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 (Kovács 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 endometriosic tissue as compared to normal tissue or eutoptic 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

somatosensorial 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

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

- Addolorato G, Marsigli L, Capristo E, Caputo F, Dall'Aglio C, Baudanza P. Anxiety and depression: a common feature of health care seeking patients with irritable bowel syndrome and food allergy. Hepatogastroenterology. 1998;45(23):1559-64.
- Ahmad A, Genovese T, Impellizzeri D, Crupi R, Velardi E, Marino A, Esposito E, Cuzzocrea S. Reduction of ischemic brain injury by administration of palmitoylethanolamide after transient middle cerebral artery occlusion in rats. Brain Res. 2012;1477:45-58.
- Anaf V, Chapron C, El Nakadi I, De Moor V, Simonart T, Noël JC. Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis. Fertil Steril. 2006;86(5):1336-43.
- Anaf V, El Nakadi I, De Moor V, Chapron C, Pistofidis G, Noel JC. Increased nerve density in deep infiltrating endometriotic nodules. Gynecol Obstet Invest. 2011;71(2):112-7.
- Anand P, Singh B, Jaggi AS, Singh N. Mast cells: an expanding pathophysiological role from allergy to other disorders. Naunyn Schmiedebergs Arch Pharmacol. 2012;385(7):657-70.
- Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126(3):693-702.
- Barbara G, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, Trevisani M, Campi B, Geppetti P, Tonini M, Bunnett NW, Grundy D, Corinaldesi R. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology. 2007;132(1):26-37.
- Beghdadi W, Madjene LC, Benhamou M, Charles N, Gautier G, Launay P, Blank U. Mast cells as cellular sensors in inflammation and immunity. Front Immunol. 2011;2:37.
- Bornstein J, Cohen Y, Zarfati D, Sela S, Ophir E. Involvement of heparanase in the pathogenesis of localized vulvodynia. Int J Gynecol Pathol. 2008;27(1):136-41

- Bornstein J, Goldschmid N, Sabo E. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. Gynecol Obstet Invest. 2004;58(3):171-8.
- Buhner S, Schemann M. Mast cell-nerve axis with a focus on the human gut. Biochim Biophys Acta. 2012;1822(1):85-92.
- Bulanova E, Bulfone-Paus S. P2 receptor-mediated signaling in mast cell biology. Purinergic Signal. 2010;6(1):3-17.
- Calabrò RS, Gervasi G, Marino S, Mondo PN, Bramanti P. Misdiagnosed chronic pelvic pain: pudendal neuralgia responding to a novel use of palmitoylethanolamide. Pain Med. 2010;11(5):781-4
- Cao J, Papadopoulou N, Kempuraj D, Boucher WS, Sugimoto K, Cetrulo CL, Theoharides TC. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. J Immunol. 2005;174(12):7665-75.
- Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther. 2011;130(2):226-38.
- Conti S, Costa B, Colleoni M, Parolaro D, Giagnoni G.Antiinflammatory action of endocannabinoid palmitoylethanolamide and the synthetic cannabinoid nabilone in a model of acute inflammation in the rat. Br J Pharmacol. 2002;135(1):181-7.
- Costa B, Comelli F, Bettoni I, Colleoni M, Giagnoni G. The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors. Pain. 2008;139(3):541-50.
- Costa B, Conti S, Giagnoni G, Colleoni M. Therapeutic effect of the endogenous fatty acid amide, palmitoylethanolamide, in rat acute inflammation: inhibition of nitric oxide and cyclo-oxygenase systems. Br J Pharmacol. 2002;137(4):413-20.
- Crupi R, Impellizzeri D, Esposito E, Cuzzocrea S. N-palmitoylethanolamine treatment exhibits antidepressant effects in a mouse model of anxiety/depressive like behavior. Experimental Biology 2012 - April 21-25 -San Diego Convention Center, San Diego, CA.
- Dai H, Korthuis RJ. Mast Cell Proteases and Inflammation. Drug Discov Today Dis Models. 2011;8(1):47-55.
- De Filippis D, Luongo L, Cipriano M, Palazzo E, Cinelli MP, de Novellis V, Maione S, Iuvone T. Palmitoylethanolamide reduces granuloma-induced hyperalgesia by modulation of mast cell activation in rats. Mol Pain. 2011;7:3.
- Dunn AJ. Cytokine activation of the HPA axis. Ann N Y Acad Sci. 2000;917:608-17.
- Esposito P, Gheorghe D, Kandere K, Pang X, Connolly R, Jacobson S, Theoharides TC. Acute stress increases permeability of the blood-brain-barrier through activation of brain mast cells. Brain Res. 2001;888(1):117-127.

