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Review article

Mast cells in neuroinflammation and brain disorders

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ABSTRACT

It is well recognized that neuroinflammation is involved in the pathogenesis of various neurodegenerative diseases. Microglia and astrocytes are major pathogenic components within this process and known to respond to proinflammatory mediators released from immune cells such as mast cells. Mast cells reside in the brain and are an important source of inflammatory molecules. Mast cell interactions with glial cells and neurons result in the release of mediators such as cytokines, proteases and reactive oxygen species. During neuroinflammation, excessive levels of these mediators can influence neurogenesis, neurodegeneration and blood-brain barrier (BBB) permeability. Mast cells are considered first responders and are able to initiate and magnify immune responses in the brain. Their possible role in neurodegenerative disorders such as multiple sclerosis, Alzheimer's disease and autism has gained increasing interest. We discuss the possible involvement of mast cells and their mediators in neurogenesis, neurodegeneration and BBB permeability and their role in neuronal disorders such as cerebral ischemia, traumatic brain injury, neuropathic pain, multiple sclerosis, Alzheimer's disease, migraine, autism, and depression.

1. Introduction

Inflammation is a protective response of the innate immune system to remove harmful stimuli and to initiate a healing process to repair any damage that has been inflicted (Skaper et al., 2014a; Bañuelos Cabrera et al., 2014; Lyman et al., 2014). Such an immune response also occurs in the central nervous system (CNS) and is termed neuroinflammation (Lyman et al., 2014; Dong et al., 2014a). Neuroinflammation is distinctive due to unique characteristics of the CNS. Firstly, no dendritic cells are involved. Instead, microglia and mast cells are the innate immune cells of the CNS and also astrocytes are immunocompetent (Xanthos and Sandkühler, 2014). Secondly, the CNS is immune privileged due to the presence of the blood-brain barrier (BBB) although, recent discovery of a brain lymphatic system may revisit the role of the peripheral immune system for the brain (Aspelund et al., 2015; Louveau et al., 2015). The permeability of the microvasculature of the CNS to plasma components and leukocytes is limited compared to the rest of the body (Xanthos and Sandkühler, 2014). Although inflammation is intended to be a protective and beneficial response, prolonged neuroinflammation can result in detrimental effects involving changes in the brain parenchyma, BBB alterations, neuronal hyperexcitability and neuronal death (Bañuelos Cabrera et al., 2014; Lyman et al., 2014; Dong et al., 2014a). Persistent neuroinflammation is now acknowledged as a mechanism that can contribute to or even cause CNS injury associated with the pathogenesis of several neurodegenerative diseases (Lyman et al., 2014; Lehnardt, 2010). Therefore, neuroinflammation has increasingly gained interest as a target to treat brain disorders (Skaper et al., 2014a; Silver and Curley, 2013).

Extensive communication takes place between the immune system and the CNS (Skaper et al., 2014a). Moreover, the interaction between glia, immune cells and neurons seems to be very much involved in the initiation and propagation of neuroinflammation (Dong et al., 2014a). Microglia are the resident immune cells of the CNS and provide the innate defence against invading microbes (Lehnardt, 2010; Lee Mosley, 2015). They express many cell surface proteins (e.g. P2Y receptors, cytokine receptors, integrins), which enable them to interact with neighbouring cells including neurons, astrocytes and immune cells (Hu et al., 2014; Amor and Woodroofe, 2014; Madry and Attwell,

Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorders; BBB, blood-brain barrier; CADM, cell adhesion molecule; CCL, chemokine (C−C motif) ligand; CGRP, calcitonin gene-related peptide; CNS, central nervous system; CRF, corticotropin-releasing factor; CSD, cortical spreading depression; EAE, autoimmune encephalomyelitis; ECs, endothelial cells; ECM, extracellular matrix; HPA axis, hypothalamic-pituitary-adrenal axis; ICAM, intracellular adhesion molecule; IDO, Indoleamine-pyrrole 2,3-dioxygenase; Ig, immunoglobulin; IL, interleukin; LTP, long term potentiation; MCP, monocyte chemotactic protein; MMP, matrix metalloproteinase; MS, multiple sclerosis; NO, nitric oxide; NSCs, neuronal stem cells; NT, neurotensin; NVU, neurovascular unit; PAR, proteinase-activated receptor; ROS, reactive oxygen species; SGZ, subgranular zone; SP, substance P; SVZ, subventricular zone; TIMP, tissue inhibitor of metalloproteinases; TLR, toll-like receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VIP, vasoactive intestinal peptide

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Table 1
Characteristics of brain mast cells, microglia and astrocytes.[a]

