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## A focus on mast cells and pain

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### Abstract

Mast cells (MCs) are immunocytes with secretory functions that act locally in peripheral tissues to modulate local hemodynamics, nociceptor activation and pain. They are also able to infiltrate the central nervous system (CNS), especially the spinal cord and the thalamus, but their cerebral function remains an enigma. A role in regulating the opening of the blood–brain barrier has been proposed. Paracrine-like action of MCs on synaptic transmission might also signal a modulation of the nervous system by the immune system. In this review, we examine the link between MCs and nociceptive process, at the periphery as well as in the CNS.

### Keywords

Mast cells

Nociception

Brain

Immuno-neuromodulation

### Introduction

Mast cells (MCs) are immune cells produced by the bone marrow ([Gurish and Boyce, 2002](#)). These cells pass the blood wall and quickly infiltrate most tissues, such as skin, mucous membranes, respiratory and gastrointestinal tracts, peritoneal cavity and meninges ([Metcalf et al., 1997](#)). MCs act by degranulation ([Florenzano and Bentivoglio, 2000](#)) and produce a plethora of mediators such as biogenic amines (histamine and serotonin), enzymes (acid hydrolases, phospholipases, chymase, tryptase and other proteases), cytokines (interleukin-1 to interleukin-6, interferon, transforming growth factor TGF, granulocyte-macrophage colony-stimulating factor, leukemia inhibitory factor, tumor necrosis factor TNF), lipid metabolites (leukotrienes, prostaglandins, platelet-activating

factor), ATP (adenosine triphosphate), neuropeptides (vasoactive intestinal peptide), growth factors (nerve growth factor, NGF) and nitric oxide ([Schwartz and Austen, 1980](#); [Johnson and Krenger, 1992](#)). MCs are also the only cells containing intra-cytoplasmic granules of proteoglycans, mainly heparin. Indeed, the principle of specific staining of MCs on histological tissues is based on a metachromatic reaction of these proteoglycans with acidified toluidine blue (pH 2.3), which results in a shift of the natural color blue dye in characteristic red purple ([Humason, 1972](#)). MCs adapt and release mediators according to local tissue conditions ([Lowman et al., 1988](#)).

## 1. Peripheral and central mast cells

In the peripheral tissues, MCs are involved in the inflammatory reaction in response to exogenous pathogens and pro-inflammatory bioactive substances, such as cytokines and prostaglandins. They are also considered to be major effectors in IgE-associated hypersensitivity and in allergic responses such as asthma. More recently, the pathophysiological role of MCs have been recognized in various diseases affecting the periphery and/or the brain, such as atherosclerosis, pulmonary hypertension, autoimmune disorders, visceral diseases, cancer, ischemia–reperfusion injury, anxiety, Alzheimer's disease, migraine... (for review see [Anand et al., 2012](#)). In addition to the periphery, numerous data indicate that MCs are also resident in the central nervous system (CNS) of many animal species, including humans ([Ibrahim, 1974](#); [Dropp, 1976](#); [Michaloudi and Papadopoulos, 1999](#); [Michaloudi et al., 2003](#)). The exact function of MCs in the central nervous system is, however, much less understood.

During development MCs enter the brain by penetrating blood vessels with which they remain associated ([Lambracht-Hall et al., 1990](#)). The number of mast cells progressively decreases until the adulthood, even if they are still able to migrate from blood to brain. Almost 97% of brain MCs lie on the vessel wall ([Fig. 1](#)). They are especially found not only in the thalamus, but also in the hypothalamus, choroid plexus, olfactory bulb and pineal gland ([Krüger, 1974](#); [Dropp, 1976](#); [Persinger, 1977](#); [Zhuang et al., 1999](#); [Khalil et al., 2003](#); [Kriegsfeld et al., 2003](#); [Michaloudi et al., 2003](#)).

