



Contents lists available at ScienceDirect

## Medical Hypotheses

journal homepage: [www.elsevier.com/locate/mehy](http://www.elsevier.com/locate/mehy)

## Migraine, neuropathic pain and nociceptive pain: Towards a unifying concept

A. Chakravarty\*, A. Sen

Department of Neurology, Vivekananda Institute of Medical Sciences, Calcutta, India

## ARTICLE INFO

## Article history:

Received 14 August 2009

Accepted 19 August 2009

Available online xxxxx

## SUMMARY

Migraine, neuropathic pain and nociceptive pain are the three commonest pain syndromes affecting human. In the present article, we first present the salient features of the pathophysiology of the three conditions particularly highlighting the core features that are similar in the three conditions. We argue on the validity of the prevailing concept that maintenance of structural integrity of the nervous system differentiates nociceptive pain from neuropathic pain and point out that the fundamental pathophysiology of lasting nociceptive pain (like cancer pain) and neuropathic pain (like nerve injury pain) is essentially same. Migraine pathophysiology is complex and complicated by two opposing views on site of migraine pain generation – peripheral versus central. We hypothesize that this dichotomy has resulted from focusing on two different sites on a single, somewhat complicated, pain mediating circuitry from the peripheral meningeal and vascular structures through several cell stations in the brain stem and thalamus up to the sensory cortical matrix. At the end, we suggest that fundamentally all the three pain syndromes referred to in the article share a common pathophysiological mechanism, namely peripheral pain perception, peripheral sensitization at dorsal root ganglion or its intracranial counterpart (like trigeminal ganglion) and central sensitization at the spinal cord (dorsal horn for somatic pain), brain stem nuclei and thalamus before final pain perception at the sensory cortical matrix.

© 2009 Elsevier Ltd. All rights reserved.

## Introduction

The International Association for the study of pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Migraine, neuropathic pain and nociceptive pain are the three common forms of pain disorders known to human and thinking a little broadly, all pain syndromes would perhaps fall into one of these three categories.

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system [1]. The spectrum covers a variety of disease states and presents with a variety of symptoms [2].

Nociceptive pain, by convention, is defined as pain induced by an external (outside the nervous system) noxious stimulus to a structurally and functionally intact nervous system. The latter point is important to distinguish neuropathic from nociceptive pain by usual convention. The question is – is it true? We shall examine this in the course of this article.

Migraine is a common head pain syndrome, often genetically determined, characterized by generally episodic but often chronic, usually throbbing pain, often unilateral in distribution and often associated with photophobia, phonophobia, osmophobia and nau-

sea and/or vomiting. The common occurrence of throbbing head pain was wrongly interpreted earlier for the pain to arise from blood vessels; but current research points to a neural origin of the migraine pain. In the present article, we would first discuss the salient features in the pathogenesis of these three major pain syndromes and would then proceed to formulate a unifying concept linking the pathophysiology of these three disorders which perhaps would be applicable to all pain syndromes affecting humans.

## Pathophysiology of neuropathic pain

Neuropathic pain is often reported as having lancinating or continuous burning character and is often associated with the appearance of abnormal sensory signs, such as allodynia (pain as a result of a stimulus which does not normally provoke pain) or hyperalgesia (an increased response to a stimulus which is normally painful) or it may be spontaneous like dysesthesia that is normally seen with thalamic lesions. The sensory phenomenon can be further characterized into static (chronic) or dynamic (episodic or paroxysmal) subtypes. The mechanistic implication of allodynia is that elements of the sensory nervous system, which normally signal innocuous sensation, have begun to encode painful stimuli, whilst in hyperalgesia the structures that subserve nociception have become hyperexcitable.

Majority of research in this field had been based on animal studies with mechanical, thermal, chemical and electrical injuries

\* Corresponding author. Address: 1E 1202, Avishikta II, Calcutta 700 078, India. Tel.: +91 33 24843283.

E-mail address: [saschakra@yahoo.com](mailto:saschakra@yahoo.com) (A. Chakravarty).

to peripheral nerve or spinal cord, and hence most available evidence relates to changes in these parts of the nervous system. Nevertheless, it is important to recognize that alteration in the brain has also been demonstrated following peripheral nerve injury. For example, phantom limb has been shown to be associated with re-organization in the cortex in humans (revealed by BTi neuro-magnetic imaging) [3]. A variety of pain-related phenomena, both central and peripheral, have been associated with peripheral nerve injury. These are not mutually exclusive, and it is entirely possible that a combination of these contributes to symptomatology in an individual patient.