	Mast cells	Microglia	Astrocytes	Refs
Origin	Derived from hematopoietic stem cells.	Yolk sac derived erythromyeloid progenitors ($CD45^-$ and $ckit^+$).	Derived from the neuroectoderm.	(Casano Alessandra and Peri, 2015; Jensen et al., 2013)
Location in CNS	Area postrema, choroid plexus, parenchyma of the thalamic hypothalamic region.	Entire nervous parenchyma.	Cover entire CNS.	(Ribatti, 2015; Polyzoidis et al., 2015; Cuadros and Navascués, 1998; Sofroniew, 2014)
Functions in CNS	Not exactly known yet. Mast cells function as first responders at sites of injury and infection and are involved in neuroimmune interactions.	Immune surveillance, phagocytosis of cell debris, synaptic pruning, and involved in neurogenesis and axonal growth.	Maintain fluid, ion and pH homeostasis, uptake and clearance of neurotransmitters, provision of neurons and axons with energy metabolites, modulation of local blood flow, support synaptic function, and contribute to blood brain barrier.	(Silver and Curley, 2013; Casano Alessandra and Peri, 2015; Sofroniew, 2014)
Numbers	Very few in the healthy human brain. In the meninges and in the perivascular area < 5 mast cells were found during autopsy. During infection mast cell numbers increase to 11–20 in the meninges and 5 to10 in the perivascular area. Mast cell numbers in the brain of mice are higher, increasing from 150 to 500 during development.	Constitute ~10% of the total cells in the adult CNS, but vary considerably in numbers throughout the CNS. Numbers vary from 0.5% in the grey matter areas of the cerebral cortex to 16.6% in the pons and medulla of the normal human brain.	In the human cortex, the ratio between astrocytes and neurons is around three or two. However, this ratio is highly region specific.	(Nautiyal et al., 2012a; Jensen et al., 2013; Maslinska et al., 2005; Mittelbronn et al., 2001; Salter Michael and Beggs, 2014)
Receptors	Fc receptors (FcεRI, FcγR), TLRs (1-7 and 9), nod-like receptors, c-Kit receptor CD117, complement receptors (CR3, CR4, CR5), cytokine and chemokine receptors, neurotensin receptor, histamine receptor (H4R), corticotropin-releasing hormone receptor, neurokinin-1 receptor	Prostaglandin receptors (e.g. PPAR-γ), complement receptors (e.g. CR1, CR3), Fc receptors (e.g. FcγRI), cytokine and chemokine receptors, lipopolysaccharide receptor, TLR, histamine receptor (H1R-H4R)	Cytokine and chemokine receptors (e.g. TNFR1, IL-6R), CD40, TLR (2–4), lipopolysaccharide receptors, histamine receptors (H1R-H3R), and PAR1.	(Yu et al., 2015; Sofroniew, 2014; Aloisi, 2001; da Silva et al., 2014)
Inflammatory mediators	Biogenic amines (e.g. histamine), proteases (e.g. chymase, tryptase), angiogenin, proteoglycans, cytokines (e.g. TNF-α, IL-4, IL-6, IL-33, IL-15), chemokines (CCL5, IL-8, MCP-1, eotaxin), growth factors (e.g. neuronal growth factor), peptides, prostaglandins, leukotrienes, complement factors.	Chemokines (e.g. IL-8, MCP-1, CCL5), cytotoxic molecules (nitric and oxygen radicals), prostanoids (e.g. PGD2, PGE2), proinflammatory cytokines IL-1β, TNF-α, IL-6, IL-12, IL-15 and IL-18, and anti-inflammatory cytokines IL-10, TGF-β, IL-1ra.	Chemokines (e.g. MCP-1, CCL5, IL-8, MIP-2), proinflammatory cytokines TNF-α, IL-1β, IL-4, IL-6, IL-12, IL-15, IL-17 and IL-23, anti-inflammatory cytokines TGF-β, IL-10, IL-11, IL-27, nitric oxide (NO) and interferons	(Jensen et al., 2013; Aloisi, 2001; da Silva et al., 2014)

[a] Abbreviations used: CCL, Chemokine (C–C motif) ligand; CNS, central nervous system; IL, interleukin; MCP, Monocyte chemotactic protein; MIP, Macrophage inflammatory protein; PAR, protease-activated receptor; PGD2, prostaglandin D2; PGE2, prostaglandin E2; TGF transforming growth factor; TLR Toll-like receptor; CR, complement receptor; TNF, tumor necrosis facor; TNFR, tumor necrosis facor receptor.

