Published in final edited form as:

Cephalalgia. 2009 December ; 29(12): 1277–1284. doi:10.1111/j.1468-2982.2009.01873.x.

Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache

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Abstract

Medication overuse headache (MOH) is a challenging, debilitating disorder that develops from the frequent use of medications taken for the treatment of migraine headache pain. MOH affects an estimated 3–5% of the general population. The mechanisms underlying the development of MOH remain unknown. Opiates are one of the major classes of medications used for the treatment of migraine at least in some countries, including the USA. Although the effects of repeated opiate use for headache are unknown, it is possible that opiate use may contribute to increased frequency and occurrence of such headaches. Recent preclinical studies exploring the neuroadaptive changes following sustained exposure to morphine may give some insights into possible causes of MOH. Peripherally, these changes include increased expression of calcitonin gene-related peptide (CGRP) in trigeminal primary afferent neurons. Centrally, they include increased excitatory neurotransmission at the level of the dorsal horn and nucleus caudalis. Critically, these neuroadaptive changes persist for long periods of time and the evoked release of CGRP is enhanced following morphine pretreatment. Stimuli known to elicit migraine, such as nitric oxide donors or stress, produce hyperalgesia in morphine- but not in saline-pretreated rats even long after the discontinuation of the opiate. CGRP plays a prominent role in initiating vasodilation of the intracranial blood vessels and subsequent headache. Furthermore, studies have demonstrated increased excitability of the nociceptive pathway in migraine sufferers, and CGRP receptor antagonists have been shown to be efficacious in migraine pain. Thus, such persistent neuroadaptive changes may be relevant to the processes that promote MOH.

Keywords

Headache; migraine; CGRP; cutaneous allodynia; central sensitization

Introduction

The American Migraine Study II estimates that 28 million Americans suffer from migraine headache. The phenomenon of frequent use of anti-headache medication that can either worsen the initial headache disorder, or even create a new form of daily headache, has been described with a variety of different names. Among the most frequently used terms are:

rebound headache, chronic migraine, daily migraine, analgesic overuse headache, and medication overuse headache (MOH). According to the International Headache Society, MOH is defined as a condition involving interaction between a therapeutic agent used excessively and a susceptible patient in which headaches occur on 15 days per month. The most common cause of migraine-like headache or tension-type-like headache is overuse of symptomatic migraine drugs and/or analgesics. Chronic tension-type headache (TTH) is less often associated with medication overuse but, especially among patients seen in headache centres, episodic TTH has commonly become a chronic headache through overuse of analgesics (1). Furthermore, the headache associated with medication overuse often has a peculiar pattern that can shift, even within the same day, from having migraine-like characteristics to those of TTH (1). The diagnosis of MOH is clinically extremely important because patients rarely respond to preventative medications while overusing acute medications (1).

The TTH (experienced by > 50% of the population) and migraine (experienced by 10%) are the most frequent forms of primary headache. MOH is now recognized as a major cause of chronic daily headache (1–4) that affects approximately 4% of the general population, representing one-quarter of those suffering from chronic daily headache (5–8). MOH can be diagnosed when headache occurs on 15 days a month and has characteristics that include: bilateral, dull pain of light to moderate intensity; drug intake including ergots, triptans and opioids for > 10 days per month; the use of analgesics for > 15 days for at least 3 months; and the resolution of the condition after discontinuation of the medication (2–4, 9). When the occasional headache strikes, most people take an over-the-counter pain medication. The overuse or misuse of pain relievers can result in ‘rebound’ into another headache, and may initiate MOH (9). The mechanisms by which MOH occurs remains unknown and can be influenced by genetic factors, neuroplastic changes and psychotropic effects (10). Genetic factors are important for the development of MOH, because only patients with TTH, but not those with cluster headache, develop MOH and frequently patients with a history of migraine, who need to take analgesics on a regular basis for non-headache painful disorders, may develop MOH.

