



Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome

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Fibromyalgia Syndrome (FMS) is a disorder of chronic, generalized muscular pain, accompanied by sleep disturbances, fatigue and cognitive dysfunction. There is no definitive pathogenesis except for altered central pain pathways. We previously reported increased serum levels of the neuropeptides substance P (SP) and its structural analogue hemokinin-1 (HK-1) together with the pro-inflammatory cytokines IL-6 and TNF in FMS patients as compared to sedentary controls. We hypothesize that thalamic mast cells contribute to inflammation and pain, by releasing neuro-sensitizing molecules that include histamine, IL-1 β , IL-6 and TNF, as well as calcitonin-gene related peptide (CGRP), HK-1 and SP. These molecules could either stimulate thalamic nociceptive neurons directly, or via stimulation of microglia in the diencephalon. As a result, inhibiting mast cell stimulation could be used as a novel approach for reducing pain and the symptoms of FMS.

Keywords: mast cells, pain, neuroinflammation, fibromyalgia syndrome, proinflammatory cytokines (TNF-alpha, IL-1 beta, IL-6)

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INTRODUCTION

Fibromyalgia Syndrome is a disorder of chronic generalized muscular pain, stiffness, generalized fatigue, sleep abnormalities, (Clauw et al., 2011; Schmidt-Wilcke and Clauw, 2011; Clauw, 2014) and cognitive problems (Theoharides et al., 2015b; Hauser et al., 2019) assessed by the FSQ (Ferrari and Russell, 2013), which has about 93% sensitivity and 92% specificity (Clauw, 2014). FMS affects about 5% of adults, primarily women 20–60 years of age (Branco et al., 2010) and belongs to a family of overlapping painful conditions (Table 1) known as CSS (Yunus, 2007; Theoharides, 2013). Central sensitization is recognized as the main mechanism involved (Woodman, 2013) and is characterized by allodynia, pain from an otherwise non-painful stimulus, (Russell and Larson, 2009) and hyperalgesia (Staud et al., 2001) due to an exaggerated response to a painful stimulus

Abbreviations: ACR, American College of Rheumatology; ASD, autism spectrum disorder; CGRP, calcitonin-gene related peptide; CIRS, chronic inflammatory response syndrome; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; CSS, central sensitivity syndromes; CXCL8, IL-8; Fc ϵ RI, high affinity surface receptors; FMS, fibromyalgia syndrome; FSQ, fibromyalgia survey questionnaire; IBS, irritable bowel syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; IgE, immunoglobulin E; MCP-1/CCL2, monocyte chemoattractant protein-1; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MRGPRX2, mas-related G-protein coupled receptor member X2; (mt)DNA, mitochondrial; NGF, nerve growth factor; PAF, platelet activating factor; PTSD, post-traumatic stress disorder; SCF, stem cell factor; SP, substance P; TLRs, toll-like receptors; TMD, myogenic temporomandibular disorder.

(Woolf, 2011). The pathogenesis of FMS remains unknown and with no objective diagnostic criteria (McBeth and Mulvey, 2012; Wolfe and Walitt, 2013). FMS patients have reduced tolerance to pain, especially extremes of heat and cold (Desmeules et al., 2003). There is considerable evidence of altered circuitry of pain networks and (Jensen et al., 2012; Flodin et al., 2014) abnormal pain processing in FMS (Staud, 2011).

The PubMed database was searched between 1960 and 2018 using the terms fatigue, fibromyalgia, hypothalamus, inflammation, mast cells, pain and stress. Only articles in English were included.

Here we discuss how brain mast cell release of neurosensitizing mediators in the thalamus leads to focal inflammation and contribute to the pathogenesis of FMS.

