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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.

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## 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 (CXCL8,

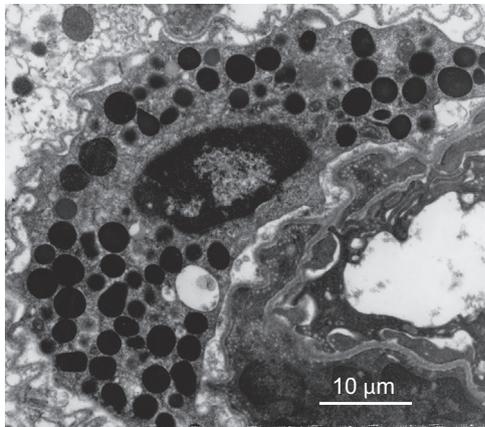
**Abbreviations:** ASD, autism spectrum disorders; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CRF, corticotropin-releasing factor; EGCG, epigallocatechin gallate; mTOR, mammalian target of rapamycin; mt, mitochondrial; NT, neurotensin; NTS, neurotensin receptor; PTEN, phosphatase 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<sub>1</sub> 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<sub>1</sub> receptor. Normal human cultured MCs express high affinity CRF<sub>1</sub> receptor, activation of which leads to selective release of VEGF (Cao et al., 2005). Moreover, CRF<sub>1</sub> 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

also reported and it was absent in W/W<sup>Y</sup> MC deficient mice (Esposito et al., 2002).

### 3. Brain inflammation and autism

Increasing evidence indicates that brain inflammation is important in the pathogenesis of neuropsychiatric disorders (Theoharides et al., 2011; Hagberg et al., 2012). ASDs are pervasive neurodevelopmental disorders characterized by varying degrees of deficiencies in social interactions, intelligence and language, as well as the presence of stereotypic behaviors (Fombonne, 2009; Johnson and Myers, 2007). Recent results from the Centers of Disease Control in the USA indicate that as many as 1/60 children have ASDs. Many such children regress at about age 3 years, often after a specific event such as reaction to vaccination, infection (Hsiao et al., 2012), trauma (Blenner et al., 2011), toxic exposures (Deth et al., 2008) or stress (Lanni et al., 2012) implying the importance of some environmental triggers (Herbert, 2010). In particular, exposure to mold has been associated with decreased cognitive function in six year old children (Jedrychowski et al., 2011). Cognitive impairment (Gordon et al., 2004) has been associated with exposure to mycotoxins that trigger MCs.

#### 3.1. Immune dysregulation

It is now recognized that ASDs are associated with some immune dysfunction (Zimmerman et al., 2005; Derecki et al., 2010; Rossignol and Frye, 2012a; Onore et al., 2012; Theoharides et al., 2012), autoimmunity (Ashwood and Van de Water J., 2004; Theoharides et al., 2013), as well as some neuroimmune component (Theoharides et al., 2009).

The markers of inflammation identified in the brain and CSF of many ASD patients include TNF, IL-6 and MCP-1, the latter of which also is chemotactic for MCs (Theoharides et al., 2010a). IL-6 expression was elevated in the brains of ASD patients (Li et al., 2009), and increased serum IL-6 was linked to the expression of an ASDs phenotype in mice (Dahlgren et al., 2006; Smith et al., 2007). Maternal immune activation in mice led to increased IL-6 and IL-17, and contributed to immune dysregulation and ASD-related behaviors in the offspring (Hsiao et al., 2012). Such cytokines could disrupt the BBB (Theoharides and Doyle, 2008), and cause “focal encephalitis” in specific brain areas, thus contributing to the pathogenesis of ASDs (Theoharides et al., 2008; Theoharides, 2013c) (Fig. 2).

#### 3.2. Mitochondrial dysfunction

A recent review connected mitochondrial dysfunction to oxidative stress and inflammation in children with ASDs (Rossignol and Frye, 2012b). We showed that MC activation leads to mitochondrial translocation to the cell surface (Zhang et al., 2011), and secretion of extracellular mitochondrial ATP and DNA (Zhang et al., 2012a). These extracellular mitochondrial components could augment MC activation and inflammation (Asadi and Theoharides, 2012). We also showed that serum of young autistic children had increased levels of extracellular mitochondrial DNA (Zhang et al., 2010), which is mistaken by the body as “innate pathogen” and induces a strong auto-inflammatory response (Zhang et al., 2012a).