In normal primary afferent neurons, it is rare for firing threshold to be reached without the input of a signal. However, following a nerve injury, it has been demonstrated that there is a large increase in the level of spontaneous firing in the afferent neurons, linked to injury site [4]. This has been termed ectopic discharge and has also been demonstrated in humans. Because of the practical problem of recording from humans, most of the studies have been carried out in animals. Ectopic discharges were originally described as arising in the neuroma itself [4] (for example, in a phantom limb). However, further studies revealed that some ectopic discharges could arise also from the dorsal root ganglion (DRG) and other points along the nerve [5]. This phenomenon in the DRG may be labelled as the peripheral sensitization following nerve injury and is an important step to understand the mechanism of neuropathic pain. But what may be the cause of this ectopic discharge? A small number of A-fibres (10%) exhibit subthreshold membrane oscillations in their resting state or under depolarization conditions [6]. Following sensory nerve lesions (SNLs), this was seen to increase to 23% at 9 days post-operation. A similar increase in membrane oscillation in both A- and C-fibres was also seen by Amir et al. [7]. This increased oscillatory behaviour leads to an increase in ectopic firing as the oscillations more frequently reach threshold and subsequent cross-excitation of other neurons serves to amplify this effect. As the DRG neurons are all effectively isolated from each other, cross-talk or emphasis is unlikely to normally occur within the DRG and does not do so after nerve injury [8]. However, chemically mediated cross-excitation has been shown to occur in the DRG [9]. Cross-depolarization has been demonstrated to occur following tetanic stimulation in most (90%) neurons within the DRG [10]. This depolarization is transient following neighbouring cell stimulation and is subthreshold for eliciting an action potential. However, following peripheral nerve injury, many DRG neurons exhibit alteration in their membrane potential to bring them closer to the firing threshold. It is, therefore, possible that the cross-excitation will then be sufficient to evoke ectopic firing. A more recent study has shown evidence of cross-excitation between A- and C-fibres [11]. These observations suggest that the development of ectopic activity may be particularly important for the development of hyperalgesia, allodynia and ongoing pain associated with nerve injury. It is now recognized that two populations of afferent fibres develop ectopic activity following nerve injury, the injured sensory neurons themselves and their uninjured neighbours [12]. This is yet another aspect of the phenomenon of peripheral sensitization.

Sprouting has been described in many animal models, but what are the consequences of such sprouting? The terminals of the sprouted neurons have been shown to form functional synapse-like structures within the cell bodies [13]. These structures could be involved in the formation and maintenance of abnormal excitation originating from the DRG, a hypothesis supported by electrophysiological studies in which sympathetic stimulation increased sensory ectopic discharge from the DRG [14]. As both sympathectomy [15] and guanethidine [16], a noradrenergic depleting agent, have been demonstrated to relieve hyperalgesia in peripheral neuropathy models, it is fair to assume that these functional interactions have some importance in the sympathetically maintained

pain subgroups of neuropathic pain patients (e.g. reflex sympathetic dystrophy).

### Central sensitization in peripheral nerve injury

There is considerable degree of re-organization of the spinal cord in response to peripheral nerve injury. Under normal physiological condition, different classes of primary afferent neuron fibres terminate in specific laminae of the dorsal horn. As a generalization, the nociceptive small diameter cells with myelinated A-fibres and unmyelinated C-fibres terminate in the superficial laminae (I and II) of the dorsal horn, whilst the large diameter neurons with myelinated A $\beta$ -fibres terminate in laminae III and IV. Lamina V is a region of convergence of inputs. Woolf and colleagues demonstrated that after sciatic nerve axotomy, the central terminals of the large myelinated primary afferent neurons sprouted into lamina II of the superficial horn [17]. Koerber et al. also showed a sprouting of A $\beta$ -fibres into laminae II of the superficial dorsal horn after axotomy [18]. Woolf et al. then demonstrated that this ectopic C-fibre activity only occurs 3–4 weeks following axotomy and may persist for many weeks [19].

Evidence has also been obtained that signals in uninjured neighbouring afferents have a role in the development of central sensitization in neuropathic pain. Pain arising as a result of peripheral nerve damage may reflect activity in both damaged and intact sensory neurons.

Na<sup>+</sup> are critical to the physiology of excitable membranes, including neuronal membranes. One important finding of potential significance to the generation of ectopic firing is alteration in the expression of Na<sup>+</sup> channels in the cell bodies and the terminal neuroma of peripheral nerves following nerve injury. In 1989, Devor and Keller demonstrated accumulation of Na<sup>+</sup> channels in the neuroma of cut sensory axons [20], and then demonstrated that the Na<sup>+</sup> channels were the cause of ectopic discharges [21]. However, molecular biology has since revealed that there are many different and distinct voltage-gated Na<sup>+</sup> channels of which at least six are expressed on the cell bodies of primary afferent neurons within the DRG [22]. These can be further split into tetrodotoxin (TTX)-sensitive and TTX-resistant subtypes. TTX-sensitive channels are expressed through the central nervous system and predominantly in the A-fibres in the DRG. TTX-resistant channels are found only within a subset of primary afferent neurons of the DRG, specifically in the smaller C-fibres associated with nociception [23]. Following peripheral nerve injury, it has been demonstrated that there is a re-organization of the natures and expression of the various channels [24]. The expression of some Na<sup>+</sup> channel subtypes in DRG cell bodies is diminished whilst others appear de novo and others translocate to different parts of the neuron, following nerve injury. More specifically, there is an upregulation of type III TTX-sensitive channel gene expression (not normally expressed in DRG) and a downregulation of SNS (aka PN3) and NaN (aka SNS 2) TTX-resistant channel gene expression [25].

The reason for this change is unclear but neurotrophin supply may be a crucial factor. However, this channel mechanism almost certainly contributes to hyperexcitability and ectopic firing in the DRG cells – with rapid repriming of the normally silent type III TTX-sensitive Na<sup>+</sup> channels.

In addition to such changes in Na<sup>+</sup> channels, loss of high voltage-activated N-type Ca<sup>2+</sup> channels seen in response to peripheral nerve injury increases the excitability of the DRG neurons. This in turn would lead to an increase in firing susceptibility and frequency, possibly resulting in not only spontaneous pain but also central sensitization as mentioned earlier. Neuropathic pain disorder can thus be assumed to arise as a result of trauma/disease-induced channelopathy. Sprouting has been mentioned earlier and

sprouting of collateral fibres for sensory axons in the skin into denervated areas has also been described following nerve crush injuries. It is likely that a local release of neurotrophic growth factor (NGF) from sources within the skin is responsible for axon sprouting.

