Neuroimmune connections between corticotropin-releasing hormone and mast cells: novel strategies for the treatment of neurodegenerative diseases

Abstract
Corticotropin-releasing hormone is a critical component of the hypothalamic–pituitary–adrenal axis, which plays a major role in the body's immune response to stress. Mast cells are both sensors and effectors in the interaction between the nervous and immune systems. As first responders to stress, mast cells can initiate, amplify and prolong neuroimmune responses upon activation. Corticotropin-releasing hormone plays a pivotal role in triggering stress responses and related diseases by acting on its receptors in mast cells. Corticotropin-releasing hormone can stimulate mast cell activation, influence the activation of immune cells by peripheral nerves and modulate neuroimmune interactions. The latest evidence shows that the release of corticotropin-releasing hormone induces the degeneration of mast cells under stress conditions, leading to disruption of the blood-brain barrier, which plays an important role in neurological diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism spectrum disorder and amyotrophic lateral sclerosis. Recent studies suggest that stress increases intestinal permeability and disrupts the blood-brain barrier through corticotropin-releasing hormone-mediated activation of mast cells, providing new insight into the complex interplay between the brain and gastrointestinal tract. The neuroimmune target of mast cells is the site at which the corticotropin-releasing hormone directly participates in the inflammatory responses of nerve terminals. In this review, we focus on the neuroimmune connections between corticotropin-releasing hormone and mast cells, with the aim of providing novel potential therapeutic targets for inflammatory, autoimmune and nervous system diseases.

Key Words: blood-brain barrier; corticotropin-releasing hormone; gastrointestinal tract; inflammatory; mast cells; neuroimmune; neurological disorders

Introduction
Corticotropin-releasing hormone (CRH) is a primary hypothalamic activator of the hypothalamic–pituitary–adrenal (HPA) axis, playing a key role in the stress response via the regulation of the immune system and neuroendocrine systems (Inda et al., 2017; Russell and Lightman, 2019; Leistner and Menke, 2020; Theoharides, 2020a). Various neurotransmitters/neuromodulators, neuropeptides and inflammatory cytokines control the release of hypothalamic CRH from the hypothalamus, depending on stress responses that modulate neuroendocrine and neuroimmune functions (Dedic et al., 2018; Naama et al., 2020; Theoharides, 2020a). The HPA axis strongly influences neuroimmune and inflammatory processes through the release of CRH. The secretion of CRH in the brain exerts pro-inflammatory effects through mast cell (MC) activation, leading to inflammation and neurological diseases (Kempuraj et al., 2017a). Stress activates the HPA axis via the release of CRH, thereby modulating the central nervous system (CNS) immune components that mainly affect immune cells, such as MCs (Kempuraj et al., 2020a; Pondejak and Luguvić-Mihić, 2020).

MCs are effector cells that connect the nervous, circulatory and immune systems (Krystal-Whittemore et al., 2015; Stakenborg et al., 2020). MCs act as sentinels of the human body and play a pivotal role in the defense mechanism against foreign pathogens and stress responses such as allergy. MCs are critical for allergic reactions and are also directly involved in innate and acquired immunity (Yamanishi and Karasuyama, 2016; González-de-Olano and Álvarez-Twose, 2018). Strong evidence indicates that CRH plays a very important role in the activation of MCs, which secrete numerous cytokines, chemokines, proteases and vasoactive compounds associated with inflammatory-related diseases (Esposito et al., 2002; Theoharides, 2020a). CRH-mediated MC activation affects gut–blood barrier and blood–brain barrier (BBB) permeability via acute psychological stress (Esposito et al., 2002; Vanuytsel et al., 2014). Acute psychological stresses activate the HPA axis via the release of CRH and significantly increase the production of glucocorticoids, resulting in the downregulation of immune responses (Herman et al., 2016; Li et al., 2019; Juruena et al., 2020). A growing body of evidence demonstrates that MCs participate in the neuroendocrine system, demonstrating that MCs are crucial for the treatment of neurodegenerative diseases.
MCs are prototypical neuroimmunoendocrine cells that regulate bidirectional communication between the nervous system and the immune system. Brain-resident MCs and CRH neurons regulate BBB permeability during the stress response (Esposito et al., 2002; Kritas et al., 2014a; Füzesi et al., 2016). However, further study is required to address how brain-resident MCs and CRH regulate BBB permeability. Over the past few years, significant advances in our understanding of the underlying molecular mechanisms has allowed us to focus on the effects of CRH and its receptors on MC activation in inflammatory and neurological diseases.

In this review, we discuss the current state of knowledge on the effects of CRH on MC activation in neuroimmune connections in inflammatory, autoimmune and neurological disorders. Moreover, we briefly address how CRH induces central and peripheral inflammation by promoting MC activation in inflammatory and neurological disorders. In this review, we describe the neuroimmune two-way information exchange between MCs and CRH, which will provide a new perspective for the treatment of inflammatory, autoimmune and neurological diseases. CRH is the initiating hormone for the HPA axis to adapt to the stress response. MCs are immune cells related to allergy, asthma and irritable bowel syndrome. Recent studies have advanced our understanding of these cells—they suggest that MCs play a dual role as sensor and effector in the neuroimmune networks. Under normal circumstances, MCs resident in the brain can secrete factors such as CRH, histamine and tryptase to regulate BBB permeability and maintain brain homeostasis. When intracranial or extra cranial homeostasis is perturbed, the stressor can activate the HPA axis, stimulate the secretion of CRH in the hypothalamic paraventricular nucleus (PVN) and activate intracranial MCs through the CRH receptor (CRH-R), causing the cells to degranulate. By causing the permeability of the BBB to increase, allowing peripheral inflammatory factors and cells to enter the brain, histamine and related mediators released by MCs can activate gial cells and participate in the occurrence and development of central inflammation-related disorders, such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and Parkinson’s disease (PD), as well as perioperative cognitive dysfunction.

Search Strategy
We searched for articles published from the year 1955 to 2020 using Google Scholar, PubMed, Web of Science and Publons to comprehensively summarize the bidirectional neuroimmune communications between MCs and CRH. Keywords used for the literature search included “MCs”, “CRH and its receptors”, “HPA”, “stress”, “Urocortin”, “neurodegenerative disease”, “blood-brain barrier (BBB)”, “neuroimmune”, “MCs activation”, “acute or chronic stress”, “neuroinflammatory processes”, “neurological diseases”, “inflammatory cytokines and neuropeptides”, “immunity”, “peripheral inflammation and central inflammation”, “gial cells”, “skin inflammatory diseases”, “irritable bowel syndrome (IBS)”, “Postoperative cognitive dysfunction (POCD)”, “Alzheimer’s disease (AD)”, “Parkinson’s disease (PD)”, “autism Spectrum Disorder (ASD)”, “multiple Sclerosis (MS)”, “amyotrophic lateral sclerosis (ALS)”, “traumatic brain injury (TBI)” and “rheumatoid arthritis”.

Corticotropin-Releasing Hormone Family
Hypothalamic CRH was first reported in 1955 (Saffran and Schally, 1955) and identified in the ovine hypothalamus in 1981 (Vale et al., 1981). CRH is a neuropeptide hormone of 41 amino acids that is a critical activator of the HPA axis, which is required for stress adaptation. CRH is released from the hypothalamus and stimulates adrenocorticotropic hormone secretion from the anterior pituitary. CRH is one of the central mediators of the excitation of the HPA axis (Herman et al., 2016), and it plays a key role in the neuroendocrine regulation of the stress response. CRH in the hypothalamus is primarily controlled by parvocellular neurons, mainly located in the hypothalamic PVN. CRH neurons that project to the median eminence are found mostly in the PVN, and regulate the release of adrenocorticotropic hormone in the anterior pituitary through the portal system, which in turn stimulates the synthesis and secretion of glucocorticoids (Aguilera and Liu, 2012), which regulate immune function, glucose metabolism and cognitive function. External and internal stress responses are modulated by feedback mechanisms, whereby glucocorticoids act to reduce drive (brainstem) and promote synaptic inhibition by limbic structures (hippocampus).