#### 3.3. Autoantibodies

Circulating auto-antibodies directed against fetal brain proteins have been reported in about 30% of ASD patients (Rossi et al., 2011; Braunschweig and Van de Water, 2012; Wills et al., 2009). The Autism Phenome Project reported that 42% of 3 year old children with ASDs had plasma antibodies against GABAergic cerebellar

neuron proteins (Rossi et al., 2011). A recent paper described a strong statistical correlation between the presence of brain auto-antibodies and allergic symptoms (Mostafa and Al-Ayadhi, 2013).

#### 3.4. Allergic diathesis and mast cells

Epidemiological studies have shown that allergic diseases are associated with psychological and behavioral problems in preschoolers (Tsai et al., 2013) and infant atopic eczema was associated with attention-deficit-hypersensitivity disorder (Genuneit et al., 2014). One large epidemiological study reported a strong correlation between eczema and both attention deficit hypersensitivity disorder (ADHD) and ASD (Yaghmaie et al., 2013). Many ASD patients suffer from food allergies (Jyonouchi, 2010) and “allergic-like” symptoms (Kogan et al., 2009; Angelidou et al., 2011), indicating MC activation (Theoharides et al., 2012; Kempuraj et al., 2010). The suggestion was, therefore, made that a subtype of ASD may be “Allergy of the brain” (Theoharides, 2013c). A recent publication actually reported neurochemical changes and autistic-like behavior in a mouse model of food allergy (de Theije et al., 2014). Interestingly, children with mastocytosis, appear to have a 5-fold higher risk of developing Autism Spectrum Disorders (ASDs) (1/10 children) than the general population (Theoharides, 2009).

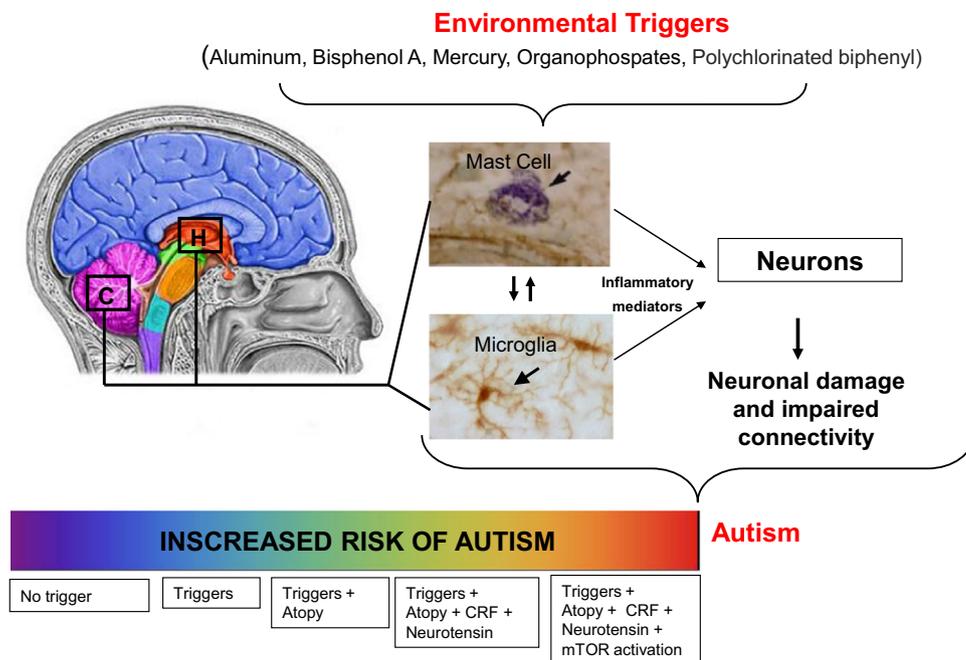
The richest source of MCs in the brain is the diencephalon (Pang et al., 1996) that regulates behavior. Neuroglial activation and neuroinflammation has been reported in brains of patients with ASDs (Vargas et al., 2005) MC-microglial interactions are important in neuroinflammatory diseases. Microglia are the innate brain immune cells that are increasingly implicated in a number of neuropsychiatric diseases. During healthy brain developments microglia may “prune” neural circuits through a complement-dependent manner (Schafer et al., 2012). However, abnormal microglia activation and proliferation could lead to focal inflammation and “choking” of normal synaptic traffic. In fact, abnormal microglial growth and activation was reported in the brains of ASD patients (Morgan et al., 2012; Rodriguez and Kern, 2011).