### Role of sympathetic nervous system

This has been briefly mentioned earlier. Sympathetic component of neuropathic pain is classically seen in Reflex Sympathetic Dystrophy – more appropriately called nowadays as Complex Regional Pain Syndrome type 1 (CRPS1). Several sites of coupling between sensory neurons and sympathetic neurons have been proposed and tested in animal models [26], the most favoured site being the DRG. Peripheral nerve injury leads to sympathetic sprouting to the DRG which is connected to the sympathetic ganglion through the grey and white rami communicantes. The factors responsible seems to be neurotrophic factors and cytokines which are often linked to the development of Wallerian degeneration following nerve injury.

### Sensitization in ascending pathways

The output from the dorsal horn to higher centres in the brain is carried by spinal projection neurones along ascending pathways. A large population of projection neurones is found superficially in lamina 1. It is estimated that 80% of these cells express neurokinin 1 (NK 1) receptor for substance P, a neuropeptide that is released by nociceptive afferents, meaning that these cells respond to noxious stimulation [27]. NK 1 positive cells in lamina 1 have been shown to project to areas in the brain such as the thalamus, periaqueductal grey (PAG), and in particular the parabrachial area (PB). In addition to transmitting pain signals up to higher centres in the brain, these cells also project into brain stem areas such as the rostral ventromedial medulla (RVM), a region that has descending projections back to the dorsal horn. Thus, lamina 1 NK1-expressing cells can modulate spinal processing by the activation of descending pathways from the brain stem [28]. These descending pathways can be influenced by limbic regions in the brain and so incorporate the emotional, affective component of the pain experience. A large number of projection neurones are also found deeper in the dorsal horn from lamina III to VI and these project predominantly to the thalamus, thereby making up a significant proportion of the spinothalamic tract. The ascending pathway carries primarily sensory information and so provides the sensory component of the pain experience. From thalamus, nociceptive information is transmitted to cortical regions. There does not exist a single pain centre within the cortex, but rather there are various cortical regions that may or may not be activated during a particular painful experience. The cortical 'pain matrix' includes the primary and secondary somatosensory, insular, anterior cingulate and prefrontal areas [29]. Descending pathways from brain stem structures are able to influence nociceptive signalling in the dorsal horn of the spinal cord. Such descending influences are both facilitatory and inhibitory in nature. Descending facilitatory pathways from RVM in the brain stem have been shown to be involved in the maintenance, but not in the initiation, of nerve injury-induced pain [30]. The origin of modulation from nuclei in the brain stem is in fact located in the superficial dorsal horn itself, thus forming the spino-bulbo-spinal loop that can modulate spinal nociceptive transmission. Pharmacological block of spinal 5 HT receptors reveals a role for a serotonergic descending facilitatory influence in the modulation of spinal nociceptive transmission. The 5HT<sub>3</sub> receptors are predominantly expressed on nerve terminals of small diameter afferents and exert pronocicep-

tive effects at spinal level [31]. Experimental studies have revealed that the beneficial effect of gabapentin (that blocks  $\alpha 2$  subunit of voltage-gated  $\text{Ca}^{++}$  channels) in neuropathic pain is partly related to the drug's activity on descending serotonergic pathways [32].

Descending inhibition largely involves the release of norepinephrine (NE) in spinal cord from brain stem nuclei such as the locus coeruleus (LC), acting predominantly at the  $\alpha 2$ -adrenoceptor subclass and inhibiting transmitter release from primary afferent terminals and suppressing firing projection neurones in the dorsal horn [33]. Clonidine, effective in neuropathic pain relief, acts by partial agonism at spinal  $\alpha 2$  adrenoceptors. It is likely that the inhibitory noradrenergic pathways from brain stem to the dorsal horn may also undergo plastic changes in chronic pain states. Such changes are essentially a homeostatic one to balance facilitatory and inhibitory drive to dorsal horn cells maintaining their excitability.

It seems there is a loss of tonic descending inhibitory control of neuronal responses to low intensity mechanical stimulation and also of spontaneous neuronal activity in the dorsal horn. Coupled with the enhancement of descending noradrenergic inhibition, this would result in an overall enhancement of dorsal horn excitability, which manifests as mechanical hypersensitivity and allodynia and spontaneous pain, common complaints of neuropathic pain patients.

Also, the dual control of spinal cord by serotonergic and noradrenergic pathways may be the route by which sleep, anxiety, coping and catastrophizing can impact upon the level of pain perceived. The use of antidepressants to control pain is related to activity in these systems. Antidepressants are used to increase either 5HT- or NE-mediated neurotransmission or both.

### Pathophysiology of nociceptive pain: Is it much different from neuropathic pain?

Traditionally nociceptive pain is believed to arise with the application of a noxious stimulus peripherally to a structurally intact nervous system. In contrast to neuropathic pain, only a scanty literature is available on nociceptive pain mechanism, the principal reason being that animal models designed to study pain mechanism almost always had neural tissue injury induced mechanically, chemically or thermally. Sorkin and Wallace [34] recently discussed acute pain mechanism and we felt that these authors meant nociceptive pain. Sorkin and Wallace [34] felt that the systems activated by peripheral tissue injury stimuli are complex. The nociceptive primary afferents have little spontaneous activity under normal conditions; however, after tissue injury, they display constantly, ongoing activity. This results, in part, because the injury elicits the release of active factors that sensitize or excite the peripheral nerve terminal. The threshold is lowered to the extent that body temperature and the pressure of oedema are adequate stimuli resulting in spontaneous pain. This phenomenon is mediated by a variety of blood-borne active factors released during plasma extravasation, by agents released from local inflammatory cells and by neurotransmitter released from terminals of the primary afferent fibres themselves. Well-defined projections into the dorsal horn convey pain message to at least two well-defined populations of neurons: those that are nociceptive specific and those that display an intensity-linked discharge over a range of stimuli from innocuous to noxious. Convergence from various fibre types, modalities and end organs permits the encoding of afferent traffic with respect to intensity and location. The convergence of axons from somatic and visceral structures reflects the mechanism for the so-called 'referred pain state'. Most importantly, these dorsal horn systems have a dynamic component in addition to hard wiring; their output can be regulated both up and down. The

