus contribute to improved delineation of neuropathic pain.6–10

This Review presents an overview of alldynia and hyperalgesia in neuropathic pain conditions, including their clinical manifestations, underlying mechanisms, and potential value as novel outcome measures.

Epidemiology of alldynia and hyperalgesia in neuropathic pain

Alldynia is Greek for other (allo) pain (odynia) according to the International Association for the Study of Pain.3 The authors of a systematic review10 showed that the prevalence of pain associated with predominantly neuropathic pain descriptors in questionnaire studies ranged from 7% to 18%, whereas studies based on diagnostic codes reported lower rates of neuropathic pain of 1% to 2%. The authors additionally stressed the variability in the prevalence of neuropathic pain associated with specific conditions; the estimated
prevalence of, for example, painful diabetic polyneuropathy ranged from 15 to 72 per 100 000 person-years. The main difficulty in epidemiological studies of pain is the subjective nature of the symptoms, preventing proper validation studies from being done.16 The prevalence of alldynia in neuropathic pain is likewise difficult to assess. In a questionnaire study of more than 1600 patients with painful diabetic neuropathy, 12% reported that light touching was painful, and 14% reported that cold or heat was occasionally painful. Only 47% with postherpetic neuralgia had touch-evoked alldynia, although this is usually reported to be present in at least 70% of cases.13 On the basis of quantitative allodynia, although this is usually reported to be present in 52% of patients with painful diabetic polyneuropathy, brush-evoked alldynia was present in 20% of all patients, 12% of patients with painful polyneuropathy, and 49% of patients with postherpetic neuralgia.14 In another study of 482 patients with different causes of neuropathic pain,15 55% had brush-evoked alldynia, whereas pain evoked by contact with cold objects was reported in 31% of patients, with pressure-evoked pain reported in 52% of patients. Any pain evoked by brush, pressure, or cold stimuli was present in 52% of patients with painful diabetic polyneuropathy and 92% of patients with postherpetic neuralgia. The presence of evoked phenomena is therefore not only dependent on the patients examined, but also on the criteria and methods used to assess these evoked responses.

Clinical assessment and manifestations of alldynia and hyperalgesia

Theoretically, alldynia can be defined as a painful response to a non-nociceptive stimulus—ie, one not encoded by nociceptors16—but this definition cannot be used in the clinical setting because it would be impossible to establish whether a stimulus is capable of activating nociceptors in the individual patient. Therefore, the clinical terms alldynia and hyperalgesia need to be defined according to the sensation experienced after a stimulus that would normally produce either no pain or pain that can be tested in a non-affected body part, usually the contralateral part.17 The clinical assessment of alldynia and hyperalgesia includes examination of trigger points, mapping of the area of abnormality, and determination of the intensity of hypersensitivity. Simple bedside tests include responses to cotton swab, finger pressure, pinprick, cold, and warm stimuli—eg, thermorollers kept at 20°C and 40°C, respectively (table).17,18

More detailed but time-consuming testing includes laser stimuli and quantitative sensory testing,17,18 with the use of monofilaments, pressure or pinch algometers, and thermotest equipment. Sensory profiles including different aspects of alldynia and hyperalgesia have been described.19 The clinical significance of these profiles is still unclear, mainly because of an absence of specific and selective compounds that can address the potential underlying mechanisms.19,20 The paradoxical presentation of areas of hyperalgesia and sites with sensory loss can pose difficulty regarding where the assessment should be done. Examination at hyperalgesic sites might mask the presence of a potential sensory loss area (figure 2), whereas examination within a hypoalgesic area might preclude the identification of hypersensitivity. In these situations, mapping of sensory abnormalities is a way to obtain additional information.

The distribution of different pain types on a phantom map represents an important initial step for pain assessment (figure 2). The area can be quantitated and the evoked intensities and qualities measured both before and after an intervention. Such procedures are useful—eg, when recording the effect of drugs. Automatic drawing systems have been proposed, which might likewise be of value for more accurate measurements. An essential element of neuropathic pain is a lesion of the afferent

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PHN=postherpetic neuralgia. CRPS=complex regional pain syndrome.