- Esposito E, Paterniti I, Mazzon E, Genovese T, Di Paola R, Galuppo M, Cuzzocrea S. Effects of palmitoylethanolamide on release of mast cell peptidases and neurotrophic factors after spinal cord injury. Brain Behav Immun. 2011;25(6):1099-112.
- Fitzgerald JJ, Ustinova E, Koronowski KB, de Groat WC, Pezzone MA. Evidence for the role of mast cells in colon-bladder cross organ sensitization. Auton Neurosci. 2013;173(1-2):6-13.
- Forsythe P, Bienenstock J. The mast cell-nerve functional unit: a key component of physiologic and pathophysiologic responses. Chem Immunol Allergy. 2012;98:196-221.
- Frenzel L, Hermine O. Mast cells and inflammation. Joint Bone Spine. 2012; doi: 10.1016/j.jbspin.2012.08.013.
- Galli SJ, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. Nat Immunol. 2005;6:135–142.
- Galli SJ, Tsai M. Mast cells: versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. J Dermatol Sci. 2008;49(1):7-19.
- Genovese T, Esposito E, Mazzon E, Di Paola R, Meli R, Bramanti P, Piomelli D, Calignano A, Cuzzocrea S. Effects of palmitoylethanolamide on signaling pathways implicated in the development of spinal cord injury. J Pharmacol Exp Ther. 2008;326(1):12-23.
- Giugliano E, Cagnazzo E, Soave I, Lo Monte G, Wenger JM, Marci R. The adjuvant use of N-Palmitoylethanolamine and transpolydatin in the treatment of the endometriotic pain. Eur J Obstet Gynecol Reprod Biol. 2013; *In Press*
- Goetsch MF, Morgan TK, Korcheva VB, Li H, Peters D, Leclair CM. Histologic and receptor analysis of primary and secondary vestibulodynia and controls: a prospective study. Am J Obstet Gynecol. 2010;202(6):614.e1-8.
- Halova I, Draberova L, Draber P. Mast cell chemotaxis - chemoattractants and signaling pathways. Front Immunol. 2012;3:119.
- Ikarashi Y, Yuzurihara M. Experimental anxiety induced by histaminergics in mast cell-deficient and congenitally normal mice. Pharmacol Biochem Behav. 2002;72(1-2):437-41.
- Ito A, Oonuma J. Direct interaction between nerves and mast cells mediated by the SgIGSF/SynCAM adhesion molecule. J Pharmacol Sci. 2006;102(1):1-5.
- Jin Y, Silverman AJ, Vannucci SJ.Mast cells are early responders after hypoxia-ischemia in immature rat brain. Stroke. 2009;40(9):3107-12.
- Kinet JP. The essential role of mast cells in orchestrating inflammation. Immunol Rev. 2007;217:5-7.
- Kovács P, Hernádi I, Wilhelm M. Mast cells modulate maintained neuronal activity in the thalamus in vivo. J Neuroimmunol. 2006;171(1-2):1-7.
- Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatry. 2012;83(5):495-502.