upregulation provides the basis for much of the facilitated processing that is believed to account for a significant percentage of the post-injury pain states. The facilitated state has a unique pharmacology, with the underlying mechanism reflecting a cascade of actions that starts with the NMDA receptor and proceeds through the spinal release of intermediaries such as prostaglandin and nitric oxide. Conversely, downregulation of dorsal horn response accounts for the powerful control exercised by a wide variety of diverse factors including the spinal delivery of opioid and non-opioid analgesics and the endogenous analgesic system. These mechanisms are part of the central sensitization that occurs induced by a peripheral noxious stimulus. The stages in nociceptive pain mechanism are thus similar to those of peripheral neuropathic pain mechanism and consist of peripheral sensitization at sensory nerve endings and DRG and then central sensitization at dorsal horn level influenced by descending brain stem pathways before final pain perception at the sensory cortex. One fundamental difference between nociceptive pain and neuropathic pain is that while nociceptive pain is well responsive to opiates, neuropathic pain is not. The possible explanations are loss of peripheral opioid effects, loss of spinal opioid receptors and increased activity in physiological opioid antagonists system [35]. Interestingly, spinal opiate analgesics offer greater pain relief than systemic administration in neuropathic pain and also cannabinoid analgesia appears more effective than opiate analgesia.

On the whole we feel that any long-lasting noxious stimulus applied to periphery induces exactly the same structural and functional re-organization in the peripheral and central nervous system as those produced by peripheral nerve injury. Furthermore, we feel that structural integrity of the nervous system (an essential differentiating feature between nociceptive and neuropathic pain disorders) cannot be maintained in any lasting nociceptive pain state. Cancer pain is often cited as a prototype of nociceptive pain state. In cancer, neural tissue may be damaged (both centrally and peripherally) by infiltrating cancer cells; neural tissue may be affected by cytokines released from cancer-induced inflammation and by antibodies released by cancer cells themselves (paraneoplastic syndromes) and also by chemotherapeutic agents and radiation. Hence, it is debatable whether cancer pain is nociceptive or neuropathic in nature.

### Pathophysiology of migraine

The pathophysiology of migraine is complex, and over 20 years of exhaustive research has failed to unravel the mystery of this common malady. Current opinions are sharply divided as to the site of migraine pain origin – the Queen Square group (recently reviewed by Goadsby [36]) believing that migraine pain originates from the trigeminal nuclear complex in the brain stem and the Dutch group (recently reviewed by Olesen et al. [37]) arguing that pain actually originates in the peripheral nociceptors located in the meninges and meningeal blood vessels and walls of venous sinuses. A throbbing quality of headache is seen in over 80% of migraine headaches and certainly raises the issue of a vascular element in the pain mechanism. While the Queen Square group [36] feels the vascular component as only an epiphenomenon in the headache mechanism, the Dutch group [37] considers it an important component in headache pathophysiology. The Queen Square group feels that extracranial vasodilatation that occurs in many migraine headaches only results from the action of norepinephrine released from the activity of locus coeruleus (LC) in the pons which causes intracranial vasoconstriction and extracranial vasodilatation and thus only an external manifestation of the central sensitizing process which occurs in migraine (like allodynia) and not a contributory factor to the pain generation.

In this article, we only highlight the key features of migraine pain mechanisms taking relevant issues pointed out by the two opposing groups, thus providing a simplified version of pain mechanism as relevant in the context of the present discussion on nociceptive and neuropathic pain.

Like most solid viscera in the body, the brain is insensitive to pain. The intracranial pain-sensitive structures include the walls of the cerebral and meningeal arteries, the walls of the veins and venous sinuses and the meninges – dura mater and leptomeninges which may be conceived as the ‘Capsule’ of the brain. Elsewhere in the body, visceral pain arises from the nociceptors located in the capsule of the solid viscera due to inflammation or stretching (described as a nociceptive pain); similarly intracranial pain (which includes migraine) should arise from the brain ‘Capsule’ – the meninges due to inflammation or stretching. This is the essential similarity between visceral nociceptive pain and migraine. Visceral pain is often referred to the corresponding sensory dermatome as a result of co-excitation at the dorsal horn level; similarly migraine pain is often ‘referred’ to pericranial and cervical muscles due to co-excitation at the trigemino-cervical nuclear complex – the brain stem counterpart of the spinal dorsal horn. This is the second sharing property between somatic nociceptive pain and migraine. But what about the initial site of pain origin in migraine?