A recent study of the transcriptomes from 104 human brain cortical tissue samples shows an inverse relationship between a gene expression module of M2-microglia activation and a neuronal module implying dysregulated microglia responses that may lead to altered neuronal activity with ASDs (Gupta et al., 2014). Furthermore wild-type microglia could prevent autism-like pathology and behavior in a mouse model of Rett syndrome. We recently compared brain inflammation and abnormal BDNF signaling in Rett syndrome and ASDs (Theoharides et al., in press).

Microglia expresses the neurotensin receptor 3 (NTS3), activation of which leads to their proliferation (Martin et al., 2003). NT is a brain peptide involved in inflammation (Mustain et al., 2011). We reported that NT and CRF synergistically stimulate MCs, leading to increase vascular permeability (Donelan et al., 2006) and contribute to BBB disruption (Theoharides and Konstantinidou, 2007). NT also increases expression of CRF<sub>1</sub> receptor, activation of which by CRF increases allergic stimulation of human MCs (Asadi and Theoharides, 2012; Alysandratos et al., 2012). In fact, brain MCs were considered the link between the immune system and anxiety (Nautiyal et al., 2008). We reported that NT was increased in the serum of young children with ASDs (Angelidou et al., 2010) and so was serum levels of CRF (Tsiloni et al., 2014a).

NT also induces expression of CRF<sub>1</sub> receptor (Zhang et al., 2012a), activation of which by CRF increases allergic stimulation of human MC (Asadi and Theoharides, 2012). NT is neurotoxic (Ghanizadeh, 2010) and can facilitate N-Methyl-D-aspartate (NMDA)-induced excitation of cortical neurons (Antonelli et al., 2004).

ASD patients are prone to stress (Gillott and Standen, 2007). Anxiety in children with ASDs was consistent with sympathetic over-arousal and parasympathetic under-arousal (Kushki et al., 2013). It is possible that heightened response to stress and comorbid



**Fig. 2.** MCs act as “mirror” of environmental triggers stimulating microglia and together secreting inflammatory and neurodamaging molecules contributing to the risk for developing ASD. This risk is higher in children with a history of atopy, even higher in children who also have high level of stress as indicated by serum levels of the neuropeptides corticotropin-releasing factor (CRF) and neurotensin (NT), and highest in those with mutations in *PTEN*, which has been linked to high risk of ASDs by permitting activation of mTOR and leading to activation/proliferation of MCs and microglia.

anxiety disorders may be due to maladaptive psychological responses in children with ASDs (Hollocks et al., 2014).

Anxiety was also strongly correlated with repetitive behaviors with children with ASDs (Rodgers et al., 2012). A meta-analysis showed a strong correlation between the presence of anxiety disorders and ASDs (van Steensel et al., 2011). Prenatal stress has been linked to increased risk of ASD (Beversdorf et al., 2005; Ronald et al., 2010). Paternal stress altered sperm micro RNA and reprogrammed the offspring stress response (Rodgers et al., 2013). Prenatal negative life events increased cord blood IgE and the risk of atopy. Amazingly, prereproductive stress in female rats alters CRF<sub>1</sub> receptor expression in ova as well as CRF<sub>1</sub> receptor expression in the brain of the offspring (Zaidan et al., 2013). Moreover, neonatal maternal deprivation stress induced long-term colonic nerve-MC interactions in rats (Barreau et al., 2008). Stress activates MC leading to BBB disruption (Esposito et al., 2002) that contributes to brain inflammation, as amply documented in multiple sclerosis (Karagkouni et al., 2013). CRF was also responsible for disruption of the gut–blood barrier (Vanuytsel et al., 2014).

We propose that atopic diathesis plus increased CRF and NT released under stress contribute to the risk of developing ASDs (Fig. 2). The risk may be further increased if children have mutations leading to decreased phosphatase and tensin homolog (PTEN) (Aldinger et al., 2011). PTEN is an upstream inhibitor of the mammalian target of rapamycin (mTOR) (Aldinger et al., 2011), which leads to microglia and MC proliferation. Activation of susceptibility genes is being increasingly invoked to explain ASD (Fig. 2). Stimulation of mTOR in subjects with overactive mTOR due to gene mutations leading to low PTEN would contribute to a form of “epigenetic” signal (Fig. 2).

