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Sensitization and pain

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Abstract Migraine is often accompanied with signs of increased intracranial and extracranial mechanical sensitivities. The prevailing view today is that migraine headache is a neurovascular disorder with intracranial origin and involvement of meningeal blood vessels and their pain nerve fibers. Allodynia, defined as perception of pain following not painful stimulation, is a common clinical feature in various pain syndromes, and as part of migraine pain, it can be considered an indicator of trigeminal neural network sensitization. The cutaneous allodynia that accompanies the migraine headache in a large percentage of patients may be considered the clinical expression of central nervous system sensitization and is characterized by pain provoked by stimulation of the skin that would ordinarily not produce pain. An altered codification process of sensory impulses in the brainstem, in particular by the nucleus caudalis trigeminalis, may justify the temporal aspects and symptoms in the course of migraine attack.

Keywords Nociception · Sensitization · Allodynia · Pain · Headache

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Introduction

Cutaneous allodynia (CA), defined as the perception of pain after application of a stimulus in itself not painful, can be considered clinical expression of sensitization of the central nervous system in the course of migraine. The first description of sensory symptoms (scalp tenderness) in the course of migraine attack was made in 1832 by Living [1] and was then subsequently described since the 1950s [2, 3].

In animal models, is possible to induce CA after a violent nociceptive stimulation, able to sensitize the second-order neurons of the dorsal horn or the trigeminal nucleus caudalis. The phenomenon of sensitization results in a corresponding reduction of the activation threshold, an increased neuronal reactivity, and an expansion of the receptive fields related to the second-order neurons themselves.

In migraineurs, pain in critical phase starts following the involvement of the trigeminal fibers surrounding the brain vessels, forming together the "trigemino-vascular system" [4]. In this activation will follow the involvement of nociception pathways (trigemino-thalamic-cortical tracts), the release of vasoactive and pro-inflammatory neuropeptides and the activation of superior salivatory nucleus by the trigeminal nucleus caudalis [5].

The sensitization of the nociceptive neurons in the trigeminal nucleus caudalis, which receives convergent afferent input from the dura mater and periorbital skin, justifies the perception of facial CA [6]. The hypothesized mechanism for CA in migraine is central sensitization of second-order neurons of the trigeminal nucleus caudalis, or third-order neurons in the thalamus [7, 8]. These central neurons receive convergent intracranial (dural and meningeal blood vessels) and extracranial (skin and hair follicle) sensory input. The CA occurs more frequently in high-frequency migraineurs and with longest history of diseases

if it results from repeated sensitization of central pain pathways over time [9] [10]. In this context, it is reasonable to affirm that the sensitization of meningeal perivascular nociceptors can explain the intracranial hypersensitivity and the throbbing pain of migraine, and that the central sensitization can produce the extracranial tenderness and cutaneous allodynia.

Repeated or prolonged noxious stimulation may lead to sensitization which in turn can manifest clinically the phenomenon of allodynia [11], through altered functions of chemical, electrophysiological, and pharmacological systems [12]. A variety of painful conditions involve diffuse changes in the function of the nociceptive nervous system and, for this reason, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and endometriosis have all been linked to central sensitization [8] as well as to migraine [13]. Here, the allodynia, expression of central sensitization, may play a role for progression from episodic to chronic migraine. Besides modifiable and not modifiable risk factors for migraine chronification, allodynia may alter the response to pain in migraineurs, especially if those suffering from frequent attacks of high intensity and coexisting analgesic over-intake [14]. Moreover, depression and anxiety occur with high frequency with chronic pain conditions, including migraine, although the mechanism still remains uncertain [15]. Neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have yielded better understanding of the cerebral processing of pain and pain stimuli. The limbic system, particularly the anterior cingulate cortex, is activated extensively in patients with chronic pain, reflecting a considerable contribution of affective-motivational aspects in the experience of this pain [16–18].

Sensitization

The dura is richly innervated by unmyelinated (C-fibers) and thinly myelinated (Að fibers) axons that originate in the trigeminal ganglion and C1–3 dorsal roots ganglions [19, 20]. First-order sensory neurons connect to peripheral corpuscular nociceptors (Að fibers from facial skin) are free-ending (C-fibers from dura or intracranial vessels) and travel in the trigeminal nerve to the brainstem, where they synapse with second-order neurons in the trigeminal nucleus caudalis [21]. Just at the spinal level ascending trigeminal neurons reach the thalamus, where third-order neurons travel to the somatosensory cortex for nociception. Moreover, collaterals to the midbrain, the reticular formations, the periaqueductal gray matter (PAG), and the hypothalamus (with further projections to forebrain limbic structures) ensure reflex responses, emotional processing, and pain modulation via descending pathways [22, 23]. Serotonin, noradrenalin, and endogenous opioids are the main transmitters of those descending pathways to the spinal dorsal horn and trigeminovascular complex. These pathways may exert both inhibitory/anti-nociceptive and facilitatory/pro-nociceptive effects [24–26].

At the brainstem level trigeminal afferents converge with afferents from the second and third cervical nerve roots (C2 and C3), which relay sensory information from meninges of the posterior cranial fossa, the occiput, and the neck including bone and muscular structures [27]. The brainstem area extending from the trigeminal nucleus caudalis to C2–C3 in the spinal cord is called the "trigeminocervical complex". The brainstem serves as a relay station and pathways descending from the periaqueductal gray matter, the nucleus raphe magnus, and the rostral ventromedial medulla modulate incoming pain from the trigeminothalamic and spinothalamic tracts [28] [29].

