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REVIEW

Migraine Headaches: the Immunologist's View

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KEY WORDS: *inflammation, mast cells, stress, vascular permeability*

List of Abbreviations:
ACS = acute coronary syndromes
CRH = corticotropin releasing hormone
IL = interleukin
SP = substance P
VEGF = vascular endothelial growth factor

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ABSTRACT

OBJECTIVE: Review evidence supporting the role of mast cells in migraine pathophysiology.

BACKGROUND: Mast cells are known for their role in allergic reactions, but they are also important in immunity and inflammatory diseases, especially those precipitated or worsened by stress. Such are migraine headaches that are associated with spreading neuronal depression and neurogenic inflammation intracranially. Migraines are also comorbid with allergies and could precipitate acute coronary syndromes (ACS). Mast cells are located perivascularly, in close association with neurons, especially in the meninges. Mast cells can be activated by trigeminal nerve stimulation and by acute stress, leading to increased vascular permeability and neurogenic inflammation dependent on NK-1 receptors, but not necessarily on substance P (SP).

METHODS: We reviewed relevant literature and summarized our own findings.

RESULTS: Corticotropin-releasing hormone (CRH), a mediator of the stress response released from the hypothalamus, can activate CRH receptors either on the sensory nuclei of the trigeminal nerve or directly on the mast cells. They, then release proinflammatory, nociceptive and vasoactive mediators including histamine, tryptase and vascular endothelial growth factor (VEGF), thereby triggering migraine headaches.

CONCLUSIONS: These results indicate that there are several novel points of intervention for the development of therapeutic agents to help alleviate migraines. Preliminary clinical studies with brain mast cell blockers and CRH receptor antagonists suggest that they could be useful prophylactically.

1. SELECTIVE RELEASE OF MAST CELL MEDIATORS

Mast cells derive from a distinct precursor in the bone marrow[1] and mature under local tissue microenvironmental factors.[2] Mast cells are necessary for the development of allergic reactions, through crosslinking of their surface receptors for IgE (FcεRI), leading to degranulation and the release of vasoactive, pro-inflammatory and nocicep-

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tive mediators that include histamine, cytokines and proteolytic enzymes (Table 1).[3,4] The multitude of mediators that could be secreted, especially in response to many non-immunologic triggers (Table 2) has given rise to new speculations about the possible role of mast cells in immune responses, especially acquired immunity[5] and inflammation.[6]

Unlike allergic reactions, mast cells are rarely seen to degranulate during autoimmune[7] or inflammatory processes.[8] Instead, mast cells can secrete mediators without overt degranulation,[9] through differential or selective release,[10] probably regulated by the action of distinct protein kinases on a unique phosphoprotein.[11,12] In such cases, mast cells undergo ultrastructural alterations of their electron dense granular core indicative of secretion, but without overt degranulation, a process that has been termed "activation",[13-15] "intragranular activation"[16] or "piecemeal" degranulation.[17] Selective release has been reported for a number of mediators,[18-20] especially serotonin,[10] eicosanoids[21-23] or IL-6.[24-27] In fact, we showed that interleukin-1 (IL-1) can stimulate human mast cells to release IL-6 selectively without degranulation, through a unique process utilizing 40-80 nm vesicles unrelated to the secretory granules (800-1000 nm).[28] We also recently showed that corticotropin releasing hormone (CRH) secreted under stress can stimulate human mast cells through specific CRH receptors to release vascular endothelial growth factor (VEGF) selectively.[29]

These findings suggest that mast cells may also be involved in inflammatory diseases[6,30] that include migraines[31] and cardiovascular disease.[32]

2. MENINGEAL INFLAMMATION AND MIGRAINES

Migraine headache is still a descriptive term that has been used primarily to refer to the brain and is usually associated with meningeal and cerebral vasodilation, as well as "spreading" neuronal depression.[33] It was hypothesized that mast cells may be involved in the pathophysiology of migraines.[31] Mast cells are located in close apposition to neurons in the meninges [34,35] and can be activated by neuropeptides,[36] by antidromic nerve stimulation,[14] as well as by acute immobilization stress.[15] Brain mast cells were also activated by acute stress leading to increased vascular permeability,[37] effects dependent on mast cells and CRH.[38]