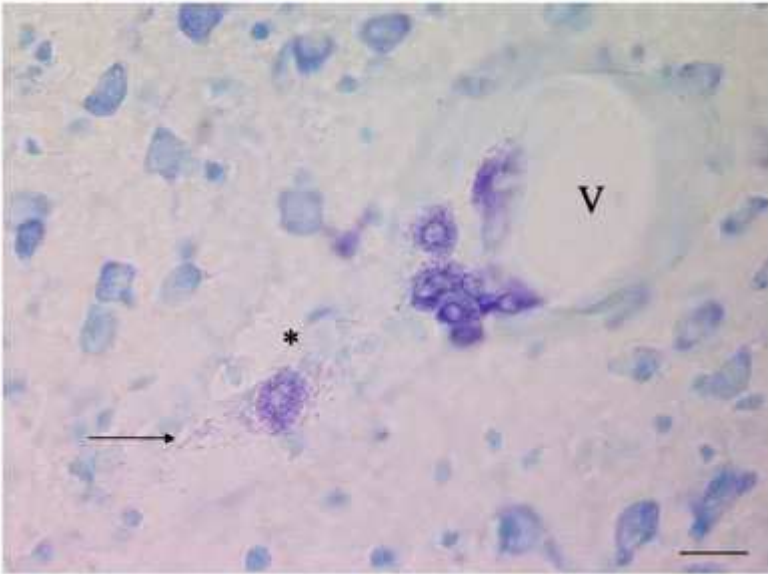


Fig. 1. Photomicrograph of thalamic mast cells (MCs) in the rat brain. MCs were identified by specific metachromatic (red-purple) staining of heparin with toluidine blue. Many MCs clung to the wall of the vessel (V). One MC entered the nervous parenchyma (\*) and showed degranulation (black arrow) evidenced by the presence of granules outside the cytoplasm (scale bar: 15  $\mu$ m).

In the thalamus, MC number can be regulated by environmental conditions or hormonal factors, such as hibernation, parturition, stress and aging (Dropp, 1976; Aydin et al., 1998). They are more numerous in females than in males (Goldschmidt et al., 1984). Unlike peripheral tissues, brain MCs do not express the c-kit receptor, which binds to stem cell factor (SCF) (Shanas et al., 1998). In accordance with these results, centrally injected SCF was not able to increase the population of MC in the thalamus (Taiwo et al., 2005). Within the CNS, MC proliferation is not possible. In this case, MC infiltration would damage neuronal tissue (Galli et al., 1994). Cerebral MC number and degranulation are regulated, not only in physiological, but also in pathological conditions. In physiological conditions, MCs are attracted by chemotaxis (Frei et al., 1985; Da Cunha and Vitkovic, 1992; Metcalfe et al., 1997; Esposito et al., 2001). This phenomenon involves many molecules produced by the brain, such as NGF, TGF- $\beta$ 1, chemokines (fractalkine), CRF (corticotropin releasing factor), neuropeptides (substance P and somatostatin) and interleukin-3. Blood MCs cling on the laminin wall of endothelium and slip between endothelial cells by diapedesis (Flood and Krüger, 1970; Silverman et al., 2000). The degranulation of the first MCs penetrating the brain parenchyma promotes the entry of others by releasing histamine, which acts as a vasodilator molecule increasing blood–brain barrier (BBB) permeability (Esposito et al., 2001; Lindsberg et al., 2010).

The reason why MCs are prevalently located within the CNS, and more particularly in the thalamus, remains to be elucidated. This raises the question of their potential roles in brain function. Considering that peripheral MCs are implicated in pain processes and that thalamus is the essential brain structure that relies on the integration of sensory messages to the cerebral cortex for conscious

perception, we postulate that thalamic MCs could be implicated in sensory processing including nociception.

## 2. Role of peripheral mast cells in pain transmission

Pain information begins at the nerve endings called nociceptors, which form a functional pain unit with the nearby tissue capillaries. Peripheral MCs are often found in proximity to sensory nerve endings and vasculature (Fig. 2). Following injury or inflammatory stimuli, mediators such as bradykinin, prostaglandins and histamine are released and stimulate nociceptive afferents. They are produced by damaged tissues, platelets, granulocytes, macrophages and MCs. Nociceptive fibers, themselves, release neuromodulators such as substance P, calcitonin gene-related peptide (CGRP), the vasoactive intestinal protein (VIP), and CRH (Corticotropin Releasing Hormone), which, in turn, can stimulate activation of MCs (Matsuda et al., 1989). Subsequently, MCs release algogenic molecules which amplify vasodilation and sensitize nociceptors (Koda and Mizumura, 2002). This positive feedback loop causes neurogenic inflammation (Kowalski and Kaliner, 1988; Ansel et al., 1990). So, MC stabilizers such as cromolyn, are able to inhibit nociception and neurogenic inflammation (Le Filliatre et al., 2001; Parada et al., 2001).

