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Pathophysiology of medication overuse headache: Insights and hypotheses from preclinical studies

Ian D Meng[1], **David Dodick**[2], **Michael H Ossipov**[3], and **Frank Porreca**[1,3]

[1]University of New England, USA

[2]Mayo Clinic Arizona, USA

[3]University of Arizona, USA

Abstract

Introduction—Medication overuse headache (MOH) is a clinical concern in the management of migraine headache. MOH arises from the frequent use of medications used for the treatment of a primary headache. Medications that can cause MOH include opioid analgesics as well as formulations designed for the treatment of migraine, such as triptans, ergot alkaloids, or drug combinations that include caffeine and barbiturates.

Literature review—Gathering evidence indicates that migraine patients are more susceptible to development of MOH, and that prolonged use of these medications increases the prognosis for development of chronic migraine, leading to the suggestion that similar underlying mechanisms may drive both migraine headache and MOH. In this review, we examine the link between several mechanisms that have been linked to migraine headache and a potential role in MOH. For example, cortical spreading depression (CSD), associated with migraine development, is increased in frequency with prolonged use of topiramate or paracetamol.

Conclusions—Increased CGRP levels in the blood have been linked to migraine and elevated CGRP can be casued by prolonged sumatriptan exposure. Possible mechanisms that may be common to both migraine and MOH include increased endogenous facilitation of pain and/or diminished diminished endogenous pain inhibition. Neuroanatomical pathways mediating these effects are examined.

Keywords

Medication overuse headache; allodynia; pain; headache; opioids; triptans; sensitization

Introduction

Medication overuse headache (MOH) (previously referred to as rebound headache, drug-induced headache or drug-misuse headache) is a secondary cause of chronic daily headache (≥15 headache days per month) that occurs in patients with a primary headache disorder

Corresponding author: Frank Porreca, Department of Pharmacology, University of Arizona, Tucson, AZ 85724, USA, frankp@u.arizona.edu.

who overuse acute medications (1). The prevalence of MOH in the general population worldwide is estimated to be at least 1% in adults and 0.5% in adolescents (2–4). Approximately one-third of individuals with chronic daily headache in the general population meet the criteria for medication overuse (MO) (2,5–7); the rates are higher in specialty and tertiary care centers (8,9). Data from a physician survey that included neurologists, headache specialists and general practitioners suggested that MOH may be the third most frequent type of headache after migraine and tension-type headaches (10).

Most patients with MOH in the population and clinical practice have migraine. While migraine is a complex paroxysmal neurological disorder with multiple symptoms, headache pain is the most disabling feature. More than 95% of migraine sufferers regularly use acute medications which include analgesics, migraine-specific medications (triptans, ergot medications), opioids, or a combination thereof. Emerging evidence suggests that the choice of acute treatment and the frequency of use have a major influence on the prognosis of migraine (11,12). Clinic-based and case-control studies evaluating the influence of acute medication use in migraine and non-migraine sufferers have suggested that individuals with migraine are uniquely vulnerable to the development of chronic daily headache (chronic migraine) and that certain acute medications, particularly opioids, barbiturate-containing combination analgesics, as well as triptans and ergots, potentiate this risk of progression (13–18).

There is considerable variability in the propensity and dose-relationship with which certain acute medications can lead to migraine progression. The speed with which certain medications result in the progression of migraine and the durability of this transformation also appears to differ between acute medications. The frequent use of triptans has been shown to result in migraine progression with fewer doses compared with ergots and analgesics (19). In a prospective German study ($n = 96$), the interval between first intake and daily headache was 1.7 years for triptans, 2.7 years for ergots, and 4.8 years for analgesics (19). Moreover, the phenotype of the daily headache differed based on the acute medication being used; patients with triptan-induced migraine progression were more likely to describe a daily migraine-like headache or an increase in migraine frequency. This suggests that the biology of migraine headache, and the biology of migraine progression caused by the overuse of triptans, is probably similar. In a prospective study of 95 patients, the same authors investigated the duration and severity of withdrawal headache after overuse of various headache drugs, including single and combination analgesics, ergots and triptans (20). The duration of withdrawal headache was less severe and shorter in patients overusing triptans (4.1 days) than in patients overusing ergots (6.7 days) or analgesics (9.5 days; $p < 0.002$). This study demonstrated that just as the time interval to the development of daily headache differs depending on the acute medication used, so too does the duration and severity of withdrawal headache and other symptoms upon discontinuation of the medication.