It is generally agreed that the initiating event in migraine is a neuronal phenomenon called Cortical Spreading Depression (CSD). Described first over 60 years ago [38,39], it suggests a spread of a wave of neuronal functional depression which starts in the occipital lobe and proceeds anteriorly at a speed which matches the spread of migraine visual aura in the opposite hemifield. This neuronal functional depression is preceded by a very brief period of neuronal excitation very similar to what occurs in epileptic seizure generation. Along with this spreading neuronal functional depression there occurs a spread of cortical and meningeal (dural and pial) hypoperfusion resulting from reduced metabolic demand of cortical neurons [40]. Initially thought to occur only in subjects with migraine with aura (MA), CSD has now been shown to occur in subjects with migraine without aura (MO) as well. The CSD is a bilateral phenomenon in humans as evidenced by the clinical observation that in subjects with hemiplegic migraine, symptoms, at times, spread to the ipsilateral side as well. Spreading neuronal depression most likely results from alteration of neuronal membrane permeability resulting in ion-channel dysfunction allowing extra- and intraneuronal ionic shifts which include  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  ions [41]. It is thus a channelopathic condition and mutations in ion-channel genes have been described in patients with hemiplegic migraine. Further CSD may be stopped using channel active pharmacological agents that might be useful in prophylaxis of migraine headaches. What is the relevance of CSD to migraine pain generation? Two neuronal mechanisms are operative in migraine pain generation – the trigemino-vascular system activation (peripheral sensitization) and brain stem nuclear activation (central sensitization). All pain-sensitive structures intracranially are supplied by the sensory division of the trigeminal nerve having its cell bodies (first-order neuron) in the trigeminal ganglion with central connection to trigeminal nuclear complex (second-order neuron) located in caudal brain stem and extending up to the C2 segment of the spinal cord where it is continuous with the dorsal horn of the spinal cord. The trigeminal nuclear complex (TNC) is thus the cranial part of the spinal dorsal horn. The trigeminal sensory nerve should better be called trigemino-vascular nerve as in addition to subserving pain, it contains fibres that may liberate vasoactive peptides at the periphery upon stimulation.

The spreading cortical and meningeal hypoperfusion release nociceptive chemicals from the neuronal cells and vascular endothelium which sensitizes the peripheral nerve endings of the trige-

mino-vascular nerve [42,43]. This sensation is carried to the trigeminal ganglion, and an 'axon reflex'-like mechanism is set in whereby impulses travel down the trigeminal sensory nerve itself to the pial and dural arteries and arterioles and release vasoactive polypeptides such as calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) which cause vasodilatation and a 'sterile inflammation' in the vessel wall with extravasation of plasma. By a similar mechanism, vasoactive peptides travel through other branches of the trigeminal nerve to reach such extracerebral arteries like middle meningeal and superficial temporal causing vasodilatation and increased pulsation. Increased pulsation in superficial temporal artery is a common accompaniment of migraine attacks. The vessel wall stretching (arterial and venous sinuses) caused by vasodilatation and altered geometry produced by the sterile inflammatory process along with the extravasated plasma in cortex and meninges stimulate the sensory trigeminal nerve endings further and produce a nociceptive sensation which is carried through trigeminal ganglion (first-order neuron) to the TNC (second-order neuron) in caudal medulla. We feel this peripheral sensitization is the initiator of pain production in migraine and in that way we tend to agree with the Dutch group's [37] argument, and this concept of pain production brings migraine at par with other syndromes like neuropathic and nociceptive pain.

Another point needs emphasis at this stage. Available evidence in the literature suggests that extra- and intracranial vasodilatation cannot just be put to side as an epiphenomenon (suggested by the proponents of the central pain generation concept) of migraine but an essential feature of migraine pathogenesis and extracerebral vessel wall dilatation and stretching are important contributors to nociception of trigeminal sensory endings at the periphery. Clinically, it is well known that carotid compression in neck can abolish ipsilateral hemicranial migraine pain.

### Central pain mechanisms in migraine

Several observations made over the past two decades raised the issue that there is likely to be a central pain generator of migraine located in the brain stem. Stimulation of periaqueductal grey (PAG) by deep brain stimulation led to generation of headache [44] and lesions (cavernomas) at or near the PAG may cause migraine like headache [45,46]. However, such headaches would rarely have the classic clinical features of migraine. Imaging studies have demonstrated activation at the PAG region in migraine and more recently in the dorsal pons at the site of locus coeruleus (LC) [47–49]. These observations have been interpreted as suggestive sites of migraine pain generation. However, many pain states mediated through the spinal cord to the brain can show PAG activation and this is not specific for migraine. Finally, 5HT receptors have been observed in the TNC and other cell stations of the brain stem and the activity of triptans in relieving migraine pain had been linked to the action of triptans in these brain stem receptors than their locations at the periphery in vessel walls and meninges [36]. This concept is somewhat overemphasized and 5HT receptors are not specific for brain and are found in spinal dorsal horns and DRG at various levels. However, triptans are only specific for migraine like pain, and hence their efficacy primarily related to activity at the peripheral cranial blood vessels and the meninges. Central activity at brain stem level may be contributory to pain relief. Thus, brain stem nuclear complexes in migraine are involved in pain modulation and not in generation exactly in the same way as they modulate spinal pain as discussed in relation to neuropathic and nociceptive pain earlier in the article. How is this modulation effected?

Afferent pain fibres from the trigeminal ganglion are relayed to the TNC which extends up to the C2 segment of spinal cord where sensory fibres from cervical structures (e.g. muscles) also converge. This convergence explains the common finding of neck pain and neck muscle tenderness during migraine headaches and the concept is very similar to the concept of referred pain from visceral pain as discussed previously.

