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Persistent medication-induced neural adaptations, descending facilitation, and medication overuse headache

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Abstract

Purpose of review—An impediment to the investigation of mechanisms that drive headache is the inability of preclinical models to measure headache. Migraine attacks are associated with the development of cutaneous allodynia in some patients. Such cutaneous allodynia suggests a state of ‘central sensitization’ of pain transmission pathways and may additionally reflect the engagement of descending facilitation from pain modulatory circuits. For this reason, cutaneous allodynia has been measured in animal models as a surrogate of marker that may be relevant to headache. Overuse of antimigraine medications can promote an increase in the frequency and intensity of headache, a syndrome termed medication overuse headache (MOH). The mechanisms leading to MOH are not known, but may involve the processes of amplification including central sensitization and descending facilitation. This review explores potential mechanistic insights that have emerged from such studies and that could contribute to MOH.

Recent findings—Development of MOH has been recently associated with long-lasting adaptive changes that occur within the peripheral and central nervous systems. Preclinical studies have shown that repeated or continuous treatment with antimigraine drugs result in persistent upregulation of neurotransmitters within the orofacial division of the trigeminal ganglia and in development of cutaneous allodynia in response to migraine triggers, even weeks after discontinuation of the antimigraine drug. Additionally, descending facilitation is critical for the expression of cutaneous allodynia and may mask the expression of diffuse noxious inhibitory controls.

Summary—Medication-induced persistent pronociceptive adaptations might be responsible for lowering the threshold and amplifying the response to migraine triggers leading to increased frequency of headache attacks.

Keywords

cutaneous allodynia; descending facilitation; medication overuse headache; migraine; triptans

Introduction

Migraine is a common neurological disorder associated with headache that is frequently unilateral and that has a pulsating, throbbing quality. Some studies suggest that as many as

80% of migraineurs patients develop cutaneous allodynia during a migraine attack [1]. Cutaneous allodynia is commonly expressed on one side of the head, ipsilateral to the headache. However, during the course of the migraine attack, cutaneous allodynia can spread to the contralateral region of the head as well as to extracephalic areas; broad distribution of allodynic areas may reflect the development of 'central sensitization' of the pain transmission pathway [2]. Central sensitization is a common description for multiple mechanisms that amplify pain signaling usually after tissue injury. In the course of a migraine attack, it is suggested that trigeminal nerve afferent fibers innervating the dura mater can become 'sensitized' (i.e. 'peripheral nociceptor sensitization'), perhaps contributing to the sensation of throbbing pain [1,3,4]. Additionally, however, as the attack progresses, it is believed that second and higher order sensory neurons of the trigeminal nucleus caudalis, and more rostral sites, also become 'sensitized' (i.e. 'central sensitization') resulting in hypersensitivity to normally nonnoxious stimuli, that is, cutaneous allodynia. The generalized expression of cutaneous allodynia may additionally reflect the central mechanisms of amplification including descending facilitation [5,6**].

Medication overuse headache and trigeminal system

It is well known that some, but not all, migraine patients develop medication overuse headache (MOH) after frequent intake of antimigraine medications, in particular opiates and triptans. The International Headache Society defines MOH as a syndrome in which migraine attacks occur 15 or more days a month, when the antimigraine drug is used for 3 or more months and when the headaches have developed or worsened during the period of medication overuse [7]. Termination of the drug administration results in amelioration of MOH. Migraineurs are more likely to develop chronic daily headache than nonmigraineurs and interruption of the drug treatment will result in a reversal of chronic migraine to episodic migraine [8,9]. The mechanisms that underlie MOH are not well understood. However, MOH might be associated with development and/or persistence of states of central sensitization. Central sensitization is thought to underlie the expression of cutaneous allodynia, and migraineurs are more vulnerable to develop cutaneous allodynia as well as MOH than patients with nonmigraine headache [1,10,11]. Additionally, MOH patients are more likely to develop cutaneous allodynia than are individuals suffering from episodic migraine [12,13*]. It is thought that the transformation from episodic to chronic headache may involve sensitization of the trigeminal system, and medications like triptans and opiates might facilitate such sensitization. Because migraineurs are more vulnerable to develop MOH, it is possible that migraine and MOH may share some common neural pathways. Additionally, as migraineurs suffer intermittent pain in the absence of any tissue injury, it is possible that the trigeminal system of these patients is in a state of persistent hyperexcitability [14]. Burstein *et al.* [1] showed that migraineurs have enhanced excitability of the nociceptive pathway both during and in-between migraine attacks.