2015). Upon recognition of pathogens, microglia become reactive and accumulate at the site of invasion. Activated microglia produce reactive oxygen species (ROS), proinflammatory cytokines and chemokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-12, chemokine (C−C motif) ligand (CCL) 5 and monocyte chemotactic protein (MCP)-1 (Table 1) (Dong et al., 2014a; Lehnardt, 2010). Besides being neurotoxic, these mediators also attract leukocytes to the affected area, thereby stimulating an adaptive immune response. Additionally, the release of inflammatory molecules can activate astrocytes. Astrocytes, a type of glial cells, are mainly involved with synaptic function and tissue homeostasis, but can also release proinflammatory signalling molecules when stimulated (Lyman et al., 2014; Rodrigues et al., 2014). Such an immune response may induce a potential unfavourable inflammatory environment, resulting in irreversible neuronal damage and BBB disruption (Lehnardt, 2010; Rodrigues et al., 2014). A positive feedback loop has been described, in which sustained recruitment and activation of leukocytes and glial cells can result in prolonged inflammation and long-term neuronal damage (Wang and Jin, 2015). Therefore, the magnitude of the immune response may be an important factor influencing the impact of neuroinflammation on the brain.

It is accepted that long-term activation of glial cells is a major pathogenic component that contributes to neurodegeneration and therefore various neurodegenerative diseases (Lyman et al., 2014; Rodrigues et al., 2014). However, microglia and astrocytes are known to respond to proinflammatory mediators released from immune cells (Skaper et al., 2012). From this perspective, the role of mast cells within neuroinflammation and the pathogenesis of several brain disorders has been a subject of increasing interest (Ribatti, 2015). Mast cells reside in the brain and are an important source of inflammatory mediators (Table 1) (Skaper et al., 2012). Increases in the number of mast cells within the CNS have been found in certain CNS diseases such as stroke and multiple sclerosis (MS) (Jin et al., 2009; Kim et al., 2010). Also, infiltrated tryptase-containing mast cells have been found in the brains of patients with Alzheimer's disease (AD) (Maslinska et al., 2007). Recently, it was shown that mast cells can promote BBB breakdown in focal ischemia in mice (McKittrick et al., 2015). This review will focus on the possible involvement of mast cells in several processes associated with neuroinflammation and will evaluate current literature on the role of mast cells in several brain disorders.

2. Mast cells: origin and activation

Mast cells, derived from hematopoietic stem cells, are the effector cells of the innate immune system (Dong et al., 2014a; Nelissen et al., 2013). Together with dendritic cells, they are the first line of defence in the immune system against invading pathogens (Nelissen et al., 2013). Their differentiation is initiated in the bone marrow under the influence of c-kit ligand and IL-3 (Nelissen et al., 2013; Galli et al., 2005). Mast cells circulate in the blood in immature form until they migrate to vascularized tissues where they complete their differentiation (Skaper et al., 2014a; Dong et al., 2014a; Nelissen et al., 2013). They are typically found in tissues in close contact with the external environment such as the airways, the gastrointestinal tract and the skin (Skaper et al., 2014a; Dong et al., 2014a; Nelissen et al., 2013). Mast cells respond to stimuli such as allergens, antigens, complement factors, neuropeptides, drugs and trauma (Nelissen et al., 2013). They are best studied for their role in the allergic response during which mast cells are activated via cross linking of FcεRI by immunoglobulin E (IgE) (Dong et al., 2014a; Silver and Curley, 2013; Nelissen et al., 2013). However, mast cells can be activated through a variety of other receptors, including toll-like receptors (TLRs), cytokine receptors, tropomyosin receptor kinase-A and the complement receptors (Dong et al., 2014a; Nelissen et al., 2013; Yu et al., 2015). Mast cells have granules that contain a variety of preformed mediators. Within seconds after mast cell activation, these preformed mediators are released (e.g. histamine, serotonin, tryptase, heparin, TNF-α) (Silver and Curley, 2013). This is quickly followed by *de novo* synthesis of lipid mediators (e.g. prostaglandins, leukotrienes, growth factors). Finally, the late phase response involves the release of newly synthesised cytokines and chemokines (e.g. TNF-α, IL-6, IL-13) (Silver and Curley, 2013; Nelissen et al., 2013). Mast cells are heterogeneous, which means the morphology, mediator content and response to activation can vary substantially (Dong et al., 2014a; Nelissen et al., 2013; Kitamura, 1989).

3. Mast cells in the brain

Mast cells are present in various areas of the brain and in the meninges (Dong et al., 2014a). They are typically found in the area postrema, the choroid plexus and the parenchyma of the thalamic hypothalamic region (Ribatti, 2015; Nelissen et al., 2013; Polyzoidis et al., 2015). Already during development, mast cells enter the brain by migration along the blood vessels (Skaper et al., 2014a). Also, mature mast cells are capable of migrating from the periphery to the brain (Nautiyal et al., 2011; Silverman et al., 2000). Most mast cells reside on the abluminal side of the blood vessels, where they are able to communicate with neurons, glial cells and the endothelial cells (ECs) of the extracellular matrix (ECM) (Dong et al., 2014a; Silver and Curley, 2013). The exact number of mast cells in the brain is difficult to measure, because numbers vary with age and species (Table 1) (Nautiyal et al., 2012a; Silver et al., 1996). Brain mast cells are not numerous and are mainly of a tryptase-chymase positive phenotype (Bañuelos Cabrera et al., 2014). However, their number and distribution can dramatically change in response to a number of environmental stimuli, such as trauma and stress (Silver and Curley, 2013). For example, stress induced in rats by social isolation resulted in a 90% reduction of the total number of brain mast cells during the first day of isolation compared to group-housed rats (Bugajski et al., 1994).

