Mast cell-mediated neuroinflammation may have a role in attention deficit hyperactivity disorder (Review)

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Received October 15, 2019; Accepted April 29, 2020

DOI: 10.3892/etm.2020.8789

Abstract. Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental and behavioral disorder with a serious negative impact on the quality of life from childhood until adulthood, which may cause academic failure, family disharmony and even social unrest. The pathogenesis of ADHD has remained to be fully elucidated, leading to difficulties in the treatment of this disease. Genetic and environmental factors contribute to the risk of ADHD development. Certain studies indicated that ADHD has high comorbidity with allergic and autoimmune diseases, with various patients with ADHD having a high inflammatory status. Increasing evidence indicated that mast cells (MCs) are involved in the pathogenesis of brain inflammation and neuropsychiatric disorders. MCs may cause or aggravate neuroinflammation via the selective release of inflammatory factors, interaction with glial cells and neurons, activation of the hypothalamic-pituitary adrenal axis or disruption of the blood-brain barrier integrity. In the present review, the notion that MC activation may be involved in the occurrence and development of ADHD through a number of ways is discussed based on previously published studies. The association between MCs and ADHD appears to lack sufficient evidence at present and this hypothesis is considered to be worthy of further study, providing a novel perspective for the treatment of ADHD.

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Key words: attention deficit hyperactivity disorder, mast cell, brain, neuroinflammation, microglia, blood-brain barrier, hypothalamic-pituitary adrenal axis

Contents

1. Introduction

ADHD is characterized by inattention, motor hyperactivity and impulsivity, affecting childhood and adolescence until adulthood. ADHD is a childhood-onset neurodevelopmental disorder with a worldwide prevalence of 1.4-3.0% (1). ADHD is associated with substance misuse, oppositional defiant disorder, conduct disorder, depression, post-traumatic stress disorder (PTSD), school or occupational failure and criminality, and these comorbidities may even lead to increased mortality in adulthood (2,3). Half of the patients with ADHD have impairing symptoms persisting into adolescence and 30-60% into adulthood (4). Therefore, the pathogenesis and causes of ADHD warrant more attention.

The etiology of ADHD is complex, and genetic and environmental factors have a role in it (1). ADHD is a familial disorder with high heritability that ranges between 60 and 90% (5). Psychosocial risks, such as low income, family adversity and hostile parenting, are strongly related to ADHD and other psychiatric disorders (6). The relative risk of ADHD is 5-9 in first-degree relatives of probands with ADHD (5). Several different classes of genomic variants have been identified to be associated with ADHD (6). Candidate gene studies have revealed the effects of genes associated with monoamine neurotransmitter systems (1). The composite genetic risk scores and copy number variants exhibit a significant overlap between ADHD and schizophrenia and mood disorders (7). In addition, environmental factors are significant risk factors for ADHD. Several lines of clinical evidence suggest that

prenatal and perinatal factors, environmental toxins, and dietary and psychosocial factors may be potential risk factors for ADHD (8). In-utero exposure to maternal stress, cigarettes, alcohol, prescribed drugs (e.g., paracetamol) and illegal drugs were reported to be associated with ADHD (9). Psychosocial risks, including low income, family adversity and harsh or hostile parenting, have also been demonstrated to be associated with ADHD and several other psychiatric disorders, such as autism spectrum disorder (ASD) and obsessive-compulsive disorder (10-12). The occurrence of ADHD is based on the combined effects of genetic and environmental factors.

Although ADHD is a heterogeneous disorder and the pathogenesis has not been fully elucidated, studies in animal models have suggested the involvement of dopaminergic, noradrenergic and serotoninergic neurotransmission (11,13). Structural and functional abnormalities in the cortical and subcortical regions of the brain are also considered to be characteristic of ADHD. For instance, a study including imaging data of >3,000 patients with ADHD suggested that the volume of the nucleus accumbens, amygdala, caudate nucleus, hippocampus and putamen was reduced (14). Methylphenidate (MPH), the first-line medical treatment for ADHD, may cause side effects, including depression, compulsion and loss of appetite (15). Furthermore, a certain proportion of patients taking MPH did not achieve the expected outcomes (16). To improve the treatment of ADHD, it may thus be worthwhile to gain novel insight into the pathological mechanisms.

Neuroinflammation acts as a double-edged sword, which is an epiphenomenon following neuronal cell damage and also an inherent host-defense mechanism to protect and restore the normal structure and function of the brain against infection and injury, contributing to the recovery of impaired neurons and to the occurrence and aggravation of neurodegeneration (17). Neuroinflammation, particularly when persistent, has an important role in central nervous system (CNS) disorders, including neuroimmune diseases, neurodegenerative diseases and other neuropsychiatric diseases, such as multiple sclerosis (MS) (18), Parkinson's disease (PD) (19), Alzheimer's disease (AD) (20), stroke (21), depression (22), autism (23), schizophrenia (24) and chronic pain (25). Neuroinflammation differs from inflammation at other sites with no dendritic cells involved. Microglia and mast cells (MCs), which are natural immune cells of the CNS, are mainly involved in the occurrence of neuroinflammation (26). Astrocytes are also involved in neuroinflammation (27).

