



Review

The role of mast cells in migraine pathophysiology

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Abstract

Mast cells are critical players in allergic reactions, but they have also been shown to be important in immunity and recently also in inflammatory diseases, especially asthma. Migraines are episodic, typically unilateral, throbbing headaches that occur more frequently in patients with allergy and asthma implying involvement of meningeal and/or brain mast cells. These mast cells are located perivascularly, in close association with neurons especially in the dura, where they can be activated following trigeminal nerve, as well as cervical or sphenopalatine ganglion stimulation. Neuropeptides such as calcitonin gene-related peptide (CGRP), hemokinin A, neurotensin (NT), pituitary adenylate cyclase activating peptide (PACAP), and substance P (SP) activate mast cells leading to secretion of vasoactive, pro-inflammatory, and neurosensitizing mediators, thereby contributing to migraine pathogenesis. Brain mast cells can also secrete pro-inflammatory and vasodilatory molecules such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), selectively in response to corticotropin-releasing hormone (CRH), a mediator of stress which is known to precipitate or exacerbate migraines. A better understanding of brain mast cell activation in migraines would be useful and could lead to several points of prophylactic intervention.

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Contents

1. Introduction	66
2. Allergic diathesis, mast cells, and migraines	66
3. Brain mast cells, stress, and vascular permeability	68
4. Therapeutic approaches	69
5. Conclusion	70
Acknowledgments	70
References	71

Abbreviations: BBB, blood–brain barrier; CGRP, calcitonin-gene related peptide; CRH, corticotropin-releasing hormone; IL-6, interleukin-6; NGF, nerve growth factor; NO, nitric oxide; NT, neurotensin; PACAP, pituitary adenylate cyclase activating peptide; SP, substance P; TNF- α , tumor necrosis factor-alpha; VIP, vasoactive intestinal peptide; Ucn, urocortin; VEGF, vascular endothelial growth factor

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1. Introduction

Migraine headache is an episodic, typically unilateral, incapacitating throbbing headache associated not only with nausea, vomiting, and photophobia, [118] but also with other neurologic dysfunctions [142,152]. It is the most common neurologic condition and is more prevalent than asthma, diabetes, and epilepsy combined. Migraines occur in about 18% of adults in the US, are precipitated by stress, and are associated with high disability [152]. The World Health Organization ranked migraine as one of the most disabling conditions, equivalent to the disability associated with quadriplegia [65]. Migraine affected more than 74 million people in the US, France, Germany, Italy, Spain, and the UK in 2002 with the migraine drug market estimated at \$2.86 billion that year and expected to double by 2012. Migraines occur in about 10% of children and adolescents, but the term migraine has also been used to describe abdominal pain in children [144] and adults [119]. Patients with interstitial cystitis (IC) often describe their bladder pain as “migraine of the bladder” [102,200] and the incidence of migraines in IC is much higher than the average population [218] (Table 1).

Migraine headache is still a descriptive term from the Greek *hemicrania*, meaning half the head. Recent evidence has increasingly linked migraines to anxiety symptoms, as well as stress experienced during childhood or adolescence [216]. Increased sensitivity to stress was strongly correlated with migraines [83,215] and the greatest risk factor for migraines among military women was a high level of job stress [79].

There is no reliable animal model for migraines. Their pathogenesis has been associated with “cortical spreading depression” (CSD) as well as with meningeal and cerebral vasodilation [177] documented by topography [141]. In fact, CSD induction regulates gene expression of vasodilatory peptides; of 1,180 genes examined, the ones regulated by CSD were involved in vascular responses that may be responsible for the propagation pain of migraine [27]. However, neither the vascular nor the CSD theories sufficiently explain the initial triggering events of migraine that could involve emotional, physical, or oxidative stress. Neurogenic inflammation continues to be considered a key pathological process [50,59,221], and activation of meningeal sensory neurons was shown to be a primary mechanism in the origin of headaches [181]. Moreover, long-term

cervical sympathectomy induced mast cell hyperplasia and increased histamine and serotonin content in the dura mater [12]. Stimulation of trigeminal meningeal afferents was reported in response to intrinsic brain activity [17]. A substantial body of evidence indicates that antidromic activation of the trigeminal nerve [43], but also of cervical [92] or sphenopalatine [38] ganglion stimulation, leads to meningeal mast cell activation, vasodilation, and neurogenic inflammation [137], as is seen in humans during the migraine attack [141]. Similarly, antidromic stimulation of the lumbosacral dorsal roots in the rat leads to plasma extravasation in the skin and pelvic organs [153].