Glucocorticoids also rapidly inhibit CRH neuronal activity via membrane glucocorticoid receptors in the PVN (Strehl et al., 2019). Recent studies have shown that CRH and its receptors are widely distributed in the body and participate in many critical physiological functions, including organ and visceral sensation, cardiovascular activity, emotional response, learning, mood and memory (Linthurst et al., 1997; Weninger et al., 1999; Kellner et al., 2003; Abelson et al., 2010; Liu et al., 2015). There are two main mammalian peptides in the CRH family—CRH and urocortin (UCN). The past decade has witnessed extensive research and an increasingly deep understanding of the central and peripheral expression and regulation of the CRH and UCN signaling pathways, as well as their role in health and diseases.

Corticotropin-Releasing Hormone
CRH is highly conserved among mammals, including humans, primates and rodents. The CRH precursor comprises 196 amino acid residues, and the mature peptide is located in the C-terminal domain of the precursor (Chrousos and Zoumakis, 2017; Dedic et al., 2018). A processing motif (Arg-X-Arg-Arg) is present at the N-terminus of CRH, while the dipeptide Gly-Lys is located in the C-terminal domain of the precursor (Vale et al., 1981). After processing by endopeptidase, the C-terminal Lys is cleaved off by an exopeptidase, and the C-terminus of the CRH precursor is amidated, with glycine as an amidation donor. CRH mRNA is widely distributed in the brain, particularly in the PVN, cerebral cortex, amygdala, hippocampus and Barrington’s nucleus (Merali et al., 2004; Peng et al., 2017). CRH is also expressed in other peripheral tissues, such as the digestive tract and placenta. CRH sequence homologies are comparatively high (76–95%) between human/rat/mouse and other species (Stenzel-Poore et al., 1992). The human CRH gene, located at 8q13, consists of two exons and one intron (Malagoli et al., 2004). It has been reported that CRH peptides of all species are composed of 41 amino acid residues (C-terminally amidated peptide). CRH plays a major role in controlling the basal and stress-induced activation of the pituitary-adrenal axis, thereby regulating androgen and glucocorticoid secretion. The release of CRH in response to acute stress is necessary for the survival of the organism (Li-Tempel et al., 2019), but CRH released as a result of exposure to chronic stress may influence mood and emotional behavioral and negatively affect physiological homeostasis.

Urocortin
UCN is a member of the CRH family of peptides with high similarity to CRH in amino acid sequence. In the brain, UCN suppresses food intake mediated by CRH-Rs and also participates in the regulation of emotions, anxiety, cognitive...
memory and body temperature, and shows neuroprotective activity (Skelton et al., 2000; Heinrichs and Kooob, 2004). UCN can be classified into the following three subtypes: UCN1, UCN2 and UCN3. UCN is expressed both in the brain and peripheral organs (Pan and Kastin, 2008). Circulating UCN may reach the brain from the peripheral organs by a unique mechanism. UCN1, UCN2 and UCN3 differentially interact with the BBB (Kastin and Akerstrom, 2002). UCN1 contains 40 amino acids, with a structure similar to CRH. UCN1 is expressed in the accessory nucleus of the oculomotor nerve in the mammalian brain, as well as the heart, vascular cells and endometrium, but generally, it is more widely expressed in peripheral tissues (Fukuda et al., 2005). UCN2 is composed of 38 amino acids expressed in the parvocellular and magnocellular parts of the PVN in the hypothalamus, as well as the locus coeruleus, the ventral horn of the spinal cord, supraoptic nucleus and cranial nerve motor nuclei (trigeminal, facial and hypoglossal nuclei). Its sequence has 34% homology with CRH in humans and rats. UCN2 is also found in peripheral tissues, especially in the skin and skeletal muscle tissues (Reyes et al., 2001). UCN3 peptide is expressed in the PVN, ventromedial hypothalamus, amygdala, lateral septum, the dorsal raphe nucleus, basomedial nucleus of the stria terminalis, and the area postrema. The correlation between UCN3 and CRH is relatively weak, and there is almost no overlap in regional expression (Deussing et al., 2010).

**Corticotropin-Releasing Hormone Receptors and Their Functions**

Three subtypes of CRH-Rs have been identified—CRH-R1, CRH-R2 and CRH-R3. All three belong to the family of seven-transmembrane-domain G protein-coupled receptors that activate adenylyl cyclase (Merali et al., 2004; Grammatopoulos and Ouralidou, 2017). CRH-R1 and CRH-R2 have been identified in mammals, amphibians, birds and teleosts (Cardoso et al., 2016). In mammals, CRH-R2 has three splice isoforms—CRH-R2α, CRH-R2β and CRH-R2γ (Catalano et al., 2003) CRH-R3 has only been found in catfish (Deussing and Chen, 2018). CRH-R1 is abundantly expressed in the brain, particularly in anterior pituitary corticotropes and lactotropes, but its expression is limited in the peripheral system. CRH-R1 is an essential neuroendocrine receptor for CRH-mediated adrenocorticotropic hormone release in the pituitary in response to stress. Single-nucleotide polymorphisms in the CRH-R1 gene are associated with a significantly increased risk of neurodegenerative diseases (Weber et al., 2016; Ketchesin et al., 2017).

CRH may activate MCs via CRH-1, leading to the release of histamine, resulting in increased vascular permeability and vasodilation (Theoharides et al., 1998). The expression of CRH-R2 in the brain is relatively limited, but its peripheral expression is relatively high, especially in cardiovascular and skeletal muscle (Sheng et al., 2012). CRHR2α and CRHR2γ are highly expressed in the brain, while CRHR2β is more predominately localized in the heart, thymus and spleen. The functional significance of CRHR2γ in the brain remains unclear. Functional studies and experimental knockout mouse models show that CRH-R1 may mediate the CRH-induced response of the HPA axis to stress, whereas CRH-R2 modulates the stress response and behaviors (Klenerova et al., 2018). CRH-R1 and CRH-R2 have differential binding affinities for ligands and different expression patterns in the brain and periphery. Although CRH-R1 and CRH-R2 share 70% amino acid sequence homology, they have different pharmacological effects owing to lower similarity in the N-terminal domain (Kuenzel et al., 2013). The binding affinity of CRH and UCN for CRH-R1 is higher than that of UCN2 and UCN3 for CRH-R2. CRH-R3 has strong sequence homology to CRH-R1. In most cell types, activation of CRH-R1 or CRH-R2 mediated by CRH results in the activation of the Gs-adenyl cyclase pathway and increased cyclic adenosine monophosphate levels; however, recent evidence suggests that different tissues and cell types express various G proteins, including Gq, Gi and Go, that are associated with the receptor, thereby resulting in the activation of various kinase pathways, including protein kinase C, mitogen-activated protein kinase and Akt (Hillhouse and Grammatopoulos, 2001; Kovalovsky et al., 2002; Grammatopoulos, 2007). After CRH-R1/2 knockout mice were injected with CRH, there was no significant change in adrenocorticotropic hormone release, indicating that the receptor may not be involved in the activation of the HPA axis (Fenzl et al., 2011; Klenerova et al., 2018). Thus, its characteristics and effects need further study. CRH-R has many subtypes with differential tissue distribution, and therefore, it can activate a variety of signal transduction pathways and produce various biological effects.