Microglia are the most widely studied cell type involved in CNS inflammation (26). As the major immune effector cells of the brain, microglia continuously monitor the surrounding environment and provide an immunosurveillance function for brain damage (26). Microglia function in maintaining the neuronal synapses, identifying pathogens, removing cellular debris and providing nutritional support (28). In addition, CNS neuroinflammation also involves neurons, astrocytes, MCs, T cells and pericytes. Microglia and MCs, both derived from hematopoietic progenitor cells, are two tracks to the path of neuroinflammation (29). Previous studies on inflammation in the brain have mainly focused on microglia and astrocytes (30-33). Recently, MCs have emerged as important factors in brain inflammation and are considered as the 'first responders' to brain injury (34). Based on the above studies, a hypothesis that ADHD onset may be associated with inflammation caused by MC activation was proposed and studies supporting this notion were discussed in the present review.

2. Overview and activation of MCs

Although the role of MCs is overlooked compared with microglia, MCs remain an important factor in the immune signaling pathway (29). MCs, the effector cells of the innate immune system, are derived from hematopoietic stem cells and multifunctional antigen-presenting cells and have a pivotal role in immunoglobulin type E (IgE)-associated allergic and inflammation-associated diseases (35). Despite their low numbers in most organs, MCs are present in both healthy and disease states. MCs are the first line of defense against invading pathogens and are distributed in almost all organs and vascularized tissues (36). Blood MCs express CD34 and contain cytoplasmic granules filled with heparin and histamine, the latter of which is released after binding to IgE. Unlike other myeloid-derived cells, tissue MCs have a hematopoietic developmental lineage (37,38). During MC development, immature lineage progenitors enter the circulation and are recruited to peripheral tissues by endothelial cells, regulating the appearance of granules with proteases (37,38). Human MCs may be classified into mucosal and connective tissue types according to the type of proteases present in their cytoplasmic granules; the mucosal type contains tryptase, whereas the connective tissue type contains both tryptase and chymase (39). MCs act as first responders and environmental 'sensors' to interact with other cellular elements involved in physiological and immune responses, promoting the neuroinflammation process (40). MCs are present in various areas of the brain and meninges. Although less distributed in the brain, they are generally found in the subthalamic nucleus, choroid plexus and the parenchyma of the hypothalamic region (41). The pathogenic roles of MCs were indicated to extend from allergic disease to autoimmune diseases and carcinogenesis (42-47).

The most common way through which MCs perform their function is degranulation. The activation of the inflammatory process results in a rapid release of MC granules into the interstitium. MC granules contain pre-formed and newly synthesized reactive chemicals known as MC mediators. These mediators include histamine, tryptase, chymase, interleukin families, tumor necrosis factor-α (TNF-α), serotonin, heparin, proteoglycans, vascular endothelial growth factor (VEGF), prostaglandins, leukotrienes, chemokines and growth factors, several of these are unique to MCs (42,48). Studies have indicated that MC degranulation may cause cognitive dysfunction (49). Large-scale MC degranulation may cause fatal anaphylaxis; however, most physiological functions of MCs, including regulation of inflammatory processes, occur without complete degranulation (50). MCs are phenotypically and functionally heterogeneous. The pathways and results of MC activation are multifaceted. In addition to IgE, MCs may also be activated through a number of other stimuli, including trauma, other immunoglobulins, complements, toll-like receptors (TLRs), neuropeptides, cytokines, chemokines and other inflammatory products, causing mast cell activation and leading to the selective release of mediators and/or stimulating T-cell proliferation, differentiation and migration (51,52). A

characteristic of MC physiology that has been overlooked is that MCs are able to secrete mediators via differential or selective release without significant degranulation. This process may be regulated by the action of distinct protein kinases on a unique phosphoprotein (53). MCs undergo changes in the core of the electron-dense granules but without overt degranulation, a process that has been termed as activation, intragranular activation or piecemeal degranulation (54). MCs are essential for the pathogenesis of numerous inflammatory diseases, but this effect may only be achieved if MCs release selective mediators without degranulation, which may otherwise cause allergic reactions (52). Under normal circumstances, the brain does not express IgE receptor (FcεRI), since the brain does not display any allergic reactions and IgE does not cross the blood-brain barrier (BBB) under normal conditions (55).

The ways in which the mediators are secreted depend on the given stimuli and microenvironmental conditions. For instance, serotonin may be selectively released without histamine or arachidonic acid metabolites (56). The combination of TLR4 and mast cells does not cause degranulation but results in the secretion of inflammation-associated mediators. TLR4 binds to the co-receptors CD14 and MD-2 expressed by MCs. Subsequently, activation by myeloid differentiation primary response protein MyD88 innate immune signal transduction adaptor results in activation of interleukin (IL) receptor-associated kinase family members and pyruvate dehydrogenase kinase isoform 1, mitogen-activated protein kinases (MAPKs) p38 and JNK and to phospholipase A2 (57). TLR4 also binds to lipopolysaccharides (LPS) and induces TNF-α release without degranulation (58). LPS induces secretion of IL-5, IL-10 and IL-13 but not granulocyte-macrophage colony-stimulating factor, IL-1 or leukotriene C_4 (LTC_4) (58). The selective release of IL-6 occurs in the MC response to LPS, provided the presence of the PI3K inhibitor wortmannin or stem cell factors (59). Corticotropin-releasing hormone (CRH) was demonstrated to stimulate the selective release of VEGF without degranulation and histamine or tryptase release from the human leukemic mast cell line HMC-1 and human umbilical cord blood-derived mast cells (60). Neurotensin (NT) induces expression of CRH receptor (CRHR)-1 on MCs and NT and CRH are released under stress via NT-CRH crosstalk (61). IL-1 stimulates human MCs to selectively release IL-6 without degranulation, via a unique process utilizing 40-80 nm vesicles unrelated to the length of secretory granules (800-1,000 nm) (62). IL-33 may serve as a potent activator of MCs and was reported to promote MC survival, maturation, migration and adhesion, and to selectively produce a variety of pro-inflammatory cytokines, including IL-4, IL-5, IL-6, IL-8 and IL-13 and chemokines including macrophage inflammatory protein-1α and monocyte chemoattractant protein 1 (MCP-1) (63,64). IL-33 enhances the role of the pro-inflammatory peptide substance P in stimulating human MCs to secrete high levels of VEGF and TNF via the interaction of neurokinin 1 and ST2 receptors without concomitant secretion of tryptase (65). In the presence of stem cell factor, IL-33 may also induce TNF production in MCs via a MAPK-activated protein kinases 2 and 3, ERK1/2- and PI3K-dependent pathways (66). Understanding the selective release of mediators may explain how MCs participate in numerous biological processes and how they are capable of exerting both immunostimulatory and immunosuppressive effects.