Neurohormonal Triggers of Mast Cells Contribute to Focal Inflammation in the Diencephalon

It was recently proposed that FMS may involve localized inflammation in the hypothalamus (Theoharides et al., 2015c). Elevations in pro-inflammatory chemokines/cytokines could negatively impact symptoms (Bazzichi et al., 2007; Carvalho et al., 2008; Nugraha et al., 2013) leading to sensitization of peripheral and central nociceptors (Uceyler et al., 2011; Behm et al., 2012; Hornig et al., 2015). Increased levels of the pro-inflammatory chemokine IL-8 (CXCL8) have been reported in the serum and CSF in patients with FMS (Ross et al., 2010; Kadetoff et al., 2012; Rodriguez-Pinto et al., 2014). Chemokines facilitate nociception by directly acting on chemokine receptors present along the pain pathway (Abbadie, 2005; Charo and Ransohoff, 2006).

The cytokines TNF and IL-17 greatly contribute to the inflammatory response (Romero-Sanchez et al., 2011; Griffin et al., 2012). Plasma levels of IL-17 were increased and correlated with levels of TNF in patients with FMS (Pernambuco et al., 2013). CSF and serum IL-17 also positively correlated with pain (Meng et al., 2013) and anxiety (Liu et al., 2012). Mast cells, themselves, can secrete IL-17; moreover, IL-6 and TGF β from mast cells contribute to the development of Th-17 cells (Kenna and Brown, 2013).

TABLE 1 | Pain Syndromes Comorbid with FMS.

- Chronic inflammatory response syndrome (CIRS)
- Functional dyspepsia
- Gulf War Illness (GWI)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
- Irritable bowel syndrome (IBS)
- Mast cell mediator disorder (MCMD)
- Mastocytosis
- Migraines
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
- Myogenic temporomandibular disorder (TMD)
- Myofascial pain syndrome
- Post-traumatic stress disorder (PTSD)
- Restless leg syndrome
- Temporomandibular pain syndrome (TMS)
- Tension headache

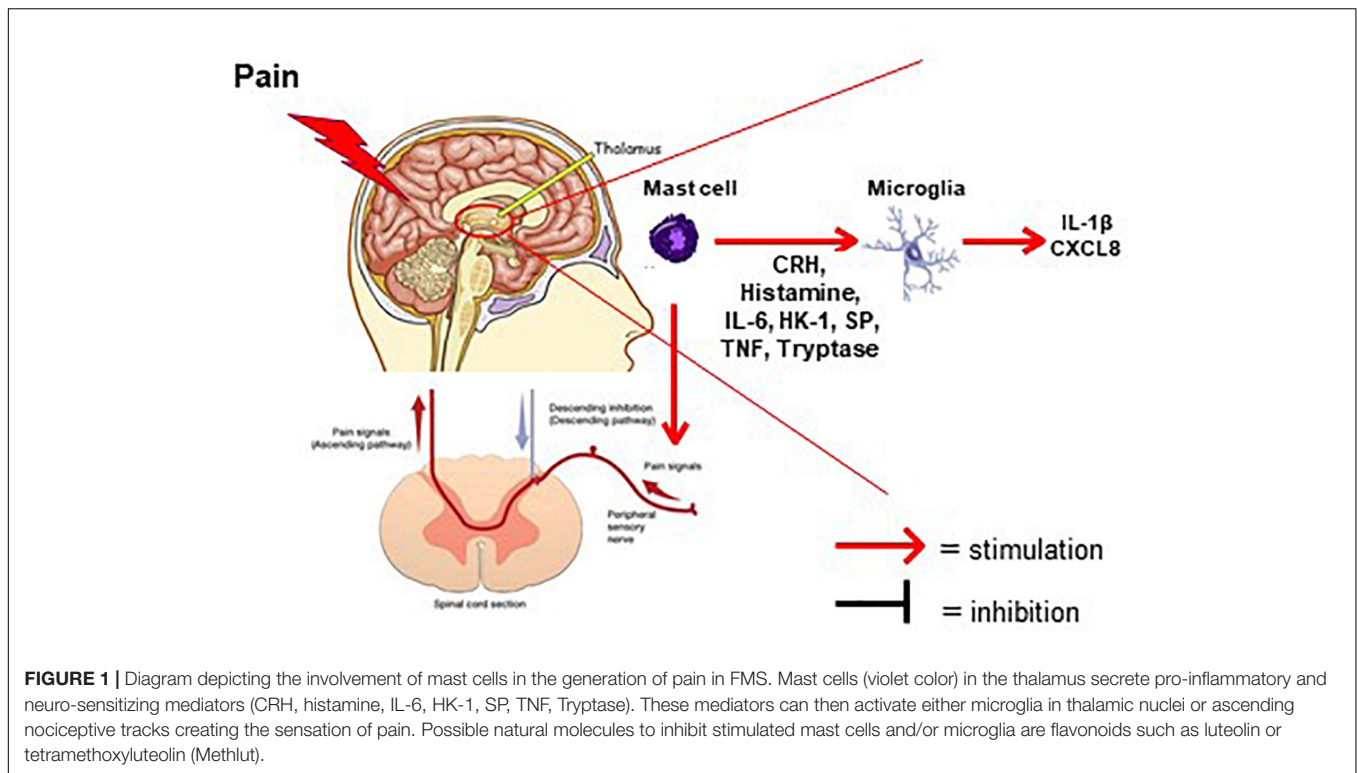
Fibromyalgia syndrome worsen by stress, (Geenen et al., 2002) which augments pain responses (Bote et al., 2012, 2013). Plasma concentrations of cortisol are increased in the evening, suggesting disruption of the circadian rhythm (Crofford et al., 2004). Serum levels of CRH, which is secreted under stress, were increased in patients with FMS (Tsilioni et al., 2016). CRH was also increased in the CSF of such patients and correlated with severity of pain (McLean et al., 2006). Physiological stress was reported to be the most common trigger in patients with systemic mastocytosis (SM) (Jennings et al., 2014) who also commonly experience FMS (Theoharides et al., 2015d, 2019). We reported increased levels of CRH in the serum of one patient with indolent systemic mastocytosis (Theoharides et al., 2014). CRH can trigger human mast cells to release VEGF without histamine or tryptase (Cao et al., 2005). CRH also has synergistic action with NT stimulating VEGF release. As a result, there is increased vascular permeability in the skin and the blood-brain barrier (BBB) (Esposito et al., 2002; Donelan et al., 2006; Theoharides and Konstantinidou, 2007). Stress also disrupts the gut-blood barrier (Theoharides et al., 1999; Wallon et al., 2008) allowing for gut microbiome-associated molecules, such as propionate (Minerbi et al., 2019) to enter the brain and contribute to focal inflammation. These results have led to the conclusion that mast cells may serve as “immune gate to the brain” (Theoharides, 1990; Ribatti, 2015).