2. Allergic diathesis, mast cells, and migraines

Migraine headaches are frequently seen by allergists and yet are largely underrepresented in the allergy literature. Further, migraines have been found to occur with increased frequency in asthma patients. Migraines are triggered by a variety of environmental conditions, foods, histamine, and smells, although the role of “allergy” as a migraine trigger remains largely speculative. Migraines are often confused with sinus headaches, an entity not recognized by allergists, otolaryngologists, or neurologists, and is erroneously treated with antibiotics [189]. However, over 90% of sinus headaches meet the International Headache Society’s criteria for migraines [189].

It was proposed almost 20 years ago that mast cells may be involved in the pathophysiology of migraines [190]. At about that time, a number of papers reported higher plasma histamine levels in patients with a history of migraines that further increased during attacks [76,78,174], histamine release also increased from basophils taken from migraineurs [168]. A few years later it was suggested that “atopic diseases” also include migraines [139] that may be linked to food allergies [128]. Recent publications indicate a strong association between allergies, asthma, and migraines, as well as between elevated histamine plasma levels and migraines [93]. In one study involving 64,678 case-control pairs, the relative risk of allergy in patients with migraines was 1.59, while that for patients with respiratory symptoms consistent with asthma or with eczema were 1.85 and 1.67, respectively [122] (Table 1). This large study concluded that understanding disease mechanisms shared between migraine and atopic disease would be useful. In another study of 70 migraine patients without aura, serum histamine and total IgE levels were 48.2 ng/ml and 38.3 IU/ml in the control group, 105.0 ng/ml and 79.1 IU/ml in the migraine without allergy group, and were 159.1 ng/ml and 303.3 IU/ml in the migraine with allergy group [63], respectively. It was concluded that a relationship between allergy and migraine could be based, in part, on an IgE-mediated mechanism and histamine release. Although an “allergic” mechanism could be involved, it does not explain the increased incidence of migraines in conditions that involve mast cell activation in

Table 1
Diseases that involve mast cells are associated with higher incidence of migraines

Conditions	Relative risk	Reference
Allergies	1.59	[63]
Asthma	1.85	[122]
Eczema	1.67	[122]
Interstitial cystitis	1.25	[102]
Irritable bowel syndrome	1.92	[218]

the absence of serum IgE elevations (Table 1), such as eczema, interstitial cystitis (IC), or irritable bowel syndrome (IBS). In addition, histamine-receptor antagonists are not helpful in alleviating migraines, suggesting that migraine involves more than just an increase in plasma histamine.

A more likely explanation is that meningeal mast cells are activated not only by allergic, but also by other, neuroimmune triggers. For instance, trigeminal nerve-induced vascular permeability was shown to depend on dura mast cell degranulation [44]; moreover, drugs which are clinically used for the symptomatic treatment of migraines inhibited trigeminal nerve stimulation-induced dura mast cell activation and vasodilation [21], as well as neurogenic dura plasma extravasation [222]. Antidromic cervical [92] and sphenopalatine [38] ganglion stimulation also activated rat dura mast cells. Additional evidence supporting the possibility that dura mast cell activation may be involved in migraines comes from studies showing that the serum histamine level of patients with cluster headache [5] is increased indicating activation of mast cells. Moreover, biopsies of the temporal artery of the painful side of cluster headache patients were shown to contain degranulated mast cells [41,116,117].