4. Mast cell–glial cells interactions

In vitro research has revealed various mediators and molecular mechanisms via which mast cells and microglia may interact (Fig. 1A and Table 2). Mast cell tryptase can activate proteinase-activated receptor 2 (PAR2) receptors on microglia, which results in the release of proinflammatory mediators such as TNF-α, IL-6 and ROS (Silver and Curley, 2013; Zhang et al., 2012a). IL-6 can induce IL-13 release from mast cells and affect expression of TLR2/TLR4 (Skaper et al., 2014a; Pietrzak et al., 2011; Zhang et al., 2010a), while TNF-α can upregulate PAR2 expression on mast cells augmenting PAR2 mediated mast cell activation and degranulation (Zhang et al., 2010c). Also, mast cell tryptase can cleave microglial PAR2 receptors, resulting in the upregulation of the P2 × 4 receptor promoting the release of brain derived neurotrophic factor (Yuan et al., 2010). Furthermore, mast cell activation induces upregulated expression of a number of chemokines, including CCL5 (Feuser et al., 2012). This chemokine was found to induce a proinflammatory profile in microglia *in vitro* (Skuljec et al., 2011). Moreover, microglia express all four histamine receptors (H1R, H2R, H3R and H4R) and stimulation via these receptors results in the production of TNF-α, IL-1β and IL-6 (Bañuelos Cabrera et al., 2014; Dong et al., 2014b; Ferreira et al., 2012). Many other molecules and receptors, such as the complement component 5a receptor (C5aR), C-X-C chemokine receptor type 4 and TLRs, might be involved in microglia-mast cell interactions (Skaper et al., 2014a; Dong et al., 2014a; Silver and Curley, 2013). This wide variety of potential bidirectional communication highly suggests mast cells and microglia might work in concert influencing neuroinflammation (Fig. 1A).

Interactions between astrocytes and mast cells are also possible as they share perivascular localization (Table 2) (Silver and Curley, 2013; Kim et al., 2010). *In vitro* work has shown that co-culture of mast cells and astrocytes results in the release of several mediators, such as histamine and leukotrienes, through CD40-CD40L interactions (Kim et al., 2010). Additionally, production of cytokines and chemokines