**Regulatory Effect of Corticotropin-Releasing Hormone on Mast Cell-Mediated Neuroinflammatory Processes**

MCs are a multifunctional immune cell. They originate from CD34+/CD117⁺ bone marrow-derived cells and differentiate into different mature MCs under the influence of different environments. MCs are generally distributed along blood vessels or body surfaces and express many cell surface receptors, and accordingly, their differentiation, migration and activation are easily affected by the external environment. Therefore, MCs are regarded as sentinels of the human body and play an important role in the defense against the outside world and the stress response such as allergy (Li et al., 2017). MCs abundantly express CRH-R1 and CRH-R2 on their surface and are highly sensitive to CRH (Ayyadurai et al., 2017). The expression levels of CRH and its receptors are increased in patients with mastocytosis (Theoharides et al., 2014). It has been reported that stress is the main risk factor for the occurrence and aggravation of MC-related diseases, such as allergy, asthma and irritable bowel syndrome (Priftis et al., 2009; Andrae et al., 2013; Heffner et al., 2014). MCs are activated by the CRH signal, which leads to degranulation and the release of various inflammatory factors such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) (Theoharides et al., 2012). Although it is known that MCs are highly activated under stress conditions, the cellular mechanisms by which stress regulates MC function and pathophysiology are still unclear. The human leukemic mast cell (HMC-1) line and human umbilical cord blood-derived MCs both express CRH and the CRH-R1α, 1β, 1c, 1e and 1f isoforms (Cao et al., 2005). CRH activates the HPA axis in the stress response, possibly through MC activation. CRH-mediated MC activation increases cyclic adenosine monophosphate levels and induces the secretion of vascular endothelial growth factor without trypase, histamine, TNF-α, IL-6 or IL-8 release (Theoharides, 2020a).

Interestingly, human MCs synthesize and secrete a large amount of CRH, suggesting this neuroendocrine peptide may regulate MCs through CRH and its receptors in an autocrine manner (Zouboulis et al., 2002; Ayyadurai et al., 2017). CRH-mediated MC activation regulates the autocrine signaling pathway under inflammatory conditions; however, its receptors remain to be identified. MCs communicate functionally with glial cells in the brain and degranulate in response to physical and psychological stress. Studies have shown that degranulation of brain MCs modulates HPA responses via centrally released histamine and CRH (Matsumoto et al., 2001; Elenkov et al., 2005).

In the model of MC-dependent IgE-mediated passive systemic anaphylaxis, treatment with antalarmin, an antagonist of CRH-R1, can alleviate the symptoms caused by MC degranulation and hypothermia. When CRH-R1 on the surface of MCs is knocked out, serum histamine content, body temperature and clinical score recover compared with the...
control group, and the degranulation of MCs and intestinal permeability changes are also inhibited (Ayyadurai et al., 2017). These studies suggest that CRH-R1 regulates MC activation mediated by CRH. Accumulating evidence indicates that CRH can induce MCs to secrete vascular endothelial growth factor by increasing cAMP, which can be blocked by antalarmin, while astressin 2B, an antagonist of CRH-R2, has no effect (Cao et al., 2006; Boucher et al., 2010). These results reveal that the CRH-R1 signal plays a key role in MC degranulation. However, the regulatory effect of CRH-R2 on MCs remains unclear. It has been shown that CRH-R1 and CRH-R2 are expressed on the surface of human cord blood MCs cultured with stem cell factor and IL-6 for 10 weeks (Papadopoulou et al., 2005; Asadi et al., 2012). Only CRH-R2 is expressed when IL-4 is added in the last 3 weeks. Further analysis showed that adding IL-1 or lipopolysaccharides within 6 hours only increased CRH-R2 gene expression. CRH could not induce human cord blood MCs to secrete IL-6, but could induce human cord blood MCs to release IL-4. These results suggest that CRH-R2 is upregulated when MCs are stimulated by inflammation (Papadopoulou et al., 2005). However, there are also experimental results contrary to the above studies; namely, the loss of CRH-R2 function has been shown to aggravate MC degranulation and promote IgE-mediated anaphylaxis and psychological stress-induced intestinal barrier dysfunction. CRH-R2 on the surface of MCs inhibits degranulation induced by various stimuli by blocking calcium-triggered calcium release channels (Vicario et al., 2010; D’Costa et al., 2019), indicating that CRH-R2 can also negatively regulate MC activation. These varied findings suggest that, at the single-cell level, the effect of CRH-R activation on MCs is modulated by multiple signaling pathways.

Theoharides (2020a) have suggested that CRH activates brain-resident immune cells (such as MCs, microglia and astrocytes) through CRH-Rs, and that these cells release numerous neuroinflammatory and neurotoxic factors that affect BBB permeability, thereby contributing to chronic neuroinflammation and neurodegenerative diseases. It is well recognized that MCs act as the first responders in the brain, and can initiate, amplify and modulate various nervous and immune responses upon stimuli. Furthermore, degranulated MCs secrete numerous mediators that trigger neuroinflammatory processes linked to several neurological disorders as well as neurovascular dysfunction. Data from clinical studies demonstrate that neurovascular dysfunction disrupts BBB permeability and is associated with neuroinflammation and cognitive decline caused by chronic stress (Najjar et al., 2013; Sweeney et al., 2018). However, further study is required to clarify the effects of stress on the neurovascular system in the brain and the relationship to CRH-mediated MC activation. MS and brain metastases may increase BBB permeability in response to acute stress that leads to the release of CRH and the activation of brain MCs, which in turn secrete vascular endothelial growth factor, IL-6 and IL-8 (Theoharides and Konstantinidou, 2007). These results indicate that acute or chronic stress may increase BBB permeability via CRH and MCs. A few studies have reported that MCs and microglia express large amounts of CRH and its receptors, and that these cells are activated by CRH released from the HPA system, which in turn has autocrine effects and modulates neuroinflammatory processes (Kritas et al., 2014a; Zhang et al., 2016d). CRH and its receptors activate MCs and microglia that release inflammatory factors (such as TNF, IL-6, IL-8, IL-33, IL-1, IL-18, nitric oxide and proteases), leading to the complication of neurological disorders via complex crosstalk between CRH, MCs and microglia (Tsilioni et al., 2016). Studies have shown that MCs are activated during acute or chronic stress through CRH released by sensory nerves, and may be involved in the disruption of neurodevelopment and the pathogenesis of neuropsychiatric disorders (Petra et al., 2015; Godoy et al., 2018). However, the mechanisms underlying the neurodevelopmental perturbation and the link with MCs and CRH remain unknown.

Surgical stress responses are connected with crosstalk interactions within the nerve–endocrine–immune network (Finnerty et al., 2013; Manley et al., 2018). Several studies reported that stress is the leading risk factor for the occurrence and aggravation of MC-related diseases, such as allergies and asthma (Kryśtel-Whittemore et al., 2015; Bischoff, 2016). MCs in the brain are widely distributed in the hypothalamus, especially near the nerve endings containing CRH, which can be activated by surgical stress (Traina, 2017). The activation of MCs in the rat brain can be observed in a model of acute stress caused by immobilization stress, and CRH antisera pretreatment can block this effect. Furthermore, injection of the MC stabilizer sodium cromoglycate in the hypothalamus can reduce BBB damage caused by CRH (Jin et al., 2007; Ocak et al., 2019). In addition, stress only causes BBB destruction in the brain of wild-type mice, but has no effect on the BBB in MC knockout mice (Theoharides and Konstantinidou, 2007). Theoharides and Konstantinidou (2007) pointed out that the increased permeability of the BBB under acute stress depends on the interaction of CRH and MCs. Kempuraj et al. (2017b) suggested that CRH might influence MC activation and their release of inflammatory mediators, resulting in peripheral and central inflammation (Figure 1). However, further study is required to investigate whether peripheral surgical trauma stress promotes the release of CRH in the hypothalamus and activates MCs in the brain, resulting in increased permeability of the BBB and neuroinflammation.

MCs are an immune cell of bone marrow origin that regulate neuroinflammation and, upon activation, secrete many inflammatory mediators in systemic and CNS inflammatory conditions (Dong et al., 2014; Hendriksen et al., 2017; Kempuraj et al., 2019). MCs are critical immune regulators and act as sentinels of brain immunity because of their unique ability to regulate the stress response via the HPA axis (Galli et al., 2008; Theoharides, 2020a). Matsumoto et al. (2001) first reported that brain-resident MCs are an immune gate to the HPA responses via histamine and CRH release. Emerging evidence demonstrates that acute and chronic stress has inflammatory effects that are mediated through MC activation (Traina, 2019; Wang et al., 2020).