The ascending afferents from TNC (second-order neuron) cross and go up the brain stem (just like somatic afferents in the spinothalamic tract from spinal dorsal horn of the opposite side) to the ventral posterior medial nucleus of the thalamus (third-order neuron). In this course, the ascending fibres relay to various brain stem cell stations that include the posterior hypothalamic grey, the PAG, the LC and the nucleus raphe magnus/rostral ventral medulla (RVM) in medulla. The spinothalamic tract, as discussed earlier, also gives relays to exactly the same structures, and thus highlights a shared anatomical substrate for migraine and neuropathic/nociceptive pain. The activation of the brain stem cell stations by relays from the ascending trigemino-thalamic tract would explain the increased activity noted in some such structures in imaging studies as mentioned earlier. Activation does not necessarily mean sites of pain generation. In fact, PAG activation in imaging can be observed in peripheral somatic pain from the opposite side as well [50]. What then is the role of the brain stem cell stations? This had earlier been mentioned in relation to neuropathic pain. In migraine also their role is the same, namely pain modulation. Descending fibres from posterior hypothalamus, PAG, LC and RVM modulate activity of TNC, and they may even go down further and even cross the midline to the dorsal horn cell stations of the spinal cord. The phenomenon of convergence is brought into play with somatic afferents passing to dorsal horn cells through the DRG. This explains that migraine allodynia may spread to extracranial sites (e.g. limbs) both on the same side as well as on the opposite side. This is similar to the allodynia mechanism in neuropathic pain and nociceptive pain crossing the dermatome barrier.

The modulation by the brain stem cell stations may be inhibitory and facilitatory, and thus determines the intensity of pain perceived. The variability of pain perception in humans – be it migraine, neuropathic or nociceptive pain – entirely depends upon the brain stem modulatory functions of PAG, LC and RVM.

Does the thalamus play a role in migraine pain modulation? Human imaging studies have confirmed activation of thalamus contralateral to pain in acute migraine [49]. Processing of vascular nociceptive signals in the thalamus occurs in the ventro-postero-medial thalamus (VPM), medial nucleus of the posterior complex and intralaminar nucleus of thalamus. The neurons in the VPM can be modulated by activation of GABA-inhibitory receptors [51] and perhaps of more direct clinical relevance by propranolol through a  $\beta_1$ -adrenoceptor mechanism [52]. Remarkably, triptans through 5HT 1B/1D mechanisms can also inhibit VPM neurons locally [53], suggesting a hitherto unconsidered locus of action of triptans in acute migraine.

We feel that the dichotomy between peripheral and central pain generation in migraine is essentially artificial – different experimental workers seem to have looked at different points of a rather complex electrical circuit – having a power source (internal and external environment) at one end and an electric bulb (sensory cortex) at the other, having three switches (trigeminal ganglion, TNC and thalamus) and several regulators/dimmers (PAG, LC and RVM) on the way. At least two of these switches have regulatory functions with on–off modes as well. As discussed, this conceptual circuit is essentially same for both peripheral neuropathic and nociceptive pain. Like neuropathic/nociceptive pain impulse transmission in migraine pain also occurs through the activity of receptors and neurotransmitters.

The most widely studied are the 5HT receptors belonging to 5HT1 B, 5HT 1D and 5HT 1F classes which, as mentioned earlier, are not only located at the peripheral endings of the trigemino-vascular nerve on the extracranial and meningeal blood vessels (necessary for initiating the sterile inflammation) but also at the trigeminal ganglion and TNC and also in the spinal DRG at various levels. This central distribution of 5HT receptors suggests more than one site of action of triptans (5HT receptor agonists) in migraine pain relief. This observation favours the central pain generation hypothesis of migraine. However, this is only one part of the story as discussed earlier.

As in neuropathic nociceptive pain pathway, in trigemino-vascular pain transmission in migraine, glutamate receptors that include the ionotropic (I Glu Rs): NMDA, AMPA, Kainate; and the metabotropic glutamate receptors (mGlu Rs) 1–8 are involved [54]. NMDA receptor channel blockers have been shown to reduce nociceptive trigemino-vascular transmission [55]. Also certain AMPA/Kainate antagonists also reduced c-fos expression after activation of structures involved in nociceptive pathways [56,57].

Involvement of the posterior hypothalamic grey in migraine pain modulation suggests involvement of two other neurotransmitters, namely dopamine and orexin. A D2 receptor-mediated mechanism may be involved in the inhibition of trigemino-vascular nociceptive transmission. Orexin A – activation of the OX1 receptors can modulate dural–vascular responses to trigeminal afferent activation and inhibit second-order trigemino-vascular neurons in the TNC [58]. Orexinergic mechanisms may be an attractive component to the central matrix of neuronal systems that are dysfunctional in migraine.

### Towards a unifying concept

Is migraine a nociceptive or neuropathic pain disorder? The term ‘nociception’ is widely used in migraine pathophysiology literature. Indeed, as discussed earlier, peripheral nociception does occur in migraine at the walls of extracerebral vessels and meninges. And like in nociceptive pain, the structural integrity of the nervous system is maintained in migraine. This brings migraine and nociceptive pain closer. On the other hand, in neuropathic pain disorders, the structural integrity of the nervous system is jeopardized. But does migraine always occur with a structurally intact neuraxis? Barring rare cases of migraine associated with brain stem cavernoma and other brain stem tumours [45,46], some structural abnormalities do indeed occur with recurrent attacks of migraine. Increased iron accumulation in PAG has been described [59] and in many migraineurs, cerebral white matter hyperintense (in T2-weighted brain MR imaging) lesions could be seen [60] (not to speak of the widespread lesions noted in migraineurs with CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy). These lesions occur as a result of recurrent migraine attacks and not the cause of the attacks. However, PAG iron accumulation may have a role in the transforming process from episodic migraine to chronic migraine, and hence may have a causal role [61]. In that way, migraine may behave like a neuropathic pain disorder. Peripheral nociception does indeed occur in neuropathic pain disorders. The peripheral nociceptors are stimulated by the inflammatory cytokines at the site of injury. Nociception also occurs as a result of ectopic discharges from DRG cells which travel downstream to the periphery to sustain and augment the peripheral nociception. In this way, the spinal DRG neurons behave much like the trigeminal ganglion neurons in migraine where from the axon reflex (discussed earlier) is generated with the liberation of peptides at the periphery causing vasodilatation and sterile inflammation and nociception follows. Thus, migraine behaves like a peripheral neu-

