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Mast cells, brain inflammation and autism

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ABSTRACT

Increasing evidence indicates that brain inflammation is involved in the pathogenesis of neuropsychiatric diseases. Mast cells (MCs) are located perivascularly close to neurons and microglia, primarily in the leptomeninges, thalamus, hypothalamus and especially the median eminence. Corticotropin-releasing factor (CRF) is secreted from the hypothalamus under stress and, together with neurotensin (NT), can stimulate brain MCs to release inflammatory and neurotoxic mediators that disrupt the blood–brain barrier (BBB), stimulate microglia and cause focal inflammation. CRF and NT synergistically stimulate MCs and increase vascular permeability; these peptides can also induce each other's surface receptors on MCs leading to autocrine and paracrine effects. As a result, brain MCs may be involved in the pathogenesis of "brain fog," headaches, and autism spectrum disorders (ASDs), which worsen with stress. CRF and NT are significantly increased in serum of ASD children compared to normotypic controls further strengthening their role in the pathogenesis of autism. There are no clinically affective treatments for the core symptoms of ASDs, but pilot clinical trials using natural-antioxidant and anti-inflammatory molecules reported statistically significant benefit.

1. Introduction

Mast cells (MCs) derive from bone marrow progenitors mature in tissues depending on microenvironmental conditions and MCs are critical for the development of allergic reactions, but also implicated in immunity (Kalesnikoff and Galli, 2008) and inflammation (Theoharides et al., 2010a). MCs can produce both pro- and anti-inflammatory mediators and may have immuno-modulatory functions (Kalesnikoff and Galli, 2008; Galli et al., 2008).

MCs are located perivascularly in close proximity to neurons in the leptomeninges (Roznieckі et al., 1999) and hypothalamus where they contain most of the brain histamine (Alstadhaug, 2014). In fact, MCs are located adjacent to corticotropin-releasing factor (CRF)-positive neurons in the rat median eminence (Theoharides et al., 1995) (Fig. 1) and could contribute to neuroinflammatory diseases (Theoharides and Cochrane, 2004).

In addition to IgE and antigen (Blank and Rivera, 2004), immunoglobulin light chains, anaphylatoxins, drugs and neuropeptides can trigger MC secretion. It is now recognized that activation of different Toll-like receptors (TLR) on MCs is important in the development of innate immunity to invading pathogens (Abraham and St John, 2010). Human umbilical cord blood-derived mast cells (hCBMCs) express viral TLR1, 3, 5, 7 and 9 (Kulka et al., 2004). Antigen can also act synergistically with TLR-2 and TLR-4 to produce cytokines from murine MCs (Qiao et al., 2006).

Neuropeptides such as substance P (SP) (Zhang et al., 2011) and neurotensin (NT) (Donelan et al., 2006) and nerve growth factor (NGF) (Kritas et al., 2014) also stimulate MCs. The ability of neuropeptides to stimulate MCs is augmented by IL-33 (Theoharides et al., 2010b). IL-33 has been considered an "alarmin" acting through MCs to alert the innate immune system (Moussion et al., 2008; Enoksson et al., 2011), and has recently been linked to brain inflammation (Chakraborty et al., 2010). MCs may, therefore, contribute to brain inflammation through different mechanisms (Table 1).

Once activated, MCs secrete numerous vasoactive, neurosensitizing and pro-inflammatory mediators. These include preformed histamine, serotonin, kinins, proteases and TNF, as well as newly synthesized, leukotrienes, prostaglandins, chemokines (CCXL8,

Abbreviations: ASD, autism spectrum disorders; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CRF, corticotropin-releasing factor; EGCG, epigallocatechin gallate; mTOR, mammalian target of rapamycin; mt, mitochondrial; NT, neurotensin; NTS, neurotensin receptor; PTEN, phosphatase and tensin homolog; SSRIs, selective serotonin re-uptake inhibitor; VEGF, vascular endothelial growth factor

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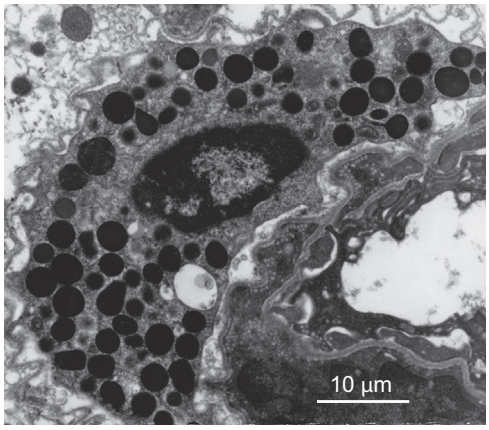

Fig. 1. Transmission electron photomicrograph of one perivascular mast cell. One normal mast cell with intact secretory granules (shown as black circles) encircles a pericyte and endothelial cell process that make up the blood–brain barrier of a blood vessel from the median eminence of a rat.

Table 1
Role of mast cells in brain inflammation.

- Activation by CRH and neurotensin
- Release of inflammatory mediators (IL-6, TNF, mtDNA)
- Release of IL-6 and TGFβ which promote IL-17 cell maturation
- Disruption of the BBB
- Recruitment of circulating lymphocytes
- Stimulation of microglia activation and proliferation
- Depletion of histamine which promotes motivation

CCL2) cytokines (IL-4, IL-6, IL-1, TNF) and vascular endothelial growth factor (VEGF), which increase blood–brain barrier (BBB) permeability (Theoharides et al., 2008). MCs are the only cell type that stores pre-formed TNF in secretory granules from which it can be released rapidly (Zhang et al., 2012b). MCs can also interact with T cells (Nakae et al., 2006) and superactivate them through TNF (Kempuraj et al., 2008).