3. MC-glia crosstalk

Microglia and MCs are the two most important cell types mediating and regulating neuroinflammation in the brain. There is a close association between MCs and glial cells. MCs are generally clustered near the glia in neuroinflammatory conditions to recruit and activate other inflammatory cells, where neuroinflammation already occurs in the brain. The contribution of MCs and glia to neuroinflammation is strongly influenced by the likelihood of their crosstalk and pathological exacerbation (29). MCs may interact with microglia and astrocytes via the complement system, proteases, TLRs and chemokines. MCs may participate in the migration and activation of glia, thereby affecting the release of inflammatory mediators. The expression of ligand-receptor pairings may be upregulated under inflammatory conditions, facilitating chemotactic actions through contact between MC and glia (27). For instance, C5a, the chemoattractant anaphylatoxin peptide and its receptor CD88 are upregulated in the glia of inflammatory CNS tissues (67-69). Complementary expression of the C5a receptor on activated MCs produces an intense chemoattractant signal to the C5a peptide and intense crosstalk between C5a and TLR4, which also has a role in neuroinflammation (67-69). TLRs are a major class of pattern recognition receptors involved in innate immunity. TLRs are associated with groups of pathogens recognized by innate immune system cells, including microglia and MCs, and act as a bridge between non-specific and specific immunity (70). Upregulation of C-C motif chemokine 5 (CCL5; also known as RANTES) by MC activation leads to a pro-inflammatory response in microglia, releasing IL-6 and CCL5, which in turn promotes chemokine expression in MC (71). IL-33 is an activator of MCs and IL-33 release from astrocytes may activate brain MCs and microglia (72). The binding of IL-33 to MC receptors leads to the secretion of IL-6, IL-13 and MCP-1 to regulate microglia activity. Furthermore, IL-33 may be stimulated from microglia pre-activated with pathogen-associated molecular patterns via TLRs (73,74). Together, MC protease and matrix metalloproteinase (MMP) activate p38, ERK1/2, MAPKs and transcription factors including NF-κB in astrocytes, microglia and MCs (75). IL-6 and TNF-α released from microglia upregulate protease-activated receptor 2 (PAR2) expression in MCs, causing MC activation and TNF-α release (76). MC tryptase may induce the release of pro-inflammatory mediators such as TNF-α, IL-6 and reactive oxygen species (ROS) via the PAR2/MAPK/NF-κB signaling pathway and activation of PAR2 receptors on MCs, which then contributes to the development of microglia-mediated inflammation in the brain (77). IL-6 induces IL-13 release from MCs, affecting the expression of TLR2/TLR4. Furthermore, TNF-α upregulates PAR2 expression in MCs and enhances PAR2-mediated MC activation and degranulation (78-80). C-X-C chemokine receptor type 4 (CXCR4; also known as stromal cell-derived factor 1) is an MC chemotaxin and studies have indicated that

CXCR4 is upregulated in hypoxia and ischemia, promoting the migration and activation of microglia (81). In addition to microglia, astrocytes sharing a perivascular localization with MCs maintain the viability of MCs. Astrocytes express histamine receptors and release cytokines/chemokines through Rho-family GTPases/Ca^{2+}-dependent protein kinase C isoforms, MAPK, NF-κB and signal transducer and activator of transcription 1 (82-84). These trigger MC degranulation and enhance CD40L and CD40 surface expression, leading to further inflammation (82-84). Both microglia and astrocytes express histamine receptor H_1 (HRH_1), HRH_2 and HRH_3 and MCs may affect the activity of microglia and astrocytes through these receptors (85,86). An *in vitro* study has indicated that MC proteases may induce demyelination and apoptosis of oligodendrocytes, while myelin promotes MC degranulation (87). Several experiments have confirmed the relationship between MCs and glia. Co-culture of microglia and HMC-1 cells revealed that activated HMC-1 cells stimulate the activation of microglia and subsequent production of pro-inflammatory factors TNF-α and IL-6 (88). MC degranulator compound 48/80 induces microglia activation and inflammatory cytokine production, triggering an acute brain inflammatory response. However, the MC stabilizer cromolyn inhibits this effect, reduces inflammatory cytokines and inhibits the MAPK, AKT and NF-κB signaling pathways. Furthermore, cromolyn inhibits HRH_1, HRH_4, protease activity, PAR2 and TLR4 in microglia (49,89). Incubation of astrocytes and neurons with 1-methyl-4-phenylpyridinium, glia maturation factor (GMF), mouse MC protease-6 (MMCP-6) and MMCP-7 increased PAR-2 expression, suggesting contact between MCs and astrocytes (90).