As migraineurs are most susceptible to development of MOH, some common neural mechanisms between migraine and MOH might be expected. A review of migraine mechanisms and neuroplastic changes that occur with chronic medication exposure reveals considerable overlap between the two. In the migraineur, the trigeminal system is likely to

be in a state of hyperexcitability. Preclinically, chronic exposure to analgesics (e.g. triptans, opioids) has been shown to induce an up-regulation of pronociceptive systems. Possible up-regulation of pronociceptive mechanisms, when paired with trigeminal hyperexcitability that probably occurs in the migraineur, may thus exacerbate and help to trigger migraine headache.

The following sections highlight the results of some recent studies that demonstrate a profound influence of prolonged exposure to migraine medications on neural events that have been hypothesized to play a role in triggering migraine headache. These events include cortical spreading depression, intracranial neurogenic inflammation, central sensitization and activation of brain pathways involved in the descending modulation of pain. The impact of prolonged exposure to migraine medications on each of these processes might thus exacerbate and help to trigger migraine headache, leading to the development of MOH.

Cortical spreading depression

While the pathophysiology of migraine is unknown, it is widely acknowledged that activation of trigeminal primary afferent neurons that innervate the intracranial blood vessels and dura is likely to be responsible for producing the headache pain. As evidence, stimulation of the large blood vessels and sinus in humans produces pain qualitatively similar to headache (21,22). How these neurons are activated during migraine or in response to headache triggers leading to migraine remains uncertain. Among the possible initiators of migraine headache pain are cortical spreading depression (CSD), vasodilation and neurogenic inflammation around the intracranial blood vessels.

Spreading depression is a transient depression of electrocorticographic waves that propagates at a rate of 3–6 mm/min following cortical depolarization (21). Recent studies suggest that CSD may have a causal relationship to migraine with aura, but not for migraine in the absence of aura (23). Tonabersat, a compound whose site and mechanism of action is still unknown, is a potent inhibitor of CSD events and was evaluated for the management of migraine (23). A placebo-controlled, double-blind crossover study revealed that tonabersat significantly reduced the incidence of migraine with aura but had no effect on development of headache without aura (23).

While CSD has been strongly linked to migraine aura, establishing a link between CSD and pain during migraine has remained a challenge. The expression of the c-fos protein in neurons is generally taken as an indicator of neuronal excitation. CSD appears to induce c-fos immunoreactivity in trigeminal nucleus caudalis in animal models, suggesting a link between spreading depression and activation of trigeminal afferents. Furthermore, sustained prophylactic treatments for migraine, such as topiramate and valproate, were shown to reduce the frequency of CSD events (24). In a potential connection with MOH, 30-day exposure to the analgesic paracetamol has recently been shown to increase the frequency of CSD events induced by application of potassium chloride to the cortex (25). Furthermore, chronic paracetamol administration increased CSD-evoked c-fos expression in superficial layers of the trigeminal nucleus caudalis, suggesting an increase in the activation of the nociceptive pathway involved in headache. CSDs initiated by KCl applied to the visual

cortex enhanced neuronal responses of the trigeminal complex in response to meningeal stimulation (26). In other studies, CSDs elicited by KCl or pinprick applied to the visual cortex, or by electrical stimulation of the visual cortex, produced a doubling of meningeal nociceptor firing, indicating that CSDs can elicit a long-lasting (i.e. 30 to >68 min) activation of meningeal nociceptors (27).