Mast cells derive from a distinct precursor cell in the bone marrow, enter the brain from the leptomeninges [108] and mature in the local microenvironment [219]. Mast cells are important not only in allergic reactions, but also in inflammation [192] autoimmunity [10,159], arthritis [224], and other inflammatory conditions, especially those worsened by stress [194,224]. Mature mast cells vary considerably [185] in their cytokine [18] and proteolytic enzyme content. Also, the phenotypic expression of mast cells does not appear to be fixed [15,112]. In addition to vasodilatory molecules, mast cells secrete various pro-inflammatory mediators, such as kinins, prostaglandins, and numerous cytokines, including IL-6 (for a review, see [194]). Mast cell-derived cytokines have recently been implicated in neuropsychiatric disorders [204]. In addition to IgE and antigen, anaphylatoxins (complement 3a, 5a), cytokines, hormones, and neuropeptides [192] can trigger mast cell secretion [57,66,87,184,192,194,219]. The latter include substance P (SP) [2,74,132], somatostatin, [195] neurotensin (NT) [24], parathyroid hormone [207,220], pituitary adenylate cyclase activating peptide (PACAP) [223], and calcitonin gene related peptide (CGRP) [154] which was found to be colocalized with SP and 5-hydroxytryptamine receptors (5-HT 1B/2D) in trigeminal ganglion neurons [125]. Moreover, SP and CGRP are secreted from rat dura mater, along with prostaglandin E₂, following electrical stimulation of the trigeminal nerve or application of neurosensitizers on the exposed dura [75]. Similar increases were noted in the serum of patients during the migraine headache [51] and a CGRP receptor antagonist was recently shown to be effective in treating acute migraine attacks [143]. Stem cell factor (SCF) [62] and nerve growth factor (NGF) [14,187], the latter of which is released under stress [37],

can promote mast cell growth [132] and can trigger mast cell secretion [188]. SCF has also been reported to induce mast cells to become responsive to PACAP [167]. SCF and NGF are also secreted by mast cells [36,225], while SP has been localized in human skin mast cells [206], indicating autocrine actions.

Increasing evidence has led to the suggestion that brain mast cells may regulate vascular permeability in the brain [191,227]. Mast cell vasodilatory molecules include histamine, nitric oxide (NO) [127], vasoactive intestinal peptide (VIP) [123], and vascular endothelial growth factor (VEGF) [16,72,107], all of which could be responsible for the vasodilatory phase of the migraine, associated with throbbing pain (Table 2). For instance, histamine administration induced intense headache [103], while NO was considered to be a key molecule in the pathophysiology of migraines [142]. In fact, upregulation of inducible NOS was noted in the dura during nitroglycerin infusion, along with induction of IL-1 β in the dura mater, IL-6 in dura macrophages, and dura mast cell activation [162]; all these changes were considered consistent with delayed meningeal inflammation [162]. Mast cells are also a rich source of most known cytokines including TNF- α [100], which is vasodilatory and induces the expression of intercellular adhesion molecule-1 (ICAM-1) [217], a prerequisite for leukocyte exit into the affected tissues. Mast cell degranulation has been shown to lead to ICAM expression [98,182]. In fact, immunologic stimulation of brain mast cells was shown to release TNF- α [32,33], which was involved in both brain inflammation [99,157] and increased vascular permeability [95]. Moreover, the unique mast cell protease tryptase caused microvascular leakage [77], as well as hyperresponsiveness of bronchi [7] and neuronal hyperexcitability [160] (Table 2). Tryptase could also induce widespread inflammation through protease-activated receptors by a neurogenic mechanism [77,180]. Brain pro-inflammatory molecules

Table 2
Neurosensitizing and vasoactive mast cell mediators

Neurosensitizing
Bradykinin
Histamine
Prostaglandins
Substance P
Tryptase
Tumor necrosis factor
Vasodilatory
Bradykinin
Histamine
Nitric oxide
Tumor necrosis factor
Tryptase
Vascular endothelial growth factor
Vasoactive intestinal peptide
Vasoconstrictive
Angiotensin II
Leukotrienes
Renin
Serotonin

have also been implicated in other neuropsychiatric disorders [204].