4. MC-neuron interactions

The connection between MCs and neurons mainly occurs through peripheral interactions. A number of studies have revealed the association between MCs and neurons in CNS neuroinflammation. In the brain, the co-localization of MCs and neurons provides a basis for neuroimmunological interactions. Cell adhesion molecule-1 (CADM1), expressed by mature hippocampal neurons, may have an important role in the development of MC neuron interactions (91). In the CNS, MC-derived products may enter adjacent neurons to insert their granular contents, a process known as granulation. In this way, MCs change the internal environment of neurons, presenting a novel form of neuroimmunological interaction (92). In addition, MCs express a series of neurotransmitter receptors, which may be directly activated, enhanced [neurokinin 1 receptor (NK1R), NK2R, NK3R and VIP receptor type 2] or inhibited (acetylcholine receptor) (93,94). Furthermore, it was reported that activated MCs enhanced excitotoxic damage to 60% when co-cultured with hippocampal neurons. In N-methyl-D-aspartate receptor-mediated synaptic neurotransmission, MC-derived histamine directly increases the death of hippocampal neurons (95). Tryptase released by MCs may directly activate proteinase-activated receptors on neurons and MC-derived TNF-α has a vital role in neuronal development, cell survival, synaptic plasticity and ionic homeostasis in the CNS (96). These MC-neuron interactions are thought to be involved in the pathogenesis of numerous neuroinflammatory diseases.

5. MCs and the HPA axis

The association between chronic stress and neuroinflammation has been confirmed by numerous studies. MCs have a vital role in the mechanism of brain damage caused by chronic stress on the brain. A variety of psychological and physiological stresses may lead to changes in the expression, distribution and activity of MCs in the CNS. Stress and pro-inflammatory cytokines activate the HPA axis, thus leading to an increase in CRH and arginine vasopressin release from the paraventricular nucleus of the hypothalamus. HPA axis activation also enhances the expression of CRH receptors, vascular permeability and MC activation (97). CRH released from MCs activates MCs and glia in the CNS in an autocrine and paracrine manner in the context of stress and neuroinflammation (98). In turn, activation of CNS MCs activates the HPA axis. MCs are located near CRH-positive neurons in the median eminence and are closely linked to corticotropin-releasing factor receptors, which may be activated by CRH (99). This may be closely associated with the meningeal vasodilation and increased secretion of cytokines during meningeal inflammation in migraines (46). Cao *et al* (100) indicated that intravesical stress, CRH, MC activation and VEGFs have a crucial role in the stress-induced deterioration of inflammation, which may provide insight into the mechanism of brain stress. MC activation and CRH release increase BBB permeability, leading to further brain damage and contributing to chronic neuroinflammation in the brain (60,101). Microglia express CRH receptors and activation of microglia by CRH leads to the release of harmful inflammatory mediators in psychiatric diseases, such as AD and pain (102,103). Human MCs synthesize and secrete CRH and express functional CRH receptors (CRHR1 and CRHR2) (104). CRHR1-mediated activation of microglia induces microglia proliferation, TNF-α release and activation of MAPK. CRHR1 also mediates stress-induced MC degranulation (105). CRH release from activated MCs may also activate glial cells in neurodegenerative diseases such as AD (103,106). Stressful conditions, including trauma or hypoxia, also activate peripheral MCs, which in turn activate CRH and substance P pathways, leading to BBB leakage and glial activation, causing further neuroinflammation and neurodegeneration (107). CRH concentrations are higher in brain regions prone to developing a pathology of AD (108). Elevated cortisol levels and HPA axis dysfunction are implicated in chronic stress, which releases amyloid beta (Aβ) that causes and/or worsens AD (109). CRHR1 antagonists have been indicated to decrease stress-mediated oxidative damage, prevent cognitive damage and loss of dendritic cells and reduce Aβ deposition in the brain (110). These results confirm the correlation between CRH and AD. Other neuropeptides, including NT, may work with CRH to enhance MC activation and release of excessive inflammatory mediators under stress (61). CRH may enhance VEGF release from human MCs and induce FcεRI expression in MCs, and this effect may be blocked by the natural flavone luteolin (111). CRH is also implicated in the pathogenesis of PD. Emotional chronic stress, which is closely associated with CRH, enhances glial activation and aggravates neuronal death

through inflammation in the substantia nigra of the brain of patients with PD (107). Furthermore, observations in animal models of PD indicate that stress-induced striatal damage may subsequently worsen motor symptoms (112).