Migraine and neural adaptation

Recent preclinical studies from our laboratory have shown that some period of persistent exposure (continuous infusion for 6–7 days) to morphine [15**] or to triptans [16**,17**] results in development of cutaneous allodynia, consistent with a state of central sensitization

[15^{••}–17^{••}]. These behavioral signs are accompanied by the increased expression of pronociceptive neurotransmitters such as calcitonin gene-related peptide (CGRP) and neuronal NOS (nNOS) in identified dural afferents of the trigeminal ganglia [15^{••}–17^{••}]. These neuroadaptive changes may underlie hypersensitivity to normally non-noxious tactile and to noxious thermal stimulation. We hypothesized that such pronociceptive neural adaptations might alter the response to triggers of migraine and enhance the frequency of the headaches.

Persistent changes were observed in trigeminal ganglion cells innervating the dura following a period of triptan or opiate treatment. Importantly, the rats also demonstrated a long-lasting state of hyperresponsiveness to stimuli that are considered migraine triggers (i.e., NO donor challenge or exposure to stress), revealing a state referred to as ‘latent sensitization’ [16^{••}, 17^{••}]. Exposure to triptans leads to the development of periorbital as well as hind-paw allodynia that is present during the time of triptans infusion and slowly resolves, within 12–14 days, after discontinuation of the drug administration (by day 18 after initiation of drug infusion). At a time point at which sensory thresholds were normal, animals previously exposed to triptans showed an increased number of identified dural afferent cell bodies in the trigeminal ganglion labeled for nNOS and for CGRP. Importantly, we observed that at this time point, when behavioral signs of hypersensitivity disappeared and neuroadaptive changes were still present, only rats preexposed to trip-tans responded to administration of an NO donor (sodium nitroprusside) or to environmental stress (unrestrained rats exposed to a 1-h period of bright light) with tactile allodynia [16^{••},17^{••}]. It should be noted that generalized allodynia is also observed clinically. Although ipsilateral cutaneous allodynia may be explained by peripheral and central sensitization, how cutaneous allodynia becomes expressed diffusely in contralateral and extracephalic regions is not known.

Preclinical models have studied the effect of directly activating nociceptive afferents by application of a mixture of inflammatory mediators on the dura mater [3,4,6^{••},18–20]. An important outcome of these studies is that neurons that innervate the dura become responsive to previously subthreshold stimuli [4]. After dural inflammation, these neurons become sensitized to mechanical stimulation applied on the dura itself, and show increased firing in response to thermal and mechanical stimulation applied to the periorbital region [3,20]. After some delay, enhanced responsiveness to stimuli occurs in the absence of increased afferent activity, suggesting the development of central sensitization. Application of the mixture of inflammatory mediators has also been applied to the dura of conscious rats. Such studies show a delayed development of a generalized state of hypersensitivity [6^{••},19] that manifests with cephalic and extracephalic cutaneous allodynia. Edelmayer *et al.* [6^{••}] showed that the periorbital and hindpaw allodynia that occurs following dural inflammation in the rat is maximal approximately 3 h after the stimulation and likely reflects a state of central sensitization possibly analogous to that observed in humans. Other studies have demonstrated that repeated application of inflammatory mediators to the dura can result in a long-lasting state of hypersensitivity, possibly reflecting a state of persistent hyperexcitability relevant to migraine states [19]. Furthermore, the activity of immune cells in the meninges has also been linked to exaggerated pain behaviors including the development of facial and hindpaw allodynia [21[•]].