3. Brain mast cells, stress, and vascular permeability

Mast cells are located perivascularly in close proximity to neurons [14,40,49,110,140,148,175,176,179,192] (Fig. 1), especially in association with SP containing neurons [108] in the leptomeninges [52,58,85,145,155,156,164,212–214], which contain a substantial amount of total brain histamine [67,91,108,146,155,213]. Mast cells can also develop functional associations with neurons [183], especially in the dura [40,42,46,164]. During neonatal development in the rat, two brain mast cell populations can be distinguished, as shown by immunohistochemistry [46]; one with typical characteristics of connective tissue mast cells and a second resembling mucosal mast cells [45]. Unlike extracranial mast cells, many brain mast cells contain heterogeneous secretory granules and lipid bodies as shown by electron microscopy [53,85,145]. Brain mast cells can undergo ultrastructural alterations of their electron dense granular core indicative of secretion, but without degranulation, a process termed “activation” [42,43,198], “intragranular activation” [110], or “piecemeal” degranulation [48]. Such activation may be associated with the ability of mast cells to release some mediators selectively [101], as shown originally for serotonin [196], and subsequently for eicosanoids [11,113,209] and IL-6 [61,109]. Moreover, in certain diseases, such as scleroderma [29] and interstitial cystitis [198], mast cells appear totally depleted of their granule content and cannot be recognized by light microscopy (phantom mast cells). Brain mast cells contain histamine and heparin, as well as express mRNA for immunoglobulin E (IgE) binding protein (FcεRI) [149] and produce FcεRI protein as shown by immunohistochem-

istry [205]; however, brain mast cells appear to lack the c-kit receptor under normal conditions [169]. These findings and the functional association between mast cells and neurons [40,46,164] have led to the review of the potential pathophysiological role of brain mast cells [73,96,158,171], but not in the context of migraines.

The ability of mast cells to increase brain vascular permeability was first hypothesized by us [191] and was confirmed later [164] when restraint stress was shown to increase vascular permeability only in brain areas containing mast cells. This effect was inhibited by the “mast cell stabilizer” disodium cromoglycate [54]; moreover, acute stress did not affect vascular permeability in W/W^v mast cell-deficient mice [54,89]. Mast cell involvement in brain vascular permeability is further supported by reports that the mast cell secretagogue, compound 48/80, stimulated brain mast cells in rats [42] and increased BBB permeability in pigeons [227]. Moreover, local application of 48/80 to the pia induced vascular permeability to fluorescein-labeled dextran [134].

A number of reports indicate that mast cells can be activated by acute stress [199]. For instance, electrical stress decreased brain histamine in the hypothalamus of guinea pigs [129], while restraint stress [9] increased plasma histamine three-fold in rats. Moreover, plasma histamine levels increased four-fold in rats exposed to water immersion stress, but did not increase in stressed W_s/W_s mast cell-deficient rats [80]. Acute stress also increased serum histamine and IL-6 levels in normal mice, but not in mast cell-deficient W/W^v mice [81,82]. Mast cell activation has also been reported in the intestine after repetitive exposure to odors [166], and after Pavlovian conditioning [126], as well as in the rat thalamus in response to isolation stress [19], to restraint stress [199], during naloxone-induced morphine withdrawal [186] and during courtship in male doves [171].