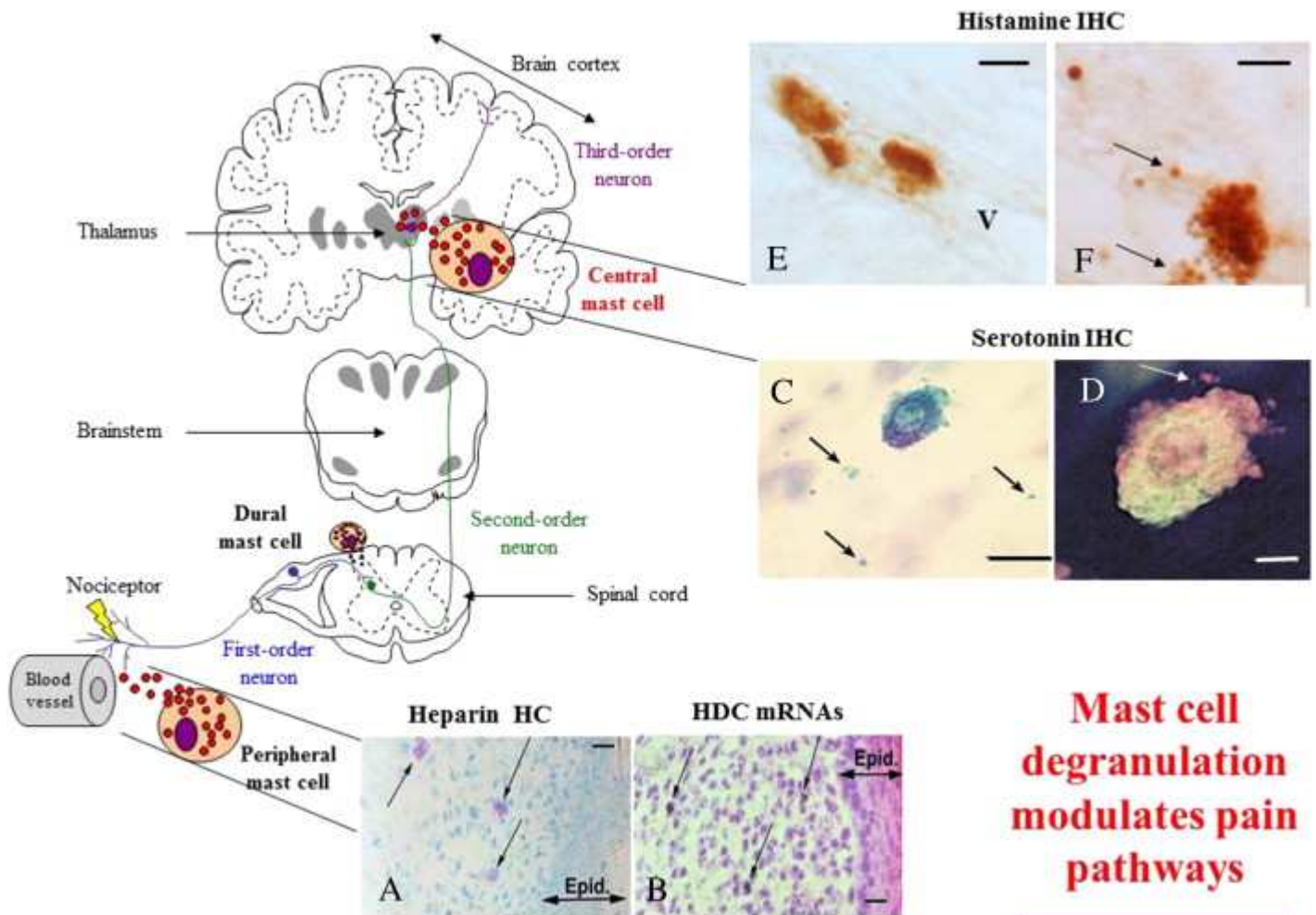


Fig. 2. Nociception is generated in the periphery but is integrated in the CNS. Pain information begins at nociceptors (yellow flash), which form a functional pain unit with the nearby tissue capillaries and peripheral MCs. Following injury or chemical stimuli, mediators released by degranulating MCs act on nociceptors and can modulate their excitability. Stimulation of first-order neurons ( $A\delta$  or unmyelinated C fibers, in blue) spreads to dorsal horn of the spinal cord where axons connect synapses with second-order neurons (in green). MCs are found in the dura matter of the spinal cord and can modulate synaptic transmission and nociception at this level. After spinal decussation, axons reach contralateral supraspinal structures, including the lateral or the median thalamus. The thalamic relay discriminates nociceptive stimulations and transmits them from the spinal cord to the sensorimotor or frontal cortex, which elaborates sensation and conscious perception of pain. MCs are particularly concentrated in the thalamus and can release mediators such as histamine or serotonin in the proximity of third order neurons targeting to the cortex (in violet). (A and B) Peripheral MCs in epidermis: heparin histochemistry (HC) by toluidine blue staining in A, and in situ hybridization labeling of histidine decarboxylase (HDC), the histamine synthesis enzyme in B. (C and D) Serotonin immunohistochemistry (IHC) with toluidine blue counterstaining of a thalamic MC: bright field illumination in C, and at higher magnification with dark field illumination in D. (E and F) Histamine immunoperoxidase staining of MCs present in a vessel (V) of the thalamus (E) and penetrating nervous parenchyma (F). Note the release of histamine containing granules in F. Arrows indicate MC granules. Scale bars AB = 20  $\mu\text{m}$ , CDEF = 10  $\mu\text{m}$ .

In addition to mediator release, communication between MCs and neurons can occur via adhesion molecules such as Cell Adhesion Molecule-1 (CADM) and N-cadherin (Suzuki et al., 2004; Ito and Oonuma, 2006; Van Diest et al., 2012), and through a transgranulation process, i.e neuronal uptake of MC particles (Wilhelm et al., 2005). The pro-inflammatory substances released by MCs can also be transported retrogradely to neuronal cell bodies of dorsal root ganglia to regulate gene expression (Murphy et al., 1999).