Table: Assessment of allodynia and hyperalgesia
Mechanical allodynia and hyperalgesia

Three types of mechanical allodynia and hyperalgesia are usually described: dynamic mechanical allodynia evoked by light touch; punctate allodynia and hyperalgesia evoked by punctate skin stimulation with a pin or monofilament (400 mN); and static allodynia and hyperalgesia provoked by pressure to skin or deep tissue. On the basis of experimental studies using capsaicin and freezing lesions, Kilo and colleagues described a fourth type, termed impact hyperalgesia, elicited in the primary hyperalgesic area by shooting small bullets against the freezing zone. To what extent this type of hyperalgesia is implicated in clinical neuropathic pain remains to be seen. Most investigators have focused their attention on dynamic mechanical allodynia and punctate hyperalgesia, probably because they are most obvious to the patient and clinician.

Dynamic mechanical allodynia

Dynamic mechanical allodynia in neuropathic pain is suggested to be perceptually similar to the same disorder driven neuronal hyperexcitability, but might be manifestations of a psychological disturbance too. Moreover, allodynia and hyperalgesia are not limited to neuropathic pain, but can be part of almost any type of chronic pain condition, ranging from simple local soreness in patients with osteoarthritis, sensitivity of facial skin in a patient with a migraine attack, and sensitivity of the abdominal wall in a patient with peritonitis, to generalised hypersensitivity in patients with fibromyalgia. Allodynia and hyperalgesia can in some, but not all, instances represent hyperexcitability in the nervous system, and it is important to note that allodynia and hyperalgesia are clinical terms that do not imply a mechanism. Allodynia and hyperalgesia are classified according to the sensory modality used to elicit pain—ie, mechanical (dynamic, punctate, and static) and thermal (cold and heat) stimuli, which are seen in various peripheral nerve disorders, such as trigeminal neuralgia, peripheral nerve injuries, and postherpetic neuralgia, as well as in central neuropathic pain conditions, such as central post-stroke pain, multiple sclerosis, spinal cord injury, and syringomyelia. The clinical presentation can be quite different in these conditions (figure 4). There has been interest in the predictive value of sensory changes for the development of pain. Studies have found that sensory hypersensitivity precedes the development of some neuropathic pain conditions. For example, after spinal cord injury and central post-stroke pain (Klit and colleagues, unpublished), early sensory hypersensitivity predicted the development of central pain, suggesting that central neuronal hyperexcitability develops gradually and precedes the development of spontaneous central pain. In peripheral neuropathic pain, early hyperaesthesia has been found to increase the likelihood of persistent pain—eg, after surgery.

Mechanical allodynia and hyperalgesia

Three types of mechanical allodynia and hyperalgesia extending beyond the innervation territory of the damaged nerve. On the basis of the symptom description, a distinction is often made between spontaneous (stimulus-independent) and evoked (stimulus-dependent) pain. This concept has been challenged by Bennett, who argues that the two types of pain are hard to separate and that spontaneous neuropathic pain might represent unrecognised allodynia or hyperalgesia due to subliminal internal or external stimuli that occur during daily life. He postulates that repeated episodes of such stimuli might summate and generate sensitisation. This hypothesis is difficult to either prove or refute. Nevertheless, the separation into stimulus-dependent and stimulus-independent pain is clinically useful because it is easy to identify on the basis of the patients’ descriptions and, as shown below, is probably important in clarification of potential mechanisms of pain. Importantly, although hyperexcitability in the pain pathways can give rise to allodynia and hyperalgesia, these symptoms and signs do not always show a peripherally
Dynamic mechanical allodynia is generally accepted to be mediated by low-threshold Aβ fibres in most

Figure 3: Mechanism for development of central sensitisation
(A) Diagram of noxious (C fibres) and non-noxious (Aβ fibres) input to second-order projection neurons in the spinal cord. (B) Following stimulation of C fibres (red area)—eg, by capsaicin amplification of spinal cord signalling systems—central sensitisation develops and non-noxious stimulation outside the injured area is sufficient to elicit a painful sensation. (C) After injury to nerves, second-order neurons are excited by abnormal and increased input form the periphery, causing central sensitisation and non-noxious input from damaged or undamaged Aβ fibres, which may now elicit activity sufficient to cause pain. Because of injury, there are also areas with a loss of sensitivity (yellow areas). (D) Additionally, a change in the balance of descending inhibitory (−) and facilitating (+) pathways from the brain to the spinal cord can affect dorsal horn neuronal activity and can therefore cause central sensitisation. Red represents sensitisation of fibres and blue represents normal fibres in A–C.