Burstein *et al.* [22] have suggested that the whole-body allodynia may be mediated by thalamic neurons that integrate sensory information from the cranial dura mater and the extracephalic skin. Alternatively, and/or additionally, descending modulatory circuits may play an important role in enhancing inputs from normally innocuous stimuli promoting altered processing and allodynia [6**]. In the study done by Edelmayer *et al.*, an inflammatory cocktail was applied to the dura mater resulting in both cephalic and hindpaw allodynia. The mechanisms that might underlie generalized allodynia were explored by the inactivation of descending modulatory circuits with local anesthetic. Microinjection of bupivacaine into the rostral ventromedial medulla (RVM) prevented and/or delayed the expression of cutaneous allodynia induced by the application of inflammatory mediators on the dura mater of the conscious rat. Additionally, the inflammatory cocktail produced a significant increase in the activity of the pronociceptive ‘on’ cells of the RVM, and inactivation of the RVM by local anesthetic resulted in a blockade of either cephalic or extracephalic allodynia [6**].

Medication overuse headache and pain modulatory circuits

Recent clinical as well as preclinical findings have suggested that abnormality of pain modulatory circuits is likely to be important in the development of MOH and in the ‘chronification’ of migraine. Patients who developed MOH showed lowered thresholds to electrically evoked reflexes that are accompanied by increased pain rating [23**]. Additionally, these patients also show diminished ‘diffuse noxious inhibitory controls’ (DNICs) [23**]. Critically, withdrawal of medications resulted in improvements of these parameters [23**]. These findings are relevant as headache may be considered in the broader category of dysfunctional pain states, in which pain is present in the absence of tissue injury. Loss of, or diminished, DNIC has been observed in patients with fibromyalgia, whiplash, irritable bowel syndrome, chronic tension-type headaches, and, as noted above, MOH [23**, 24–28]. The apparent loss of DNIC in dysfunctional pain states or in MOH has not been explained mechanistically. As noted above, preclinical studies showed that sustained exposure to triptans or to morphine elicits a generalized state of cutaneous allodynia that is blocked by inactivation of the RVM [29]. Additionally, sustained exposure to morphine results in lowering the thresholds for the activation of neurons at the medullary dorsal horn and in expansion of the receptive field of these cells, as well as a loss of DNIC [30**]. However, in these studies, inhibition of the RVM resulted in a re-establishment of DNIC function in morphine pretreated animals, suggesting that sustained morphine exposure increased descending facilitation from the RVM masking the inhibition elicited by DNIC [30**]; thus, the apparent ‘loss of DNIC’ may actually reflect enhanced descending facilitation. Such preclinical and clinical observations [23**] are consistent with reports demonstrating an apparent loss of DNIC in patients suffering from chronic daily headache and may help explain why overuse of medications used to treat migraine can increase the incidence of headache attack [31,32].

Conclusion

Considerable evidence shows that migraine is often associated with cutaneous allodynia and that this allodynia is related to central sensitization that likely occurs during a migraine

attack. Moreover, frequent use of migraine medications leads to MOH that may share neuronal pathways with migraine. Administration of triptans or opiates produces neuroadaptive changes that might be responsible for an increased hyperexcitability of the trigeminal system as well as engagement of descending facilitation. Importantly, enhanced descending facilitation may manifest as loss of DNIC. These observations may suggest mechanisms that contribute to pain in the absence of tissue injury as occurs with migraine. Further exploration of the medication-induced adaptive changes that occur both peripherally and centrally may offer insights into the underlying pathophysiology of migraine as well as into the mechanisms leading to MOH. Importantly, the use of medications that do not engage descending facilitation or elicit such adaptive changes may offer improved therapy for migraine without or with diminished risk of MOH.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 300).

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Key points

- Migraineur patients may develop cutaneous allodynia during a migraine attack, which is related with central sensitization.
- Frequent intake of antimigraine drugs may induce a syndrome called medication overuse headache.
- Sustained administration of triptans or opiates produces neuroadaptive changes.
- These neural adaptations might be responsible for hyperexcitability of the trigeminal system and engagement of descending facilitation.
- Enhanced descending facilitation may manifest as loss of diffuse noxious inhibitory control.