Panic Disorder, Interstitial Cystitis, and Mast Cells

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Panic disorder (PD) is a psychiatric condition characterized by neuropsychologic symptoms including recurrent episodes of sudden unpredictable apprehension and associated autonomic manifestations involving cardiorespiratory systems, neurologic, gastrointestinal, and cognitive symptoms.[1] It is associated with high levels of stress.[1] Genetic evidence has mapped a PD syndrome to chromosome 13q in 60 multiplex families with PD and bladder problems suggestive of interstitial cystitis (IC)[2]; other evidence from genetic linkage studies associated PD with a polymorphism in the adenosine 2A receptor.[3] Families with PD also had a higher incidence of migraines,[2] which are also prevalent in IC patients.[4] The genetic linkage studies focused on families with PD and did not have definitive diagnosis of IC. A recent paper published in the *Archives of General Psychiatry*[4] reported findings from a collaboration between psychiatry and urology. The study began with patients with well-characterized IC and found increased rates of PD in the IC patients and their first degree relatives. IC is a disorder of the urinary bladder characterized by urgency, frequency, nocturia, and chronic pelvic pain.[5] IC patients can be broadly grouped in those with bladder inflammation (some of whom may also have Hunner ulcers) on biopsy, presenting with more pronounced symptoms[6] and those with minimal or no inflammation.[6,7] The only pathologic finding that was correlated to IC symptoms was an increased number of mast cells[8] that have been repeatedly documented and shown to be activated in the bladder of IC patients. A number of other conditions occur with higher frequency in IC patients and include allergies, irritable bowel syndrome, fibromyalgia and migraines.[9]

The publication by Weissman et al[4] is the first report linking IC genetically to PD, let alone to any other disorder; this paper discussed the possibility that mast cells may serve as a link between the two disorders.[2] This is an exciting development since we had proposed that IC is a neuroimmunoendocrine syndrome[10] and that stress-related molecules may be involved.[11] Stress has been shown to stimulate mast cells,[12] as well as worsen the symptoms of IC.[13] Moreover, acute stress was shown to activate bladder mast cells and lead to sterile bladder inflammation.[14] Neurotransmitters and neuropeptides secreted under stress could then further activate mast cells[15]; in fact, adenosine has been shown to activate mast cells.[16] One of the molecules released from mast cells is serotonin that has been implicated in the pathophysiology of panic disorders.[17] It is, therefore, of interest that drugs used for the treatment of PD, benzodiazepines,[18] and tricyclic antidepressants[19] can inhibit mast cells. In fact, mast cells have been proposed as an immune gate to the brain,[20] as well as a sensor of

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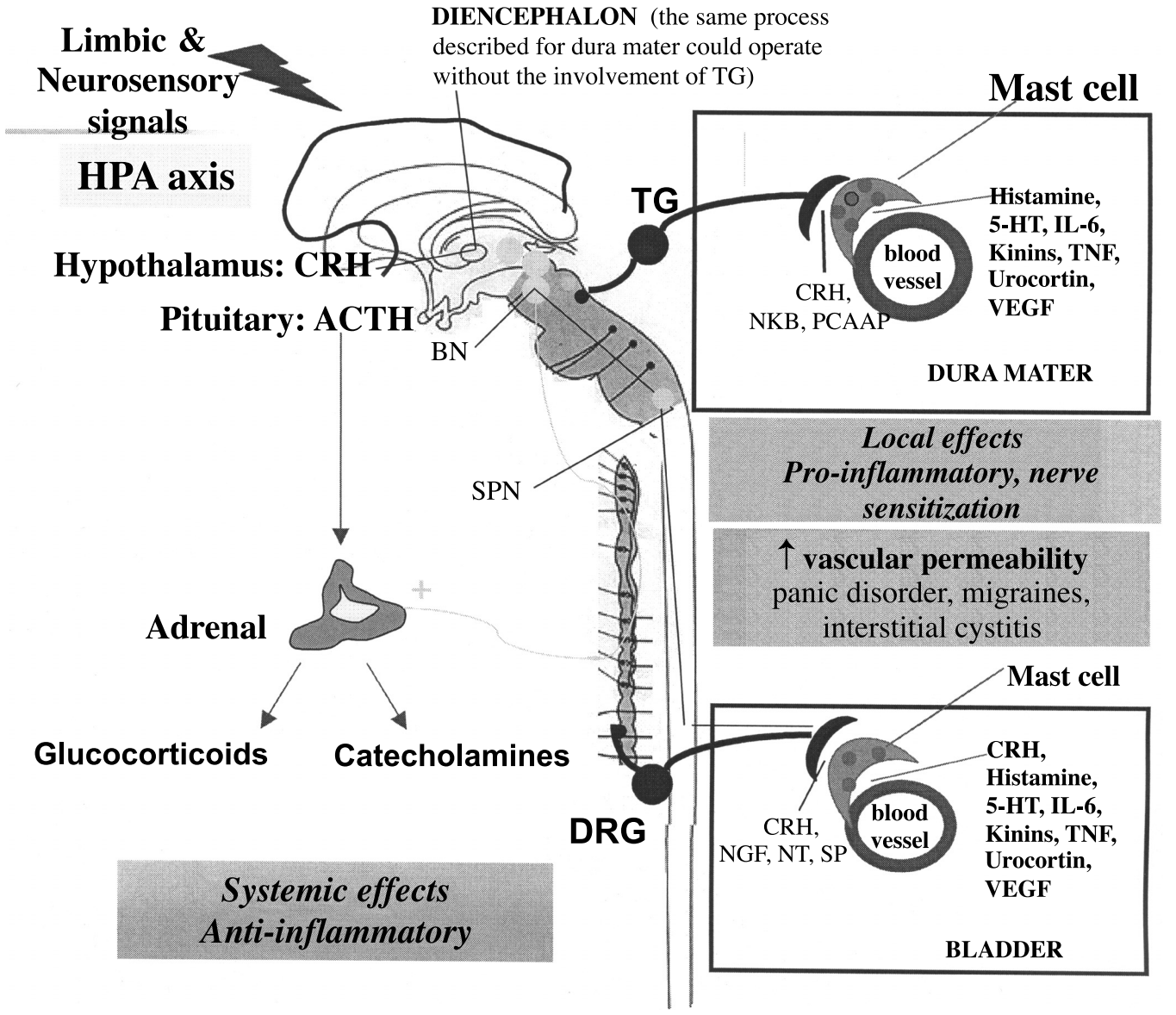