Figure 4: Three different neuropathic pain conditions with separate and distinguishable types of allodynia and hyperalgesia

seen in the secondary hyperalgesic area after capsaicin application, with similar temporospatial stimulus parameters and pain descriptors. 15–17 This similarity suggests, but does not prove, that the mechanisms underlying dynamic mechanical allodynia in some neuropathic pain states are similar to those seen after experimental capsaicin application, which produces a zone of primary hyperalgesia at the site of injury and secondary hyperalgesia extending beyond the injury site. 18–20 Stimulus-dependent pain is, by nature, only present in areas with preserved ascending sensory pathways and, consequently, patients with allodynia and hyperalgesia often have fewer sensory deficits compared with patients with spontaneous pain only. 21–23 In patients with partial nerve injury, a deficit to one or several modalities can be masked by an associated hyper-sensitivity in intact or regenerating nerve fibres in the same or adjacent territories. 24

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instances. In a classic investigation by Gracely and colleagues, a local anaesthetic block of nerve injury trigger points attenuated both continuing pain and brush-evoked allodynia, with a return of both pain and allodynia as the anaesthetic effect disappeared. Moreover, by selectively blocking A fibre input in patients with nerve injury, dynamic mechanical allodynia disappeared, whereas burning pain mediated by continuing C fibre activity remained. Studies of reaction times in dynamic mechanical allodynia confirm that large myelinated fibres mediate the disorder. The Aβ input might be necessary not only for the presence of allodynia, but also for the quality of the pain felt. A gradually increasing compression block of Aβ input in patients with nerve injury pain showed that the modality of the evoked sensation changed from dynamic mechanical allodynia to dynamic mechanical dysesthesia, which suggests that dysesthesia and allodynia are part of the same spectrum, and that both are orchestrated by the degree of input from non-noxious mechanosensitive fibres.

Small-fibre input seems to be an important driver of allodynia. In experimental studies using capsaicin or mustard oil to elicit pain and hyperalgesia in human volunteers and patients with nerve injury pain, elicited burning pain and dynamic mechanical allodynia increased after warming of the skin. The authors of another study found that preservation of thermal pain pathways (estimated using laser-evoked potentials) rather than large fibre pathways (estimated using nerve conduction recordings) were more common in patients with peripheral neuropathy and dynamic mechanical allodynia. Whether or not the testing was done in the area of dynamic mechanical allodynia was not certain, but the authors do suggest a role for at least partly preserved and sensitised thin fibres. Dynamic mechanical allodynia might, in some cases, be mediated through unmyelinated, low-threshold mechanosensitive afferents that signal the pleasantness of gentle skin stroking, although the role of these fibres in patients with neuropathic pain is still unsettled. In central pain conditions such as central post-stroke pain, tactile allodynia has been shown to occur in patients with disturbances of thermal pathways but spared tactile signalling pathways, which suggests that disruption of the thermal input is necessary for the development of pain.

Punctate allodynia and hyperalgesia

Punctate allodynia and hyperalgesia present in the innervation territory of the affected nerve usually involve a larger area compared with dynamic mechanical allodynia and depend on central changes in addition to peripheral input. Based on differential nerve fibre blocks by compression, punctate hyperalgesia is driven by activity in Aδ fibres and a minor input from C fibres, by contrast with the Aβ-mediated dynamic mechanical allodynia. Various animal models of nerve injury pain use a monofilament stimulation method to evoke motor responses, which is similar to that used in human studies to examine for punctate hyperalgesia.

Static evoked allodynia or hyperalgesia

Static (ie, pressure) evoked allodynia or hyperalgesia is another important, but less recognised, form of allodynia and hyperalgesia. Static hyperalgesia is phenomenologically different from dynamic and punctate allodynia and hyperalgesia produced by chemical irritants such as capsaicin or mustard oil. Static allodynia is generally short lasting and confined to the primary hyperalgesic area (primary hyperalgesia), whereas dynamic and punctate hyperalgesia extends beyond this area (secondary hyperalgesia). Based on nerve compression blocks, static allodynia—by contrast with dynamic mechanical allodynia and similar to heat hyperalgesia—is mediated by sensitised peripheral nociceptors. Importantly, the authors of a clinical study showed the simultaneous presence of static and dynamic allodynia in 28 patients with nerve injury, and found that these two signs represented distinct and separable types of sensory hypersensitivity. The clinical significance of static hyperalgesia has been mentioned only briefly in the literature. However, deep (static) mechanical hyperalgesia has subsequently been noted in other peripheral neuropathic pain conditions, such as traumatic nerve injuries and diabetic neuropathies.

