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GUEST EDITORIAL

Mast Cells and Stress—A Psychoneuroimmunological Perspective

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The complexity of interactions among neurotransmitters and neuromodulators in the brain continues to expand. The involvement of immune molecules has added a new dimension. An important new contributor that is of interest to psychopharmacology is a unique cell, named "mast cell" by Paul Erlich in 1887 because its numerous metachromatic granules reminded him of a "well-fed cell" (German = Mastzellen).[1] These cells are particularly active in atopic individuals, who also have higher incidences of affective disorders.[2–5] Moreover, the allergy season has been shown to affect mood and cognitive function in these patients.[6] Stress is known to exacerbate many neuroinflammatory conditions[7], but, until recently, mast cells were not suspected of being involved in conditions such as dermatoses[8], irritable bowel syndrome[9], interstitial cystitis[10], migraines[11], and multiple sclerosis (MS).[12] Although Hans Seyle wrote the first definitive work on stress[13] and one on mast cells[14], he did not link the two at that time. The effect of acute stress is particularly evident in systemic mastocytosis, a rare condition characterized by abnormal proliferation and activation of mast cells.[15,16] For these patients, and possibly many others who have a neuroinflammatory syndrome with an affective component worsened by stress (Table 1), when anxiety rises, they know there will be a flare-up in symptoms, which may include flushing of the skin, intestinal upset, palpitations, migraines, and changes in mood and cognitive function.[12] These latter symptoms could be due to activation of brain mast cells, which are plentiful in the thalamus and hypothalamus.[17–19]

Mast cells are found in most parts of the body and are well known for their involvement in allergic and anaphylactic reactions[20]; then, surface bound immunoglobulin E (IgE) complexes with specific antigen, causing degranulation, like a foil package of popcorn popping until the contents overflow.[21] Many of these molecules are preformed and stored in almost 500 secretory granules, while others are made *do novo* during or following stimulation.[22,23] It is fascinating that one cell should have such plethora and diversity of potent molecules that include arachidonic acid products, biogenic amines, chemoattractants, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes (Table 2). Although the mast cell is ubiquitous in the body—including the brain, which does not suffer from allergic reactions because IgE does not cross the blood-brain barrier—degranulation occurs only in about 10% or so of atopic individuals. Moreover, increasing evidence indicates that some molecules are released from mast cells without degranulation, a process termed "differential release" and first reported for serotonin.[24] Other biogenic amines[25], arachidonic acid products[26], and cytokines[27] may also be released differentially. The morphological appearance of this process is characterized by a more subtle set of changes within the electron dense content of the secretory granules[28] and has been called "piece-meal degranulation"[29] or "intergranular activation".[30] The type(s) of molecule(s) released may vary from person to person, and/or from organ to organ, depending on hormonal and psychological state and the specific trigger.

Anatomical and functional associations have been reported between mast cells and neurons.[31,32] Scanning electron microscopy has documented mast cells close to endothelial cells and to neuronal processes.[33] Molecules released from nerves[34–36], such substance P (SP), neurotensin (NT), nerve growth factor (NGF), and opioids[37] could trigger mast cells (Table 3), from which histamine

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TABLE 1. Neuroinflammatory syndromes with an affective component involving mast cells

Asthma
Atopic dermatitis
Fibromyalgia
Irritable bowel syndrome
Interstitial cystitis
Migraines
Multiple sclerosis
Neurofibromatosis
Rheumatoid arthritis
Unstable angina

could stimulate neuronal depolarization[38], which could lead to further activation of mast cells. Moreover, mast cell derived chondroitin sulfate or heparin complexes with NGF and extends its half-life from a few minutes to many hours.[39,40] Therefore, mast cell activation could lead to abnormal nerve proliferation (i.e., in neurofibromatosis I).[41] Intracranial mast cells could also be activated by stimulation of the trigeminal[42], sympathetic[43], or sphenopalatine[44] nerves and by acute restraint stress[45], in the absence of any allergic diathesis. Some molecules from these mast cells could have direct effects on the brain, while others could make the blood-brain barrier "leaky" and permit circulating chemicals to enter the brain.[46,47] Breakdown of the blood-brain barrier has been shown to precede any clinical or radi-

TABLE 2. Mast Cell Mediators

Mediators	Main pathophysiologic effects
Prestored	
Biogenic amines	
Epinephrine, dopamine, phenylalanine (not synthesized, but taken up and stored)	Neuromodulation
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8, MCP-1, MCP-3, MCP-4, RANTES	Chemoattraction
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, pain, angiotensin II synthesis
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, inflammation, pain
Growth Factors	
CSF, GM-CSF, b-FGF, NGF	Growth of a variety of cells
Peptides	
Chemotactic factors	Infiltration of leukocytes
Corticotropin-releasing factor (CRH)	Vasodilation, inflammation
Endorphins	Analgesia
Kinins (bradykinin)	Vasodilation, pain
Somatostatin (SRIF)	Antiinflammatory (?)
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, antiinflammatory, NGF stabilization
Heparin	Angiogenesis, NGF stabilization
Hyaluronic acid	Connective tissue synthesis, NGF stabilization
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration, pain
INF-γ; MIF	Inflammation, leukocyte proliferation/activation
TNF-α	Inflammation, vascular adhesion molecule expression
Arachidonic acid products	
Leukotriene B_4 (LTB_4)	Leukocyte chemotaxis
Platelet Activating factor (PAF)	Platelet activation & serotonin release
Prostaglandin D_2 (PGD_2)	Vasodilation, pain
Leukotriene C_4 (LTC_4)	Vasoconstriction, pain
Nitric oxide (NO)	Vasodilation, neurotransmission

CSF, colony stimulating factor; INFγ, interferon-γ; MIF, macrophage inflammatory factor; b-FGF, fibroblast growth factor; NGF, nerve growth factor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; SRIF, somatostatin; GM-CSF, granulcyte monocyte-colony stimulating factor.