Levels of the neuropeptide SP (Russell, 1998) and NGF (Giovengo et al., 1999) are elevated in the CSF of FMS patients. NGF has been reported to increase nociception and hyperalgesia (Maren, 2017). The SP receptor NK-1 has been involved in the pathophysiology of pain (Greenwood-Van et al., 2014). We reported increased serum levels of SP, its structural analogue Hemokinin-1 (HK-1) and TNF in patients with FMS (Tsilioni et al., 2016). SP (Theoharides et al., 2010a,b) and NGF (Levi-Montalcini, 1987) can stimulate mast cells. Moreover, SP induced mast cell expression of CRHR-1 (Scholzen et al., 2001). Cerebrovascular mast cells were stimulated by CGRP, (Reynier-Rebuffel et al., 1994; Ottosson and Edvinsson, 1997) which is now well established to participate in the pathophysiology of headaches (Edvinsson, 2018). In addition to neuropeptides, sex hormones can also affect mast cell reactivity. For instance, estradiol augments immune (Kovats, 2015) and allergic (Hox et al., 2015) processes. In particular, we had reported expression of estrogen receptors on rodent mast cells (Pang et al., 1995). We also reported that 17 β -estradiol further increased stimulation of mast cells by SP (Theoharides et al., 1993). Such findings may help explain why FMS is more common in women.

In addition to allergic reactions, mast cells contribute to innate immunity, (Galli et al., 2011) autoimmunity (Rottem and Mekori, 2005) and inflammation (Theoharides et al., 2010a).