MCs also contribute to the recruitment of other immune cells such as neutrophils, macrophages and T cells, which release pro-nociceptive mediators and reinforce the maintenance of inflammatory reactions (Zuo et al., 2003). As a consequence, inflammation can affect not only injured zones, but also adjacent territories, creating a secondary, widespread hyperalgesia. Hyperalgesia is an excessive pain response. For example, in a mouse model of autoimmune prostatitis, the application of culture supernatant of activated MCs induced hyperalgesia, accompanied by a significant long-term potentiation of spinal C-fiber synapses (Done et al., 2012). Hyperalgesia is observed in cases of peripheral nerve damage and in pathology such as multiple sclerosis, accidental injury, limb amputation, diabetes or sciatica (Xanthos et al., 2011). MCs could play a direct role and histamine would be the mediator responsible of this type of pain hypersensitivity (Smith et al., 2007).

Many experimental data show that MCs play a role in chronic pain, particularly at the visceral level. Indeed, peripheral MC degranulation increases excitability of vagal, splanchnic and mesenteric afferents, contributing to nociceptive processes associated with visceral pain. So, the degranulation of MCs, in close proximity to the nerves innervating the colonic mucosa, is correlated with abdominal pain in patients with Irritable Bowel Syndrome (IBS) (Barbara et al., 2004). The administration of ketotifen, a MC stabilizer, is therefore able to reduce rectal sensitivity, abdominal pain and other IBS symptoms (Klooker et al., 2010). Furthermore, an increased number of MCs associated with an increased number of serotonin cells have been demonstrated in colonic biopsies of IBS patients, suggesting that release of serotonin directly or indirectly from the intestinal MC may be responsible for sensory neuron activation and abdominal pain in this pathology (Cremon et al., 2011). MC tryptase and histamine would also cause activation of enteric nerves, resulting in neuronal hyperexcitability (Traver et al., 2010).