Levels of TNF and IL-6 were increased in the cerebrospinal fluid (CSF) of Autism Spectrum Disorder (ASD) patients (Li et al., 2009). MC can release some mediators, such as IL-6 selectively (Theoharides et al., 2007). We also showed that IL-1 can stimulate selective release of IL-6 (Kandere-Grzybowska et al., 2003), and CRF could stimulate selective release of VEGF (Cao et al., 2005). Selective release of IL-6 could have profound effects on brain function (Theoharides et al., 2004b) and could activate the HPA axis (Kalogeromitros et al., 2007), while selective release of VEGF could lead to increased BBB permeability (Theoharides and Konstantinidou, 2007). MC-derived IL-6 along with TGFβ are critical for the development of Th-17 cells (Nakae et al., 2007) and MCs secrete IL-17, themselves (Nakae et al., 2007). MCs can also secrete exosomes that can deliver microRNAs (Bryniarski et al., 2013) and could be involved in brain pathology (Tsilioni et al., 2014b).

2. "Brain fog" and headaches

A number of reviews have stressed the importance of MCs in brain pathophysiology especially through their ability to interact with endothelial cells, glia and neurons (Silver and Curley, 2013; Skaper et al., 2013). In addition, increasing evidence links MCs to pain (Heron and Dubayle, 2013; Chatterjea and Martinov, 2014).

Stress and CRF could activate brain MCs (Theoharides et al., 2004a) particularly in the diencephalon and cerebellum where they are most abundant (Theoharides and Konstantinidou, 2007). MC activation can also occur after restraint stress (Theoharides et al., 1995), and during courtship following isolation of male doves (Silverman et al., 1994).

2.1. "Brain fog"

Patients with systemic mastocytosis or MC activation syndrome, a spectrum of diseases characterized by increased number of activated MCs, present with allergies, skin problems hyperactivity and other symptoms (Petra et al., 2014). Such patients commonly complain of loss of attention, focus, short term memory and ability to multitask, symptoms they collectively refer to as "brain fog" (Jennings et al., 2014; Moura et al., 2012). In fact, it was recently reported that more than 90% of patients with mastocytosis experienced moderate to severe "brain fog" almost daily (Moura et al., 2012). Cognitive impairment in such patients was also reported using a validated instrument (Jennings et al., 2014). Mastocytosis patients also experience other neurologic (Smith et al., 2011) and psychiatric (Jennings et al., 2014) symptoms.

Brain fog is also common in patients with other diverse conditions involving neuro-inflammation, such as chronic fatigue syndrome and fibromyalgia syndrome (Theoharides, 2013a). Brain fog may be due to inflammatory cytokines released from MCs, especially in response to stress (Theoharides et al., 2014) since brain expression of pro-inflammatory genes was increased in deceased patients with neuropsychiatric diseases (Theoharides et al., 2011). However, it should be noted that histamine from brain MCs may promote wakefulness (Chikahisa et al., 2013) and motivation (Torrealba et al., 2012). Hence complete blockade of histamine receptors may not be desirable.

2.2. Headaches

MCs have been implicated in the pathogenesis of migraines (Theoharides et al., 2005) through the development of neurogenic inflammation (Theoharides et al., 1995; Rozniecki et al., 1999). Activation of the trigeminal nerve leads to vasodilation and neurogenic inflammation (Zhang et al., 2007; Alhelal et al., 2014). The serum histamine level of patients with migraine and cluster headaches was increased indicating activation of MCs (Alstadhaug, 2014). Histamine administration led to intense headache and dilation of meningeal blood vessels. The frequency of migraines was also higher in patients with allergic rhinitis, who have activated nasal MCs (Ozturk et al., 2013).

Acute stress can exacerbate inflammatory disorders, such as migraines and multiple sclerosis (MS) (Mohr et al., 2000; Karagkouni et al., 2013). Restraint stress resulted in activation of dura MCs and elevation of rat MCs protease, effects abolished by pretreatment with polyclonal antiserum to CRF (Theoharides et al., 1995) or pretreatment the CRF_1 receptor antagonist Antalarmin (Theoharides et al., 1995). CRF can be secreted from MCs (Kempuraj et al., 2004). CRF and CRF receptor mRNA is expressed in rodent and human skin (Slominski et al., 2013). Intradermal administration of CRF activates skin MCs and increases vascular permeability in rodents and humans (Crompton et al., 2003), through activation of CRF_1 receptor. Normal human cultured MCs express high affinity CRF_1 receptor, activation of which leads to selective release of VEGF (Cao et al., 2005). Moreover, CRF_1 receptor is expressed on bone marrow MCs in a mastocytosis patient with high serum CRF levels (Theoharides et al., 2014).

The involvement of MCs in BBB regulation was first hypothesized by us (Theoharides, 1990) and was confirmed later (Rozniecki et al., 1999). Acute stress increased BBB permeability in rats and mice only in brain areas containing MCs (Esposito et al., 2001). Increased BBB permeability due to forced swimming was