Thalamic Mast Cells Secrete Neurosensitizing Mediators

Increasing evidence supports the involvement of mast cells in FMS (Lucas et al., 2006; Pollack, 2014) and comorbid disorders (Theoharides, 2013) as well as other inflammatory (Galli et al., 2008; Theoharides et al., 2010a) and painful conditions, (Heron and Dubayle, 2013; Chatterjea and Martinov, 2014) as well



as neuroimmune interactions (Skaper et al., 2017) (Figure 1). Chronic urticaria, which involves stimulation of skin mast cells is more common in FMS (Torresani et al., 2009). Moreover, mast cells are significantly increased in the papillary dermis of FMS patients (Blanco et al., 2010). The chemokines monocyte chemoattractant protein-1 (MCP-1/CCL2) and eotaxin (CCL11) are elevated in plasma of FMS patients (Zhang et al., 2008). MCP-1 is a strong mast cell chemoattractant (Conti et al., 1998) and also triggers mast cells in rodents (Conti and Theoharides, 1994). MCP-1 induced prolonged muscle hyperalgesia in rats via activation of its high-affinity receptor, CC Chemokine receptor 2 (CCR2), on the peripheral nerve terminals (Alvarez et al., 2014). Myoblasts treated with MCP-1 secreted significant amounts of the key pro-inflammatory cytokine IL-1 β (Zhang et al., 2008). C-reactive protein (CRP) is now considered a marker of chronic inflammation. CRP may be useful in the diagnostic of FMS (and depression/anxiety that often accompany FMS), even though there is no direct correlation reported (De Berardis et al., 2006, 2017; Orsolini et al., 2018).

Mast cells derive from the bone marrow and mature in response to SCF, which acts via the cell surface tyrosine kinase KIT receptor (Galli et al., 2011). Mast cell progenitors then migrate in all tissues. As a result, mast cell mediators can affect all organs and lead to multiple symptoms. Mast cells are found adjacent to blood vessels and nerve endings; in the brain, mast cells are located in the thalamus, hypothalamus and median eminence (Edvinsson et al., 1976; Lambracht-Hall et al., 1990; Theoharides et al., 2015d).

Mast cells are known to be stimulated by IgE, via activation of its unique surface receptors (Fc ϵ RI) (Rivera et al., 2008). Mast

cells can also be stimulated via TLRs, (Abraham and St John, 2010; Zhang et al., 2010). Stimulated mast cells secrete multiple vasoactive, pro-inflammatory and neuro-sensitizing molecules (Galli and Tsai, 2008; Theoharides et al., 2010a). Stimulation of mast cells can be augmented by the cytokine IL-33, (Fux et al., 2014) which synergizes with SP to induce release of impressive amounts of VEGF, (Theoharides et al., 2010b) TNF (Taracanov et al., 2017) or IL-1 β (Taracanov et al., 2018). As a result, mast cells can serve as “sensors of cell danger” (Theoharides, 1996; Enoksson et al., 2011; Theoharides et al., 2015a).

Mast cell secretory granules store many preformed pro-inflammatory and neuro-sensitizing mediators including bradykinin, histamine, TNF and tryptase (Nakae et al., 2005; Olszewski et al., 2007). Mast cells also release *de novo* synthesized molecules: (a) lipid mediators (leukotrienes, prostaglandins, and PAF), (b) cytokines (IL-6, IL-13, IL-33, TNF) and (c) chemokines (CXCL8, CCL2, CCL5), (Theoharides et al., 2015d; Mukai et al., 2018). Mast cell could often release mediators selectively without histamine or tryptase (Theoharides et al., 2007). Mast cells also release IL-31, which is important in the sensation of itching and pain, in response to IgE and SP, IL-33 and specifically their combination (Petra et al., 2018). We reported that mast cells can release mtDNA, which is mistaken as a pathogen and stimulates inflammatory responses (Zhang B. et al., 2012).

Finally, mast cells can release extracellular vesicles (exosomes) (Skokos et al., 2002, 2003) that could deliver regulatory molecules, including mtDNA and microRNAs (Kawikova and Askenase, 2014). Such microvesicles have been implicated in brain disorders (Tsiloni et al., 2014;

Kawikova and Askenase, 2014) and pain disorders (Rafiee et al., 2018; Silva-Freire et al., 2019). We recently reported that extracellular vesicles are increased in the serum of children with ASD, contained mtDNA and stimulated cultured human microglia to secrete the pro-inflammatory molecules IL-1 β and CXCL8 (Tsilioni and Theoharides, 2018).

