Migraine Pain, Meningeal Inflammation, and Mast Cells

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Migraine pain has been attributed to an episode of local sterile meningeal inflammation and the subsequent activation of trigeminal primary afferent nociceptive neurons that supply the intracranial meninges and their related large blood vessels. However, the origin of this inflammatory insult and the endogenous factors that contribute to the activation of meningeal nociceptors remain largely speculative. A particular class of inflammatory cells residing within the intracranial milieu, known as *meningeal mast cells*, was suggested to play a role in migraine pathophysiology more than five decades ago, but until recently the exact nature of their involvement remained largely unexplored. This review examines the evidence linking meningeal mast cells to migraine and highlights current experimental data implicating these immune cells as potent modulators of meningeal nociceptors' activity and the genesis of migraine pain.

Introduction

Migraine is a debilitating, throbbing headache that afflicts about 15% of the Western population [1]. The origin of a migraine attack remains a matter of speculation, but now it is widely accepted that the intracranial pain of migraine itself is mediated by nociceptive primary afferent neurons that innervate the cerebral meninges and their related large blood vessels [2,3]. Despite major advances in the understanding of the anatomical, biochemical, and electrophysiological properties of meningeal nociceptors, how these neurons become activated during a migraine attack remains poorly understood.

According to the neurovascular theory of migraine, an episode of sterile inflammation localized to the intracranial meninges is the main culprit responsible for driving the activation of meningeal nociceptors during a migraine attack [4]. Although direct evidence for meningeal inflammation during a migraine attack remains lacking, its occurrence is supported by clinical findings showing increased levels of inflammatory mediators in the intracranial circulation during a migraine attack [5,6] as well as the therapeutic efficacy of NSAIDs in aborting migraine [7]. The neurovascular hypothesis further maintains that meningeal inflammation arises during a migraine attack as a consequence of single or multiple episodes of cortical spreading depression (CSD), an intrinsic brain activity that is now considered the neural substrate of the migrainous aura [8]. CSD is associated with local release of mediators, such as potassium ions and glutamate [9], that have the potential ability to promote a brief activation of nearby meningeal sensory neurons [10]. From their peripheral terminals, the activated nociceptors release proinflammatory neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P [11]. In turn, the local action of these neuropeptides has been suggested to promote a local inflammatory response that is characterized by vasodilatation and increased endothelial permeability. This vascular response may occur as a result of either a direct action of the neuropeptides on the meningeal blood vessels or through an indirect pathway that involves the local activation of local immune cells and the ensuing release of additional inflammatory mediators [4]. This neurogenic inflammation may further promote and sustain the activation and sensitization of meningeal nociceptors, a process that ultimately gives rise to the persistent throbbing headache and its intensification during physical activities associated with increased intracranial pressure (eg, straining, coughing, bending over) [12].

Evidence for Mast Cell Involvement in Migraine

One potential endogenous source of inflammatory mediators during a migraine attack is a group of immune cells known as *mast cells* (MCs). These tissue-resident granulated cells, which are mostly known for the role they play in mediating immunoglobulin E–associated allergic disorders, also have emerged as important modulators of inflammatory conditions in other diseases such as arthritis, irritable

bowel disease, and interstitial cystitis [13•]. Upon their activation, MCs degranulate and release a host of preformed inflammatory mediators such as histamine, serotonin, and various cytokines and proteases. Activated MCs also are capable of synthesizing de novo additional proinflammatory agents, including leukotrienes, prostaglandins, and nitric oxide [14]. Within the intracranial meninges, MCs are mostly localized to the dural layer [15,16], where they reside near blood vessels and in close apposition to terminals of meningeal nociceptors [17].

A clinical study conducted by Sicuteri [18] in 1963 was one of the first to suggest a direct involvement of intracranial MCs in migraine pathogenesis by showing that injection of the MC secretagogue agent, *compound 48/80*, into the cranial circulation can give rise to an episode of a hemicranial migraine–like headache. A more causative role for MC activation in migraine has emerged two decades later from studies showing a potent migraine prophylactic action for the MC stabilizing agent cromolyn [19]. Through the years, additional indirect lines of evidence further supporting the involvement of MCs in migraine came from studies on the role of the major MC constituent, histamine, in migraine. These studies have shown the following: 1) that plasma histamine levels are elevated during migraine attacks in a subpopulation of migraineurs [20]; 2) the ability of histamine infusion to promote a migraine-like headache in most patients [21]; and 3) that antihistaminergic drugs can serve as potent prophylactic agents in migraine [22–24]. Recent studies also have implicated other proinflammatory MC-derived molecules in migraine pathophysiology, including leukotrienes [25], tumor necrosis factor (TNF)-α, interleukin (IL)-6 [6], and endothelin-1 [26]. Finally, a role for MC in migraine has been suggested based on epidemiological studies showing a significantly higher prevalence of migraine in patients afflicted with other MC-related disorders such as asthma, eczema, rhinitis, and interstitial cystitis [27].