Molecular mechanisms of mechanical allodynia and hyperalgesia

Several molecular mechanisms underlie neuronal hyperexcitability and allodynia, with much knowledge gained from preclinical studies, but a detailed description is beyond the scope of this Review. After injury, cytokines, nerve growth factors, and other algogenic substances invade the injured tissue area, which contributes to a change in the expression and trafficking of non-specific ion channels and specific sodium and potassium channels.

Spontaneous ectopic activity in nerve endings or along the axon is important for spontaneous pain, but might also be a driving factor of allodynic responses. After nerve injury, the expression of sodium channels is changed, particularly the isoforms Na,1-3, Na,1-7, Na,1-8, and Na,1-9. Other channels in the development of ectopia are the neuronal hyperpolarisation-activated cation channels, which, together with calcium channels, are important to neurons to display repetitive firing patterns. This peripheralised increased input—whether caused by sensitised nociceptors or ectopia—is an important driving force for central sensitisation and its clinical expression with spread of pain outside the damaged nerve innervation territory, the increase of pain despite the same stimulus intensity, and the persistence of pain after stimulation has stopped.

Many signalling molecules are implicated in the sensitisation and include several glutamate receptor
types, substance P, proinflammatory cytokines, tyrosine kinase B receptors, and different protein kinases.4,5,38

Another potential mechanism underlying mechanical allodynia is a phenotypic switch in which Aβ fibres start to express neuropeptides such as calcitonin-gene-related peptide, substance P, and the neurotrophin BDNF, which are usually only expressed by small fibres.47,48 Postsynaptic changes probably contribute to allodynia too. These include increased activity at NMDA, AMPA, and metabotropic glutamate receptors, different kinases, and other signalling systems that increase synaptic strength.4

Reduction of normal GABA and glycine inhibition of second-order neurons will probably be involved too. Downregulation of potassium-chloride exporters leads to a shift in the transmembrane anion gradient and a net excitation rather than an inhibition of second-order neurons.47,48 A range of molecular mechanisms is probably involved in these sensitisation phenomena and the activation of nociceptive spinothalamic pathways by normally non-painful stimuli. Understanding the contribution of each of these mechanisms to the different symptoms and signs seen in individual neuropathic pain conditions and individual patients remains a future challenge.

**Thermal allodynia and hyperalgesia**

**Cold perception and allodynia**

The authors of early psychophysical studies in human beings showed that the perception of cold can usually be separated into three categories: perception of innocuous cool temperatures when the skin is cooled by between 0–5°C and 1–0°C in the most sensitive areas; cold pain sensation that is perceived in the range of 30–15°C; and a sensation that is perceived in the range of 0·5°C and 1·0°C in the most sensitive areas; cold pain tolerance further cooling from the pain threshold.76 Cold allodynia is often the sole finding in patients with cold injury, by contrast with those with neuropathic pain, who might have additional signs of sensitisation.79

Cold allodynia is a frequent finding in neuropathic pain, but it is also seen in patients with permanent sequelae after cold injuries69 and in ciguatera, a neurological disease caused by consumption of ciguatoxins, which are a group of compounds that accumulate in some tropical and subtropical fish.70 The character of cold allodynia differs between patients. For example, it might be perceived as a deep aching and burning sensation in a patient with small-fibre neuropathy,71 a pricking sensation in a patient with acute oxaliplatin neuropathy, or an intense cold or burning sensation in a patient with central pain. Patients with cold injury have normal detection thresholds, but report pain at non-painful cold temperatures. By contrast with patients with neuropathic pain, those with cold injury tolerate further cooling from the pain threshold.74 Cold allodynia is often the sole finding in patients with cold injury, by contrast with those with neuropathic pain, who might have additional signs of sensitisation.79

These differences in the clinical expression of cold hypersensitivity indicate differences in the underlying neurophysiological mechanisms and suggest that phenotyping of patients based on quantitative sensory testing should be coupled with a more detailed description and analysis to achieve a more distinct classification (panel).