## 4. Possible treatments

### 4.1. Psychotropic drugs

Unfortunately, there are no approved effective treatments for the core symptoms of ASD (Broadstock et al., 2007; Rogers and

Vismara, 2008; Parikh et al., 2008). Moreover, children with ASDs are prescribed multiple vitamins, supplements and medications (Spencer et al., 2013) making the chance of unwanted drug interactions very high (Theoharides and Asadi, 2012).

The antipsychotic agents risperidone and aripiprazole are approved for use in children with ASD; however, these medications only address the disruptive, aggressive, and self-mutilative behaviors and not the core symptoms of the disorder. A recent publication on psychotropic drug use in children with ASDs in 30 countries reported heavy use of antipsychotics followed by antidepressants and anti-anxiety medications (Wong et al., 2014). However, two meta-analysis showed that use of psychotropic drugs in children with ASDs were not helpful (Williams et al., 2010; Sochocky and Milin, 2013). In fact, a double-blind, placebo-controlled trial using the antidepressant citalopram showed not only that there was no benefit, but actually worsened ASD symptoms (King et al., 2009; Volkmar, 2009).

### 4.2. Other drugs

A recent paper reported that a single-dose of the antipurinergic drug suramin, restored normal social behavior in 6-month-old adult mice with a phenotype similar to autism developed after maternal immune activation (Naviaux et al., 2014). However, suramin has different actions and also has serious side effects making it unlikely to be used in children with ASDs (Theoharides, 2013b).

### 4.3. Natural molecules

A recent, double-blind, clinical trial used the broccoli sprout extract sulforaphane or placebo for 18 weeks in adult patients with ASDs whose behavioral symptoms evidently improved with high fever ( $n=29$ ); patients receiving sulforaphane showed significant improvement of behavior (34% for ABC as compared to < 3.3% for those receiving placebo,  $n=17$ ), an usually low placebo effect (Singh et al., 2014). Sulforaphane may be acting as a strong

anti-oxidant and could be used in association with other natural compounds inhibiting neuroinflammation.

Natural flavonoids, such as quercetin and luteolin, have potent anti-oxidant and anti-inflammatory actions (Middleton et al., 2000). Quercetin and luteolin inhibit the release of histamine, leukotrienes and prostaglandin D2 from human cultured MCs in response to cross-linkage of FcεRI (Kimata et al., 2000). Quercetin also inhibits histamine, IL-6, IL-8, TNF-α and tryptase release from human MCs (Kempuraj et al., 2005; Park et al., 2008). Luteolin inhibits MC cytokine release (Asadi and Theoharides, 2012) and thimerosal-induced inflammatory mediator release (Asadi et al., 2010).

Luteolin also inhibits IL-6 release from microglia (Jang et al., 2008) and from astrocytes (Sharma et al., 2007) as well as microglial activation and proliferation (Dirschler et al., 2010; Jang et al., 2010a; Kao et al., 2011). Quercetin reversed acute stress-induced autistic-like behavior and reduced brain glutathione levels in mice (Kumar and Goyal, 2008), while luteolin prevented the development of an autistic-like phenotype in mice (Parker-Athill et al., 2009). A recent clinical trial reported statistically significant benefit of a luteolin containing dietary supplement in children with autism (Taliou et al., 2013). Flavonoids are safe (Harwood et al., 2007) and have been discussed as possible treatment of CNS disorders (Jager and Saaby, 2011; Braunschweig and Van de Water, 2012).

Luteolin also protects mitochondria against methylmercury-induced damage (Franco et al., 2010) and dopaminergic neurons from inflammation (Chen et al., 2008). Luteolin (5,7,3',4'-tetrahydroxyflavone) is structurally closely related to 7,8-dihydroflavone, which was shown to have brain-derived neurotrophic factor (BDNF) activity (Jang et al., 2010b). In fact, absence of BDNF was associated with autistic-like-behavior in mice (Scattoni et al., 2013), while 7,8-dihydroflavone was recently shown to reduce symptoms in a mouse model of Rett syndrome, most patients with which have symptoms of ASDs (Johnson et al., 2012).

## 5. Conclusion

Mast Cells could contribute to focal brain inflammation and autism through different ways and their regulation could have important therapeutic benefit.

## Conflict of interest

The authors declare they have no conflict of interest.

## Disclosures

TCT has been awarded US Patent No 8,268,365, entitled "Anti-inflammatory compositions for treating brain inflammation."

## Authors' contributions

TCT conceived and wrote the manuscript, while JMS and IM contributed useful comments and discussions, and SP prepared the graphics.

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