6. MCs and the BBB

The BBB is composed of functional cerebral blood vessels, which create a stable CNS environment and protect brain parenchymal cells from harmful substances in the immune cells and blood. The BBB consists of tightly connected endothelial junctions and several intact transmembrane proteins, including claudin and occludin, that ensure its integrity. The basal lamina, which is part of the extracellular matrix, connects the endothelial cells of the BBB to adjacent cell layers (113). BBB destruction involves the accumulation of multiple vascular and neurotoxic molecules within the brain parenchyma, decreased cerebral blood flow and hypoxia (114). MCs are present in the dura mater and meninges, as well as on the cerebral side of the BBB, and MCs are in contact with the distal ends of the astrocytes (115). MCs may cross the BBB and blood-spinal cord barrier when the barrier is damaged by CNS pathologies. Inflammatory factors released by MC activation, including histamine, tryptase, chymotrypsin and TNF-α, may regulate BBB permeability (116). Furthermore, TNF-α induces the expression of intercellular adhesion molecule 1 (ICAM-1) and allows leukocytes to enter the affected tissues in the brain (117). The me chanism by which MCs destroy the BBB and promote basal layer degradation may involve vascular activity and matrix degradation components of MCs. MCs affect the integrity of the BBB through MMPs, whose enzymatic activity may be regulated by tissue MMP inhibitors. These include histamine and protease chymase, trypsin and cathepsin G (118). Cathepsin G activates MMPs, which degrade most of the protein components of the neurovascular matrix (118). In cerebral ischemic disease, MC degranulation increases, and brain MCs affect the activation of acute microvascular gelatinases (MMP-2 and -9) by releasing proteases to affect BBB destruction. In addition, elevated levels of VEGF may cause BBB rupture, vascular leakage and edema, which in turn causes stroke (119,120). This process extravasates glutamate and albumin, activates astrocytes, alters K^+ homeostasis in the brain parenchyma and leads to excessive neuronal excitation and inflammatory cell entry (119,120). In experimental autoimmune encephalomyelitis (EAE), activation of meningeal MCs leads to TNF-α production and early neutrophil recruitment (121). This promotes local BBB destruction, allowing initial immune cells to enter the CNS and aggravate neuroinflammation (121). An *in vitro* study revealed that TNF-α induces downregulation of tight junction proteins occludin, claudin-5 and vascular endothelial-cadherin via an increase in ROS, which leads to increased paracellular permeability (122). IL-6 participates in the effect of TNF-α on endothelial monolayers. TNF-α upregulates the expression of ICAM-1 and vascular cell adhesion molecule-1 on brain microvascular endothelial cells (123). ICAM-1 is involved in leukocyte adhesion to the endothelium and its upregulation and leukocyte-mediated BBB breakdown are one of the pathological mechanisms and characteristics of various brain inflammatory diseases, including MS (123). Brain MCs may induce post-operative cognitive dysfunction by destabilizing the BBB and acute stress may cause BBB breakdown by activating MCs (88,124). In addition to cerebral ischemia, BBB destruction has also been detected in dementia, motor neuron disease, MS, AD and other neuropsychiatric disorders (125-128). Substance P, which is released following traumatic brain injury or under stress, activates MCs and glia, releasing neuroinflammatory mediators and increasing BBB permeability (129). The release of CRH from MCs contributes to the subsequent release of various neuroinflammatory and neurotoxic mediators, leading to BBB rupture and glial cell activation, chronic neuroinflammation in the brain and causing autism (130). Cromoglycate, a MC-stabilizing agent, reversed BBB destruction, brain edema and neutrophil recruitment post-ischemia by inhibiting MC activation in a stroke model (131).

7. Inflammation/MCs and ADHD

There appears to be a high comorbidity between ADHD and allergic, inflammatory and autoimmune diseases. Epidemiological studies revealed that allergic diseases or conditions are closely associated with psychological and behavioral problems in pre-school children (132). A prospective birth cohort study examining the association between atopic eczema (AE) and ADHD was conducted. The results of the study indicated that children with AE were susceptible to ADHD, which was more obvious when they were at a younger age (133). Among early preterm-born children, systemic inflammation during the first post-natal month appears to increase the risk of teacher-identified ADHD characteristics (134). A prospective cohort study of 23,645 patients in Denmark suggested that a personal or maternal history of autoimmune disease was linked to a high risk of ADHD (135). A cross-sectional study involving 2,500,118 individuals in Norway indicated that ADHD was associated with psoriasis and Crohn's disease among females (136).

Several clinical studies have reported elevated levels of pro-inflammatory factors in the blood of children with ADHD. A clinical trial in Taiwan involving 216 children with ADHD and 216 non-ADHD controls indicated that the levels of hemoglobin and 5-hydroxytryptamine receptor 3A (5-HT) in fasting venous blood were significantly lower in children with ADHD compared with controls, whereas IgE and eosinophil counts were elevated compared with controls (137). A genome-wide association analysis identified a link between ADHD and the gene encoding IL-1 receptor antagonist (138). An association study of 546 patients with ADHD and 546 controls demonstrated an association between cytokine family ciliary neurotrophic factor receptor and both adult and childhood ADHD (139). Inflammatory processes may also increase the risk of ADHD in obese individuals and peripheral inflammatory factor levels may aggravate the severity of ADHD core symptoms (140,141). The incidence of obesity and neuropsychiatric diseases has risen rapidly over the past three decades in the US (142,143). Epidemiological studies indicated that maternal obesity and metabolic dysfunction increase the risk of ADHD, ASD, anxiety, depression, schizophrenia and food addiction via the neuroinflammatory pathway (144,145). A review revealed that microbiota-gut-brain axis interactions