In esophagi, local MC activation plays an important role in inflammatory nociception (Yu et al., 2007). Esophageal MCs are mainly distributed along the lamina propria of the mucosal layer and release mediators such as histamine and tryptase. These MCs sensitize the nociceptive afferent nerve terminals located in their proximity, to produce pain and hyperalgesia. In guinea pigs, it has been reported that MC tryptase, via Protease-Activated Receptor 2 (PAR2) and Transient Receptor Potential A1 (TRPA1), induces mechanical hypersensitivity of vagal C-fibers (Yu et al., 2009). Pretreatment with the MC stabilizer cromolyn decreases the esophageal distension-induced mechano-excitability of esophageal C-fibers (Gao et al., 2011).

The pathogenesis of bladder pain syndrome associated with interstitial cystitis is unknown. However, the accumulation of bladder MCs in the muscular layer, lamina propria and submucosa seems to play an important role, as well as localized allergic reaction and inflammation (Theoharides et al., 2001; Sant et al., 2007). Indeed, clinical studies have shown an increased level of MC mediators including histamine, tryptase and IL-6 in the urine of patients suffering from cystitis (Theoharides et al., 2001). The critical role of neural-immune interactions in pathogenesis of interstitial cystitis has been well documented. It has been proposed that activation of urinary bladder-associated circuits in the CNS initiates substance P release by peripheral nerves in the bladder, which then promotes substance P-mediated MC activation. This MC activation, in turn, would induce bladder inflammation by action on the epithelium lining the bladder.

In skin, the role of MCs in chronic granulomatous inflammation-induced hyperalgesia has also been well documented. In rat, the presence of degranulated MCs was evidenced in the granuloma and nearby nerve fibers. Furthermore, palmitoylethanolamide reduced granuloma-induced hyperalgesia by modulation of MC activation (De Filippis et al., 2011). In the dermis of patients with Fibromyalgia Syndrome, a significantly increased number of MCs has also been described (Blanco et al., 2010). Thus, one might ask what is the role of MCs in the genesis of this pathology with painful and inflammatory components, as shown in rheumatoid arthritis. Indeed, in this autoimmune pathology, MCs have been shown to accumulate in arthritic lesions of patients (Maruotti et al., 2007) and mediators released by MC degranulation (chymases, tryptases, IL-17) contribute to the severity of the disease (Tchougounova et al., 2005; McNeil et al., 2008; Suurmond et al., 2011).

### 3. Do mast cells have a role in central integration of pain?

While MCs are clearly involved in the genesis of pain during inflammatory processes at the peripheral level, they could also be implicated in central integration of nociception. Pain is generated in the periphery and is integrated in the CNS (Fig. 2). Depolarization induced by stimulation of primary fibers spreads to the dorsal horn of the spinal cord via two pathways. One, corresponding to fast pain, is mediated by A-delta fibers (A $\delta$ ) responsible for localized pain and able to discriminate the precise topography. It joins the lateral thalamus by the neo-spinothalamic tract, then the S1 and S2 areas of the sensory cortex (path of sensation). The second way of pain dissemination is conveyed by unmyelinated C fibers, responsible for slow, widespread pain. After passing through a relay in the brainstem, pain information is transmitted to the medial thalamus, the limbic structures, the insula, the cingulate cortex and the frontal cortex (path of emotion and behavior). The thalamus is thus an essential nociceptive relay. It discriminates nociceptive stimulations and transmits some of them from spinal cord to the cortex, which then elaborates the conscious perception of pain sensation. In turn, the thalamus can be influenced by the cortex as well as by the limbic system. Then, the painful process acquires psycho-affective coloration. Signals from the supraspinal centers are also integrated in the periaqueductal gray, which modulates descending facilitation and inhibition of nociceptive input via the rostral ventromedial medulla. Supraspinal afferents influence the activity of spinal interneurons releasing a variety of neurotransmitters to modulate nociception (McHugh and McHugh, 2000). Spinal interneurons themselves exert inhibitory effects on the processing of pain signals. The dural MCs are found at a significant density at the cervical, thoracic, and lumbar regions of spinal cord (Majeed, 1994) and can modulate synaptic transmission and nociception at these levels (Sandkühler, 2009).