**Molecular mechanisms of cold sensation**

The exact cellular and molecular mechanisms of cold sensation are not wholly understood. However, both voltage-gated ion channels and members of the transient receptor potential (TRP) ion channel family are associated with the transduction of cold sensation and cold-related pain.74,75

TRPM8 and TRPA1 are two cation channels expressed in trigeminal and dorsal root ganglion cells that both respond to cooling temperatures.82 Essentially, TRPM8 is exclusively expressed in neurons that participate in cold signalling. Low-threshold cold cells expressing TRPM8 have been suggested to activate a postsynaptic channel resulting in a cool sensation, and high-threshold cells83

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**Panel: The thermal grill illusion as a model for cold allodynia**

After studies by Thunberg80 in the 19th century on what was termed the thermal grill illusion, there has been an interest in mechanisms giving rise to thermal allodynia. The thermal grill illusion showed how simultaneous application of innocuous cold and warm stimuli to skin elicited a warm sensation or a noxious sensation, described as a “cold burning pain sensation” or the thermal grill illusion. Different theories have been proposed to explain the thermal grill illusion.

Cold neurons, which are exclusively activated by cool stimuli, have a lower activity during the illusion stimuli compared with when a real cold stimulus is present.81 In the polymodal neurons termed heat-pinch-cold cells, the neuronal firing pattern was similar for pure cold or illusion conditions. On the basis of these findings, investigators postulated that the thermal grill illusion represents an unmasking phenomenon in which the simultaneous presentation of cool and warm stimuli disinhibits activity in cold-sensitive polymodal lamina 1 spinothalamic neurons (figure 5).82 Functional imaging has shown that the thermal grill activates the anterior cingulate cortex, which is frequently excited by noxious stimuli, whereas separate presentation of warm and cold stimulation alone does not activate the anterior cingulate cortex.82 This could show an imbalance between the activity of cold-specific and cold-nociceptive cells, resulting in differential excitation of the insular cortex and medial and lateral aspects of the thalamus.

Few investigators have tried to alter the illusion phenomena pharmacologically. However, studies by Bouhassira and his group83 have shown that the paradoxical pain produced by the grill can be reduced by the NMDA ion channel antagonist ketamine, suggesting that NMDA receptor-mediated systems play a part in this thermal hyperalgesia.

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Molecular mechanisms of cold allodynia and hyperalgesia

Several hypotheses exist for the mechanisms of cold allodynia and hyperalgesia. These include peripheral and central sensitisation, or central disinhibition, such as sensitisation of C nociceptors or Aδ fibres (figure 5). Micro-neurographic recordings in a patient with small-fibre neuropathy and cold allodynia showed sensitisation to cold and menthol responsiveness of subtypes of C nociceptors, which provides a potential explanation for cold allodynia. TRPM8 upregulation might explain this sensitisation. Although supported by animal studies, the role of TRPM8 upregulation in human neuropathic pain is less clear, and patients with neuropathic pain with cold allodynia might have both increased and decreased sensitivity to menthol.

Sodium channel dysfunction is another mechanism that could explain peripheral sensitisation. Changes in axonal excitability, indicating sodium channel dysfunction, have been documented in sensory neurons immediately after oxaliplatin infusion. In these patients, cold allodynia might therefore be due to increased excitability of cold-sensitive neurons through changes in transient Na+ conductances. Additionally, ciguatoxins elicit cold allodynia via complex mechanisms, including activated sodium channels. Authors of experimental studies suggest that different sodium channels are important. Whereas Na1.7 expression within the peripheral nervous system has been proved necessary for mechanical or cold-evoked responses in some models, this is not true for oxaliplatin-induced cold behaviour, in which Na1.6 expression plays an essential part, as likewise found in an earlier study. The authors of studies in rodents have also implicated TRPA1 receptors, potassium hyperpolarisation-activated cation channels, and calcium channels in cold allodynia and hyperalgesia. Additionally, central sensitisation of spinothalamic or cortical neurons caused by the same molecular mechanisms implicated in mechanical allodynia and hyperalgesia might underlie cold allodynia and hyperalgesia in both central and peripheral neuropathic pain.

Blockade of Aδ fibres during nerve compression or disease causes an increase in cold detection thresholds, a decrease in cold pain thresholds, and a change in the quality of cold sensation to icy, stinging, hot, and burning sensations. This is thought to result from disinhibition of C-polymodal nociceptive fibres (heat-pinch-cold fibres) by loss of Aδ fibres and could provide an explanation for cold allodynia in neuropathic pain patients (figure 5). A similar mechanism has been proposed to explain cold allodynia in patients with central pain, in whom loss of central innocuous cold pathways or disruption of a thermosensory area in the insular cortex is proposed to disinhibit polymodal nociceptive heat-pinch-cold-sensitive pathways, causing cold to be experienced as burning pain. Red represents sensitisation of fibres, grey represents loss of fibres, and blue represents normal fibres in A–D. Blue areas show where a cold stimulus is applied.

