Mast cells in chronic inflammation, pain and depression

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Background

Mast cells derive from hematopoietic stem cells and circulate as immature progenitors; maturation occurs upon reaching their destination tissue (Galli et al., 2005; Galli and Tsai, 2008). Mast cells are characterized by a high density of cytoplasmic granules which undergo partial or complete degranulation in response to a wide range of immunological and non-immunological stimuli. These granules contain plethora of mediators, including histamine, heparin, serotonin, chemotactic factors and various proteases such as peroxidase, tryptase, chymase, carboxidase, and beta-glucuronidase (Frenzel & Hermine, 2012). Mast cells are unique in that they are the only cell type that stores pre-formed tumor necrosis factor alpha (TNF-α) in secretory granules (Olszewski et al., 2007), which positions them as early responders in acute inflammatory responses (Jim et al., 2009). Moreover, activated mast cells are capable of elaborating secondary mediators such as prostaglandins, leukotrienes, numerous cytokines (e.g. interleukins (IL)-1, -3, -4, -5, -6, -10, -4 and -17, as well as transforming growth factor beta and nerve growth factor (Leon et al., 1994; Halova et al., 2012).

By synthesizing and releasing diverse types of inflammatory mediators, mast cells may provoke pathophysiological changes in various organs and systems, leading to intersystemic homeostasis imbalance and development of pathological conditions often associated with persistent inflammation and chronic or neuropathic pain (Ren & Dubner, 2010; Dai & Korthuis, 2011; Anand et al., 2012).

Mast cells and pain

Mast cells, being located in proximity to sensory nerve endings, may modulate nociceptive nerve ending excitability (Kovacs et al. 2006; Forsythe & Bienenstock, 2012). Neurogenically-generated mediators such as substance P and other inflammatory neuropeptides may also cause mast cell degranulation, thus creating a bidirectional positive feedback-loop (Matsuda et al. 1989; Messlinger et al., 2011).

Meningeal mast cells play a key role in pain etiopathogenesis by promoting neurogenic inflammation, with activated meningeal nociceptors contributing significantly in the pathophysiology of migraine (Theoharides et al. 2005a; Levy et
al. 2007; Levy, 2009; Messlinger et al., 2011; van Diest et al., 2012). At the spinal level, dural mast cells have a high density in the cervical, thoracic, and lumbar regions (Majeed, 1994; Michaloudi et al., 2008). In spinal trauma, mast cells enter the spinal cord parenchyma, an event reduced by treatment with the fatty acid amide palmitoylethanolamide (Genovese et al., 2008; Esposito et al., 2011). Interestingly, central nervous system (CNS) neurons may acquire mast cell products via transgranulation, a novel form of brain-immune system communication (Wilhelm et al., 2005). As very little white matter separates the lumbar dorsal horn from the subarachnoid and dura mater, mediators released from dural mast cells (e.g. serotonin, prostaglandins, and histamine) may reach the superficial laminae (a key relay station for nociception) to modulate synaptic transmission and nociception (Sandkühler, 2009). CNS-located mast cells may play a role in capsaicin- and carrageenan-induced peripheral inflammatory nociception: spinal application of supernatant from activated cultured mast cells reportedly induced significant mechanical hyperalgesia, long-term potentiation at the spinal synapses of C-fibers and increased the number of mast cells in the lumbar, thoracic and thalamic preparations (Xanthos et al., 2011). In a spinal nerve ligation model in the female rat, increased numbers of mast cells were seen in the thalamus contralateral to the ligation site, coincident with development of mechanical hyperalgesia (Taiwo et al., 2005). In chronic granulomatous inflammation-induced hyperalgesia in rats, degranulated mast cells were observed in the granuloma and nearby nerve fibers (De Filippis et al., 2011).