Recent preclinical studies suggest that medications themselves can elicit neuroadaptive changes that may contribute to this phenomenon. In the case of opiates, morphine has been shown to produce increased expression of excitatory neurotransmitters in primary afferent fibres as evaluated in dorsal root ganglion cells from the lumbar spinal cord in rodents. Among these adaptive changes is an increase in expression of calcitonin gene-related peptide (CGRP) (11, 12). Furthermore, in tissues taken from animals pretreated with morphine for some period of time (i.e. days) evoked release of CGRP from primary afferents is greatly enhanced, suggesting a mechanism for increased excitatory transmission that may be relevant to headache pain (11). In addition to such adaptive changes that can be observed in primary afferents, sustained delivery of opiates can enhance processes of descending pain facilitation arising from the rostral ventromedial medulla (13–16). Collectively, these neuroadaptive changes result in a state of hypersensitivity to normally non-noxious tactile and to noxious thermal stimulation. Such pronociceptive neuro-adaptations might be hypothesized to alter the response to triggers of migraine and enhance the frequency of the headaches.

Migraine and the trigeminal system

The trigeminal sensory complex comprises two nuclei, the main nucleus responsible for the messages resulting in tactile sensation, and the spinal nucleus, which includes three subnuclei, the oralis, interpolaris and caudalis. Several investigations regarding nociceptive transmission in the nucleus caudalis have revealed similarities with spinal nociceptive transmission, and this region has been referred to as the medullary dorsal horn (17). The integration between trigeminal sensory neurons and cranial blood vessels has been termed the trigeminovascular system. Local vasodilation of intracranial extracerebral blood vessels, such as those supplying the dura mater, and consequent stimulation of surrounding trigeminal perivascular afferent neurons may be important mechanisms underlying migraine headache pain (18). In addition to relaying nociceptive information, meningeal perivascular nociceptive afferents have also been suggested to release sensory neuropeptides, including CGRP and substance P, which cause vasodilation and inflammation of intracranial blood vessels. Activation of the primary afferent neurons that innervate the blood vessels and the dura elicits nociceptive signals relevant to headache pain (17, 19, 20). Multiple studies have shown that stimulation of the blood vessels and sinus can produce headache-like pain (21, 22). Additionally agents that produce vasodilation of the intracranial blood vessel have been used to induce migraine headache experimentally.

Many studies have shown that injection of nitro-glycerin, a potent vasodilator and nitric oxide (NO) donor, induces experimental migraine headache in human volunteers (23–26). Infusion of a NO donor in normal subjects induces a rapid-onset headache that usually disappears within minutes of stopping infusion, whereas migraineurs experience a more severe initial headache that persists at a moderate level for several hours before developing into a full-scale migraine headache (27). NO appears to produce vasodilation at least in part through the evoked release of CGRP from primary afferent neurons that innervate the intracranial blood vessels (28).

Migraine and CGRP

Several lines of evidence indicate a prominent role for CGRP, a potent vasodilator, in the pathogenesis of migraine. Administration of CGRP to humans can produce migraine headache (29–33). In non-migraineurs, intravenous (i.v.) infusion of CGRP causes a feeling of fullness in the head, but headache has not been reported. In contrast, i.v. CGRP infusion to migraineurs causes immediate headache and induces migraine-like disorders or migraine without aura (33). During migraine attacks, the release of CGRP into the cranial circulation is increased (34, 35). A direct relationship between CGRP and migraine has been demonstrated with nitroglycerin-induced migraine, in which plasma CGRP concentration significantly increased during the migraine attack, and returned to baseline after cessation of migraine. Additionally, the magnitude of the CGRP increase was related to the severity of the migraine attack (24). Furthermore, the critical role of CGRP in migraine has been confirmed by the effective use of the CGRP antagonist, BIBN 4096, to treat migraine (36). BIBN 4096 blocks trigeminal-induced facial vascular dilation in the marmoset (37) and CGRP-induced dilation of both human and bovine cerebral vessels (38). Similarly, triptans, 5-HT_{1B/1D} receptor agonists, can block meningeal vascular dilation (32), a response that