Stress conditions are known to suppress the immune responses and worsen neuroinflammatory conditions. Stress and environmental stimuli can trigger MC degranulation, which may induce glial cell activation that results in abnormal synaptic pruning and dysfunctional neuronal connectivity in the CNS (Boscolo et al., 2008; Paolicelli and Ferretti, 2017; Theoharides et al., 2019). We previously reported that activation of brain-resident MCs and microglia by a combination of stress and environmental triggers may disrupt neuronal connectivity in the amygdala and hippocampus, thereby altering BBB homeostasis linked to the neuroinflammatory response in the CNS (Zhang et al., 2016e). Several lines of experimental evidence indicate that stress, acting through the HPA axis or the sympathetic nervous system, stimulates peripheral nerves to release CRH and other neuropeptides that bind to receptors on the MCs, causing them to activate (Galli et al., 2018; Podobnik and Lugovic-Mihic, 2020). Bidirectional interaction between stress and MCs enhance the stress response in the CNS and stimulate the release of inflammatory cytokines and neuropeptides, leading to neuroinflammation and the disruption of the BBB that results in the pathophysiology of many neuroinflammatory conditions, such as AD, PD, MS and autism spectrum disorder (ASD) (Figure 1) (Hendriksen et al., 2017; Jones et al., 2019).
Crosstalk between the Blood–Brain Barrier, Mast Cells and Corticotropin-Releasing Hormone in Brain Inflammation

The BBB maintains microenvironmental homeostasis in the CNS for brain functional integrity (Chow and Gu, 2015). Stress, environment and lifestyle may independently and/or synergistically influence brain inflammation, causing BBB dysfunction and pericyte degeneration, resulting in neuronal death (Zhao et al., 2015b). The intact BBB can effectively block the entry into the brain of harmful substances in the circulation, thereby maintaining the homeostasis of the CNS environment (Li et al., 2017). The BBB is an essential gateway for peripheral inflammatory factors and immune cells (MCs and glial cells) to invade the brain parenchyma. Lacrochelle et al. (2011) found that the activation of peripheral immune cells can lead to the destruction of the BBB. Leukocytes can then migrate into the brain through the BBB, further increasing its permeability and inducing more white blood cells to infiltrate into the CNS (Chow and Gu, 2015; Keaney and Campbell, 2015). Therefore, the change in BBB permeability is an essential condition for peripheral trauma to induce acute central inflammation. Our team previously reported that activated MCs contribute to CNS inflammation and cognitive dysfunction by promoting BBB disruption (Zhang et al., 2016c). Therefore, based on our knowledge, we propose that interactions between MCs and the BBB could constitute a new and unique therapeutic target for neurological disorders.

The MC is a multifunctional effector cell of the body’s innate immune system. It is mainly located in the brain around the hypothalamus and the BBB. Under normal conditions, MCs in the brain secrete histamine, tryptase and other mediators through degranulation to regulate sensation, mood and cognition (Kempuraj et al., 2017a; Li et al., 2017). When peripheral inflammation occurs, the MCs in the brain immediately respond to the immune signal in the blood and quickly degranulate, releasing mediators that trigger the central inflammatory response. Because of its rapid response and signal transmission capabilities, the MC is involved in various CNS diseases such as AD, PD, ASD, stroke and cerebral ischemia-reperfusion injury (Theoharides and Konstantinidou, 2007; Galli et al., 2008; Skaper et al., 2018). In follow-up animal experiments, our team further found that surgery for tibial fractures in rats can cause an increase in MCs in the brain, increased BBB permeability, microglial activation and neuronal apoptosis, leading to increased central inflammation and a decline in learning and memory functions. Pretreatment with injection of an MC stabilizer into the lateral ventricle can prevent these changes (Zhang et al., 2016e). We showed that MC degranulation increases BBB permeability in the brain after peripheral surgery and the occurrence of acute central inflammation. Therefore, we speculate that the release of factors such as histamine and tryptase by degranulating MCs induce the destruction of the BBB and aggravate the central inflammatory response (Figure 1).

The Effects of Corticotropin-Releasing Hormone on Mast Cells: Implication for Inflammatory, Autoimmune and Neurological Disorders

Skin inflammatory diseases

The skin is the largest organ of the human body and is always in contact with the external environment. Skin MCs act as functional sensors of emotional and environmental stress, and can be directly activated by CRH released under stress and related neuropeptides. CRH and its receptors may activate MCs that stimulate pro-inflammatory actions to result in the pathogenesis of various skin disorders that are triggered by acute stress, such as atopic dermatitis, psoriasis, eczema and urticaria (Suárez et al., 2012; Căruntu et al., 2014; Chen and Lyga, 2014; Siiskonen and Harvima, 2019; Figure 3). MC-related atopic dermatitis and psoriasis are triggered by CRH/CRH-R-mediated MC activation, causing the production and release of numerous cytokines and chemokines (Nedoszytko et al., 2014). Psoriasis is triggered by acute and chronic stress and is associated with increased serum CRH-mediated MC activation, but decreased CRH-R1 gene expression, in the lesioned skin, possibly because of downregulation (Vasiadi et al., 2012; Tampa et al., 2018). MC activation and accumulation are critical to the pathogenesis of psoriasis and are involved in keratinocyte proliferation and inflammation. CRH increases the incidence rate of skin allergy and other skin diseases by activating MCs near sensory nerve terminals (Gupta and Harvima, 2018). Recent studies show that many genes that are expressed in the CNS are also expressed in the epidermis of animals, indicating an actual “skin brain” (Martins et al., 2020). The skin has also been shown to have an equivalent to the HPA axis (Holland, 2003).
Skin stress reactions, such as to ultraviolet radiation, can promote the release of CRH, leading to the degranulation of skin MCs, resulting in increased local vascular permeability (Slominski et al., 1998; Pisarchik and Slominski, 2002). Acute stress can also exacerbate delayed hypersensitivity, and chronic contact dermatitis of the skin in rats directly depends on CRH and its receptors, which are related to the upregulation of vascular permeability (Lytinas et al., 2003). CRH/CRH-R-mediated MC activation also causes peripheral blood vessel dilation and blush. Intraepithelial administration of CRH and UCN can activate CRH-R1 on the surface of mouse and human skin MCs to promote MC activation and increase skin vascular permeability. However, this does not occur in MC-deficient mice or in animals treated with the CRH-R1 antagonist antalarmin, indicating that CRH functions through MCs in skin lesions (Singh et al., 1999).

Irritable bowel syndrome

CRH is a crucial mediator of the stress response in irritable bowel syndrome (IBS) pathogenesis, which is a disorder of bidirectional interaction between the gut and brain. It has been proposed that IBS pathogenesis is linked with the HPA axis and autonomic imbalances in the prefrontal–amygdala circuitry. Studies have shown that exogenous CRH administration produces IBS-like symptoms, including anxiety behaviors, perturbed gut homeostasis, increased colonic motility, hyperalgesia to colorectal distention, watery stool/diarrhea, increased colonic mucosal permeability and autonomic responses, as well as altered brain activity (Kano et al., 2017). Studies show that colon mucosal CRH content in IBS patients is significantly higher compared with the control group (Santos et al., 2008). When CRH or UCN are injected intraperitoneally or intravenously in rats, the long-term collective explosive peak potential of the ileocecum and proximal colon and the transit time of the colon are shortened. The administration of alpha-helical CRH, a non-selective CRH-R antagonist, significantly stimulates the rectum and results in higher motility indices of the colon in IBS patients compared with the control group (Sagami et al., 2004). Numerous studies have identified CRH and UCN as well as CRH-R1 and CRH-R2 in the colonic mucosa of IBS patients (Taché et al., 2004; Sato et al., 2012; Komuro et al., 2016). However, the pathological mechanisms underlying the CRH-mediated adrenocorticotropic hormonal responses induced by MC degranulation in the IBS remain unclear.

MCs are widely distributed in the gastrointestinal tract. It has been

**Figure 1** The neuroimmune connections between CRH and MCs associated with central and peripheral inflammation result in neurological disorders.

