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Update on Medication-overuse Headache

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Abstract

Medication-overuse headache (MOH) is a syndrome that can develop in migraineurs after overuse of antimigraine drugs, including opiates and triptans especially. MOH manifests as increased frequency and intensity of migraine attacks and enhanced sensitivity to stimuli that elicit migraine episodes. Although the mechanisms underlying MOH remain unknown, it is hypothesized that repeated use of antimigraine drugs could elicit increased headache attacks as a consequence of neuronal plasticity that may increase responsiveness to migraine triggers. Preclinical studies show that exposure to either opiates or triptans can induce pronociceptive neuroadaptive changes in the orofacial division of the trigeminal ganglia that persist even after discontinuation of the drug treatment. Additionally, medications can elicit increased descending facilitatory influences that may amplify evoked inputs from trigeminal afferents leading to behavioral hypersensitivity reminiscent of cutaneous allodynia observed clinically. Importantly, enhanced descending facilitation may manifest as an inhibition of diffuse noxious inhibitory control. Persistent, pronociceptive adaptations in nociceptors as well as within descending modulatory pathways thus may jointly contribute to the development of MOH.

Keywords

Migraine; Medication-overuse headache; Opiates; Triptans; Neuroadaptive changes

Introduction

Migraine is a common neurological disorder characterized by episodic, unilateral, throbbing pain that may be accompanied by photophobia or phonophobia, and may occur with or without aura. One of the troubling aspects of migraine therapy is that the overuse of antimigraine medications, notably opiates and triptans, can result in the development of medication-overuse headache (MOH). The International Headache Society (IHS) defines MOH as a condition in which headaches occur on 15 or more days per month when the therapeutic agent is used excessively and on a regular basis for 3 or more months and when headaches have developed or markedly worsened during the period of medication overuse [1].

Recent studies support the idea that frequent intake of antimigraine drugs is caused not only by the intensity of headache pain and frequency of the attacks, but also by fear and loss of social function, observations highlighting the importance that psychology can have on intake behavior [2]. Comorbidity of anxiety and depression frequently exists in patients with

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chronic daily headache [2]. Fritsche and colleagues [2] recently demonstrated that behavioral minimal-contact training as well as use of the bibliotherapy method are significantly effective and cost-saving in prevention of MOH in high-risk populations. They conclude that, in this population of migraineurs, both methods not only prevented the development of MOH but also decreased the frequency of medication intake. MOH also is suggested to be sustained by substance abuse disorders in some patients. In fact, with other kinds of drug dependence, MOH seems to share some common neurobiological pathways, including those that modulate motivation, reward, and behavioral control [3]. In addition, studies from Fuh and colleagues [4] showed that a large proportion of patients with chronic daily headache and with the potential to develop MOH fulfilled the criteria for substance dependence in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). They also demonstrated that prevalence of DSM-IV dependence differed among the different types of symptomatic medication overusage [4]. Moreover, according to the DSM-IV criteria, about 66% of patients with MOH also were considered to be dependent on acute treatments of headaches [5]. Additionally, most of the dependent MOH patients had migraine as preexisting primary headache and current migraine-type headaches, and most of them overused opioid analgesics [5]. A different study also showed that there is a correlation between high Severity of Dependence Scale score and people with secondary chronic headache [6]. Collectively, such evidence suggests that behavioral as well as pharmacological management should be considered for the treatment of MOH.

Several studies have shown that patients with migraine are more vulnerable to development of chronic daily headache after intake of acute medication relative to nonmigraine sufferers. Moreover, the reversal of chronic migraine to episodic migraine is achieved by terminating the drug administration [7, 8]. Among the therapeutic agents employed against migraine, opiates, barbiturates, and triptans are most likely to be associated with the risk of developing MOH [9, 10••, 11, 12]. There is considerable variability in the ability of migraine treatments to lead to development of MOH. Evidence exists that triptan overuse can cause MOH at a faster onset and with lower doses than with other drugs. For example, Limmroth and colleagues [13] showed that triptan use can cause MOH with an average onset of 1.7 years, whereas opioid analgesics lead to MOH in an average of 4.8 years. Furthermore, triptans showed the lowest monthly intake frequency (18 single doses per month) whereas analgesics were associated with the highest intake frequency (114 doses per month) [14, 15]. The duration of withdrawal headache was found to be shorter in patients overusing triptans than in those overusing analgesics [14, 15]. Moreover, patients overusing ergots and analgesics typically report development of a daily tension-type headache, while patients with triptan-induced MOH were more likely to describe development of a (daily) migraine-like headache or an increase in migraine frequency [13].