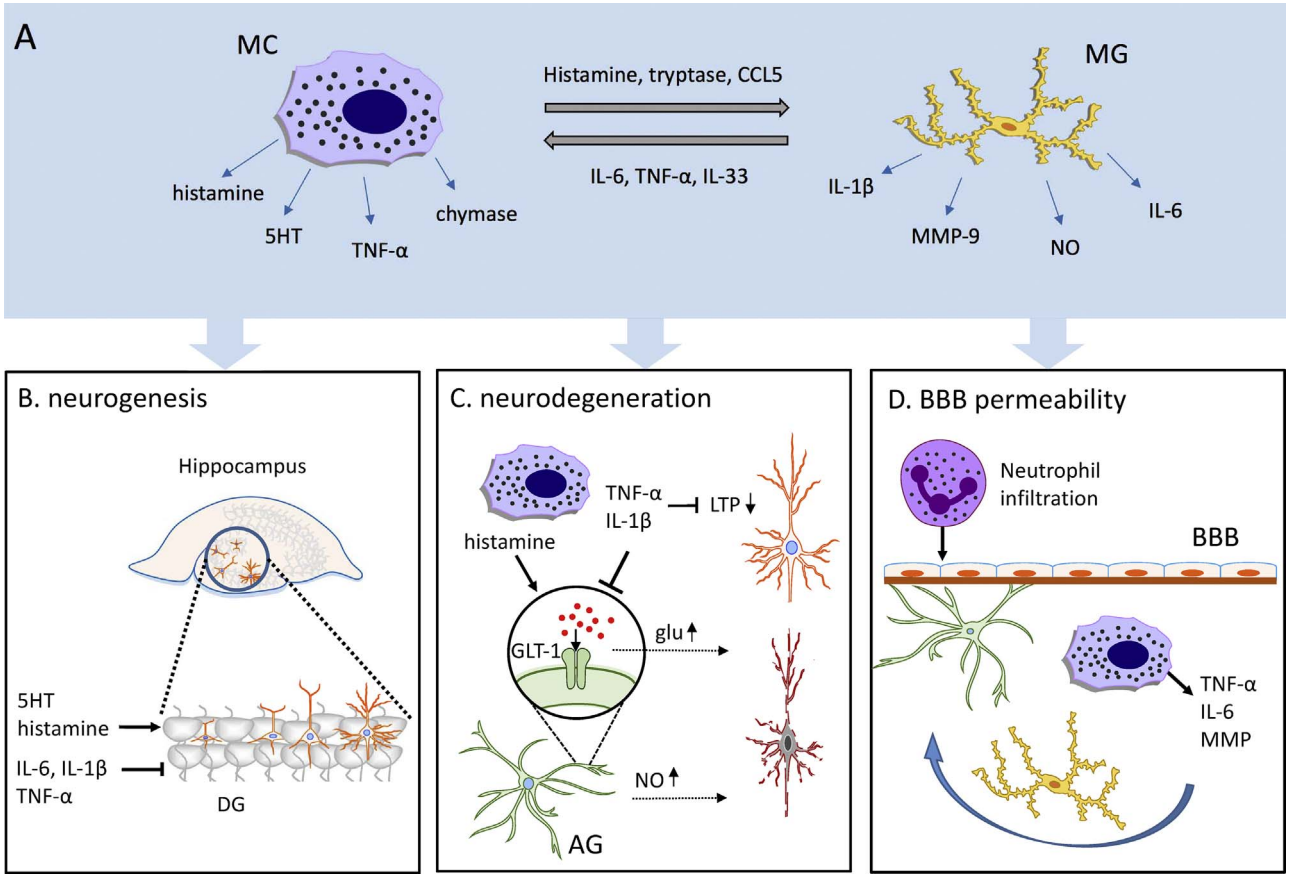

Fig. 1. Potential involvement of mast cells in physiological and pathological mechanisms involved in brain disorders.
Panel A. The cross talk between mast cells and microglia can result in changes in the functional state of these cells and release of different mediators. Panel B. Different mediators released by mast cells modulate the amount of cell proliferation in the dentate gyrus of the hippocampus. Panel C. Both IL-1β and TNF-α have been shown to inhibit LTP. Mast cells mediators are able to modulate the glutamate transporter (GLT-1) function on astrocytes resulting in either protection or induction of excitotoxicity. Moreover, NO released from TNF-α stimulated astrocytes may result in neurotoxicity. Panel D. histamine and TNF-α have vasoactive properties and mast cells can release matrix degrading molecules such as proteases. Via these mediators, mast cells can influence BBB permeability.
Abbreviations: 5HT5-hydroxytryptamine; AGastroglia; BBBblood brain barrier; CCLChemokine (C—C motif) ligand; DGdentate gyrus; gluglutamate; GLTglutamate transporter; ILinterleukin; LTPlong-term potentiation; MCMast cell; MGMicroglia; MMPmatrix metallopeptidase; NOnitric oxide; TNF-αtumor necrosis factor-α.

Table 2
Interactions between mast cells and the resident cells of the CNS.[a]

	Interaction	Effect of mast cells	Effect on mast cells	Refs
Microglia	Mast cell tryptase via PAR2	Release of TNF-α, IL-6 and ROS		(Zhang et al., 2012a)
	Upregulation P2 × 4 expression via mast cell tryptase	Release of brain-derived neurotrophic factor		(Yuan et al., 2010)
	Mast cell-derived CCL5	Induction of proinflammatory profile in microglia		(Skuljec et al., 2011)
	Histamine via H1R, H2R, H3R and H4R	Release of TNF-α, IL-1β and IL-6		(Dong et al., 2014b)
	Microglial IL-6		Release IL-13; upregulation of TLR2/TLR4	(Pietrzak et al., 2011; Zhang et al., 2010a)
	Microglial TNF-α		Upregulation PAR2 expression	(Zhang et al., 2010c)
Astrocytes	Histamine via H1R	Production of MMP-9		(Patel et al., 2015)
	Bidirectional activation via CD40L:CD40	Production of cytokines and chemokines IL-1β, IL-6, TNF-α, MCP-1 and CCL5	Release of histamine and leukotrienes and production of cytokines and chemokines IL-6, TNF-α, MCP-1, MIG and CCL5	(Kim et al., 2010; Kim et al., 2011)
	Astroglial IL-33 via ST2 on mast cells		IL-6, IL-8, and IL-13 production	(Iikura et al., 2007; Moulin et al., 2007)
Neurons	Mast cell transgranulation	Alter the neuronal response and/or supply with mediators for re-release		(Wilhelm et al., 2005)
	CADM1		Adhesion of mast cells to neurons	(Furuno et al., 2012)
	Neuropeptides (SP, neuronal growth factor, NT)		Degranulation and release of cytokines and chemokines such as MCP-1, IL-8 and CCL5	(Kulka et al., 2008)

[a] Abbreviations used: BBB, blood brain barrier; CADM1, Cell adhesion molecule 1; CCL, Chemokine (C—C motif) ligand; H1R, histamine 1 receptor; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metallopeptidase; NO, nitric oxide; NT, neurotensin; P2 × 4, purinergic 2 × 4 receptor; PAR2, protease activated receptor 2; ROS, reactive oxygen species; SP, substance P; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α.