**Figure 5: Potential mechanisms for cold allodynia and hyperalgesia**

(A) Peripheral sensitisation of cold-sensitive C fibres through abnormal expression or function of, for example, TRPM8 and TRPV1 receptors, or sodium, potassium, or calcium channels, can cause decreased thresholds and exaggerated responses to cold. (B) Peripheral sensitisation of Aδ fibres might likewise cause cold allodynia and hyperalgesia. (C) Loss of peripheral Aδ fibres or (D) of central innocuous cold pathways (eg, by disruption of a thermosensory area in the insular cortex) might disinhibit cold-sensitive polymodal nociceptive heat-pinch-cold-sensitive pathways, causing cold to be experienced as burning pain. Red represents sensitisation of fibres, grey represents loss of fibres, and blue represents normal fibres in A–D. Blue areas show where a cold stimulus is applied.

ACC=anterior cingulate cortex. INS=insular cortex. S1=primary somatosensory area. THAL=thalamus.
and A fibre mechanoheat nociceptors, which respond to mechanical and heat stimuli. There seem to be two types of thermosensitive C nociceptors: one quickly adapting type that discharges during an increment of temperature and a more slowly adapting type that responds throughout a gradually maintained temperature increase.39 The key transducer in warm and heat pain-responiding neurons is TRPV1, the activity of which increases gradually with temperature.90 Other channels of the TRP family—ie, TRP ion channels V2–4—and purinergic receptors might also participate in the transduction of heat. Hyperalgesia to heat, which is prominent in inflammatory disorders, can likewise be seen in neuropathic pain disorders. Such heat hyperalgesia can be either peripherally or centrally mediated. Resiniferatoxin—a potent capsaicin analogue—produces long-lasting desensitisation of TRPV1 receptors91 and blocks heat but not tactile hypersensitivity in experimental nerve injury, suggesting that peripheral sensitisation of the nerve fibres that express TRP channels plays a part in heat hyperalgesia.92

Heat hyperalgesia is probably likewise a result of central mechanisms and is present in 10% of patients with central pain.44 Hyperalgesia to laser stimuli in both peripheral and central neuropathic pain has been found to coexist with decreased, delayed, and desynchronised laser-evoked potentials.43 In some of these patients, the ultra-late components of heat-evoked potentials, which are described in healthy controls after C fibre sensitisation and Aδ fibre blockade,115 have been seen. Such responses have been hypothesised to show activation of a slowly conducting multisynaptic medial pain system because of either sensitisation or disinhibition.44

A classic example of heat hyperalgesia is inherited erythromelalgia—a condition characterised by bilateral severe burning pain in distal extremities, particularly the feet—associated with vasodilatation and reddening of the feet or hands.114 This condition, which is an autosomal dominant disorder, is caused by a missense mutation in the Na1.7 channel, resulting in a reduction of the activation threshold.115 With microneurography, ectopic activity has been noticed in C fibres from these patients, which represents one example of increased membrane excitability.116

In nerve injury, expression of the key heat transducer TRPV1 changes. TRPV1 is downregulated in injured nerve fibres, but upregulated in uninjured fibres,107,118 and has a de-novo expression in cells belonging to the Aδ and Aβ type.90 Taken together, these findings suggest that both peripheral—and TRPV1-sensitised nociceptors—and central mechanisms might have a role in the development and maintenance of heat hyperalgesia after damage to the nervous system. It can also be envisioned that the general lowering of thresholds to stimuli such as warm stimuli could lead to spontaneous activity, which could provide a mechanism for other sensory perceptions, such as sticking or burning sensations.