Recently, it has been hypothesized as many types of prolonged or chronic pain are associated with long-lasting activation and sensitization of peripheral nociceptors and/or central nociceptive neurons in the dorsal horn. In animal model, a prolonged activation and subsequent sensitization of the trigeminovascular system in response to a brief exposure of the dura to a mixture of inflammatory agents consisting of serotonin, bradykinin, histamine, and prostaglandin was obtained. Using this animal model, Burstein [30] found that a brief chemical irritation of the dura activates and sensitizes meningeal nociceptors (first-order trigeminovascular neurons) over a long period of time, rendering them responsive to mechanical stimuli to which they showed only minimal or no response prior their sensitization.

Central sensitization is thought to be the physiologic process underlying cutaneous allodynia as clinical counterpart in a considerable percentage of migraine patients. Brief stimulation of the dura with inflammatory agents also activates and sensitizes second-order trigeminovascular neurons located in the medullary dorsal horn that receive convergent input from the dura and the skin. In this vision, the central trigeminovascular neurons are likely to develop hypersensitivity in the periorbital skin, manifested as increased responsiveness to mild stimuli (brush, heat, cold) to which they showed only minimal or no response prior to their sensitization.

The induction of central sensitization by intracranial stimulation of the dura, and the ensuing extracranial hypersensitivity could be essential in the development of ongoing pain during migraine [31]. Development of allodynia follows a clear temporal pattern where intracranial hypersensitivity results from peripheral sensitization of dural/perivascular trigeminal neurons, where the onset of ipsilateral extracranial allodynia is caused by central sensitization of second-order trigeminal neurons in the

trigeminal nucleus caudalis and finally where extended extracranial/extracephalic allodynia occurs when central sensitization extends to third-order trigeminal neurons in the thalamus [29]. It looks like sustainable that central sensitization depends on incoming impulses from meninges at the beginning of the crisis, and maintains itself in the absence of such sensory input later on.

About the process of chronification, a literature suggests that migraine patients are mostly non-allodynic during the first years of their migraine experience, and are eventually destined to develop allodynia during their migraine attacks over the time [7, 32–35].

It is reasonable to assume that repeated migraine attacks over the years have cumulative adverse consequences on the function of the trigeminovascular pathway, one of which is susceptibility to develop central sensitization. The threshold for a central trigeminovascular neuron to develop a state of sensitization is related to the balance between incoming nociceptive inputs and their modulation by spinal and supraspinal pathways [36] [37].

Burstein et al. showed the presence of allodynia in cutaneous areas is not related to trigeminal innervation and that thalamic sensitized neurons showed an ongoing firing, an increased response in amplitude and a low response threshold. These functional characteristics appeared after mechanical or thermal stimulation of extracephalic skin areas [34, 7]. The same group, through fMRI studies during migraine attack in patients with whole-body allodynia, described a specific thalamic activation after brush and heat stimuli [38].

Early intervention with triptans prevented both peripheral sensitization and central sensitization. Late intervention with triptans did not reverse the spontaneous firing rate and enhanced response to skin brush [39]. The authors proposed that this peripheral effect of triptans explains the control of the throbbing pain of migraine by triptans in humans, and that the persistent increased firing of trigeminal nucleus caudalis neurons explains the persistence of non-throbbing pain.

It was also found as the triptans were able to stop the migraine headache in 93 % of cases if taken before the development of allodynia, while the response rate decreased to 15 % when the triptan was taken already in the presence of allodynia [32]. More recently, it was confirmed that early treatment is more effective compared to later treatment and also ensures less headache recurrence [40].

Anatomic studies have identified 5-HT 1D receptors on the peripheral terminals of meningeal nociceptors, but these receptors are not found on the cell bodies of central nociceptive neurons of the spinal and medullary dorsal horn [41]. These findings support the theory that triptans work peripherally at the level of meningeal nociceptors counteracting the peripheral sensitization and its symptoms. Instead, there is evidence that triptans do not inhibit central sensitization once it becomes activity independent [42]. For these reasons, if administered sufficiently early triptans can block the development of cutaneous allodynia and the symptoms associated with a migraine attack, but once cutaneous allodynia has appeared in the progression of a migraine, triptans are ineffective in countering the central sensitization [43].

Conclusion

A considerable body of evidence now supports the view that activation of the trigeminovascular pathway is fundamental in the pathogenesis of pain during a migraine attack. The characteristic throbbing pain of the initial phase of migraine is due to peripheral sensitization of the meningeal trigeminovascular neurons. Moreover, the development of cephalic allodynia is due to sensitization of second-order trigeminovascular in the spinal trigeminal nucleus which includes afferents fibers from meninges, scalp and facial skin. Finally, the development of extracephalic allodynia sees the involvement and the sensitization of third-order trigeminovascular neurons in the posterior thalamic nuclei, which receive converging sensory input from meninges, facial and body skin. We must always take into account that intensity and persistence of allodynic symptoms are a function of duration of migraine attacks, frequency of attacks, and migraine history. Cutaneous allodynia and consequent sensitization have significant implications for our understanding of the pathophysiology of migraine attacks, for the implementation of treatment, and for assessing prognosis.

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

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