(e.g. IL-6, TNF-α, MCP-1 and CCL5) is induced via bidirectional activation of astrocytes and mast cells (Kim et al., 2010; Kim et al., 2011). Furthermore, astrocytes express IL-33, which is released upon injury (Yasuoka et al., 2011; Saluja et al., 2015). IL-33 is considered an alarming cytokine that, by stimulating mast cells, alerts the innate immune system. IL-33 can activate both microglia and mast cells via the ST2 receptor by which it promotes proliferation of microglia and stimulates mast cells to produce IL-6, IL-8, and IL-13 (Gadani et al., 2015; Iikura et al., 2007; Moulin et al., 2007). Like microglia, astrocytes express histamine receptors (H1R, H2R and H3R) via which mast cells may influence the activity of astrocytes (Silver and Curley, 2013; Hösli et al., 1984; Mele and Juric, 2013). Recently, Patel et al. demonstrated that histamine induces the production of matrix metalloproteinase (MMP)-9 in human astrocytic culture via the H1 receptor (Patel et al., 2015).

5. Mast cell-neuron interactions

The functional interaction between mast cells and neurons *in vivo* is not yet well characterised. However, research has provided information on the communication between mast cells and peripheral nerves (Silver and Curley, 2013). These associations between mast cells and peripheral nerves suggest that such interactions might also take place between mast cells and neurons within the CNS (Fig. 2 and Table 2) (Silver and Curley, 2013; Skaper et al., 2012). The co-localisation of mast cells and neurons is considered essential for neuro-immune interactions. Cell adhesion molecule-1 (CADM1) mediates the adhesion and communication between sensory neurons and mast cells (Silver and Curley, 2013; Hagiyama et al., 2011). CADM1d, an isoform of CADM1, is expressed by mature hippocampal neurons. It was shown that mast cells strongly adhere to this isoform *in vitro,* suggesting CADM1 might play an important role in the enhancement of mast cell-neuron interactions (Hagiyama et al., 2011). Furthermore, neuropeptides released from neurites, such as substance P (SP), neurotensin (NT) and nerve growth factor, can bind to mast cells and activate them either by direct G protein binding or by ligand binding to for example the neurokinin 1 receptor (Kulka et al., 2008). *In vitro* SP activation induced degranulation and release of cytokines and chemokines, such as MCP-1, IL-8 and CCL5 (Kulka et al., 2008). Moreover, *in vitro* stimulation of murine mast cells with SP resulted in the production of leukotriene C4 and prostaglandin D2 without degranulation (Karimi et al., 2004). Furthermore, cytokine IL-4 enhanced neurokinin-1 receptor expression on mast cells resulting in an increased sensitivity of mast cells to SP (van der Kleij et al., 2003). Lastly, a process termed transgranulation has been described in CNS neurons (Wilhelm et al., 2005). Mast cell-derived products can enter adjacent neurons, thereby inserting their granule contents. In this way, mast cells can alter the internal environment of neurons, which points to a novel form of neuro-immune communication (Wilhelm et al., 2005). For example, it has been suggested that mast cells can alter the responsiveness of neurons by transgranulation of heparin. Intracellular heparin is known as a pharmacological tool to block the release of intracellular calcium, resulting in the inhibition of the neuronal response (Wilhelm et al., 2005). Also, mast cells can supply products that neurons can re-release (e.g. gonadotropin-releasing hormone) (Wilhelm et al., 2005).

6. Neuroinflammation and mast cells

Despite their small numbers in the brain, activated mast cells can have an important impact on different processes of neuroinflammation (Fig. 1). They can act indirectly via their interactions with glial cells and neurons (resulting in the release of molecules such as IL-6, IL-1β and nitric oxide (NO)), but also directly via the release of mediators (e.g. TNF-α, histamine, chymase) (Zhang et al., 2016). In particular, mast cells are an important source of histamine and are the only cells within the brain storing preformed TNF-α (McKittrick et al., 2015). Up to 50% of whole brain histamine level in rats is attributable to the presence of mast cells, while TNF-α comprises almost 25% of the mast cell granule content (Skaper et al., 2001). During neuroinflammation, mast cells may act as catalysts and amplify cellular and molecular responses, influencing neurogenesis, neurodegeneration and BBB permeability (Fig. 1). Below we discuss the possible roles of mast cells and individual mediators associated with mast cell interactions in the context of neurogenesis, neurodegeneration and BBB permeability.