ropathic pain disorder and the two share mostly similar receptors and neurotransmitters. Essentially, in migraine a structurally intact nervous system responds abnormally to apparently non-noxious stimuli resulting from changes in the external and internal milieu. Barring such finer issues, we feel all neurally mediated pain syndromes (which include migraine, neuropathic and nociceptive pain) share a common structural and functional organization consisting of peripheral nociception (often involving a channelopathic... mechanism), peripheral sensitization (at DRG or equivalent level) and central sensitization and modulation at spinal, brain stem and thalamic levels before final pain perception at the cortical pain matrix consisting of the primary and secondary sensory cortices, prefrontal cortex, anterior cingulate region, insula and amygdala.

### Conflicts of interest statement

None declared.

### References

- [1] Merskey H, Bogduk N. Classification of chronic pain. 2nd ed. Seattle: IASP Press; 1994. p. 394.
- [2] Woolf CJ, Mannion RJ. Pain: neuropathic pain: aetiology, symptoms, mechanisms and management. *Lancet* 1999;353:1959–64.
- [3] Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995;375:482–4.
- [4] Wall PD, Gutnick M. Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. *Exp Neurol* 1974;43:580–93.
- [5] Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve ligated rats. *Pain* 1983;17:321–39.
- [6] Liu CN, Amir R, Devor M. Effect of age and nerve injury on cross-excitation among sensory neurons in rat dorsal root ganglia. *Neurosci Lett* 1999;259:95–8.
- [7] Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999;19:8589–96.
- [8] Devor M, Wall PD. Cross-excitation in dorsal root ganglia of nerve-injured and intact rats. *J Neurophysiol* 1990;64:1733–46.
- [9] Amir R, Devor M. Chemically mediated cross-excitation in rat dorsal root ganglia. *J Neurosci* 1996;16:4733–41.
- [10] Utzschneider D, Kocsis J, Devor M. Mutual excitation among dorsal root ganglion neurons in the rat. *Neurosci Lett* 1992;146:53–6.
- [11] Amir R, Devor M. Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. *Neuroscience* 2000;95:189–95.
- [12] Gold MS. Spinal nerve ligation: what to blame for the pain and why. *Pain* 2000;84:117–20.
- [13] McLachlan EM, Janig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature* 1993;363:543–6.
- [14] Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. *J Neurophysiol* 1994;71:38–47.
- [15] Shir Y, Seltzer Z. Effects of sympathectomy in a model of causalgiform produced by partial sciatic nerve injury in rats. *Pain* 1991;45:309–20.
- [16] Neil A, Attal N, Guilbaud G. Effects of guanethidine on sensitization to natural stimuli and self-mutilating behaviour in rats with a peripheral neuropathy. *Brain Res* 1991;565:237–46.
- [17] Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992;355:75–8.
- [18] Koerber HR, Mirnics K, Brown PB, Mendell LM. Central sprouting and functional plasticity of regenerated primary afferents. *J Neurosci* 1994;14:3655–71.
- [19] Woolf CJ, Shortland P, Reynolds M, Ridings J, Doubell T, Coggeshall RE. Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy. *J Comp Neurol* 1995;360:121–34.
- [20] Devor M, Keller CH, Deerinck TJ, Levinson SR, Ellisman MH. Na<sup>+</sup> channel accumulation on axolemma of afferent endings in nerve and neuromas in *Apterionotus*. *Neurosci Lett* 1989;102:149–54.
- [21] Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na<sup>+</sup> channels. *J Neurophysiol* 1994;72:349–59.
- [22] Waxman SG, Dib Hajj S, Cummins TR, Black JA. Na<sup>+</sup> channels and pain. *Proc Natl Acad Sci USA* 1999;96:7635–9.
- [23] Akopian AN, Sivillotti L, Wood JN. A tetrodotoxin-resistant voltage gated Na<sup>+</sup> channel expressed by sensory neurons. *Nature* 1996;379:257–62.
- [24] Waxman SG, Kocsis JD, Black JA. Type III Na<sup>+</sup> channel mRNA is expressed in embryonic but not adult spinal sensory neurons, and is re-expressed following axotomy. *J Neurophysiol* 1994;72:466–70.