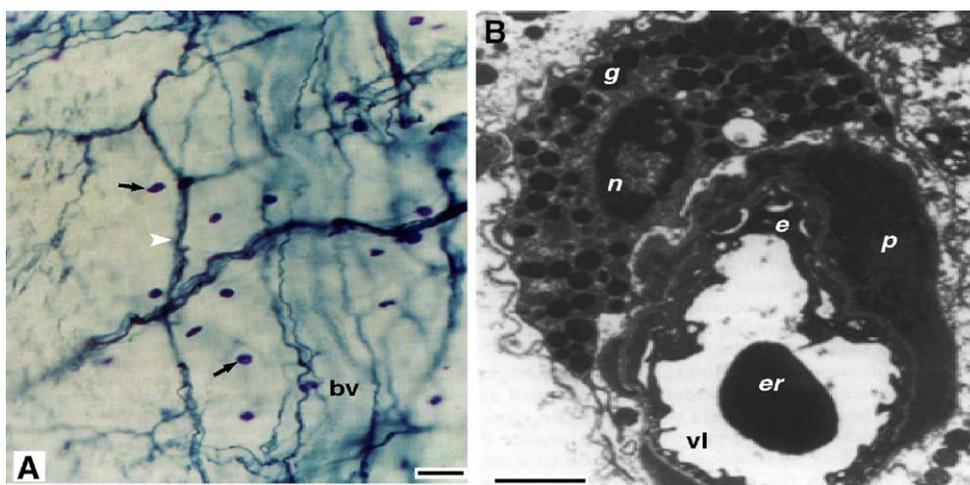


Fig. 1. Photomicrographs of rat dura mater mast cells. (A) Light photomicrograph of mast cells stained with toluidine blue; note numerous mast cells (blue) around a blood vessel and nerve endings stained for acetylcholinesterase (brown). Scale bar = 20 μ m. (B) Electron micrograph showing one mast cell around to an endothelial cell and a pericyte at a cross-section of a blood vessel. bv = blood vessel; vl = vessel lumen; er = erythrocyte; e = endothelial cell; p = pericyte; n = nucleus; g = granule. Scale bar = 4 μ m.

The stress response is coordinated by corticotropin-releasing hormone (CRH) or factor (CRF), a 41 amino acid peptide that is typically released from the hypothalamus and regulates the hypothalamic–pituitary adrenal (HPA) axis [28] through activation of the sympathetic nervous system [161]. CRH acts through specific receptors [25], which include CRHR-1 [26] and CRHR-2 [121]. CRHR-2 has two isoforms, CRHR-2 α and CRHR-2 β [120] for which urocortin (Ucn), a peptide with about 50% structural similarity to CRH, is a more potent agonist than CRH; [210] two additional forms of Ucn, Ucn II [136], and Ucn III [115] have also been identified and are selective CRHR-2 agonists. CRH could have a direct action on blood vessels since CRHR-2 was identified on rat brain arterioles [120], CRH induced vasodilation of fetal circulation [30], and both CRH and Ucn could stimulate cAMP production by brain endothelial cells [55]. However, this effect could be quantitatively and temporally distinct from that induced by mast cell activation.

Mast cells have been identified in the rat median eminence close to CHR-positive neurons [199]. Human mast cells are particularly rich in CRH and Ucn, both of which are secreted in response to immunologic stimulation [94]. Human mast cells also express multiple CRH-Rs [23], of which CRH-R2 is upregulated by IL-4 and bacterial lipopolysaccharide [150]. Restraint stress increased CRH-R gene expression on the primary sensory nuclei of the trigeminal nerve [163] that could lead to secretion in the meninges of NK-1 receptor agonists such as SP, NKA, NKB, and hemokinin A, all of which are known to induce mast cells activation. SP-reactive fibers were localized close to mast cells [46,164,213], and SP released from sensory afferents stimulated mast cell secretion in vivo [87]. CRH could be secreted from sensory nerve endings or DRG [176], as was shown in the skin [124], or NK-1 receptor agonists may stimulate CRH release from mast cells, as was shown in the dura mater [89]. The stress-induced increase in dura vascular permeability does require NK-1 receptors, since it is absent in NK-1 knockout mice, but is not dependent on SP since it is unaffected in SP knockout mice [89], implying the involvement of other NK-1 agonists such as hemokinin [8,22].