The schematic diagram shows the effect of stress-induced neuroimmune interactions between CRH and MCs and the link to neurological diseases. Stress conditions activate the HPA axis to induce neuroimmune communication between CRH and MCs to release numerous inflammatory mediators from MCs upon their activation, which in turn disrupts the BBB, leading to neuroinflammatory processes associated with neurological diseases. AD: Alzheimer’s disease; ASD: autism spectrum disorder; BBB: blood–brain barrier; CRH: corticotropin-releasing hormone; HPA: hypothalamic-pituitary-adrenal; IL: interleukin; MC: mast cell; MS: multiple sclerosis; NT: neuropeptide Y; POCD: postoperative cognitive dysfunction; TNF: tumor necrosis factor.

**Figure 2** The interactions between CRH and MCs that may affect the BBB under acute and chronic stress.

Acute and chronic stress trigger HPA axis activation to induce the release of CRH, resulting in MC activation and their secretion of histamine, tryptase and proinflammatory cytokines in the hippocampus that affect the BBB and central inflammation. Two CRH receptors are localized on the surface of MCs, and these receptors have different biological effects during stress-induced MC activation. The MCs interact with astrocytes and microglia, which release CRH, histamine, neuropeptides and serotonin, leading to disruption of the BBB. BBB: Blood-brain barrier; CRH: corticotropin-releasing hormone; CRHR: corticotropin-releasing hormone receptor; HPA: hypothalamic-pituitary-adrenal; MC: mast cell.

**Figure 3** Schematic diagram showing the acute and chronic stress-associated neuroimmune connections between CRH-mediated MC activation in inflammatory and neurological diseases.

Acute and chronic stress dysregulate the HPA axis via the release of CRH in the brain. The secretions of CRH in the brain trigger MCs activation by releasing various preformed and newly synthesized inflammatory mediators. Activated MCs also trigger other neuroimmune cells activation, including astrocytes, microglia, which decrease the synaptic plasticity, disrupt BBB integrity and mediate neuroinflammation associated with AD, POCD, MS, and ASD. Degranulations of MCs increase gut motility related to the severity of abdominal discomfort and pain in IBS patients. Activate MCs stimulate pro-inflammatory actions to result in the pathogenesis of various skin disorders such as atopic dermatitis, psoriasis, eczema, and urticaria. BBB: Blood-brain barrier; CRH: corticotropin-releasing hormone; MC: mast cell; MMP: matrix metalloproteinase; NT: neuropeptide Y; ROS: reactive oxygen species; SP: substance P; VEGF: vascular endothelial growth factor; VIP: vasoactive intestinal peptide.
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reported that MCs in the intestinal mucosa are upregulated, along with increased gut motility in IBS patients and increased MC degranulation, which are related to the severity of abdominal discomfort and pain. Therefore, MCs play a key role in the pathogenesis of IBS (Ohman and Simrén, 2010; Figure 3). CRH and its receptors are widely expressed on MCs in the gastrointestinal tract. The high content of CRH and its receptors is positively correlated with the number of intestinal MCs in IBS mice, suggesting that MCs may be one of the major cells producing intestinal CRH and its receptors (Lee and Lee, 2016; Zhang et al., 2016b). Descending colon activity in IBS patients is significantly higher after intravenous CRH injection than in the healthy control group, and CRH promotes the secretion of colonic mucus and the release of MC proteases (Vicario et al., 2010). Castagliuolo et al. (1998) found that injecting CRH into the peritoneal cavity and the ventricles of MC-deficient mice did not stimulate colonic electrical activity, suggesting that the biological function of CRH and its receptors in the intestinal tissue is related to MCs. The stress response increases the permeability of the colonic mucosa in mice. This effect can be antagonized by CRH-R antagonists and the MC stabilizer cromolyn sodium, indicating that CRH and MCs are jointly involved in stress-induced intestinal barrier dysfunction (Santos et al., 2008; Wallon and Söderholm, 2009).

Surgical stress and postoperative cognitive dysfunction

In recent years, the stress response has attracted increasing attention from researchers. Scientists have put forward stress theory and the concept of systemic adaptive syndrome for the physiological changes after stress. Common stressors include tension, fear, cold and surgical trauma, as the most common stressor in the scope of surgery, as its intensity and effect on the body are far greater than that of common stressors (Aroma et al., 2010; Finnerty et al., 2013). Surgical stress can lead to an increase in BBB permeability, and inflammatory signals enter the CNS through the damaged BBB, causing irreversible damage. Our team previously showed that the degranulation of MCs in the brain plays an essential role in the increase in BBB permeability after peripheral surgery (Zhang et al., 2016e). However, it remains unclear how surgery causes MCs in the brain to become activated and degranulate.

During the stress of surgery, the hypothalamic PVN receives information about the CNS and excites the HPA axis. CRH is considered to be the triggering hormone of the HPA axis. MCs in the brain are widely distributed in the hypothalamus, especially near the nerve endings containing CRH, which can be activated by surgical stress. It has been shown that acute stress can activate MCs in the rat brain, and this can be blocked by CRH antiserum pretreatment (Eutamene et al., 2003). The BBB injury induced by CRH can be alleviated by pre-injecting the MC stabilizer sodium cromoglycate into the hypothalamus (Nelissen et al., 2013). Stress only causes BBB damage in brain areas where MCs are present and has no effect on the BBB in MC knockout mice (Esposito et al., 2002). Although little is known about how CRH regulates MCs in surgical stress, MCs can potentially deliver neuroprotective agents released from their storage granules into the hypothalamus (Nelissen et al., 2013). Stress only causes BBB damage in brain areas where MCs are present and has no effect on the BBB in MC knockout mice (Esposito et al., 2002). Although little is known about how CRH regulates MCs in surgical stress, MCs can potentially deliver neuroprotective agents released from their storage granules (Dong et al., 2014). We believe that surgical stress leads to a large amount of CRH release, probably by activating nearby MCs. We propose that CRH/CRH-R-mediated MC activation in the brain is associated with inflammatory responses, and the development of neuroinflammation is associated with postoperative cognitive dysfunction and brain damage.

AD

AD is the leading cause of dementia in the aging population worldwide. AD is characterized by the accumulation of β-amyloid peptide (Aβ) deposits and neurofibrillary tangles within the brain along with the hyperphosphorylated and the cleaved form of the microtubule-associated protein tau, which cause synaptic dysfunction and cognitive impairment (Lane et al., 2018; Soria Lopez et al., 2019). Accumulation of Aβ is one of the critical triggers of pro-inflammatory responses leading to neuroinflammation and neurodegeneration in AD (Kinney et al., 2018). Aβ modulates synaptic plasticity, synaptogenesis, axonal growth and guidance, oxidative stress, learning and memory (Parihar and Brewer, 2010; Cuestas Torres and Cardenas, 2020). In addition, changes in neuroinflammatory signaling occur in AD pathology, as evidenced by activated MCs and glial cells (Skaper et al., 2014b).

The HPA axis induces MC degranulation under chronic stress, releasing excessive pro-inflammatory mediators that cause synaptic loss, disruption of BBB integrity and neuroinflammation in brain regions affected by AD (Galli et al., 2008; Du and Pang, 2015; Justice, 2018; Kempter et al., 2019; Figure 3). Dysregulation of the HPA axis in AD is accompanied by other clinical alterations, including memory impairment and synaptic plasticity deficits. Accumulating evidence illustrates that MC-derived inflammatory mediators may accelerate AD pathogenesis associated with neuroinflammation in the CNS (Machado et al., 2014; Chelomibitko et al., 2016; Shaik-Dasthaigirisaheb and Conti, 2016). Because MCs play a key role in neuroinflammation, chronic stress and psychiatric disorders, it is essential to study its roles in the pathogenesis of AD. However, the mechanisms by which chronic stress-mediated MC activation and HPA axis changes contribute to the pathogenesis of AD remain unclear. The early stage of AD is associated with perturbation of the HPA axis and high levels of CRH in biofluids in patients (Popp et al., 2015; Peña-Bautista et al., 2019). CRH may also work with other neuropeptides, including neurotensin, which enhances MC activation, leading to the release of many inflammatory mediators under acute stress (Alysandratos et al., 2012). CRH and its receptor CRH-R1 mediate stress-induced MC degranulation and the secretion of neuropeptides that activate glial cells in neurodegenerative diseases such as AD (Kempter et al., 2004, 2019; Ayyadurai et al., 2017).