7. Neurogenesis

Neurogenesis is the process of generating new neurons from neuronal stem/progenitor cells (NSCs) (Wang and Jin, 2015; Borsini et al., 2015). This process mainly takes place in two brain areas: the subgranular zone (SGZ) and the subventricular zone (SVZ) of the hippocampus (Fig. 1B) (Wang and Jin, 2015; Fuster Matanzo et al., 2013). The NSCs in both areas give rise to neural progenitor cells that migrate and subsequently differentiate into new neurons of the hippocampus (SGZ neurogenesis) or the olfactory bulb (SVZ neurogenesis) (Fuster Matanzo et al., 2013). NSCs have the potential to differentiate into neurons, oligodendrocytes and astrocytes (Felling and Levison, 2003). Neuroinflammation may play a complex role in

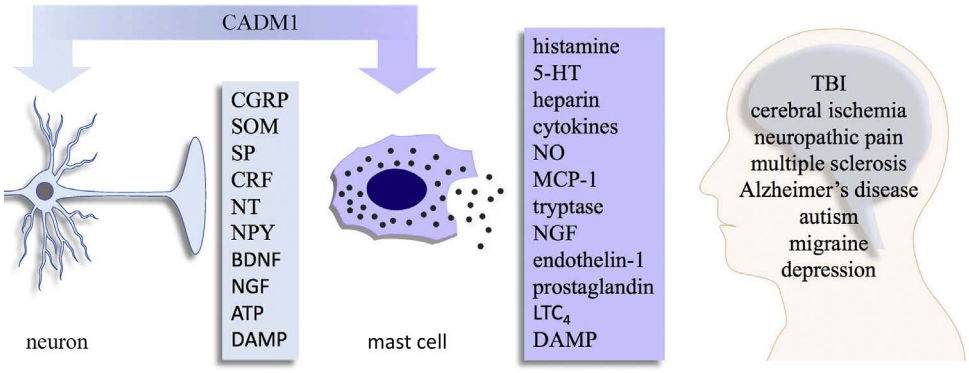

Fig. 2. The role of the mast cell in neuroinflammation.
Neurons can activate and modulate mast cells via several mediators enabling the release of a plethora of factors depending on the specific stimulation. The released mast cell mediators can in turn modulate the function of neuronal, glia, microglia, astroglia, endothelial cells and cells from the immune system. The CADM1 molecule is involved in the adhesion and communication between neurons and mast cells. Ultimately, shortcomings in the interplay between neurons and mast cells can pay a contribution to the pathology of several brain diseases.
Abbreviations: 5HT, 5-hydroxytryptamine; AG, astroglia; BDNF, brain-derived neurotrophic factor; CADM1, cell adhesion molecule-1; CGRP, calcitonin gene-related peptide; CRF, corticotropin-releasing factor; DAMP, danger-associated molecular patterns; LTC4, leukotriene C4; MCP, monocyte chemotactic protein; NGF, nerve growth factor; NO, nitric oxide; NPY, neuropeptide Y; NT, neurotensin; SP, substance P; TBI, traumatic brain injury.

modulating neurogenesis, both negatively and positively. The extent of the inflammatory response, the type of mediator, and the timing determine whether the effect is detrimental or protective (Barone and Feuerstein, 1999). While several proinflammatory cytokines have shown to be harmful, cytokines may also provide neuroprotection by promoting growth and repair. The role of these mediators within neurogenesis has been extensively reviewed by others (see (Wang and Jin, 2015; Borsini et al., 2015)), so only the mediators produced and released by mast cells will be discussed.

7.1. IL-6 and IL-1β

In physiological conditions, the proinflammatory cytokine IL-6 can have neuroprotective effects and seems to be important for proliferation and survival of NSCs (Bowen et al., 2011). However, during inflammation, IL-6 levels increase and excessive levels may be associated with neurotoxicity (Vallières et al., 2002). Recombinant IL-6 was found to inhibit hippocampal neurogenesis *in vitro* (Monje et al., 2003). Furthermore, IL-6 was found to increase NSC proliferation and astrogliogenesis, but to decrease neurogenesis in both astrocyte- and microglia-conditioned medium (Nakanishi et al., 2007; Wang et al., 2011). IL-1R1, the receptor for IL-1β, is expressed by NSCs in the SGZ (Koo and Duman, 2008; Wu et al., 2013). Exposure to IL-1β showed to decrease the rate of hippocampal NSC proliferation *in vitro* (Koo and Duman, 2008; Wu et al., 2013). However, *in vivo* disruption of IL-1 signalling, did not affect the changes in neurogenesis caused by IL-1β. Possibly, IL-1β might induce these changes in concert with IL-6 and TNF-α (Fig. 1B) (Wu et al., 2013).