Besides mast cell-mediator activation of neurons, cell-to-cell communication between mast cells and neurons can operate via adhesion molecules expressed by mast cells and neurons, such as cell adhesion molecule-1 and N-cadherin (Ito & Oonuma, 2006; Suzuki et al. 2004; van Diest et al. 2012). Moreover, a bidirectional cross talk between mast cells and microglia (the brain’s resident immune cells), has been reported (Bulanova et al., 2010; Yuan et al., 2010; Zhang et al., 2012) proposing that mast cells, in some settings, might initiate CNS inflammatory processes, as suggested for the inflammatory cascade of blood-borne neutrophil and phagocyte infiltration in ischemia (Jin et al., 2009). In particular, peripheral mast cells may sensitize primary sensory ganglionic neurons leading to co-release of glutamate and neurotransmitters such as substance P and calcitonin gene-related peptide, leading to voltage-gated Ca\(^{2+}\) currents and activation of spinal microglia (thought to initiate CNS neuroinflammation) (Milligan & Watkins, 2009). Noteworthy, molecules targeting mast cells and glia, such as palmitoylethanolamide, inhibit pain behavior in models of acute, chronic and neuropathic pain (Mazzari et al., 1996; Conti et al., 2002; Costa et al., 2002; Costa et al., 2008; Wise et al., 2008, De Filippis et al., 2011).

In humans, degranulation of mast cells in close proximity to the nerves innervating the colonic mucosa correlates with abdominal pain in irritable bowel disease patients (Barbara et al. 2004). It is worth pointing out that, most of the pathological conditions associated with chronic pelvic pain are characterized by significant increases mast cell numbers in the affected area, most of which are found in an activated and degranulating state. Elevated numbers and activation of mast cells has been consistently reported in endometriotic tissue as compared to normal tissue or eutopic endometrial tissue (Sugamata et al., 2005; Anaf et al., 2006; Menzies et al., 2011). This augmentation in mast cells is more evident in deep infiltrating lesions and in proximity to nerve fibers. A concomitant alteration of
somatosensory fibers, namely an augmentation of nerve fiber density, parallels the alteration of mast cells in the affected tissues (Wang et al., 2009; Anaf et al., 2011). A similar picture is present in interstitial cystitis/painful bladder syndrome (Theoharides et al., 1995b; Pang et al., 1996; Pang et al., 1998; Nazif et al., 2007; Larsen et al., 2008; Menzies et al., 2011; Liu et al., 2012) as well as in irritable bowel syndrome (Barbara et al., 2007; Buhner and Schemann, 2012) and vestibulodynia (Bornstein et al., 2004; Bornstein et al., 2008; Goetsch et al., 2010; LeClair et al., 2011). The bidirectional positive feedback-loop between mast cells and nociceptors plays a fundamental role in the development of cross-sensitization in the pelvis, in other words the transmission of noxious stimuli from a diseased pelvic organ to an adjacent normal structure, which results in functional changes in the latter (Ustinova et al., 2007; Ustinova et al., 2010; Fitzgerald et al., 2013). In support of a primary role for mast cells in chronic pelvic pain, recent clinical studies have shown that treatment with Pelvilen®, a “dietary food for special medical purposes” based on the combination between micronized palmitoylethanolamide and polydatin, results in a significant and long-lasting relief of pelvic pain symptomatology (Indraccolo et al., 2010; Calabrò et al., 2010; Murina et al., 2013; Lo Monte et al., 2012; Giugliano et al., 2013).

Altogether, the reported data support the involvement of peripheral and central mast cells in the development of pain processes; moreover, mast cell-derived mediators such as cytokines and chemokines could conceivably provoke a shift in inflammatory state, resulting in the transition from acute to chronic and neuropathic pain.

**Mast cells in anxiety and depression**

An increasing body of evidence now points to an intricate network of bi-directional relationships between the immune system and the brain. Alterations in immune function, specifically an increased inflammatory state, have been found in depressed patients with major depression (Miller et al., 2006; Capuron & Miller, 2011; Krishnadas & Cavanagh, 2012; Zunszain et al., 2012). Pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α, released by activated immune cells during psychosocial stress not only help orchestrate cellular responses to immune challenge, but also coordinate the behavioral changes that are necessary for recovery. Importantly, when immune challenge becomes chronic and/or unregulated, as in patients receiving chronic cytokine treatment or those exposed to chronic medical illness and/or stress (Raison et al., 2006; Zunszain et al., 2012), the behavioral effects of cytokines and the resultant inflammatory response may contribute to the development of clinically relevant behavioral symptoms and neuropsychiatric diseases, including major depression.

A growing body of evidence supports the hypothesis that mast cells behave as cellular sensors, directing tissue responses in peripheral inflammation (Kinet, 2007; Beghdadi et al., 2011) and, in some cases, initiating CNS inflammatory processes (Jin et al., 2009). Conceivably, that mast cells might represent the immune cells that peripherally and centrally coordinate inflammatory processes in neuropsychiatric diseases.