Although the mechanisms that underlie MOH remain unknown, evidence exists to suggest that MOH may be associated with development of “central sensitization.” Studies by Bigal and colleagues [16, 17] have shown that migraineurs present a greater prevalence of cutaneous allodynia than do patients with nonmigraine headaches; cutaneous allodynia is thought to reflect a state of central sensitization [18, 19]. Additionally, the possibility of developing cutaneous allodynia in the MOH population is greater than in patients suffering from episodic migraine [10••, 20••]. Because migraineurs are more vulnerable to develop MOH, it is hypothesized that migraine and MOH may share some neural mechanisms, and because migraineurs suffer from intermittent pain in the absence of tissue injury (ie, “dysfunctional” pain), the trigeminal system in these patients is likely to be in a state of hyperexcitability [16, 17]. It is possible that overuse of triptans and opiates may be a risk factor for this transformation.

Evidence also supports a role for genetic factors in the development of MOH. Studies from Burstein and colleagues [18] and Moulton et al. [21••] have demonstrated increased excitability of the nociceptive pathway in migraine sufferers, both during and in-between migraine episodes. Preclinical studies have relied on clinical symptoms for insights into a possible mechanism. Migraineurs can experience cutaneous allodynia during a migraine attack. Initially, the allodynia is restricted to the region of the head ipsilateral to the headache; however, throughout the course of the migraine, the area of allodynia can spread to include other regions of the head, and also may extend to extracephalic regions of the body [22]. Because cutaneous allodynia may reflect a state of central sensitization likely resulting from sustained activation of trigeminal afferents, preclinical models have attempted to drive these afferents by application of a mixture of inflammatory mediators to the dura mater [23, 24••, 25]. After application of inflammatory mediators, neurons that innervate the dura become sensitized and respond to previously insensitive mechanical stimulation [26]. Neurons that innervate the middle meningeal artery, superior sagittal sinus, and the dura typically receive convergent input from the skin [27, 28]. After dural inflammation, these neurons become sensitized to mechanical stimulation of the dura and increase their responses to thermal and mechanical stimulation of the facial region [27, 28]. After 2 to 4 h, these enhanced cutaneous responses appear to no longer require primary afferent input from the dura, and therefore, can be considered signs of altered central processing. Behavioral studies have shown that application of inflammatory mediator cocktail to the dura of awake rats resulted in mechanical hypersensitivity at both the cephalic and extracephalic levels [24••]. The generalized expression of cutaneous allodynia after activation of dural afferents suggests a likely role for central modulation that is likely of clinical significance

Descending modulation is bidirectional and contributes to both pain relief and to hyperalgesia [29]. Many studies in rats have shown the importance of the descending inputs from the rostral ventromedial medulla (RVM) in morphine-induced hyperalgesia [30]. Enhanced pain facilitation may be due in part to an increase in the activity of pronociceptive “on cells” of the RVM [31], suggesting that an enhancement in descending facilitation from the RVM may contribute to MOH. Application of inflammatory mediators to the dura of the rat resulted in increased on-cell discharge and cutaneous allodynia that was blocked by inactivation of the RVM with local anesthetic [24••]. Sustained exposure to morphine also elicits generalized cutaneous allodynia that is blocked by inactivation of the RVM [32••]. Furthermore, morphine treatment results in lowering of thresholds for activation of neurons in the medullary dorsal horn and expansion of the receptive fields of these cells [33••]. Additionally, stimulation of the cutaneous receptive field in the ophthalmic region to activate these cells was inhibited by placing the tail in hot water in control rats, demonstrating the presence of diffuse noxious inhibitory controls (DNIC) [33••]. Importantly, however, the DNIC effect was not observed in rats that had been treated with morphine [33••]. The loss of DNIC after morphine treatment is consistent with many clinical observations in states of dysfunctional pain [34, 35]. Critically, however, our studies have shown that inactivation of the RVM re-established the DNIC effect in morphine-treated rats, suggesting that chronic morphine increased descending facilitation from the RVM that likely masks inhibition arising from nucleus reticularis dorsalis [33••]. These preclinical results are consistent with studies demonstrating an apparent loss of DNIC in patients suffering from chronic daily headache and may partially explain why overuse of medication used to treat migraine can induce headaches. Recent work has shown that patients with MOH show lowered thresholds to electrically evoked reflexes that are accompanied by increased pain rating, and additionally, these patients show apparent diminished DNIC; importantly, these parameters are ameliorated after withdrawal of medications [36••]. Collectively, such studies suggest that abnormality of pain modulatory circuits resulting in a net loss of inhibition,

possibly due to increased facilitation, are likely to be important in the development of medication overuse and chronification of migraine.