Putative Mechanisms Underlying Mast Cell Activation in Migraine

Despite the supporting evidence of MC involvement in migraine, the mechanism by which dural MCs release their inflammatory mediators during a migraine attack remains unknown. Studies using animal models have shown that dural MCs can become degranulated and release their inflammatory mediators following exposure to the sensory neuropeptides substance P, CGRP, and pituitary adenylate cyclase–activating peptide (PACAP) [17,28–30]. The possibility that these neuropeptides are released from the peripheral nerve endings of activated meningeal nociceptors during a migraine attack therefore provides a potential mechanism that can promote the activation of dural MCs and, consequently, the development of neurogenic inflammation and the genesis of the headache [4]. Indeed, infusion of CGRP [31] or PACAP [32] has been shown to promote headache in nonmigraineurs and to trigger a delayed migraine-like episode in susceptible migraine patients. In the case of CGRP, the finding that meningeal nociceptors do not express CGRP receptors [33] and that CGRP does not activate meningeal nociceptors in animals depleted of their dural MCs [34] point to the possibility that CGRP promotes the headache through a mechanism that involves, at least in part, the activation of dural MCs.

In addition to the putative role of CSD and its related neurogenic inflammation, other exogenous and endogenous triggers of migraine also have been proposed to promote dural MC degranulation. For example, stress, a known migraine trigger, has been shown to induce dural MC degranulation through a mechanism that involves the action of corticotropin-releasing factor [35]. Infusion of nitroglycerin, one of the most reliable migraine triggers, also is associated with dural MC degranulation, although the underlying mechanism is still unknown [36]. Activation of the parasympathetic nervous system, which is now also considered to be one of the mechanisms that play a role in the triggering of a migraine attack [37], may also promote dural MC degranulation, likely through a cholinergic mechanism [17,38]. Changes in estrogen levels (which are believed to play a role in promoting migraine in women, especially those changes related to the menstrual cycle) are also potent modulators of dural MC secretion [17]. Finally, various dietary products that precipitate migraine attacks are likely to do so by inducing MC degranulation [19].

Experimental Evidence for the Ability of Mast Cell Degranulation to Activate Meningeal Nociceptors

The notion that dural MCs degranulate and release their inflammatory mediators in response to a number of exogenous and endogenous putative triggering factors of migraine points to the possibility that MC activation may promote the activation of meningeal nociceptors. MC-related enhancement of sensory nerve function already has been demonstrated in tissues other than the meninges, particularly those of visceral origin. For example, MC degranulation has been shown to increase the excitability of vagal [39], splanchnic [40], and mesenteric afferents [41].

To begin testing whether dural MCs can promote the activation of meningeal nociceptors, we conducted a series of electrophysiological studies using an animal model [42••]. In these studies, we recorded changes in the activity of these neurons prior to and following induction of dural MC degranulation using the secretagogue agent compound 48/80 (the same agent that Sicuteri [18] employed in his earlier investigation of MC involvement in migraine). We found that such chemical activation of dural MCs provides

a powerful inflammatory stimulus that, in most of the neurons tested, promotes an increase in the neuronal activity that persists for many hours [42••]. As expected, we also found that 48/80–evoked nociceptor activation can be blocked either by prior depletion of dural MCs or by stabilizing MCs with sodium cromoglycate, the same agent used by Monro et al. [19] to treat prophylactically food-induced migraines. In another set of studies using the anatomical labeling technique with c-fos as a marker of activation of pain neurons, we noticed that dural MC degranulation provides a sufficient nociceptive stimulus that can promote the activation of the second-order dorsal horn neurons in the medullary dorsal horn that receive nociceptive input from meningeal nociceptors [42••]. We further noticed the ability of the migraine drug sumatriptan to suppress this MC-related activation of medullary dorsal horn neurons, thus providing further indication of the importance of dural MC degranulation to the activation of the migraine pain pathway. In another series of electrophysiological experiments, we have examined which of the MC mediators could play a role in the activation of meningeal nociceptors. As indicated above, MCs can release a plethora of inflammatory mediators that, in theory, can activate the migraine pain pathway. To investigate the potential relative contribution of the various MC mediators to migraine pain, we tested their ability to modulate the activity of meningeal nociceptors. We found that serotonin, prostacyclin (PGI_2), and to a lesser extent, histamine and tryptase, are likely to serve as the mediators through which dural MCs promote the activation of meningeal nociceptors [43,44]. It should be emphasized that among all of the MCs mediators we have tested thus far, serotonin was found to be the most potent. It is noteworthy that although serotonin may be involved in migraine pathophysiology mainly through its central nervous system action, its potent modulatory action on meningeal nociceptors also points to a potential peripheral serotonergic involvement in migraine pathophysiology.

Conclusions

Clinical and preclinical studies suggest the involvement of meningeal MCs in the pathophysiology of migraine. During migraine with aura, activation of meningeal nociceptors by CSD could hypothetically promote dural MC degranulation via a neurogenic axon reflex. This MC degranulation could further prolong and sustain the activation of meningeal nociceptors and the migraine pain pathway. The finding that dural MCs can also become affected by other migraine triggers such as stress, nitroglycerin, various dietary products, and activation of the parasympathetic nervous system point to a more general role of these immune cells in the activation of meningeal nociceptors, and particularly as an essential part of the triggering mechanism that promotes the pain of migraine. Targeting the process of MC degranulation may be considered as an additional therapeutic target for migraine prophylaxis.

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Disclosure

No potential conflict of interest relevant to this article was reported.

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