TABLE 3. Triggers of mast cell activation

Anaphylatoxins
C3a and C5a
Bacteria
Adherent *E. coli*
Chemicals
Detergents; food additives; xenoestrogens
Contrast media used in radiology
Cytokines
IL-1, IL-2, IL-4, TNF-α
Drugs
Local anesthetics; neuromuscular junction blockers, opioids
Free radicals
Growth factors
Nerve growth factor, NGF; stem cell factor, SCF
Hormones
Adrenocorticotropic hormone, ACTH; corticotropin releasing hormone, CRH; estradiol; parathormone, PTH; urocortin, Ucn
IgE and antigen
Neuropeptides
Bradykinin; calcitonin gene related peptide, CGRP; myelin basic protein, MBP; neurotensin, NT; somatostatin, SRIF; substance P, SP; vasoactive intestinal peptide, VIP
Neurotransmitters
Acetylcholine
Physical conditions
Cold; exercise; pressure
Preservatives
Monosodium glutamate
Radiation
Electromagnetic, UV
Toxins
Bacterial (Clostridium difficile); insect (fire ants); jelly fish (man of war); plants (poison ivy)
Viruses
Measles; parainfluenza; Sendai

ographic signs of MS.[48] Therefore, it is of interest that chemical[49] or stress-induced stimulation of brain mast cells[50] increased blood-brain barrier permeability. Moreover, experimental allergic encephalomyelitis could not be induced in mast cell deficient mice.[51] These findings support the possible relationship between intracranial mast cells and migraines[52], as well as MS[53], that are often precipitated or worsened by stress.[54–57] Dura mast cells also express estrogen receptors[33], a finding that, along with the report that estrogen augments mast cell secretion[58], may possibly explain the higher incidence of migraines in women or their frequent occurrence during ovulation.

Many patients also experience tachycardia and arrhythmias related to stress. Such cardiovascular symptoms may be associated with increased sympathetic activity or reflex tachycardia in response to histamine-induced hypotension. However, such symptoms may also be explained by the recent finding that acute stress triggers mast cell activation in the heart[59], with subsequent release of histamine[60] and IL-6.[61] This action of histamine is not blocked by the usual antihistamines and appears to be mediated through the type 3 histamine receptor.[62] IL-6, a key inflammatory cytokine[63], is known be released from the hearts of patients with acute coronary syndrome, and is now considered a critical player in coronary artery disease.[64] Stress-induced cardiac mast cell activation may be involved in unstable angina and myocardial infarction triggered by acute stress.[65–67] Acute stress also results in bladder[68] and intestinal[69,70] mast cell activation, which may explain why symptoms in interstitial cystitis (IC) and irritable bowel syndrome (IBS) patients worsen under stress.

Corticotropin-releasing hormone or factor (CRH or CRF) is the first molecule released under stress and activates the hypothalamic-pituitary-adrenal (PHA) axis.[71] We have shown that CRH[72] and structurally related urocortin[73] are powerful triggers of mast cell activation in the skin. In fact, urocortin was 10 times more potent than CRH and much more potent than SP.[73] These actions were mimicked by acute stress[74] and may be responsible for stress-induced alopecia areata.[75] Such findings and the presence of both CRH and CRH receptors in the skin[76] have led to the hypothesis that the skin has the equivalent of a local "pituitary-adrenal axis".[77] Recent findings showed that hypothalamic mast cell activation by chemical[78] or immunologic means[79] triggered activation of the HPA axis. This action could be mediated either through activation of CRH neurons directly or the release of IL-6, a CRH independent activator of the HPA axis.[80] CRH or urocortin then could be further released from recruited immune cells.[81]

Recognizing the involvement of mast cells and regulating their secretion may be more important than simply addressing the effects of individual mediators. A case in point is the clinical report (Pehlivanidis and associates, page 221 in this issue) of a young boy mistakenly diagnosed and unsuccessfully treated for epilepsy. When it was recognized that his seizures were induced by acute stress and were associated with his mastocytosis, he was successfully treated with a combination of the anxiolytic antihistamine hydroxyzine and the tricyclic doxepin. The efficacy of these compounds may be explained by the fact that mast cell activation can be inhibited by certain tricyclic anxiolytic medications, such as amitriptyline and hydroxyzine[82], and benzodiazepines.[83] In fact, mast cells have been reported to express high affinity benzodiazepine receptors.[84,85] Hydroxyzine was recently shown to inhibit neurogenic inflammation and experimental allergic encephalomyelitis in rats.[86] In humans, hydroxyzine has been used successfully to treat acute pain[87] and remitting-relapsing MS.[88] Such anxiolytic molecules could be combined with naturally occurring flavonoids[89] or proteoglycans[90] for more efficient inhibition of mast cell

activation. Behavioral modification for stress reduction also contributed to the treatment of the child described in the case report by Pehlivanidis and associates. We used this approach because of our finding that training in relaxation led to a sharp decline in the frequency and severity of migraines and the release of the mast cell marker tryptase[11] in children.

The mast cell has been considered an immune gate to the brain[91], as well as a sensor of environmental and emotional stress.[92] It has also been linked to many neuropathological processes.[93–95] This versatile role of mast cells[96] compels a more appropriate name to indicate its polydimensional potential, perhaps "pleiotropocyte" (Greek = multifaceted cell).

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