Stress is known to precipitate or exacerbate migraines, raising the possibility of some underlying pathologic mechanism. One such possibility comes from one study of children migraineurs, in whom the frequency and severity of migraines was reduced, along with the unique mast cell biochemical marker tryptase, when they were taught relaxation techniques.[39] Recent studies have shown that stress-induced neurogenic inflammation depends on NK-1 receptors, but does not require SP,[40]

TABLE 1. Mast cell Triggers

Antigen + IgE
Anaphylatoxins
CRH
IL-1
Immunoglobulin – free light chains
LPS
NGF
NT
SCF
SP
Superantigens
Ucn
VIP
Viral DNA sequences

while it may involve a direct action of CRH on brain microvessels.[41] Yet, delayed responses may also involve IL-6 and nitric oxide elevations in dura macrophages.[42] These findings have led to a new model for the pathogenesis of intracranial neurogenic inflammation (Fig. 1) that calls for hypothalamic CRH acting on the sensory nucleus of the trigeminal nerve, which has been reported to express CRH receptors;[43] CRH

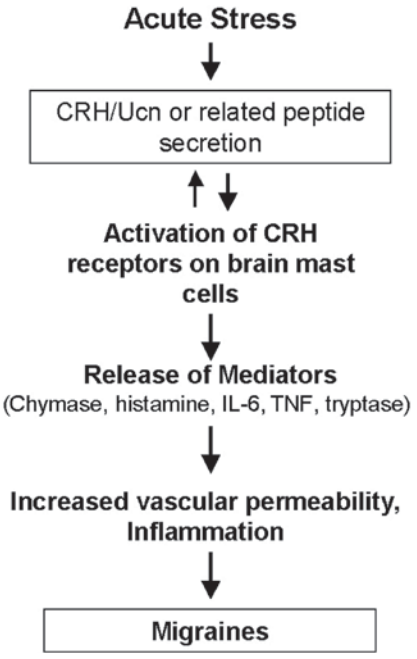

Figure 1. Schematic representation of the sequence of events that may induce brain mast cell activation and neurogenic inflammation, leading to migraines.

TABLE 2. Mast Cell Mediators

Mediators	Main Pathophysiologic Effects
Prestored	
Biogenic Amines	
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8, MCP-1, MCP-3, MCP-4, RANTES	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, angiotensin II synthesis, cholesterol liberation
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation, pain
Peptides	
Corticotropin-releasing hormone (CRH)	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Somatostatin (SRIF)	Anti-inflammatory (?)
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Urocortin	Inflammation, vasodilation
Vascular endothelial growth factor (VGEF)	Neovascularization, vasodilation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration, pain
INF-γ; MIF; TNF-α	Inflammation, leukocyte proliferation/activation
Growth Factors	
SCF, GM-CSF, b-FGF, NGF, VEGF	Growth of a variety of cells
Phospholipid metabolites	
Leukotriene B_4 LTB_4	Leukocyte chemotaxis
Leukotriene C_4 (LTC_4)	Vasoconstriction, pain
Platelet activating factor (PAF)	Platelet activation, vasodilation
Prostaglandin D_2 (PGD_2)	Bronchonstriction, pain
Nitric oxide (NO)	Vasodilation

CRH = corticotropin-releasing hormone
CSF = colony stimulating factor
INFγ = Interferon-γ
MIF = macrophage inflammatory factor
b-FGF = fibroblast growth factor
SCF = Stem cell factor
TGF-β = transforming growth factor-β
TNF-α = tumor necrosis factor-α
SRIF = somatomedin release inhibitory factor, somatostatin
GM-CSF = granulocyte monocyte-colony stimulating factor
NGF = nerve growth factor
VEGF = vascular endothelial growth factor

could then secrete mast cell stimulating peptides and/or have a direct action on mast cells and/or on the vasculature.[6] These processes have recently been reviewed,[44] as has been the important role of mast cells in migraine pathophysiology.[45]

CONCLUSION

In summary, the mast cell has emerged as a unique immune cell that could be activated by many non-immune processes, including acute stress, [46] and could participate in a variety of inflammatory diseases including the brain. [30]

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