Peripheral events

Vasodilation was once thought to play a significant role in migraine headache pain. It was believed that migraine occurred after an initial vasoconstriction and ischemia that was then followed by a rebound vasodilation that would activate trigeminal nerves innervating the dural and meningeal blood vessels (28). This theory was attractive because specific and effective anti-migraine medications such as triptans and ergotamine possess vasoconstrictive properties. However, intravenous infusion of vasoactive intestinal peptide (VIP), a potent vasodilator, does not cause headache in migraineurs (29). Moreover, brain imaging studies show no relationship between migraine attacks and cerebral blood flow, leading to the conclusion that “vasodilation is neither necessary nor sufficient to trigger migraine” (28). Although these recent findings call into question the necessity of vasodilation to the induction of migraine, evidence indicates a prominent role for two potent vasodilators, nitric oxide and calcitonin gene-related peptide (CGRP), in migraine.

A role for nitric oxide in the pathogenesis of migraine is suggested by observations that exposure to nitroglycerin produces an immediate headache in normal individuals as well as migraineurs and produces a secondary headache hours after exposure that is described as identical to a migraine attack in migraineurs (30). Furthermore, nitroglycerin-induced headache is more intense in individuals with migraine or tension-type headaches than in normal volunteers (30). Interestingly, although nitric oxide causes vasodilation of intracranial and extracranial arteries, the secondary migraine-like headache induced by sildenafil (31) or nitroglycerin (32) occurs in the absence of vasodilation. Recent clinical studies showed that the inhibitor of inducible nitric oxide synthase (iNOS) GW274150 failed in the prophylaxis (33) and acute (34) treatment of migraine. However, a recent preliminary study presented in abstract form suggested that selective inhibitors of neuronal NOS (nNOS) may show promise in the treatment of migraine (35). Based on these data showing a potential role for nNOS rather than iNOS, it is likely that the role of nitric oxide in the pathogenesis of migraine is related to its ability to promote nociceptive processing in the trigeminal system (30).

Although the mechanisms are not well established, CGRP is released from primary afferent neurons that innervate the intracranial blood vessels and plays a prominent role in the initiation of migraine headache. Administration of CGRP produces a migraine-like headache in humans (36). Increases in CGRP have been measured in the cranial circulation during migraine attacks (37). However, this remains controversial as others have also reported no release of CGRP during the onset of migraine with aura (38). Importantly, CGRP antagonists have been demonstrated to be clinically effective in treating migraine (39,40).

A potential connection between nitric oxide and CGRP has been found in both migraine and cluster headache. Nitroglycerin provoked headache in patients with cluster headaches only during the active period, and not during the headache-free remission period (41). In addition, basal blood levels of CGRP were elevated during the active period in patients with cluster headaches, and nitroglycerin further elevated blood CGRP levels coincident with the appearance of the evoked headache (42). These results suggest that nitric oxide activates an already sensitized trigeminal system to provoke headache and increase CGRP release. This is further demonstrated by the recent observation that intravenous infusion of nitroglycerin over a 20-minute period to healthy volunteers did not increase jugular levels of CGRP during the period of a mild immediate headache (43). Increased blood levels of CGRP have been observed during the late-phase migraine-like headache, but not during the immediate headache after nitroglycerin infusion (44).

Prolonged exposure to analgesics may lead to MOH through the up-regulation of neural regulators of vasodilation and neurogenic inflammation. It has been known for some time that sustained systemic delivery of morphine exposure increases CGRP content in dorsal root ganglion neurons (45–47). More recently, studies have shown that the number of dural afferent neurons that express CGRP and/or nNOS increased following morphine exposure (48). Prolonged morphine exposure also produced an increase in the expression of the transient receptor potential channel, TRPV1, in the dorsal root ganglia and trafficking to the periphery (49). This increase in TRPV1 expression was accompanied by an increase in capsaicin-induced plasma extravasation (49).