affect the pathogenesis of a variety of inflammation-associated disorders, including mood disorders, ASD, ADHD, MS and obesity (146). Evidence suggested that patients displaying symptoms of ADHD have higher serum cytokine levels compared with normal controls, including IL-1β, IL-2, IL-6, IL-10, IL-13, IL-16, interferon (IFN)-γ and TNF-α (147-150). An investigation on serum cytokine levels in children with ADHD indicated that Purkinje cell antibodies were associated with the ADHD group, suggesting that neuro-antibodies and cytokines may contribute to ADHD (151). Patients with ADHD administered MPH had lower cytokine levels compared with those of unmedicated patients with ADHD (152). These data suggested that patients with ADHD may be in a high inflammatory state and ADHD treatment reduces cytokine levels. However, most studies involving a number of cases only identified a slight association between ADHD and peripheral inflammation but did not further explore the underlying mechanisms. Several retrospective studies have indicated that perinatal infection, preterm birth and low birth weight are closely associated with the risk of ADHD-like symptoms (150,153). White matter injury caused by preterm birth is associated with maternal inflammation, perinatal infections and oxygen supply interruption, and occurs through the activation of glia, excitotoxicity and oxidative stress. Inflammation and hypoxia in this process are risk factors for ASD, ADHD and other psychological disorders (154). However, several studies found no evidence supporting a link between ADHD and inflammation in the brain. In a study on depression and anxiety in from the Netherlands including 2,307 subjects indicated that there was no evidence that ADHD development was associated with dysregulation of inflammatory markers, and there was no interaction between ADHD symptoms and stress-associated affective disorders (155). Examination of the early gestational maternal C-reactive protein in maternal serum and the risk of ADHD in offspring suggests a lack of correlation (156). In addition to clinical studies, several animal studies have identified or confirmed the association between ADHD and inflammation. Kozlowska *et al* (157) concluded that there is an interaction between neurological and immune systems in ADHD pathogenesis. This conclusion was reached by examining the concentration of cytokines, chemokines, oxidative stress markers, metabolic parameters, steroid hormones and steroidogenic enzymes in the serum and/or tissues of spontaneously hypertensive rats (ADHD model) and Wistar Kyoto rats (control animals).

Several pieces of evidence indirectly revealed a possible association between ADHD and inflammation. For instance, vitamin D has a significant protective effect on inflammation, oxidative stress and certain neurotrophic factors. Neurotransmitter and vitamin D levels are lower in patients with ADHD compared with those in healthy children (158). Dietary antioxidant treatment may have a positive effect on nerve damage caused by inflammation, oxidative stress and immune dysfunction in ADHD (159). Iron deficiency is considered to be a possible physiological etiology in subsets of patients with ADHD and serum ferritin may be affected by a variety of conditions, including inflammatory status (160). A randomized double-blinded controlled trial revealed that children with ADHD have lower blood levels of long-chain polyunsaturated fatty acids (PUFAs) compared with children with no ADHD. Furthermore, following PUFA supplementation, children with ADHD exhibited improvements in ADHD-associated symptoms, thus supporting a link to pathways responsible for inflammation in the body (161).

The intestines have a profound effect on the entire body including the brain, and the role of gut-brain connections has gradually been discovered. Food allergy is a common condition in children and adolescents and is suggested to be one of the gastrointestinal tract triggers for numerous psychological and psychiatric conditions including depression, anxiety and ADHD (162,163). A study indicated that the majority of food allergies/intolerances are mediated by IgE. Following continuous food exposure, allergens may bind conjugated IgE to induce MC degranulation and the secretion of inflammatory mediators, including cytokines, histamines, leukotrienes and prostaglandin (164). IgE-mediated allergic reactions are referred to as immediate type hypersensitivities. In non-IgE-mediated reactions, the allergic response may be mediated by Ig-free light chains or other cells such as eosinophils, T cells and mast cells. Cell-mediated food allergy, which is classified as delayed-type hypersensitivity, does not involve Igs and symptom onset is observed from 1 h to days after ingestion of the food protein (165,166). Food intake may affect the behavior of children with ADHD through a mechanism that involves a non-IgE-mediated, cell-mediated or non-allergic response (167). A cross-sectional study from China suggested that early food allergies in school-age children are associated with ADHD (168). Children with ADHD reacted severely to allergenic foods including cow's milk, wheat and eggs (167,169). Studies have pointed out that for certain patients with ADHD, dietary restrictions may provide significant benefits (170). A case study reported on a 7-year-old boy with ADHD and severe IgG-mediated food allergy who presented reduced IgG antibody levels and improved behavior with dietary supplement intervention (171). However, several studies obtained negative results regarding the association between ADHD with food allergies (172). One potential reason for this may be the complexity of the IgE immune response to food allergens in the gastrointestinal tract falling between the tolerance and sensitization mechanisms (173). Based on conflicting results of research, it was hypothesized that ADHD is not caused by allergic reactions, but that ADHD itself is a (non-)allergic hypersensitivity disorder (174,175). Food-derived allergens trigger a hypersensitivity reaction that causes ADHD-like symptoms, possibly via an IgE or non-IgE allergic response or a non-allergic mechanism (174). Food allergy is closely linked to MCs. MCs express various substances that may trigger enteric neurons, including tryptase, histamine, 5-HT, nerve growth factor and TNF-α (176). Allergic reactions in the intestines may affect behavior through intestinal mast cells, which may trigger intestinal neurons to transmit information to the CNS via afferent sensory pathways (177). Activated MCs increase IL-6 production through the mTOR pathway (178). IL-6 was indicated to induce behavioral defects and is enhanced in post-mortem brains of patients with ASD (179). In addition, gut microbes affect host social behavior through the alteration of brain neural circuits and food allergies may affect behaviors through gut bacteria. For instance, the bacteroidete/firmicute ratio was increased

