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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 (Rozniecki 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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