Mast Cell Interactions With Microglia

Mast cells communicate with microglia (Skaper et al., 2012, 2014b). Mediators secreted from mast cells, (Zhang et al., 2016) such as histamine (Dong et al., 2014) and tryptase, (Zhang S. et al., 2012) can activate microglia leading to secretion of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF. Microglia can also be activated by CRH secreted from mast cells (Wang et al., 2002; Kempuraj et al., 2004). Stimulation of brain mast cells in mice led to activation of microglia, which was decreased by administration of a mast cell inhibitor (Dong et al., 2017).

Microglia are involved in synapse plasticity, (Shemer et al., 2015; Wu et al., 2015; Reu et al., 2017) but are responsible for innate immunity of the brain (Ransohoff and Brown, 2012; Aguzzi et al., 2013). Microglia contribute to brain inflammation (Hagberg et al., 2012; Aguzzi et al., 2013; Nakagawa and Chiba, 2016) and the pathogenesis of different brain disorders, (Takeda et al., 2014; Reus et al., 2015; Faden et al., 2016; Garden and Campbell, 2016; Groh and Martini, 2017; Koutsouras et al., 2017; Pennisi et al., 2017; Jiang et al., 2018; Thonhoff et al., 2018) especially ASD (Vargas et al., 2005; Morgan et al., 2010; Suzuki et al., 2013; Edmonson et al., 2014; Gupta et al., 2014). Microglia in the thalamus have been discussed in the context of pain, especially maintaining the pain sensation even after the original painful stimulus is not present (Banati, 2002; Hansson, 2010; Saghaei et al., 2013; Blaszczyk et al., 2018).

CONCLUSION

Mast cells have been implicated in headaches (Theoharides, 1983; Theoharides et al., 2005) and pain (Xanthos et al., 2011; Aich et al., 2015; Gupta and Harvima, 2018). Activation of the mast cell-specific receptor, MRGPRX2, (McNeil et al., 2015) and its mouse analogue, Mrgprb2, mediated inflammatory mechanical and thermal hyperalgesia (Green et al., 2019). Hence, mast cells are key players of neuroendocrine (Theoharides, 2017) and painful disorders (Theoharides et al., 2019).

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In this context, inhibitors of mast cells (Harvima et al., 2014) would be useful in the treatment of FMS. Natural molecules could include the flavonoids, luteolin (Kempuraj et al., 2008; Theoharides et al., 2015c; Ashaari et al., 2018) and tetramethoxyluteolin, (Theoharides et al., 2017; Theoharides and Tsilioni, 2018) alone or in combination with other substances selected to reduce stress (Theoharides and Kavalioti, 2018). Other natural molecules could include palmitoylethanolamide, (Schweiger et al., 2019) which apparently inhibits neuro-inflammation (Skaper et al., 2013, 2015) and reduces pain (Skaper et al., 2014a; Impellizzeri et al., 2016).

FUTURE DIRECTIONS

Research should focus on identifying in serum of patients with FMS novel molecules that are involved in pain transmission such as bradykinin, CGRP and IL-31. Extracellular vesicles should also be isolated from the serum and CSF of FMS patients, their content identified, and their effect investigated on cultured human mast cells and microglia. Such possible interactions would serve as useful *in vitro* assays for the screening of potential novel treatment agents. Recent reports have also stressed the possible use of the cytokine IL-37, (Mastrangelo et al., 2018) which is known to have anti-inflammatory actions (Cavalli and Dinarello, 2018). It would be important to explore the possible use of IL-37 isoforms in the treatment of FMS.

AUTHOR CONTRIBUTIONS

TT, IT, and MB participated in searching the literature. TT and IT wrote or contributed to the writing of the manuscript. IT prepared the figure.

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Conflict of Interest Statement: TT is the inventor of US patents No. 7,906,153 and No. 8,268,365 for the treatment of neuroinflammatory conditions.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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