It has been reported that CRH and norepinephrine levels are significantly upregulated in the CSF of AD patients, compared with control subjects (Wang et al., 2018). Similarly, a significant correlation between brain glucose metabolism and CRH levels has been observed in AD (Mosconi et al., 2008), suggesting a bidirectional relationship between the HPA axis and AD progression. The degranulation of MCs induced by CRH under stress could cause dysfunction of the HPA axis, producing other immune cell alterations such as in microglia. CRH and its receptors also play a pivotal role in the development of AD pathology (Machado et al., 2014). Accumulating evidence demonstrates that CRH and its receptors modulate γ-secretase activity, increasing Aβ production (Kempter et al., 2004, 2019; Mosconi et al., 2008; Park et al., 2015; Popp et al., 2015; Chelomibitko et al., 2016; Shaik-Dasthaigirisaheb and Conti, 2016; Ayyadurai et al., 2017; Wang et al., 2018; Peña-Bautista et al., 2019; Vandel and Gounko, 2019). CRHR1 knockout mice exhibit blocked phosphorylation of tau, but not CRHR2 knockout mice, suggesting a specific role for CRHR1-mediated signaling in AD (Rissman et al., 2007).

CRHR1 signaling pathways show that women are more vulnerable to AD than men (Futch et al., 2017; Vuppaladhadiam et al., 2020). The CRHR1 antagonist R121919 has been shown to decrease stress-mediated neuroinflammation, prevent cognitive damage and reduce Aβ deposition in the AD mouse model (Vuppaladhadiam et al., 2020). Similarly, another study reported that administering a CRHR1 antagonist reduced the expression levels of phosphorylated tau (Rissman et al., 2007; Zhang et al., 2016a). Therefore, antagonism of CRHR1 could be a new therapeutic strategy for AD.
PD is a chronic and progressive movement disorder characterized by motor symptoms (such as resting tremor, rigidity, postural instability and bradykinesia) and numerous non-motor disturbances. The pathological hallmarks of PD are intraneuronal and intra-axonal inclusions of α-synuclein (Lewy bodies and Lewy neurites) and the degeneration of dopaminergic neurons in the substantia nigra and other brain regions (Tan et al., 2020). Recent studies show that inflammatory responses by MCs and glial cells, T cell infiltration and increased expression levels of inflammatory mediators in the MCs and neuronal cells are the most prominent features of PD (Kempuraj et al., 2017b, 2018; Selvakumar et al., 2018). Neuroinflammation is another key factor in PD pathogenesis and may further induce progressive loss of dopaminergic neurons (Kempuraj et al., 2016b; Tan et al., 2020). The activation of MCs releases many pro-inflammatory mediators responsible for neurodegeneration in the pathogenesis of PD (Kempuraj et al., 2016a; Sugama et al., 2016). However, the etiology of PD pathogenesis remains unclear.

De Souza and colleagues (De Souza et al., 1987) reported that the expression levels of CRH were decreased in the cerebral cortex in PD. UCN and CRH have been proposed as cytoprotectants via CRH-R1 (Pedersen et al., 2002; Facci et al., 2003). UCN was found to arrest the development of Parkinsonian-like features in the 6-hydroxydopamine-lesioned hemiparkinsonian rat model (Abuirmeileh et al., 2007). UCN, acting via the CRH-R1 receptor, has shown anti-inflammatory activity in the periphery (Gonzalez-Rey et al., 2006). UCN significantly reduces the development of Parkinsonian-like pathology (Abuirmeileh et al., 2008; Whitton, 2010). CRH and UCN reduce weight gain in a rodent PD model, but only CRH produced consistent effects with improved sympathetic activity (Oki and Sasano, 2004). It has been reported that UCN acts via the CRH-R1 receptor and can maintain nigrostriatal function in the neuroinflammatory model of PD (Abuirmeileh et al., 2007, 2009). These findings suggest that UCN-mediated neuroprotection is a potential therapeutic strategy for PD.

Although PD is mainly an idiopathic disease, it can still have a hereditary or an environmental origin, and both can be related to early life stress (Dauer and Przedborski, 2003; Lupien et al., 2009; Tsang and Chung, 2009; Hemmerle et al., 2012). Chronic stress activates the HPA axis and may trigger the dopaminergic neuron loss in the substantia nigra in PD (Mposiana et al., 2016). CRH-R1 receptors expressed in dopaminergic neurons may have an anxiolytic effect depending on the brain region (Refojo et al., 2011). MCs are surrounded by microglia and astrocytes that can become activated in PD, releasing inflammatory cytokines, CRH, neurotensin and neuropeptides that trigger bidirectional communication to damage dopaminergic neurons (Kempuraj et al., 2018; Figure 3). However, additional studies are needed to elucidate the molecular and cellular communication mechanisms between MCs, CRH neurons and glial cells in PD pathogenesis.

ASD
ASD is a complex neurodevelopmental disorder characterized by impaired communication, obsessive behaviors and language problems (Ousley and Cermak, 2014; Muotri, 2018; Theoharides et al., 2019; Marrus and Constantino, 2020). This disorder also includes repetitive and limited patterns of behavior. The incidence of ASD is increasing worldwide, with the most recent prevalence studies indicating that they will be present in 1 in 40 children by 2025 (Leigh and Du, 2015). ASD has neither a distinct pathogenesis nor an effective treatment, yet evidence continues to mount demonstrating immune abnormalities and autoimmune or brain inflammation in specific brain regions as well as neurodevelopmental perturbations.

Neuroinflammation linked to neuroimmune dysfunction has been well established in ASD as an essential factor in its development and maintenance (Onore et al., 2012; Rossignol and Frye, 2012; Estes and McAllister, 2015). Emerging evidence illustrates that neuroinflammation plays a key role in the pathogenesis of ASD and may result from the activation of MCs (Cao et al., 2005; Skaper et al., 2014a; Girolamo et al., 2017; Siniscalco et al., 2018; Theoharides et al., 2019). Brain-resident MC activation by psychological stress or environmental stimuli may trigger the release of pro-inflammatory cytokines and neuropeptides (CRH, neurotensin) that could disrupt BBB integrity and cause allergies in specific brain regions, thus contributing to neuroinflammation in ASD (Siniscalco et al., 2018; Theoharides et al., 2019; Figure 3). Pro-inflammatory cytokines and neuropeptides (CRH, neurotensin) are significantly increased in children with ASD compared with non-ASD controls (Molloy et al., 2006; Tsilioni et al., 2014; Prata et al., 2019). However, further study is needed to clarify whether hyperactive MCs induce the release of inflammatory mediators via CRH neurons and HPA axis activation and directly regulate neuroinflammatory processes in the pathogenesis of ASD.

ILs are involved in neuroinflammatory modulation and have been studied for their roles in inflammatory states and neurodevelopmental disorders (Xu et al., 2015; Siniscalco et al., 2018). IL-6 can be selectively released from MCs upon activation (Kandere-Grzybowska et al., 2003; Theoharides et al., 2007). In addition, IL-6 expression levels are upregulated in the brain of ASD patients (Li et al., 2009; Saghazadeh et al., 2019). Furthermore, the expression levels of serum IL-6 are linked to the autistic phenotype in mice (Dahlgren et al., 2006; Smith et al., 2007). Interestingly, patients with mastocytosis show increased proliferation and activation of MCs and upregulated serum levels of IL-6 (Brockow et al., 2005). Additionally, postnatal mice exhibit increased expression levels of IL-6 and IL-17 and altered immune regulation associated with ASD-related behaviors (Hsiao et al., 2012). Tsilioni et al. (2019) reported that IL-37 is significantly increased along with the pro-inflammatory cytokine IL-18 and its receptors in the amygdala and dorsolateral prefrontal cortex of children with ASD. Therefore, we propose IL inflammatory proteins as potential therapeutic targets for ASD.