- Langley PC, Van Litsenburg C, Cappelleri JC, Carroll D. The burden associated with neuropathic pain in Western Europe. J Med Econ. 2013;16(1):85-95.
- Larsen MS, Mortensen S, Nordling J, Horn T. Quantifying mast cells in bladder pain syndrome by immunohistochemical analysis. BJU Int. 2008;102(2):204-7;
- Leclair CM, Goetsch MF, Korcheva VB, Anderson R, Peters D, Morgan TK. Differences in primary compared with secondary vestibulodynia by immunohistochemistry. Obstet Gynecol. 2011;117(6):1307-13.
- Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. J Asthma. 1993;30(1):5-21.
- Leon A, Buriani A, Dal Toso R, Fabris M, Romanello S, Aloe L, Levi-Montalcini R. Mast cells synthesize, store, and release nerve growth factor. Proc Natl Acad Sci U S A. 1994;91(9):3739-43.
- Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. Pain. 2007;130(1-2):166-76.
- Levy D. Migraine pain, meningeal inflammation, and mast cells. Curr Pain Headache Rep. 2009;13(3):237-40.
- Liu HT, Shie JH, Chen SH, Wang YS, Kuo HC. Differences in mast cell infiltration, E-cadherin, and zonula occludens-1 expression between patients with overactive bladder and interstitial cystitis/bladder pain syndrome. Urology. 2012;80(1):225.e13-8.
- Lo Monte G, Soave I, Marci R. Utilizzo del N-Palmitoiletanolamide (PEA)-transpolidatina nel trattamento del dolore pelvico cronico in donne affette da endometriosi:risultati preliminari. Minerva Ginecol 2012; G4:1-2
- Majeed SK. Mast cell distribution in mice. Arzneimittelforschung.1994;44:1170-1173
- Manchanda RK, Jaggi AS, Singh N. Ameliorative potential of sodium cromoglycate and diethyldithiocarbamic acid in restraint stress-induced behavioral alterations in rats. Pharmacol Rep. 2011;63(1):54-63.
- Matsuda H, Kawakita K, Kiso Y, Nakano T, Kitamura Y. Substance P induces granulocyte infiltration through degranulation of mast cells. J Immunol. 1989;142(3):927-31.
- Mazzari S, Canella R, Petrelli L, Marcolongo G, Leon A. N-(2-hydroxyethyl)hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation. Eur J Pharmacol. 1996;300(3):227-36.
- Meltzer-Brody S, Leserman J. Psychiatric Comorbidity in Women with Chronic Pelvic Pain. CNS Spectr. 2011. doi:pii: Meltzer-Brody.
- Menzies FM, Shepherd MC, Nibbs RJ, Nelson SM. The role of mast cells and their mediators in reproduction, pregnancy and labour. Hum Reprod Update. 2011;17(3):383-96.
- Messlinger K, Fischer MJ, Lennerz JK. Neuropeptide effects in the trigeminal system: pathophysiology and clinical relevance in migraine. Keio J Med. 2011;60(3):82-9.

- Michaloudi H, Batzios C, Chiotelli M, Grivas I, Papadopoulos GC. Mast cells populations fluctuate along the spinal dura mater of the developing rat. Brain Res. 2008;1226:8-17.
- Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732-41.
- Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci. 2009;10(1):23-36.
- Moura DS, Sultan S, Georgin-Lavialle S, Barete S, Lortholary O, Gaillard R, Hermine O. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. PLoS One. 2012;7(6):e39468.
- Moura DS, Sultan S, Georgin-Lavialle S, Pillet N, Montestruc F, Gineste P, Barete S, Damaj G, Moussy A, Lortholary O, Hermine O. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. PLoS One. 2011;6(10):e26375.
- Murina F, Graziottin A, Felice R, Radici G, Tognocchi C. Vestibulodynia: Synergy Between Palmitoylethanolamide + Transpolydatin and Transcutaneous Electrical Nerve Stimulation. J Low Genit Tract Dis. 2013; *In press*.
- Nautiyal KM, Dailey CA, Jahn JL, Rodriquez E, Son NH, Sweedler JV, Silver R. Serotonin of mast cell origin contributes to hippocampal function. Eur J Neurosci. 2012;36(3):2347-59.
- Nautiyal KM, Ribeiro AC, Pfaff DW, Silver R. Brain mast cells link the immune system to anxiety-like behavior. Proc Natl Acad Sci U S A. 2008;105(46):18053-7.
- Nazif O, Teichman JM, Gebhart GF. Neural upregulation in interstitial cystitis. Urology. 2007; 69(4 Suppl):24-33
- Olszewski MB, Groot AJ, Dastych J, Knol EF. TNF trafficking to human mast cell granules: mature chain-dependent endocytosis. J Immunol 2007;178: 5701–5709
- Pang X, Boucher W, Triadafilopoulos G, Sant GR, Theoharides TC. Mast cell and substance P-positive nerve involvement in a patient with both irritable bowel syndrome and interstitial cystitis. Urology. 1996;47(3):436-8.
- Pang X, Sant G, Theoharides TC. Altered expression of bladder mast cell growth factor receptor (c-kit) in interstitial cystitis. Urology. 1998; 51(6):939-44.
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24-31.
- Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep. 2011;13(6):467-75.
- Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nat Med. 2010;16(11):1267-76.
- Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. Physiol Rev. 2009;89(2):707-58.
- Sugamata M, Ihara T, Uchiide I. Increase of activated mast cells in human endometriosis. Am J Reprod Immunol. 2005;53(3):120-5.