Activation of mast cells by CRH can vary in magnitude from differential release of select mediators to overt degranulation, as shown by intradermal injection of CRH in the rat skin [173,201]. CRH may be acting directly on mast cells or together with yet other neuropeptides, such as NT since a NT-receptor antagonist blocked stress-induced mast cell activation [203]. Intradermal CRH administration induced histamine-dependent swelling [34], activation of mast cells [201], and Evans blue extravasation [201]. Moreover, stress-induced exacerbation of chronic contact dermatitis in rats was shown to involve CRHR-1 [90]. Iontophoretic application of CRH increased human skin vasodilation that was dependent on CRHR-1 and mast cells [31,35]. Finally, CRH administration in humans caused

peripheral vasodilation and flushing reminiscent of mast cell activation [105,172,208].

4. Therapeutic approaches

A recent comprehensive review of the treatment of migraines (Headache 44:846–850, 2004) focused primarily on acute treatments. Yet the prevalence and treatment pattern showed that as many as 42% of migraineurs reported >24 attacks in the previous few months, making the need for effective prophylactic therapy necessary. However, behavioral interventions have also been reported to reduce migraines up to 50% [151]. In one study of children migraineurs, the frequency and severity of migraines were reduced, along with the unique mast cell biochemical marker tryptase, when children were taught relaxation techniques [144]. Reduction of stress-induced CRH release could, therefore, be beneficial in the prophylaxis of migraines. The mixed histamine/serotonin receptor antagonist cyproheptadine is still used especially for migraines in children [114]. Pretreatment with cyproheptadine inhibited brain vascular permeability induced by forced swimming in rats [170], suggesting that both histamine and serotonin may be involved in BBB permeability in rodents. However, cyproheptadine was also shown to inhibit mast cell activation [197] as did the heterocyclic histamine-receptor antagonist hydroxyzine [56,197], which also inhibited neurogenic inflammation [47]. These additional properties of hydroxyzine, along with its weak anxiolytic action, may explain why it was useful in the treatment of pain [84]. It is interesting that other drugs reported to be useful in the prophylaxis of migraines, such as amitriptyline [197], chlorpromazine [197], and promethazine [197], also inhibit mast cells to various degrees (Table 3). Inhibition of mast cells would also prevent CGRP release and could be of significant benefit since a CGRP receptor antagonist was shown to be effective in the acute treatment of migraine [143].

Unlike the current treatments for migraines that are mainly abortive (symptomatic) [6,39], we propose a model that will permit screening of drugs and complementary medicine molecules that could act at a number of sites of possible prophylactic intervention (Fig. 2): (a) interruption of the action of CRH on the trigeminal ganglion by non-peptide CRH receptor antagonists that

Table 3
Prophylactic migraine therapies that inhibit mast cells

Drug	Trade name	Reference
Amitriptyline	Elavil	[198]
Chlorpromazine	Thorazine	[198]
Cyproheptadine	Periactin	[198]
Hydroxyzine	Atarax	[56,198]
Prochlorperazine	Compazine	[88]
Promethazine	Phenergan	[198]