involves CGRP (32) and NO (39). Different studies have shown that trigeminal ganglion neurons containing CGRP co-localize with both 5-HT_{1B} and 5-HT_{1D} receptors (40–42), and it is likely 5-HT_{1B/1D} agonists can produce antimigraine effects, in part through inhibition of CGRP release from trigeminal primary afferent neurons (43–45). It is also possible that CGRP contributes to neurogenic inflammation by potentiating the release of inflammatory agents such as histamine, serotonin, bradykinin and prostaglandins into the perivascular space (46–49). One prominent theory of migraine holds that vasodilation of the intracranial vasculature combined with neurogenic inflammation in the perivascular space leads to activation of the trigeminal primary afferent neurons responsible for producing migraine headache pain (50–53).

Migraine and cutaneous allodynia

Several studies have demonstrated increased excitability of the nociceptive pathway in migraine sufferers, both during and between migraine episodes (54–58). Observations from both human and animal studies have demonstrated a sequence of events that occur during a migraine attack, leading from peripheral sensitization of primary afferent neurons to central sensitization of neurons in the nociceptive pathway (50, 58). Humans undergoing a migraine attack can develop an area of cutaneous allodynia that spreads over time (54–59). Initially, the area of hypersensitivity is restricted to the region of referred pain ipsilateral to the headache. Throughout the course of the migraine, the area of allodynia can spread to include large regions of the head and face, and can also include other regions of the body. These results are consistent with recent preclinical studies that examined neuronal discharges following inflammation of the dura. Following application of a mixture of inflammatory mediators, the primary afferent neurons that innervate the dura become sensitized and respond to previously insensitive mechanical stimulation (60). Response properties of second-order neurons in the trigeminal nucleus caudalis following craniovascular stimulation have also been examined following dural inflammation (61–63). Neurons that receive input from the middle meningeal artery, superior sagittal sinus and dura typically receive convergent input from the skin (61, 64, 65). Following 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 (61, 63). After 2–4 h, these enhanced cutaneous responses no longer require primary afferent input from the dura, and can therefore be considered signs of central sensitization. Although this model can explain the basis for headache and referred pain from trigeminal regions, it does not account for the extracranial hypersensitivity associated with migraine. The mechanisms by which extracranial and contralateral sensitivity occur are currently unknown.

Sustained exposure to morphine induces tactile and thermal hypersensitivity

Numerous studies in humans report that opioids can elicit abnormal pain (i.e. hyperalgesia), which includes allodynia and hyperalgesia, and typically the abnormal pain differs in location and quality from the original complaint (66, 67). Thermal hyperalgesia and tactile allodynia can also be demonstrated in animal model by repeated systemic or spinal injection

of opioids (68–71). Furthermore, many studies have reported that the thermal hyperalgesia, induced by repeated opioid administration, persists even after termination of drug administration, suggesting that sustained opioid can elicit long-lasting neuroadaptive changes (68, 72). One of the hypotheses for sustained opioid-induced hypersensitivity is that these changes in sensory thresholds result from mini-withdrawals from opioid administration, analogous to the explanation of rebound headache for MOH (73). Although this may be the case for studies with repeated injections of opiates, other studies have used continuous infusion of opiate by pellets or osmotic minipumps in order to provide stable blood levels, thus mitigating concerns of a contribution of withdrawal. An additional possibility is that sustained exposure to opiates can lead to the activation of pronociceptive circuits (72, 74, 75).

Multiple studies have demonstrated that sustained exposure to morphine over a period of days produces a decrease in evoked sensory thresholds in rodents (76, 77). The hypersensitivity observed during and following sustained morphine may engage mechanisms analogous to those that can elicit cutaneous allodynia observed during migraine in humans. Studies in our laboratory have shown that the mechanical allodynia following sustained exposure to subcutaneous morphine delivered by osmotic minipump is not localized to the rat hind paw. Animals receiving sustained morphine show hypersensitivity to touch in the facial region, suggesting the possibility of neuroadaptive changes in the trigeminal system as well as in afferents innervating other parts of the body. Sensory thresholds were determined using von Frey filaments applied to the infraorbital region of the face across 7 days of subcutaneous morphine (osmotic minipumps) (manuscript in preparation). The results of this study showed a similar time course to previous studies with the hindpaw, with sustained morphine producing facial tactile hypersensitivity (i.e. ‘allodynia’) beginning approximately on day 4 of exposure.