Resident MCs located in the cerebral dura mater promote neurogenic inflammation, activate meningeal nociceptors and contribute significantly to the pathophysiology of migraine (Theoharides et al., 2005; Levy, 2009). Electrical stimulation of the trigeminal ganglion which activates meningeal nociceptors, promotes the degranulation of dural MCs (Dimitriadou et al., 1991). The activation of meningeal nociceptors induces substance P and CGRP. This phenomenon accompanies migraine with aura (Pietrobon and Striessnig, 2003). The local release of inflammatory molecules by MCs during this neurogenic inflammation would prolong activation of the trigeminal pain pathway by stimulating further meningeal nociceptors, thus prolonging headache (Levy et al., 2007).

Experimental data show that nociceptive signals influence the distribution of MCs in the brain during the development of hyperalgesia. Indeed, MCs infiltrate the thalamus from blood to brain within a few hours in response to chemotactic molecules directly released by peripheral sensory afferents. In animal model of cystitis associated with a referred cutaneous hyperalgesia, left (or right) repetitive punctures of the abdominal wall generate an infiltration of MCs in some parts of the contralateral thalamus (paraventricular pars anterior and reuniens nucleus; Dubayle et al., 2007). Because of the asymmetrical distribution of MCs, they might thus be involved in thalamic sensory processes, implicated in some aspect of visceral pain. In other studies, the number of MCs increased in contralateral thalamus (posterior and lateral geniculate nuclei) after a painful unilateral ligation of



the spinal nerve lasting several days in female mice (Taiwo et al., 2005). It is interesting to see that in rodents, thalamic MCs are more numerous in females than in males (Goldschmidt et al., 1984), and that females are more sensitive to nociceptive stimuli in models of neuropathic and inflammatory pain (Coyle et al., 1995; Tall and Crisp, 2004). Sex hormones and thalamic MCs could be modulators of the basic processes involved in nociception (Kovács et al., 2006).

MCs might also be implicated in psycho-affective integration of nociceptive processes. Cyclophosphamide is an antineoplastic drug that generates cystitis, nausea, headache, vomiting, asthenia, taste aversion, dizziness, photo and phonophobia in humans (Cubeddu et al., 1990). After intra-peritoneal cyclophosphamide administration in rats, a significant infiltration and degranulation of MCs appeared in the part of the thalamus localized at the border of the third ventricle: the medial habenular nucleus (Servièrè et al., 2003). This nucleus belongs to the limbic system. The presence of MCs in the habenula suggests that they could be implicated in modulation of emotional reactions occurring in painful conditions.

Several pharmaceutical molecules known to act on nociception are able to modulate infiltration and degranulation of thalamic MCs. An intraperitoneal injection of sumatriptan (a 5-HT<sub>1B/D</sub> agonist, an anti-migraine agent with large analgic effects) doubles the number of degranulated MCs and especially those containing serotonin (Menétrey and Dubayle, 2003; Dubayle et al., 2005a). In less than 4 h, MCs cross the BBB to infiltrate the thalamus. Serotonin is known to modulate pain mechanisms with pro-nociceptive effect at the periphery and anti-nociceptive effect at the central level (Viguièr et al., 2013). Indeed, microinjection of serotonin into the submedial thalamic nucleus produced anti-nociception, in a rat model of allodynia induced by peripheral electrical stimulation (Xiao et al., 2005). From these results, we postulate that the specific thalamic MC population which releases serotonin may exert an anti-nociceptive effect. In turn, considering the effect of two analgesic drugs, we observed that Morphine chlorhydrate, a mu opioid agonist, has no effect on thalamic MCs infiltration; only acetylsalicylic acid, a non-steroidal anti-inflammatory drug, decreased the number of thalamic MCs (Dubayle et al., 2005b). It should be noted that the effect of all these pharmaceutical drugs is not due to direct action on MCs, but rather derives from systemic vasoactive molecules which would be able to increase or decrease the infiltration of MCs.