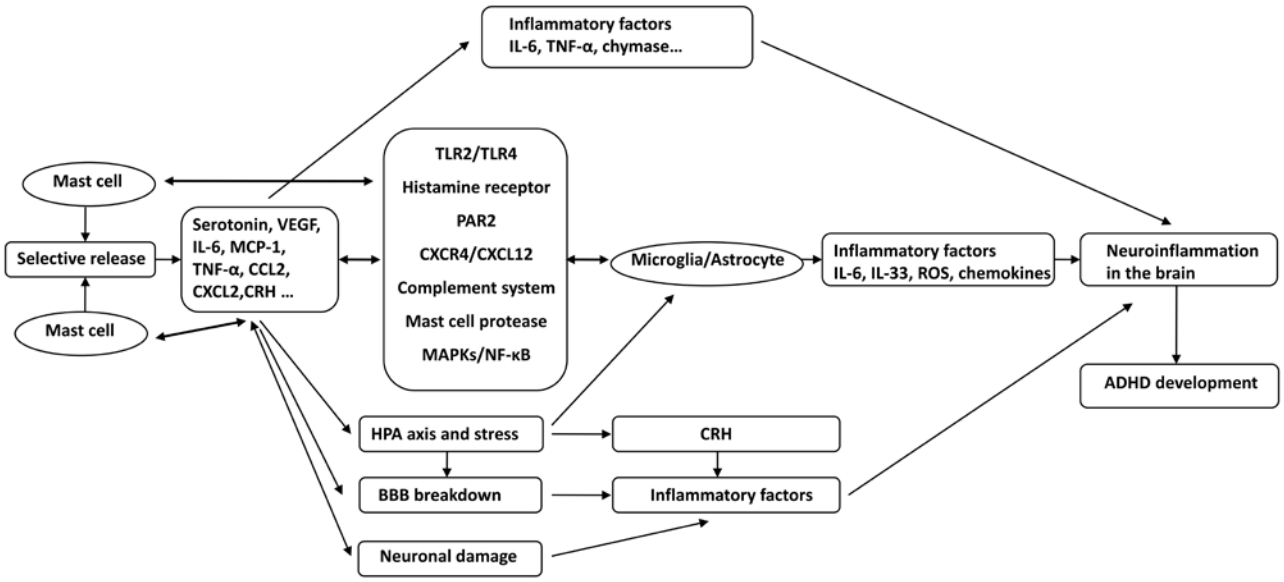

Figure 1. Possible association between ADHD and mast cells. Mast cells may cause ADHD via the following mechanisms: Selective release of inflammatory factors, interacting with glia via CD40L, TLR2/TLR4, histamine receptor, PAR2, CXCR4/CXCL12, complement system, mast cell protease, MAPKs and NF-κB, causing neuronal damage, activating the HPA axis and resulting in BBB breakdown. These pathological processes trigger the neuroinflammation in the brain, resulting in the development and progression of ADHD. ADHD, attention deficit hyperactivity disorder; MAPK, mitogen-associated protein kinase; BBB, blood-brain barrier; CXCL/R, C-X-C motif chemokine ligand/receptor; CCL, C-C motif chemokine ligand; HPA, hypothalamic-pituitary adrenal; IL, interleukin; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor; TLR, Toll-like receptor; CRH, corticotropin-releasing hormone; PAR2, protease-activated receptor 2.

in children with ASD and propionic acid produced by gut bacteria may increase locomotor activities and stereotyped behavior (180,181).

8. MCs in brain disorders

Although the possible association between MCs and ADHD has not been previously reported, the role of MCs in other brain disorders has been confirmed. For instance, studies have suggested that patients suffering from PTSD have immune disorders with an excessive inflammatory response. Patients with PTSD exhibit chronic stress responses along with low-grade inflammation in the body. Furthermore, MCs are also dysregulated in combat soldiers (182). The number of MCs in the skin, gastrointestinal tract and respiratory tract of patients with PTSD is higher compared with that in individuals without PTSD (183). In addition, patients with PTSD have high levels of CRH and inflammatory factors, including serum IL-6, IL-1β, TNF-α and IFN-γ. Increased expression of these factors may be linked to MC activation (184). MC-derived substance P markedly contributes to pain in patients with PTSD (185). Furthermore, PTSD is an important risk factor for several autoimmune and MC-associated diseases, including MS, rheumatoid arthritis, thyroiditis, lupus erythematosus and IBD (186). Multiple lines of evidence suggested that MC activation accelerates the pathogenesis of AD in high-risk brain injury, trauma, stress and PTSD. MCs are one of the first type of brain cell involved in the pathogenesis of AD and respond early to Aβ formation (187). GMF regulates neuroinflammation via the NACHT, LRR and PYD domains-containing protein 3 inflammasome in brains of patients with AD (188). Enhanced IL-33 and GMF expression was observed in the vicinity of amyloid plaques and neurofibrillary tangles in human AD brains (189). In AD, increased ROS activates MCs to release inflammatory mediators and several MC-derived inflammatory mediators were reported to be involved in the pathogenesis and severity of AD (190). Mitochondrial uncoupling proteins (UCPs) are implicated in neurodegenerative diseases and MCs express UCP2 and UCP4 (191). The concentration of CRH is higher in areas prone to AD-associated pathological changes (108). In the brain of a rat model of AD, chymotrypsin-like proteases surrounded the meninges and Aβ highly accumulated in cortical blood vessels, and these proteases are thought to affect Aβ accumulation (192). MS is a chronic inflammatory disease of the CNS, characterized by demyelination, immune cell infiltration and axonal damage. MCs are present in perivascular demyelinating lesions associated with immune cell infiltration and in the CNS parenchyma and leptomeninges of patients with MS (193). MCs may regulate the transport of inflammatory cells through the BBB, thereby exerting effects on MS and EAE (107,121). Levels of histamine and tryptase are elevated in the cerebrospinal fluid of patients with MS (194). MCs may also be involved in the pathogenesis of ASD. Serum and brain NT levels as are elevated in patients with ASD, which may cause MC activation (195). TNF-α, IL-6, MCP-1 and granulocyte macrophage colony-stimulating factor were significantly increased in the brain tissue of patients with ASD (179). Inflammation may induce depression through different pathways. Elevated kynurenine levels are associated with depression in humans. Kynurenine promotes IgE-mediated reactions of MCs, including degranulation, LTC_4 release and IL-13 production through activation of phospholipase C-γ1, Akt, MAPK p38 and intracellular calcium release in an aryl hydrocarbon receptor-dependent manner, possibly modulating MC responses (196). Mastocytosis is a rare disease characterized by the accumulation and activation of MCs,