- Taiwo OB, Kovács KJ, Sun Y, Larson AA. Unilateral spinal nerve ligation leads to an asymmetrical distribution of mast cells in the thalamus of female but not male mice. Pain. 2005;114(1-2):131-40.
- Tajima Y, Hamada K, Houzenn H, Tsukishima E, Owada Y, Moriwaka F, Musashi M, Miyazaki T, Hamada T, Tashiro K. Sequential magnetic resonance features of encephalopathy induced by systemic mastocytosis. Intern Med. 1994;33(1):23-6.
- Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A. The role of mast cells in migraine pathophysiology. Brain Res Brain Res Rev. 2005;49(1):65-76.
- Theoharides TC, Sant GR, el-Mansoury M, Letourneau R, Ucci AA Jr, Meares EM Jr. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. J Urol. 1995b;153(3 Pt 1):629-36.
- Theoharides TC, Spanos C, Pang X, Alferes L, Ligris K, Letourneau R, Rozniecki JJ, Webster E, Chrousos GP. Stress-induced intracranial mast cell degranulation: a corticotropin-releasing hormone-mediated effect. Endocrinology. 1995a;136(12):5745-50.
- Ustinova EE, Fraser MO, Pezzone MA. Cross-talk and sensitization of bladder afferent nerves. Neurourol Urodyn. 2010;29(1):77-81.
- Ustinova EE, Gutkin DW, Pezzone MA. Sensitization of pelvic nerve afferents and mast cell infiltration in the urinary bladder following chronic colonic irritation is mediated by neuropeptides. Am J Physiol Renal Physiol. 2007;292(1):F123-30.
- van Diest SA, Stanisor OI, Boeckxstaens GE, de Jonge WJ, van den Wijngaard RM. Relevance of mast cell-nerve interactions in intestinal nociception. Biochim Biophys Acta. 2012;1822(1):74-84.
- Wang G, Tokushige N, Markham R, Fraser IS. Rich innervation of deep infiltrating endometriosis. Hum Reprod. 2009; 24(4):827-34.
- Wilhelm M, Silver R, Silverman AJ. Central nervous system neurons acquire mast cell products via transgranulation. Eur J Neurosci. 2005;22(9):2238-48.
- Wise LE, Cannavacciulo R, Cravatt BF, Martin BF, Lichtman AH.Evaluation of fatty acid amides in the carrageenan-induced paw edema model. Neuropharmacology. 2008;54(1):181-8.
- Xanthos DN, Gaderer S, Drdla R, Nuro E, Abramova A, Ellmeier W, Sandkühler J. Central nervous system mast cells in peripheral inflammatory nociception. Mol Pain. 2011;7:42.
- Yu HL, Deng XQ, Li YJ, Li YC, Quan ZS, Sun XY. N-palmitoylethanolamide, an endocannabinoid, exhibits antidepressant effects in the forced swim test and the tail suspension test in mice. Pharmacol Rep. 2011;63(3):834-9.
- Yuan H, Zhu X, Zhou S, Chen Q, Zhu X, Ma X, He X, Tian M, Shi X. Role of mast cell activation in inducing microglial cells to release neurotrophin. J Neurosci Res. 2010;88(6):1348-54.

- Zhang S, Zeng X, Yang H, Hu G, He S. Mast cell tryptase induces microglia activation via protease-activated receptor 2 signaling. Cell Physiol Biochem. 2012;29(5-6):931-40.
- Zunszain PA, Hepgul N, Pariante CM. Inflammation and Depression. Curr Top Behav Neurosci. 2012; *In Press*