MCs act as early responders in the regulation of the BBB in pathological conditions, such as ischemia, hemorrhage, multiple sclerosis, Alzheimer disease and contention stress (Esposito et al., 2001; Graves et al., 2004; Biran et al., 2008; Fiala et al., 2010; Lindsberg et al., 2010). Disruption of the BBB involves vasoactive components of MCs including histamine and proteases. These enzymes can degrade basal lamina and activate metalloproteinases localized in the neurovascular matrix (Tchougounova et al., 2005; Mattila et al., 2011). In opening the BBB, we speculate that MCs could then permit access of circulating molecules such as pro-inflammatory mediators to CNS parenchyma, particularly in conditions where inflammation is important. Pro-inflammatory molecules could act on neurons and regulate nociceptive integration occurring at spinal and/or brain levels. The interplay between MCs, pro-inflammatory molecules and the vasculature could enhance the responses of neurons, as described during inflammation of meninges and visceral tissues (Barbara et al., 2007; Coldwell et al., 2007; Yu et al., 2007; Levy, 2009). In other cases such as

weak inflammatory conditions, down regulation of MC degranulation would prevent the opening of BBB in detecting the early hallmarks of putative bacterial infection (Dubayle and Héron, 2012).

At the neuronal cell level (Fig. 3) within the thalamus, the presence of degranulated MCs exerts a paracrine-like action on synaptic transmission of thalamocortical tracts. These cells could be the mark of a modulation of the thalamic activity by the immune system (Persinger, 1977; Hough, 1988; Silver et al., 1996). The thalamic micro-iontophoretic application of 48/80, a specific compound inducing MCs degranulation, causes serotonin and histamine release, with subsequent increase in the activity of thalamic neurons (Kovács et al., 2006). MCs could then be implicated in immuno-neuromodulation processes and may be at the origin of a new form of synaptic plasticity. In other nervous structures, such as the superior cervical ganglion, MC degranulation increases the activity of postsynaptic neurons and promotes the efficiency of synaptic transmission, a mechanism of long-term potentiation (Weinreich et al., 1995). Moreover, spinal application of supernatant from activated cultured MCs was also reported to induce long-term potentiation at the synapses of nociceptive C-fibers (Xanthos et al., 2011). We suggest that the same mechanism of immuno-neuromodulation could occur in the thalamus after MC infiltration.