Stress is linked to the onset and worsening of ASD. This link may involve brain MCs activated by CRH from the hypothalamus, thereby contributing to neuroinflammation (Theoharides, 2020a). MCs widely express CRH, and its receptors lead to selective production of vascular endothelial growth factor (Cao et al., 2005). MCs are closely linked to CRH nerve endings in the median eminence of the PVN (Rozniecki et al., 1999). It has been reported that UCN1 induces activation of cultured human MCs (Singh et al., 1999). Acute stress results in the secretion of CRH, which activates the HPA axis, leading to stimulation of MCs and increased vascular permeability and disruption of BBB integrity associated with neuroinflammation in ASD pathogenesis (Theoharides et al., 1998; Crompton et al., 2003; Lytnas et al., 2003; Ribatti, 2015; Joshi et al., 2019; Welcome and Mastorakis, 2020). Investigating the interaction between MCs and CRH neurons in the amygdala could uncover novel therapeutic targets for ASD.

MS
MS is a neurological autoimmune disorder causing severe non-traumatic disability in young adults. The pathological hallmarks of MS are inflammatory demyelinating lesions and neurodegeneration within the CNS (Oh et al., 2018; Reich et al., 2018; Wasko et al., 2020). The mechanisms of MS involve disruption of the innate and adaptive immune systems, leading to the inflammatory infiltration of immune cells (composed of MCs, T and B cells, dendritic cells and
natural killer cells) into the brain and spinal cord through an increasingly leaky BBB (Hemmer et al., 2015; Baecher-Allan et al., 2018). MCs may promote demyelination at the early stage because MCs interact with other immune cells (astrocytes and microglia) to mediate neuroinflammation (Elieh-Ali-Komi and Cao, 2017; Pinke et al., 2020; Zusso et al., 2020).

Chronic stress, CRH-mediated MC activation and BBB dysfunction may participate in the pathogenetic progression of MS (Theoharides et al., 2012; Figure 3). MCs are tightly associated with CRH-positive neurons in the median eminence and widely express CRH and its receptors (Theoharides et al., 1995). Hyperactivation of hypothalamic MCs can stimulate the HPA axis through histamine and CRH, which regulate hypothalamic function and can also increase CRH/CRH-R mRNA expression in the hypothalamus (Bugaïski et al., 1995; Kjaer et al., 1998; Ayyadurai et al., 2017). It has been reported that human MCs can produce and release large amounts of CRH, as well as IL-1 and IL-6, which are critical activators of the HPA axis (Bethin et al., 2000; Cao et al., 2005). MC-derived mediators such as neuropeptides (CRH, neurotensin and SP) may increase BBB permeability (Tsilioni et al., 2016). CRH and MCs regulate BBB permeability, and possibly, neurological inflammatory disorder exacerbated by chronic stress. Benou et al. (2005) reported that CRH-deficient mice are resistant to experimental autoimmune encephalomyelitis and show decreased clinical disability and brain infiltration of immune cells. This suggests that CRH contributes to immune cell activation and the peripheral inflammatory response in experimental autoimmune encephalomyelitis. It is hypothesized that the subsequent chronic activation of MCs may activate the HPA axis that contributes to MS pathogenesis. Further studies are needed to elucidate the neuroimmune connections between MC-mediated BBB disruption, HPA axis activation and tissue damage in MS.

ALS
ALS—also known as motor neuron disease or Lou Gehrig’s disease—is an idiopathic, fatal neurodegenerative disease that is characterized by the progressive degeneration of motor neurons with heterogeneity in the age and site of disease onset. The pathophysiological mechanisms involved in the motor neuron degeneration underlying ALS are multifactorial and complex processes with interactions between genetic and environmental factors (Brown and Al-Chalabi, 2017). Mutations in numerous genes have been linked to ALS, including TARDPB (also known as TDP-43; TAR DNA-binding protein) (Sreedharan et al., 2008), SOD1 (copper/zinc ion-binding superoxide dismutase) (Zetterström et al., 2007), FUS (fused in sarcoma) (Vance et al., 2009), OPTN (optineurin) (Maruyama et al., 2010) and ANG (angiogenin, ribonuclease, RNase A family, 5) (Greenway et al., 2006). Transgenic mice expressing these mutations exhibit neuroinflammation and immune dysregulation, which lead to microglial and MC activation and reactive astrocytosis, immune cell dysfunction and the release of proinflammatory mediators from peripheral lymphocytes, monocytes and macrophages (Malyshchev and Malysh, 2015; Zhao et al., 2015a, 2017; Liu and Wang, 2017). ALS is characterized by significantly increased spinal and brain inflammation, particularly mediated by microglia and MCs (Clemente, 2012).

Emerging evidence now points to a fundamental role of neuroinflammatory mechanisms in pathophysiology onset and progression, with the interaction of MCs and microglia playing a key role in neurodegenerative diseases such as ALS (Taylor et al., 2017). Neuroinflammatory disorders are typically associated with dysregulation of immune cells (MCs, microglia) in the nervous system (Ransohoff et al., 2015). Numerous studies demonstrate that chronic stress is an integral part of neuroinflammatory processes, which may accelerate the risk of developing neurodegenerative diseases including ALS (Glass et al., 2010; Zhang et al., 2019). The ability of MCs to respond to many diverse molecules, especially CRH during stress and neuroinflammatory processes, suggests a role in the pathogenesis of stress-related neurological disorders such as ALS (Jones et al., 2019). CRH acts as a neuropeptide and major regulator of the stress response. Dysregulation of protein levels of CRH is involved in the pathogenesis of ALS (Vandael and Gounko, 2019), but little is known of the underlying mechanisms. The neuroinflammatory processes involving MC–CRH interactions in ALS pathogenesis have yet to be elucidated.

Traumatic brain injury
Traumatic brain injury (TBI) is a form of acquired brain injury where a sudden trauma causes damage to the brain, resulting in tissue destruction and distortion (Garvin and Mangat, 2017; Stein et al., 2017b). Secondary injuries from TBI cause changes in immune cell function, depolarization, excitotoxicity, the formation of edema, BBB disruption and imbalance of calcium homeostasis (Fehily and Fitzgerald, 2017; Galgano et al., 2017). TBI has been linked with long-term cognitive deficits including impaired memory and attention, changes in immune and functional activity, and emotional instability, resulting in trauma-induced neurological disorders (Rabinowitz and Levin, 2014). Recently, research into TBI has mainly focused on stress, disruption of the BBB, cerebral blood flow and neuroinflammatory activities (Pavlova et al., 2018). Neuroinflammation associated with TBI involves the activation of immune cells (MCs, microglia and astrocytes) and the subsequent release of inflammatory mediators within the brain (Barrett et al., 2020).

In secondary injury in TBI, MCs directly communicate with glial cells and release neuroinflammatory mediators, leading to neurological diseases (Simon et al., 2017). Chronic stress conditions influence MC activation via CRH and other neuropeptides to release numerous neuroinflammatory mediators such as IL-1β, TNF-α, IL-6, C–C motif chemokine ligand 2, IL-8, tryptase, histamine, reactive oxygen species, CRH and matrix metalloproteinases (Liezmann et al., 2012). These neurotoxic inflammatory mediators lead to activation of microglia, which release additional pro-inflammatory mediators, resulting in neurological diseases and neuronal death. TBI also disrupts BBB permeability and recruits other immune cells such as MCs, microglia, astrocytes and T cells into the brain (Chodobski et al., 2011). Activated immune cells release neuroinflammatory mediators at the site of brain injury and accelerate neuroinflammatory reactions (Kempuraj et al., 2020b). Moreover, MCs also increase the expression of CRH in the brain. TBI induces neuroinflammation, which in turn causes neurological diseases via immune cells.