FIGURE 1. Schematic representation of the hypothesized common pathological basis of stress-induced panic disorder, migraines, and interstitial cystitis through mast cell activation by CRH or related neuropeptides released locally or through the pontine Barrington nucleus acting through CRH on the spinal parasympathetic nucleus that innervates the bladder. BN indicates Barrington nucleus; DRG, dorsal root ganglion; 5-HT, 5-hydroxy tryptamine, serotonin; IL-6, interleukin-6; NGF, nerve growth factor; NKB, neurokin B; PCAAP, pituitary cyclic AMP-activating peptide; SP, substance P; SPN, spinal parasympathetic nucleus; TG, trigeminal ganglion; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

environmental and emotional stress,[12] and have been linked to many neuropathologic processes.[21–23]

Mast cells are essential not only for allergies, but also for innate and acquired immunity[24,25] and inflammation[12] by releasing histamine, proteases (tryptase, chymase), proteoglycans, prostaglandin D_2, leukotriene C_4, and several multifunctional cytokines including IL-8. Mast cells are ubiquitous in the body and are particularly active in atopic individuals, who also have a higher incidence of affective disorders.[26–29] Stress is known to exacerbate many neuroinflammatory conditions,[12] especially IC[13] and migraines.[30] These latter conditions could be due to activation of mast cells, which are plentiful both in bladder,[31] as well as in the dura,[32] the thalamus and hypothalamus.[33–35] Mast cell participation, however, would require release of some molecules either from distinct granules[36] or without degranulation, a process termed ''differential release,'' as first reported for serotonin.[37] Other biogenic amines,[38] arachidonic acid

products,[39] and cytokines,[40] especially IL-6,[41] may also be released differentially.

Anatomical and functional associations have been reported between mast cells and neurons in the brain[32] and bladder.[42] Molecules released from nerves, such as substance P, neurotensin, nerve growth factor, and opioids could trigger mast cells,[12] from which histamine could then stimulate neuronal depolarization[43] leading to further activation of mast cells. Intracranial mast cells could also be activated by stimulation of the trigeminal,[44] sympathetic,[45] or sphenopalatine[46] nerves, as well as by acute restraint stress[47] 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 serotonin from activated platelets to enter the brain.[48,49] Dura[32] and bladder[50] mast cells also express estrogen receptors, a finding that, along with the fact that estrogen augments mast cell secretion,[51] may possibly explain the higher incidence of IC and migraines in women or their frequent occurrence during ovulation.[10]

Corticotropin-releasing hormone (CRH) is released under stress and activates the hypothalamic-pituitary-adrenal axis.[52] CRH[53] and its structurally related urocortin[54] are powerful triggers of mast cell activation. These actions were mimicked by acute stress[55] and may be responsible for alopecia areata that occurred under panic conditions.[56] Mast cells were recently shown to be one of the richest sources of CRH and urocortin[57] as well as express CRH receptors,[58] indicating that there could be an autocrine feedback loop. Preliminary evidence also indicates that CRH could induce selective release of interleukin-6 (IL-6) from human mast cells,[59] and IL-6 has been reported to increase brain serotonin metabolism through activation of the HPA axis.[60] A model that could explain both PD and IC could involve release of CRH or related molecules under stress that could then activate mast cells in the brain, dura, and bladder contributing to the pathophysiology of PD, migraines, and IC (Fig. 1).

The efficacy of tricyclic antidepressants and benzodiazepines in PD[61] may be explained by the fact that mast cell activation can be inhibited by amitriptyline and hydroxyzine,[62] as well as by benzodiazepines.[19] In fact, mast cells have been reported to express high affinity benzodiazepine receptors.[63,64] Hydroxyzine can also inhibit neurogenic inflammation in the brain[65] and bladder,[66] as well as reduce symptoms of IC in susceptible patients.[67]

It is becoming apparent that comorbid conditions may have similar underlying pathology and even be linked genetically. It is, therefore, important to consider such conditions as a continuum and attempt to treat the patients with multimodal therapy that addresses not only the symptoms, but also the underlying common mechanism.[68] The mast cell is emerging as a powerful effector cell in many comorbid disorders that involve the hormonal, immune, and nervous systems[69] as well; as such, the mast cell deserves closer scrutiny and may prove to be a unique target for new therapies.

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