Recent studies have begun to examine the effect of prolonged exposure to triptans in initiating peripheral neuroplasticity that may promote headache. Continuous, persistent exposure of rats to triptans for a period of days resulted in a marked increase in the numbers of trigeminal ganglion cell bodies expressing CGRP and a modest increase in expression of substance P (50). The increase in CGRP was especially pronounced when only dural afferent nerves, identified by application of the retrograde tracer fluorogold to the dura, were considered. In addition, CGRP was increased in unmyelinated C-fibers that expressed binding for the isolectin IB4 (presumed to be ‘peptide-deficient’ nociceptors), as well as in myelinated afferents. Additionally, recent data demonstrate a marked increase in numbers of trigeminal ganglion neuronal profiles, and especially labeled dural afferents, that express nNOS after persistent exposure to sumatriptan (51). As triptans and opiates produce MOH in some patients, one possibility is that prolonged exposure to these medications produces long-lasting, apparently pronociceptive, neuroplastic changes in the peripheral nerves of the trigeminal system, that may lower the threshold to stimuli (i.e. ‘migraine triggers’) capable of precipitating migraine in the migraineur. For example, animals exposed to sumatriptan, but not saline, for 6 days and allowed to recover so that behavioral responses were returned to baseline levels showed sensitivity to subsequent exposure to environmental stress or to an NO donor (51). In addition to these potential peripheral mechanisms, several observations point to a potential contribution of centrally-mediated events in the onset of migraine and the development of MOH.

Trigeminal nucleus hyperexcitability

Increased excitability of the trigeminal nociceptive pathway in migraine sufferers has been demonstrated both during and in between migraine episodes (52–60). The most commonly used clinical correlate of this increased excitability has been the presence of cutaneous allodynia, which occurs in the head and face region during migraine. In the interictal period, increased temporal summation of pain produced by repeated mechanical stimulation (wind-up) suggests a reduced threshold for the induction of central sensitization in migraineurs (59).

Dural inflammation, produced in animal studies by a solution of proinflammatory mediators in high concentrations applied to the dura, has been used to examine the neural events leading to headache pain during migraine (61). In results that parallel the findings of allodynia in humans with migraine, intracranial mechanical hypersensitivity has been reported following dural inflammation in the rat (62–64). Following inflammation, primary afferent neurons become sensitized to mechanical stimulation of the dura, which could account for the throbbing pain associated with headache. In addition, dura sensitive neurons recorded in the trigeminal nucleus, which typically receive convergent input from the skin, become sensitized to both dural and cutaneous stimulation (65–67). Because these animal studies produce behavioral and neurophysiologic results that appear to correlate to some degree with clinical observations of sensitization and allodynia, such studies may lead to further insights into potential causes of MOH (50,52,61,65). Such sensitization is likely to be relevant to the cephalic allodynia observed during migraine headache.

Consistent with evidence for the development of central sensitization, exposure of rats to either morphine or triptans for a period of days results in behavioral responses to tactile stimuli suggestive of cutaneous allodynia, including allodynia of the periorbital region (48,50). In the case of triptans, these behavioral changes resolve over the 14 days following discontinuation of exposure to the drug. The elevation in expression of CGRP and of nNOS in identified dural afferents of the trigeminal ganglion is maintained even after behavioral responses to tactile stimuli have returned to baseline levels (50,51). Such pronociceptive adaptations may underlie a state of ‘latent sensitization’ in which animals previously exposed to triptans become hyper-responsive to presumed triggers of migraine such as environmental stress or challenge with a nitric oxide donor (51). Thus, migraine triggers elicit cutaneous allodynia only in animals previously exposed to triptans. Moreover, the cutaneous allodynia evoked in this animal model can be abolished by CGRP, but not NK-1, receptor antagonists (50), and by nNOS inhibitors (51). These observations mirror the clinical results showing that CGRP, but not NK-1, antagonists or iNOS inhibitors can effectively treat migraine headache in humans (68–70). Challenge of rats previously exposed to triptans with an NO donor also produced significant elevations in plasma levels of CGRP, similar to observations of elevated CGRP blood levels found during spontaneous and NO-precipitated migraine headaches (44,71,72).