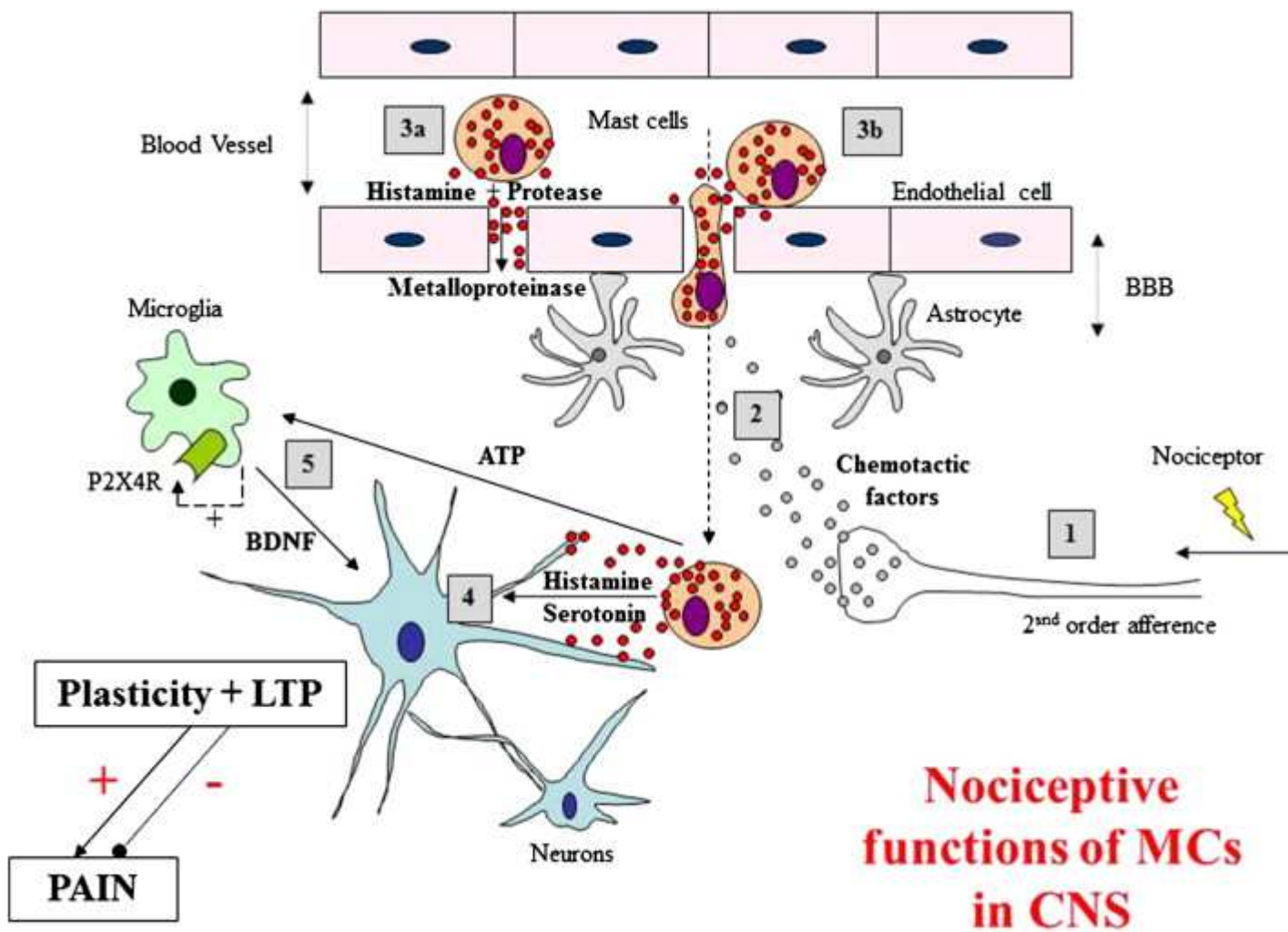


Fig. 3. Diagrammatic representation of the possible nociceptive role of MCs in CNS. (1) The nociceptive information (yellow flash) is transmitted from nociceptor to second-order afference. (2) Axon terminal releases chemotactic factors in the parenchyma, which attract blood MCs at the vessel wall level. (3a) MCs open the BBB by the release of histamine, a vasodilator mediator, and protease which activates metalloprotease localized in neuronal matrix. (3b) This phenomenon induces the infiltration of MCs by diapedesis. (4) In the parenchyma, MCs activate neurons by releasing histamine or serotonin, which subsequently modulate central integration of pain in regulating synaptic plasticity and/or long term potentiation processes. (5) MCs also indirectly communicate with neurons via microglial cells. MCs release ATP, which activates and amplifies P2X4R receptor expression and BDNF release. This mechanism could influence activity of neurons implicated in nociception.

At the level of glial cells (Fig. 3), MCs could act on microglia to indirectly influence neuronal activity (Skaper et al., 2012). Indeed, emerging evidence suggests a role of mast cell-glia communications in the control of pain transmission pathways. For example, co-culture of mouse cortical microglial cells and human MCs promotes brain-derived neurotrophic factor (BDNF) release and P2X4R (BDNF receptor) expression by microglial cells (Yuan et al., 2010). P2X4R maintains the capacity of microglial cells to release high levels of BDNF. In neuropathic pain hypersensitivity, ATP-activated microglia releases BDNF which induces a depolarizing shift in neuronal anion gradient (Tsuda et al., 2003; Coull et al., 2005). MCs contain ATP, so this mechanism could be influenced by the release of ATP by MCs (Johnson and Krenger, 1992) and thus modulate nociception.

#### 4. Conclusion

MCs are immune cells localized at the peripheral and central levels. In the periphery, they amplify nociception, particularly after injury or inflammatory stimuli. In the CNS, MCs could modulate painful sensation. Depending on the subtype of MCs that infiltrate the parenchyma, MCs could stimulate or inhibit neuronal activity. In most cases, they could increase the pain perception by histamine release, but in some rare cases they could infiltrate the thalamus and exert an anti-nociceptive effect via serotonin release. In conclusion, in addition to its peripheral function, MCs could also be considered as cerebral immuno-neuromodulators of pain perception.

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