Multiple potential sites can be identified as potential contributors to increased excitability after exposure to medications. It long has been known that prolonged exposure to morphine (ie, several days) elicits a time-dependent development of cutaneous allodynia and an increased expression of excitatory transmitters, in particular calcitonin gene-related peptide (CGRP) in dorsal root ganglia of rats [30]. Additionally, in tissues taken from animals pretreated with morphine for some period of time, evoked release of CGRP from primary afferents is greatly enhanced, suggesting a mechanism for increased excitatory transmission that may be relevant to headache pain [30]. In addition to such adaptive changes, more recent studies have shown that prolonged exposure to morphine resulted in upregulation of expression of CGRP as well as neuronal nitric oxide synthase (nNOS) in identified dural afferents of the trigeminal ganglia [32••]. These neuroadaptive changes result in a state of hypersensitivity to normally non-noxious tactile and noxious thermal stimulation. Such pronociceptive neuroadaptations may alter the thresholds and degree of response to triggers of migraine, and thus, contribute to the increase in frequency of headache.

Analogous studies from our laboratory also have demonstrated that persistent exposure of rats to triptans over a period of 6 days leads to a long-lasting state of enhanced responsiveness to either evoked stimuli or to challenge with putative triggers of migraine, referred to as “triptan-induced latent sensitization” [37••, 38••]. Triptan exposure leads to a state of generalized cutaneous allodynia, present both at periorbital regions and the hindpaw, suggesting the possibility of central sensitization. Triptan-induced cutaneous allodynia was observed during the time of the triptan infusion and slowly resolved after discontinuation of the drug treatment, within 12 to 14 days. Importantly, during the triptan infusion, neuroadaptive changes were observed within the dural afferents of the trigeminal ganglia. These changes consisted of a marked upregulation of identified dural afferents labeled for CGRP and nNOS and only a slight increase in substance P. Critically, these changes were persistent even after discontinuation of the drug treatment (ie, day 20–21) and at a time where signs of behavioral hypersensitivity had resolved. After discontinuation of triptan administration and at times when sensory thresholds were at baseline levels, challenge with a nitric oxide (NO) donor or with environmental stress reestablished cutaneous allodynia [37••, 38••].

Moreover, studies in humans had suggested that migraine that can be induced by administration of nitroglycerin may be accompanied by increased CGRP in the blood, and this increase is directly linked to the severity of headache pain [39–41; see work from Friberg and colleagues: 42]. Similarly, increased levels of CGRP were observed in the plasma of rats with triptan-induced latent sensitization after NO donor challenge [37••].

Hyper-responsiveness to NO donor or environmental stress in triptan-induced latent sensitization can be blocked by a CGRP antagonist or selective inhibitors of nNOS; CGRP antagonists and nonselective NOS inhibitors have efficacy in migraine in humans. Consistent with a role for NO in promoting excitation, work from our laboratory has demonstrated that inhibition of nNOS can prevent the expression of hyper-responsiveness to presumed migraine triggers [38••]. Thus, cutaneous allodynia that results from environmental stress in animals with latent sensitization is prevented if the animals receive coinfusion of sumatriptan and NXN 323, a selective nNOS inhibitor [38••].

Stress may be considered to be one of the major trigger of migraine. However, how stress induces migraine still is not known. It is hypothesized that stress may induce a cortical spreading depression (CSD) event that will lead to migraine attack. CSD has been suggested

to activate and sensitize primary afferent neurons innervating the dura mater, resulting in sensitization of second-order neurons in the trigeminal nucleus caudalis (TNC) and higher brain centers, to cause cephalic and extracephalic cutaneous allodynia. Whether this occurs in animals with latent sensitization is not known, but recent data suggest that induction of CSD events in untreated rats can result in activation of trigeminal afferent fibers [43••].

It is possible that medications may increase the incidence of CSD events, or consequence of CSDs, to initiate signaling in the trigeminovascular system to enhance the frequency of migraine headaches. Recent studies from Supornsilpchai and colleagues [44••] have demonstrated that acute administration of paracetamol did not change the frequency of CSD after application of solid potassium chloride (KCl) on the rat cortex. However, a daily dose of paracetamol, up to 30 days, significantly increases the frequency of CSD events and c-fos expression in the TNC induced by CSD, indicating increase of cortex excitability as well as increased activation of the nociceptive pathways involved in headache pain [44].

Conclusions

Considerable evidence shows that prolonged and frequent use of medications used to treat migraine headache may lead to the development of MOH, turning migraine from an episodic disorder to a near-daily or daily migraine. The different medications used to treat migraine headache may lead to MOH through distinct mechanisms because the time and the risk of the progression is different. However, common mechanisms also may exist. While the effects of repeated triptan or opioid use for headache are unknown, the recent studies summarized above show that neural adaptations that occur after sustained triptans are seen in the primary afferent that project to the dura, and that these adaptations are pronociceptive and persistent. Additionally, however, the data indicate an important role for descending modulation, especially in descending facilitatory influences that may be important in overcoming or counterbalancing normally present descending inhibition. Further exploration of the medication-induced adaptive changes that occur in primary afferents and in descending modulatory circuits as well as possible cortical hyperexcitability may offer insights into the mechanisms underlying MOH, but additionally, also may offer insights into the underlying pathophysiology of migraine.

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