Additional central mechanisms may promote increased excitability after chronic medications. An up-regulation of pronociceptive systems at the level of the spinal cord occurs after prolonged exposure to morphine, probably contributing to opiate-induced

hyperalgesia and possibly antinociceptive tolerance (66,73–75). In spinal cord tissue, sustained morphine administration increased capsaicin-evoked release of CGRP and substance P, indicating an increase in excitatory neurotransmission (47,76). Additional studies have found a down-regulation of glutamate transporters after chronic morphine (77). Morphine-induced down-regulation of glutamate transporters may cause an increase in glutamatergic transmission and provide a mechanism for studies demonstrating increased activation of excitatory amino acid receptors following chronic administration of opiates. In particular, NMDA receptor activation, which contributes to central sensitization following inflammation, has been shown to also underlie, in part, opioid-induced tolerance and hyperalgesia (78–89). Whether similar changes occur in the trigeminal system is still unknown.

Studies indicate that many of the changes that occur in the spinal cord and trigeminal nucleus following inflammation and chronic drug exposure depend on brainstem neurons involved in the descending modulation of pain. The dysfunction of brainstem pain modulating neurons has also been implicated in migraine headache.

Descending control mechanisms

Throughout the course of a migraine, the region of hypersensitivity can spread from the head and face to encompass extracranial regions as well. The correlation of migraine headache with activation of the neuronal centers and pathways of the central nervous system that contribute to pain processing is not well established. However, an examination of descending pain modulatory pathways may provide some insights into the progression of migraine pain and allodynia to extracranial regions. The ventrolateral periaqueductal gray (PAG) and nucleus cuneiformis modulate pain through projections to the rostral ventromedial medulla (RVM). The RVM, in turn, can either inhibit or facilitate pain transmission through direct projections to the spinal and medullary dorsal horn (90). In a recent study in animals, dural inflammation produced extracranial allodynia that required the activation of pain facilitating ‘on’ cells in the RVM (62). Importantly, inactivation of the RVM prevented the cutaneous allodynia that resulted from dural inflammation (62). In humans, the PAG appears to be activated prominently in migraine and demonstrates significant structural abnormalities in migraine patients (91–95). The function of the nucleus cuneiformis also seems compromised in the interictal period (96), which may explain the reduced threshold required for induction of central sensitization that exists between migraine episodes (59).

A separate pain modulatory pathway, one involved in producing diffuse noxious inhibitory controls (DNIC), has also been found to be dysfunctional in chronic daily headache patients (97–99). Sometimes referred to as counter-irritation, the effect of DNIC is observed as an inhibition of pain produced by a noxious stimulus applied to a remote part of the body. Chronic daily headache patients demonstrate a profound loss in DNIC, leading some to suggest that a reduction in descending inhibition may be responsible for migraine chronicity. Whether the loss of DNIC in chronic daily headache is related to changes in PAG and nucleus cuneiformis function remains unknown. Studies that have examined DNIC after chronic opiate exposure, however, have provided evidence for an interaction between these two descending modulatory systems (Figure 1).

Morphine-induced cutaneous allodynia and increased spinal cord neuronal excitability depends on descending input from the RVM (47). While acute administration of morphine inhibits pain through the activation of pain inhibitory 'off' cells in the RVM, it appears that more prolonged exposure to morphine can increase pain by enhancing the influence of pain facilitating 'on' cells (100). In addition to increasing descending facilitation from the RVM, chronic opiate exposure also inhibits DNIC. A study of chronic opiate users found that, although baseline pain thresholds remained unchanged, inhibition of pain produced by a remote noxious stimulus was greatly reduced when compared to control subjects (101). This result is consistent with a recent study that examined dura-sensitive neurons in morphine-treated animals (102). In rats exposed to chronic morphine, dura-sensitive neurons recorded from the trigeminal nucleus caudalis were not inhibited by noxious stimulation of the tail. The loss of DNIC in these animals could be re-established by inactivating the RVM, providing evidence that morphine exposure produces an increase in descending facilitation from the RVM that masks inhibition from DNIC. Results from these studies suggest that the transformation of periodic migraine to chronic daily headache, whether due to medication overuse or other factors, may be caused by an increase in descending facilitation from the RVM. The emergence of advanced imaging techniques has led to a growing interest in the examination of the role of these pain modulatory systems in the processing of nociception and pain perception in humans. It seems likely that as our understanding of these pain processing systems grows, the integration of these systems in the development of migraine headache or of MOH will become an important area of clinical research in the development of novel therapeutics and management protocols.