Rheumatoid arthritis
Rheumatoid arthritis (RA), a chronic long term inflammatory autoimmune disorder, is characterized by inflammation of the synovial membrane associated with various immune cells, including B cells, T cells, NK cells and MCs (Smolen et al., 2016). MCs are the tissue-resident innate immune cells that contribute to RA pathogenesis (Min et al., 2020); however, the mechanisms of MC involvement in RA remain unclear. Synovium from RA patients has a significantly increased population of MCs compared with healthy controls (Crisp et al., 1984; Pitzalis et al., 2013) and shows increased MC infiltration in the end stage of the disease (Rivelles et al., 2018). Rivelles et al. (2015) and Rossini et al. (2016) have suggested that synovial MCs are associated with the severity of RA disorder, including synovial inflammation, lympho-myeloid infiltrate, systemic inflammation, autoantibodies and disease progression. Activated synovial MCs release several endogenous toll-like receptor ligands, pro-inflammatory cytokines and chemokines, including TNF-α, IL-1β and IL-1Rα (Min et al., 2020). The induction

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of osteoporosis can be mediated directly by MC-derived proteases (Ragipoglu et al., 2020). Lee et al. (2002) found that MC-deficient mice were resistant to the development or progression of RA. These studies suggest that MCs may act as a complex cellular link with inflammatory signaling pathways in RA. The number of MCs are increased 5- to 24-fold in human RA compared with healthy controls (Nigrovic and Lee, 2007). Furthermore, degranulated MC numbers increase more than 3-fold in multiple RA animal models (Shin et al., 2006; Kambayashi et al., 2009). Activated MCs produce cytokines and proteases that are involved in the pathogenesis of RA, particularly Il-1β, TNF-α and microglia (Kempuraj et al., 2017). Tryptase directly triggers synovial fibroblasts by interacting with the protease-activated receptor 2, resulting in degraded cartilage and bone (Shin et al., 2009; Sawamuki et al., 2010). The neuropeptide substance P induces MC activation through Mas-related X2 expression in RA synovium. MCs accumulate in the synovial fluids and joint tissue of patients with RA and with osteoarthritis and RA (Crofford et al., 1993). Stress induces the HPA axis response through CRH and its receptors and is differentially modulated by CRH gene promoter polymorphisms in RA patients (Zhou and Fang, 2018). HPA axis activation is induced by both arginine vasopressin and CRH in acute mono-arthritis (Nishimura et al., 2020). The HPA axis secretes CRH which initiates an immune and inflammatory cascade of events leading to the release of cortisone (Herman et al., 2016). Studies have reported that CRH and its receptors are identified on MCs from RA joints as well as UCN (Baerwald et al., 2016). Synovial fibroblasts in RA that modulate MCs containing proteases, tryptases and chymase may be considered a novel potential therapeutic target.

CRH is locally secreted in synovial tissue and fluids of patients with osteoarthritis and RA (Crofford et al., 1993). Stress induces the HPA axis response through CRH and its receptors and is differentially modulated by CRH gene promoter polymorphisms in RA patients (Zhou and Fang, 2018). HPA axis activation is induced by both arginine vasopressin and CRH in acute mono-arthritis (Nishimura et al., 2020). The HPA axis secretes CRH which initiates an immune and inflammatory cascade of events leading to the release of cortisone (Herman et al., 2016). Studies have reported that CRH and its receptors are identified on MCs from RA joints as well as UCN (Baerwald et al., 2000; Gonzalez-Gay et al., 2003). Furthermore, other studies have shown that activated MCs express mRNAs for CRH and its receptors in RA patients (Huang et al., 2002). Therefore, it has been postulated that degranulated MCs releasing CRH may be a major contributor to RA pathogenesis.

The Link between MCs and Stress in Neurological Disorders

Stress triggers HPA axis activation through the release of CRH and vasopressin from the PVN of the hypothalamus in the brain, leading to enhanced MC activation (Kempuraj et al., 2017a). Stress conditions activate MCs through CRH, neurotensin and substance P to release inflammatory mediators that lead to perturbed BBB permeability and the recruitment of peripheral immune and inflammatory cells into the brain, thereby contributing to neuroinflammation and inflammatory disease (Kempuraj et al., 2017a, 2019; Theoharides, 2020a). Acute stress directly increases BBB permeability through brain-resident MCs and microglial activation and CRH release (Esposito et al., 2001). MC activation plays a critical role in the pathogenesis of neurological disorders. Social stress exposure leads to long-term increases in the recruitment of macrophages, activated MCs and microglia in the brain (Bryan and Rudd, 2015; Stein et al., 2017a). Social stress also accelerates activation of these cell types, resulting in increased expression of pro-inflammatory cytokines. Pro-inflammatory cytokines are pleiotropic molecules that play an important role in the pathogenesis of neurological diseases and can communicate with the CNS via direct interaction with the BBB or via the neuroinflammatory signaling pathway by way of the vagus nerve (Kim et al., 2016; Sinagra et al., 2020). Stress induces the release of pro-inflammatory cytokines, which leads to chronic neuroinflammation, and ultimately contributes to the pathology of depression. Inflammatory cytokines and their neuroimmune signaling pathways, via complex cytokine networks, perturb the HPA and hippocampal glucocorticoid receptors by activating microglia that are closely associated with depression, thereby leading to structural and functional changes in the brain, including impaired spatial memory, neuronal loss and altered neuroplasticity (Pace and Miller, 2009). Crosstalk between inflammatory cytokines and neural circuits via neuroimmune cells can affect behavioral responses such as depression. Increasing evidence suggests that pro-inflammatory cytokines (i.e., IL-1β, IL-6 and TNF-α) induce microglial activation and cause neuroinflammation, leading to oxidative imbalance and stress, which are correlated with depression and subsequent neuronal death in neurological diseases (Pace et al., 2007).

Long-term psychological stress triggers neuroimmune cell activation (MCs, microglia) (Walker et al., 2013; Lehmann et al., 2016; Kempuraj et al., 2020a). These activated neuroimmune cells secrete numerous inflammatory mediators under stress, and together with MCs and microglial activation, could be a major contributor to the pathogenesis of neurological diseases. Psychological stress worsens anxiety and depression, induces oxidative stress, enhances immune responses and induces the activation of MCs and microglia, resulting in neuroinflammation (Grippo and Scotti, 2013; Calcia et al., 2016; Lehmann et al., 2018; Kempuraj et al., 2020a). Inflammatory pathways are linked to MCs and stress, leading to chronic depression in mastocytosis patients (Georgin-Lavialle et al., 2016). A single exposure to social stress may promote increased neuroinflammatory processes in response to spontaneous stress exposure (Audet et al., 2011). Stress induces or worsens migraines through activation of MCs that release inflammatory cytokines and chemokines (Maleki et al., 2012; Theoharides et al., 2012; Theoharides, 2020a). Therefore, we postulate that the interaction between stress and MCs may be a major contributor to neurological disorders.

Conclusion and Future Prospects

MCs are multifunctional neuroimmune cells that participate in the stress response. Under normal conditions, brain-resident MCs secrete CRH, histamine, tryptase and other mediators that regulate BBB permeability. When peripheral inflammation occurs, the MCs in the brain immediately respond to the neuroimmune signal in the blood and quickly degranulate via CRH and its receptors, releasing neuroinflammatory mediators and acting as the initiator and catalyst of the inflammatory response in the CNS. Acute or chronic stress can activate the HPA axis within seconds and increase the secretion of CRH and other neuropeptides from the PVN of the hypothalamus, thereby activating MCs, which in turn disrupt the BBB, leading to neuroinflammation in the brain. Accumulating evidence suggests that bidirectional neuroimmune interactions between MCs, CRH and BBB tight junctions result in neuronal dysfunction, neuroinflammation and neurological diseases. However, a deeper understanding of these complex neuroimmune networks is needed to clarify their role in inflammatory and neurological disorders. Further study is required to elucidate the cellular and molecular mechanisms underlying the neuroimmune connections between CRH and MCs to uncover new therapeutic targets for inflammatory and neurological disorders.

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