Mast cells are localized not only in the periphery but are also resident in mammalian brain. Constitutively active brain mast cells respond to a broad range of stimuli, including immune and non-immune signals such as corticotropin releasing hormone, various neuropeptides like substance P and neurotensin (Johnson & Krenger, 1992). Acute
Mast cells in chronic inflammation, pain and depression

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stressors or injury to CNS have been shown to change both activational state and numbers of brain mast cells. For example, non-traumatic immobilization stress as well as traumatic injury induces mast cell degranulation above baseline levels and mast cell recruitment (Esposito et al., 2001; Ahmad et al., 2012). Activation of brain mast cells leads to release of neuroactive mediators into the brain parenchyma, which may be tied to emotionality. Indeed, patients with mast cell-mediated diseases such as food allergies, asthma, and irritable bowel syndrome often complain of associated anxiety (Lehrer et al., 1993; Addolorato et al., 1998). Moreover, patients with systemic mastocytosis also report low arousal states, lethargy, and coma (Tajima et al., 1994; Moura et al., 2011, Moura et al., 2012) a symptomatology reversed by treatments with sodium cromoglycate or masitinib. The KitW−sh/W−sh genetic model of mast cell-deficient mice has been used to show that mast cells mediate the expression of anxiety-like behavior without affecting sensory arousal and locomotor responses. Additionally, blockade of central mast cells attenuated anxiety-like behavior, suggesting a role of centrally located mast cells in affecting anxiety (Nautiyal et al., 2008). Moreover, systemic treatment with sodium cromoglycate attenuated restraint stress-associated behavioral alterations (Manchanda et al., 2011). The endogenous fatty acid amide palmitoylethanolamide, which is also able to modulate mast cell and microglia activation, exerted an antidepressant-like effect comparable to the reference drug fluoxetine (Yu et al., 2011; Crupi et al., 2012).

Mast cell-dependent effects on behavior may be mediated by multiple interacting chemicals and neural systems. For example, histamine has both anxiolytic and anxiogenic effects, with opposing roles attributed to H1 versus H2 receptors (Ikarashi & Yuzurihara 2002; Nautiyal et al., 2008). Serotonin functions both as a transmitter affecting aggression, appetite, and mood, and as a trophic factor influencing neurogenesis and thereby affecting emotionality and memory (Nautiyal et al., 2008; Anand et al., 2012). Selective serotonin reuptake inhibitors increase serotonin signaling and decrease anxiety; therefore, a lack of mast cell-derived serotonin may increase anxiety-like behaviors (Nautiyal et al., 2012). Mast cell-derived cytokines act as neuromodulators having effects on systems controlling behavior. Indeed, TNF-α, IL-1, and IL-6 are known to act on the hypothalamic-pituitary-adrenal axis and control stress behavior (Dunn, 2000). In addition, mast cells express receptors for and can be stimulated by corticotropin-releasing hormone, with the release of histamine, IL-8, tryptase and vascular endothelial growth factor (Cao et al., 2005). Given their repertoire of mediators, it would not be surprising for mast cells to have multifaceted interactions with brain systems controlling behavior.

Concluding remarks

Preclinical and clinical studies have demonstrated a key role for mast cells in the pathophysiology of pain as well as in anxiety and depression. Mast cell degranulation-induced persistent release of cytotoxic mediators is responsible for producing deleterious effects in different tissues where mast cells reside and for the shift from acute to chronic inflammation and pain. In addition, the release of mast cell neuroactive mediators might contribute to the development of clinically relevant behavioral symptoms and neuropsychiatric diseases, including anxiety and major depression.
There is increasing evidence that chronic and neuropathic pain is associated with a higher incidence of co-morbidities such as depression and anxiety disorders, supporting the hypothesis of common or complementary pathways/mechanisms in the etiopathogenesis of these conditions (Meltzer-Brody & Leserman, 2011; Langley et al., 2013). Collectively, these observations propose that a pharmacological strategy targeting complementary pathways or mechanisms might concomitantly contrast the symptomatology of both diseases, limiting the adverse effects that may occur, for example, in elderly individuals, following multiple therapies due to drug interactions. In this context, it is important to emphasize that micronized palmitoylethanolamide exerts analgesic effects at the preclinical and clinical level, and shows antidepressant-like effects in preclinical studies. Taken as a whole, these observations suggest mast cells to be the key pharmacological target to modulate for the effective management of both diseases.

References


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