Conclusions

Evidence from observational, prospective clinic-based, case-control, and population-based studies indicates that the frequent use of acute medications to treat migraine headache, in a substantial subgroup of individuals, leads to the progression of migraine from an episodic disorder to a syndrome of daily or near daily migraine. The risk of and time to progression, the phenotype of the daily headache, and the duration of withdrawal symptoms appears to vary based on the acute medication and its frequency of use. These features, together with the unique and selective vulnerability of migraine patients to this phenomena, highlights the possibility that the mechanism(s) by which acute medications lead to this progression may differ depending on the particular drug, and may be similar to the underlying biology of acute attacks of migraine.

Preclinical studies have now provided evidence for several potential mechanisms for the development of MOH, including increases in evoked CSD, a possible role for neurogenic inflammation, peripheral and central sensitization, and descending facilitation. A more thorough examination comparing the effect of different classes of medication on each of these factors should provide further insight into the pathophysiological mechanisms of both MOH and migraine.

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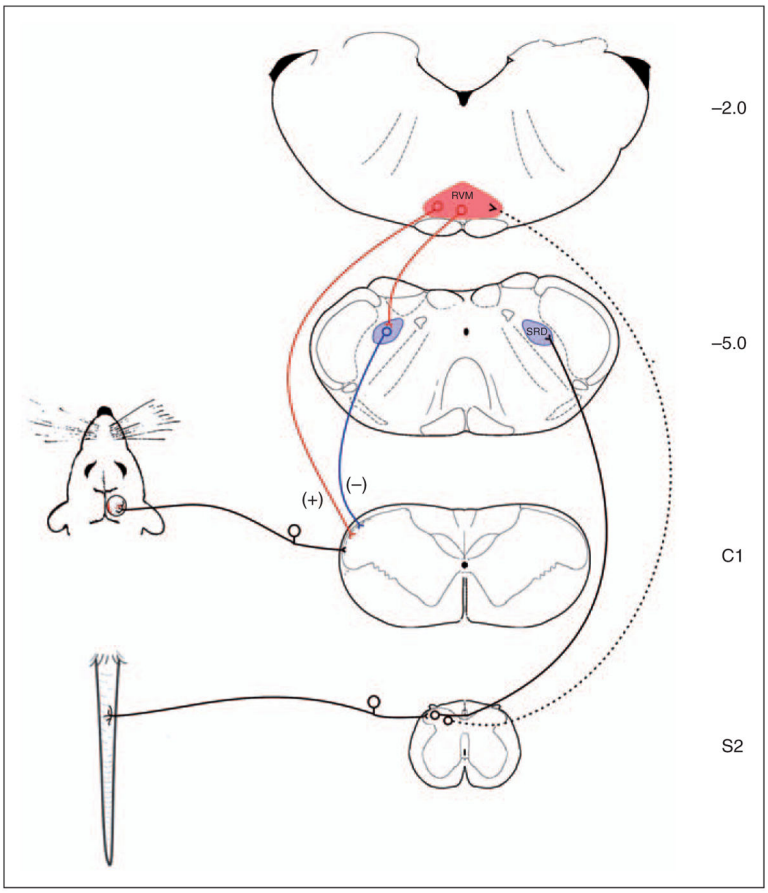

Figure 1.

Schematic diagram illustrating the interaction of descending projections involved in the inhibition and facilitation of pain. Placement of the rat's tail in hot water activates dorsal horn nociceptive neurons that project to the subnucleus reticularis dorsalis (SRD). Descending projections from the SRD inhibit nociceptive transmission produced by the activation of dural afferents. In addition, noxious tail stimulation activates pain-facilitating neurons in the rostral ventromedial medulla (RVM), mainly through indirect projections. Evidence indicates a shift in the balance between these two systems following chronic morphine exposure, such that descending facilitation dominates, masking DNIC.