The mechanisms responsible for the tactile and thermal hypersensitivity observed following sustained morphine exposure are unknown. However, it is likely that the hypersensitivity requires activation of opioid receptors. Previous studies have evaluated the contribution of non-opioid activities of active metabolites such as M3G (78–82, 87–90). Such molecules are unlikely to be responsible for opiate-induced hyperalgesia, as this phenomenon has been reported in humans for many structurally diverse opioids including remifentanyl, fentanyl, sufentanil, heroin and methadone, and most of these compounds have been shown to produce hyperalgesia in preclinical studies as well (69, 83–87). Data from our laboratory have also shown that agonists for δ opioid receptors including peptidic (i.e. [D-Ala², Glu⁴]deltorphin) and non-peptidic (i.e. SNC80) molecules also produce hyperalgesia (77).

Several independent observations have consistently shown that prolonged exposure to morphine results in up-regulation of the pronociceptive neurotransmitter CGRP in the peripheral nervous system (11, 12, 88–90). We have also consistently demonstrated that prolonged morphine exposure results in enhanced capsaicin-evoked release of CGRP from primary afferent terminals in the spinal dorsal horn, suggestive of increased nociceptive transmission (11). More recently, we found that similar changes occur in the trigeminal nociceptive system as well (De Felice and Porreca, unpublished observations). Notably, subcutaneous morphine infusion significantly increased the number of trigeminal ganglion

cells that expressed CGRP and/or neuronal nitric oxide synthase (nNOS). Using fluorogold as a retrograde marker, we found that the up-regulation of cells expressing CGRP and nNOS was particularly increased in cells specifically projecting to the dura. These changes in expression appeared to be of functional significance since, like our results within the spinal cord, morphine exposure increased the capsaicin-evoked release of CGRP in sections of the nucleus caudalis, as well as in dural preparations (i.e. the ‘cranial cup’), indicating enhanced release from both central and peripheral terminals of the trigeminal ganglion fibres (De Felice and Porreca, unpublished observations). Critically, CGRP and nNOS expression was still elevated 14 days after termination of morphine infusion. At that time point, morphine-induced behavioural hypersensitivity had resolved. However, in rats previously exposed to morphine as described here (i.e. for a 7-day period), but not in animals that had received saline, exposure to a NO donor or exposure to non-nociceptive environmental stress 14 days later evoked hyperalgesia. These observations suggest that prolonged exposure to morphine results in long-lasting neuroadaptive changes that promote a state of increased susceptibility to stimuli that may promote activation of the nociceptive trigeminal system. Under these conditions, putative sub-nociceptive stimuli may convert to nociception. These observations may have implications for clinically relevant conditions such as MOH that occur with prolonged morphine use, possibly by increasing the likelihood of migraine attack from normally ineffective triggers.

Conclusions

Although the effects of repeated opiate use for headache are unknown, it is possible that opiate use may contribute to increased frequency and occurrence of such headaches. Preclinically, it is clear that sustained morphine modulates the central and peripheral neural systems that are likely to underlie aspects of migraine headache pain. Our recent studies, summarized above, show that neural adaptations that occur following sustained morphine are seen in the trigeminal system and that these adaptations are pronociceptive and persistent. Moreover, they are especially prominent in fibres that project to the dura. Furthermore, we found that a period of exposure to opiates (over days) can result in increased responsiveness to stimuli known to trigger migraine attacks in humans (i.e. NO donors, stress). These findings suggest that such persistent and pronociceptive neural adaptations may contribute to opiate-induced MOH by (i) increasing the responsiveness of the nociceptive system to previously sub-threshold ‘triggering’ stimuli, as well as (ii) increasing the transmission of the pain signal at the level of the medullary dorsal horn. These processes may contribute to increase the likelihood and perhaps the severity of headache, and may reflect a neural basis for the development of opiate-induced MOH.

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