Modulation of allodynia and hyperalgesia
Pharmacological treatment
Pharmacological treatment is the mainstay of neuropathic pain treatment. A series of compounds has been used to modulate neuropathic allodynia and other manifestations of neuropathic pain. These include drugs acting at voltage-gated and ligand-gated ion channels, metabotropic glutamate receptor ligands, opioids, cannabinoid receptor modulators, and glycine transporter inhibitors.128,129

Few trials have specifically addressed the treatment of evoked pain. Several randomised, double-blind, placebo-controlled studies with the primary aim to study the effect of pharmacological treatment in neuropathic pain conditions have reported on the effect of the drug on allodynia or hyperalgesia, assessed by history, at the bedside, or by quantitative sensory testing. Dynamic mechanical allodynia to a brush or cotton swab is the outcome most often assessed, followed by hyperalgesia to pinprick and allodynia to cold. Allodynia or hyperalgesia was made an inclusion criterion in only a few studies, and most had too few patients with a specific type of evoked pain or the intensity was too low to be able to show an effect. Tricyclic antidepressants,122 serotonin-norepinephrine reuptake inhibitors,123,124 gabapentinoids,125–127 opioids,128–132 cannabinoids,131 lamotrigine,132 mexiletine,135 lidocaine gel,134 and botulinum toxin-A135 have been found to relieve dynamic mechanical allodynia, cold allodynia, or pinprick hyperalgesia in different peripheral and central neuropathic pain conditions. The authors of studies with intravenous treatment additionally investigated the effect on different types of evoked pain, and sodium channel blockers, opioids, NMDA antagonists, and propofol have shown effect on mechanical and cold allodynia.127,129,132–134

Studies have also been done to examine whether allodynia or hyperalgesia are predictors of overall treatment effect. Pinprick hyperalgesia predicted an overall effect of pregabalin in HIV polyneuropathy44 and dynamic mechanical allodynia or temporal summation to repetitive pinprick predicted the response to lamotrigine in spinal cord injury.38 whereas dynamic mechanical allodynia was a negative predictor of the overall effect of pregabalin in postherpetic neuralgia129 and levetiracetam in multiple sclerosis.136 These results were all based on posthoc analyses. Six intravenous treatment trials133,138–142 were done to examine alldynia or hyperalgesia as predictors of overall pain-relieving effect, but only as a predefined outcome in one of them.139 In one study, static or dynamic mechanical alldynia predicted the response to intravenous lidocaine,146 whereas authors of the other studies failed to find evoked pain to predict the response to lidocaine,138,140 morphine,144 or ketamine.139

Recently, a study was done to try to establish whether a reduction of spontaneous pain is matched by a similar reduction of evoked pain. In a group of patients with peripheral nerve injury pain and evoked pain who underwent a complete block of afferent input to the CNS,
blockade of spontaneous continuing pain additionally blocked aspects of evoked pain, which suggests that the afferent drive from the periphery is necessary for the centrally mediated evoked pain.10

Non-pharmacological modulation

Allodynia and hyperalgesia produced by nerve injury can be modified from the brain. Psychological and physical modulations have been shown to alter allodynic phenomena in patients with peripheral nerve injury. The authors of systematic reviews covering different electrical or magnetic stimulation techniques for neuropathic pain after spinal cord injury showed that these techniques might have a beneficial effect in neuropathic pain and the associated dysaesthesia and allodynia.12,13 The authors of these neuromodulation studies took advantage of the powerful control exerted by the brain on dorsal horn pain processing—eg, Wittering and colleagues12 showed that a paradigm with diffuse noxious inhibitory control, in which a painful stimulus was applied at a distance from a neuropathic pain area, could reduce the perceived intensity of allodynia in patients with nerve injury when exposed to a cold pressor test. Results of another study in patients with post-thoracotomy pain13 showed that placebo responses could modify the area of allodynia. In general, larger studies are needed to establish the value of stimulation on allodynia and hyperalgesia.

Conclusions and future directions

Allodynia and hyperalgesia in neuropathic conditions, together with sensory loss, represent an important imprint of the activity in the nociceptive system. On the one hand, the extent and degree of sensory loss will show the magnitude of peripheral deafferentation or the CNS structures that have lost their normal patterned input. The areas of allodynia and hyperalgesia in neuropathic pain, on the other hand, provide a measure of those structures within the nervous system where signs of neuronal hyperexcitability are present. By further classification of allodynia or hyperalgesia according to different types of stimuli, additional insight might be gained into the underlying pain mechanisms, which can then be targeted by different types of management.

Existing drugs are rather non-specific in their mode of action.14 This non-specificity limits the possibility of dissection of the underlying pathophysilogies. However, with novel and more specific drugs, these subtypes of allodynia and hyperalgesia could be used as additional endpoint measures in clinical trials.

Contributors

TSJ wrote the first draft. TSJ and NBF both searched for studies and edited the Review.

Declaration of interests

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