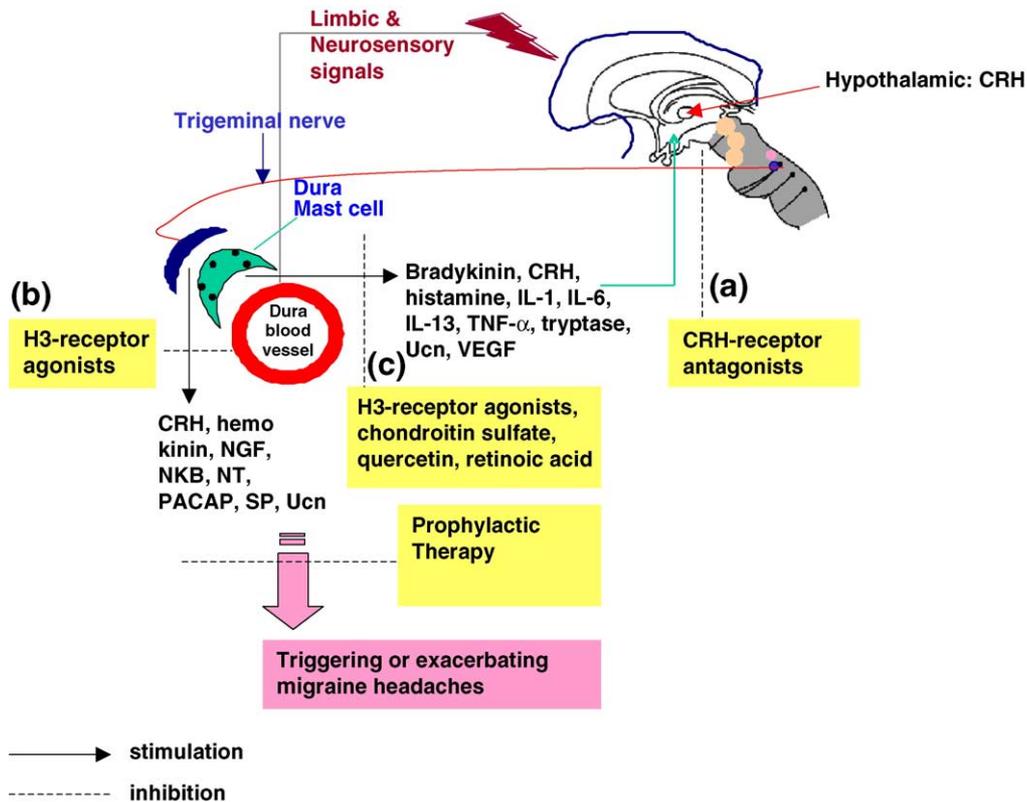


Fig. 2. Emotional, physical, or oxidative stress could trigger CRH secretion from the hypothalamus, which activates CRH receptors on the sensory nuclei of the trigeminal nerve, leading to release of NK-1 agonists (i.e., neurokinin B or hemokinin) in the meninges, especially dura. These could then trigger dura mast cells, either directly or synergistically together with CRH, Ucn, or other neuropeptides, such as NT or PACAP. Mast cell-derived vasoactive, pro-inflammatory, and neurosensitizing mediators then increase vascular permeability and [98,182] contribute to the pathogenesis of migraines. Points of possible prophylactic intervention include: (a) CRH-R antagonists that could block central CRH action; (b) H₃-receptor agonists that could block mast cell triggers such as NKB, PACAP, and hemokinin; (c) H₃-receptor agonists, chondroitin sulfate, quercetin, or retinoic acid which could block release of mast cell mediators.

can cross the BBB [64,71]; (b) presynaptic inhibition of the release of NK-1 agonists and other neuropeptide by histamine-3 receptor agonists known to stimulate presynaptic autoinhibitory H₃ receptors [165]. Even though neurokinin-1 (NK-1) receptor (for NKA, SP) antagonists failed to prevent migraines [68,69], these do not block neuropeptides such as CGRP or hemokinin [8,22,106] from stimulating mast cells; (c) blockade of neuropeptide induced mast cell activation [147] by proteoglycans such as chondroitin sulfate [202] or inhibition of mast cell mediator degranulation [98,131,182] with select flavonoids such as quercetin [135] that was recently shown to cross the BBB [226] or retinoic acid [1,86]. Formulations combining some of these molecules may provide synergistic benefit [193].

5. Conclusion

Mast cells could serve both as key “sensor” and “effector” cells in migraines locally in the meninges, as well as in the hypothalamus [60,133,191]. For instance, histamine increased CRH mRNA expression in the hypothalamus [97] and mast cells could stimulate the

HPA axis [20,60,133]. Moreover, IL-1 and IL-6, [13,104,109,130,138,178] both of which are released from mast cells [70], could trigger CRH secretion; conversely, CRH stimulates IL-6 release [3,4,111,211].

The premise discussed above may offer a more realistic explanation of migraine headaches than the vascular or CSD theories presented so far [177], and could account for a purely physical (sunstroke), emotional (fear of exam failure), or molecular (oxidative stress) trigger of migraines.

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