- [25] Dib Hajj S, Black JA, Felts P, Waxman SG. Down-regulation of transcripts for Na<sup>+</sup> channel alpha-SNS in spinal sensory neurons following axotomy. *Proc Natl Acad Sci USA* 1996;93:14950–4.
- [26] Janig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. *Prog Brain Res* 1996;113:161–84.
- [27] Todd AJ. Anatomy of primary afferents and projection neurons in the rat spinal dorsal horn with particular emphasis on substance P and the neurokinin 1 receptor. *Exp Physiol* 2002;87:245–9.
- [28] Suzuki R, Morcuende S, Webber M, Hunt SP, Dickenson AH. Superficial NK 1 expressing neurons control spinal excitability through activation of descending pathways. *Nat Neurosci* 2002;5:1319–26.
- [29] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron* 2007;55:377–91.
- [30] Vera Portocarrero LP, Zhand ET, Ossipov MH, et al. Descending facilitation from the rostral ventromedial medulla maintains nerve injury induced central sensitization. *Neuroscience* 2006;140:1311–20.
- [31] Oyama T, Ueda M, Kuraishi Y, Akaike A, Satoh M. Dual effect of serotonin on formalin-induced nociception in the rat spinal cord. *Neurosci Res* 1996;25:129–35.
- [32] Miquel MC, Emerit MB, Nos Jean A, et al. Differential subcellular localization of the 5-HT<sub>3</sub>-As receptor subunit in the rat central nervous system. *Eur J Neurosci* 2002;15:449–57.
- [33] Millan MJ. Descending control of pain. *Prog Neurobiol* 2002;66:355–474.
- [34] Sorkin LS, Wallace MS. Acute pain mechanisms. *Surg Clin North Am* 1999;79:213–29.
- [35] Rowbotham MC, Kalso E, McQuay HJ, Wiesenfeld-Hallin Z, editors. The debate over opioids and neuropathic pain. Opioid sensitivity of chronic non-cancer pain, vol. 18. Seattle: IASP Press; 1999. p. 307–17.
- [36] Goadsby PJ. Pathophysiology of migraine. *Neurol Clin* 2009;27:335–60.
- [37] Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitization. *Lancet Neurol* 2009;8:679–90.
- [38] Leao AAP. Spreading depression of activity of cerebral cortex. *J Neurophysiol* 1944;7:359–80.
- [39] Leao AAP. Pial circulation and spreading activity in the cerebral cortex. *J Neurophysiol* 1944;7:391–6.
- [40] Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. *Ann Neurol* 1981;9:344–52.
- [41] Lauritzen M, Kraig RP. Spreading depression. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, editors. The headaches. Philadelphia: Lippincott, Williams & Wilkins; 2006. p. 269–74.
- [42] Lambert GA, Michalick J, Storer RJ, et al. Effect of cortical spreading depression on activity of trigeminovascular sensory neurons. *Cephalalgia* 1999;19:631–8.
- [43] Moskowitz MA, Nozahi K, Kraig RP. Neocortical depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanism. *J Neurol* 1993;13:1167–77.
- [44] Raskin NH, Hosobuchi Y, Lamb S. Headache may arise from perturbation of brain. *Headache* 1987;27:416–20.
- [45] Afridi S, Goadsby PJ. New onset migraine with a brain stem cavernous angioma. *J Neurol Neurosurg Psychiatry* 2003;74:680–2.
- [46] Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. *Cephalalgia* 2002;22:107–11.
- [47] Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1995;1:658–60.
- [48] Denuelle M, Fabre N, Payoux P, et al. Brainstem and hypothalamic activation in spontaneous migraine attacks. *Cephalalgia* 2004;24:775–814.
- [49] Afridi S, Giffin NJ, Kaube H, et al. A PET study in spontaneous migraine. *Arch Neurol* 2005;62:1270–5.
- [50] Petrovic P, Ingvar M, Stone-Elander S, Petersson KM, Hansson P. A PET activation study of dynamic mechanical allodynia in patients with mononeuropathy. *Pain* 1999;83:459–70.
- [51] Shields KG, Kaube H, Goadsby PJ. GABA receptors modulate trigeminovascular nociceptive transmission in the ventro-posteromedial (VPM) thalamic nucleus of the rat. *Cephalalgia* 2003;23:728.
- [52] Shields KG, Goadsby PJ. Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: a role in migraine? *Brain* 2005;128:86–97.
- [53] Shields KG, Goadsby PJ. Serotonin receptors modulate trigeminovascular responses in ventroposteromedial nucleus of thalamus: a migraine target? *Neurobiol Dis* 2006;23:491–501.
- [54] Storer RJ, Goadsby PJ. Trigeminal nociceptive transmission involves N-methyl-D-aspartate and non-N-methyl-D-aspartate glutamate receptors. *Neuroscience* 1999;90:1371–6.
- [55] Mitsikostas DD, Sanchez del Rio M, Waeber C, et al. The NMDA receptor antagonist MK-801 reduces capsaicin-induced c-fos expression within rat trigeminal nucleus caudalis. *Pain* 1998;76:239–48.
- [56] Johnson KW, Nisenbaum ES, Johnson MP. Innovative drug development for headache disorders: glutamate. In: Olesen J, Ramadan N, editors. Innovative drug development for headache disorders. Oxford (United Kingdom): Oxford University Press; 2008. p. 185–94.
- [57] Sang CN, Ramadan NM, Wallihan RG, et al. LY293558, a novel AMPA/GluR5 antagonist, is efficacious and well-tolerated in acute migraine. *Cephalalgia* 2004;24:596–602.
- [58] Holland PR, Akerman S, Goadsby PJ. Modulation of nociceptive dural input to the trigeminal nucleus caudalis via activation of the orexin 1 receptor in the rat. *Eur J Neurosci* 2006;24:2825–33.
- [59] Kruit MC, Leuner LJ, Over Bosch J, VanBuechem MA, Ferrari MD. Iron accumulation in deep brain nuclei in migraine: a population based magnetic resonance image study. *Cephalalgia* 2009;29:351–9.
- [60] Kruit MC, Launer LJ, VanBuechem MA, Tiedarindt GM, Ferrari MD. MRI findings in migraine. *Rev Neurol (Paris)* 2005;161:661–5.
- [61] Boes CJ, Black DF, Dodick DW. Pathophysiology and management of transformed migraine and medication overuse headache. *Semin Neurol* 2006;26:232–41.