with a prevalence of depression ranging from 40-70% (197). A study of 54 patients with mastocytosis identified the role of MCs in the tryptophan (TRP) catabolic pathway leading to depression. The levels of TRP and serotonin were significantly lower in patients with mastocytosis compared with healthy subjects, with higher indoleamine-2,3-dioxygenase activity and higher levels of kynurenic and quinolinic acids (198). This demonstrated a TRP metabolism disorder in mastocytosis, and its association with perceived stress and depression, thereby indicating a close association between MCs and the development of depression.

9. Possible association between ADHD and MCs

Various pieces of evidence suggested that ADHD may be a neuroinflammatory disease and is closely linked to the activation of MCs. The role of neuroinflammation and MCs in various neuropsychiatric diseases, including ASD, AD, PD and depression, has been elucidated. However, no studies have assessed the role of MCs in ADHD. In the present review, it was hypothesized that ADHD is a neuroinflammatory disease in which MCs have an important role. The association between other brain diseases and MCs and the inflammation-associated signal cascade induced by MC activation allow for the hypothesis that MCs may induce the development and progression of ADHD through the following mechanisms: i) MCs selectively release various neuroinflammatory mediators, including IL-6, TNF-α, CRH and MCP-1. ii) Microglial and astrocyte activation by MCs via CD40L, TLR2/TLR4, HRH, PAR2, CXCR4/CXCL12, the complement system, MC protease, MAPKs and NF-κB, causes an increased release of IL-6, IL-33, TNF-α, ROS and other inflammatory factors; in turn, glia affect the activation of MCs through the above-mentioned pathways. These pathological processes trigger and exacerbate the state of inflammation in the brain. iii) MCs mediate alterations of co-localized neurons through CADM1, enhancing neuroimmune responses through a process called transgranulation. Mediators released from MCs affect neurodevelopment in the CNS, cause neuronal damage and trigger neuroinflammation. iv) Chronic stress-mediated activation of the HPA axis, which enhances CRH receptor expression and CNS MC activation, leads to microglia activation, increased BBB permeability and release of inflammatory mediators. v) Inflammatory mediators released by MC activation, including histamine, tryptase, chymase and TNF-α, result in increased expression of MMPs, VEGF, ICAM-1, as well as decreased expression of occludin and claudin-5 and destruction of BBB integrity. Inflammatory factors and inflammatory cells then enter the brain tissue, aggravating neuroinflammation in the brain and causing the occurrence and progression of ADHD (Fig. 1). Our group will endeavor to explore and validate these hypotheses using clinical and *in vivo* experiments.

10. Conclusions

With the enhanced requirement for life quality, behavioral disorders such as ADHD are gaining increased attention. However, at present, there is no consensus on the etiology, pathogenesis and effective treatment of ADHD. The association between ADHD and immunity or inflammation has recently been discovered, but the underlying mechanisms have remained to be elucidated. Previous studies (34,41,49,199) have reported that MC activation is an important mechanism in the progression of neuroinflammatory diseases. MCs are of significance and easily overlooked in the immune system of the CNS. Based on the study of ADHD and inflammation, as well as the association between MCs and other neuropsychiatric diseases, it is reasonable to speculate that MC-meditated neuroinflammation has a vital role in ADHD. MC activation may lead to the selective release of inflammatory factors and also affect the function of glial cells via a number of ways, which in turn promotes the occurrence of CNS neuroinflammation. In addition, brain MCs interact with neurons, the BBB and the HPA axis, aggravating neuroinflammation and disrupting brain function. MCs may promote CNS inflammation through various pathways, further leading to the occurrence and exacerbation of ADHD. In the present review, this hypothesis was discussed based on previously published studies. To the best of our knowledge, the association between MCs and ADHD appears to lack sufficient evidence at present and this hypothesis is worthy of further investigation using clinical studies and well-designed experiments. The present study provided a perspective of inflammatory mechanisms being accountable for ADHD. This hypothesis may expand the current understanding of the onset of ADHD and provide a novel target for the treatment of the condition.

Acknowledgements

The authors thank Dr Rongyi Zhou (The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, China) and Dr Jichao Sun (The First Affiliated Hospital of Guangxi University of Chinese Medicine, Nanning, China) for their helpful advice, supervision and early studies in the field of ADHD.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 81674023 and 81873342).

Availability of data and materials

Not applicable.

Authors' contributions

XH conceived and designed the topic of the review. YS and ML performed the literature search and wrote the manuscript. HY and TC reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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