7.2. TNF-α

this cytokine can both stimulate and inhibit neurogenesis, depending on the receptor that is being activated. Activation of TNF-R1 was found to suppress NSC proliferation, while activation of TNF-R2 increases proliferation and survival of newly formed neurons (Chen and Palmer, 2013; Montgomery and Bowers, 2012). TNF-R1 is expressed on almost all cells, while TNF-R2 expression is limited to hematopoietic lineage cells. Human NSC cells, however, express both TNF-R1 and TNF-R2 (Montgomery and Bowers, 2012). *In vitro* studies demonstrated that TNF-α did affect the differentiation phase but not the proliferation phase of neurogenesis. Under differentiation conditions, TNF-α decreased neuronal development and stimulated astroglial development (Keohane et al., 2010). However, in a murine model for stroke, TNF-α was found to be protective and to promote neurogenesis after stroke (Heldmann et al., 2005). TNF-α might have a dual role and whether the effect is detrimental or protective not only depends on the receptor subtype it is binding to, but also on the level and time of release (Heldmann et al., 2005).

7.3. Serotonin

Both neurons and mast cells are responsible for the production of serotonin in the CNS. Although this mediator is only present in low levels within mast cells, 20–40% of the serotonin might originate from mast cells (Nautiyal et al., 2012a; Wernersson and Pejler, 2014). A study by Nautiyal et al., indeed, found a mast cell-mediated increase in serotonin in the hippocampus after stimulation with compound 48/80 (used to promote degranulation) and increases in serotonin level may promote hippocampal neurogenesis (Nautiyal et al., 2012a). Mast cell-deficient W^{sh}/W^{sh} mice showed reductions in the volume of granule cell layer and decreased cell proliferation compared with $W^{sh}/+$ mice (Nautiyal et al., 2012a).

7.4. Histamine

Histamine receptors H1R, H2R and H3R are present on NSCs, suggesting histamine may be able to influence neurogenesis (Eiriz et al., 2014; Hu, 2012; Molina Hernández and Velasco, 2008). *In vitro* studies demonstrated that H1R activation on NSCs seems to be critical for neuronal differentiation and cell survival, while cell proliferation seems to depend upon H2R activation (Molina Hernández and Velasco, 2008). After differentiation, histamine increased the number of neurons in 3-fold, mainly by activation of H1R. Furthermore, the proportion of astrocytes was significantly decreased compared to control (Molina Hernández and Velasco, 2008). Histamine did not increase NSC proliferation, but instead induced neuronal differentiation. It may increase the number of neuroblasts that reach the olfactory bulb, and therefore, the number of newly-generated olfactory bulb neurons (Eiriz et al., 2014). According to these findings, histamine might play a role in neurogenesis by promoting NSC proliferation through the activation of H2R, while favouring neuronal differentiation through H3R (Hu, 2012). Further *in vivo* research demonstrated reduced levels of adult hippocampal neurogenesis in H1R-deficient mice (Ambrée et al., 2014). However, they did not find any significant differences in the number of cells that develop into neurons or astrocytes (Ambrée et al., 2014).

8. Neurodegeneration

8.1. Neuronal death

Neuronal death may either be necrotic or apoptotic. Necrotic neuronal death occurs when cell death is caused by acute ischemia or trauma. Apoptotic neuronal death is a controlled process that is part of natural physiology. However, it can also be induced during acute and chronic neurodegeneration (Lyman et al., 2014). Possibly, neuroinflammation directly affects neuronal apoptosis through the production of excessive levels of inflammatory molecules, thereby accelerating neurodegeneration (Lyman et al., 2014). Activated mast cells might also play a role in accelerating neurodegeneration during neuroinflammation. Mast cell activation was found to result in delayed neurodegeneration in mixed neuron-glia cultures. No acute neurodegeneration was found, suggesting that the immediate release of mast cell mediators is not alone sufficient to cause injury (Skaper et al., 1996). Mast cell-derived TNF-α, in concert with other cytokines, possibly induces the release of NO by astrocytes, resulting in neurotoxicity (Fig. 1C) (Skaper et al., 1996; Hendrix et al., 2013).

8.2. Synaptic dysfunction

Before neuronal cell death, synaptic impairment may lead to damaged neurons and inadequate neurotransmission. Therefore, also synaptic dysfunction is considered a measure of neurodegeneration (Lyman et al., 2014). Impairment of synaptic plasticity is one of the manifestations of synaptic dysfunction and concerns the variability of synapse impulse strength (Lyman et al., 2014). Long-term potentiation (LTP), one of the forms of synaptic plasticity seen in the hippocampus, increases synaptic efficacy and is considered important for learning and memory processing (Di Filippo et al., 2008; Pickering et al., 2005). At physiological levels, cytokines may be important for the induction and maintenance of synaptic plasticity. For example, IL-6 and IL-1β gene expression is upregulated in the hippocampus following LTP induction, suggesting a physiological role (del Rey et al., 2013). However, overexpression of cytokines during neuroinflammation might impair synaptic plasticity (Fig. 1C) (Di Filippo et al., 2008). High levels of both IL-1β and TNF-α have been shown to inhibit LTP (Butler et al., 2004; Curran et al., 2003). Additionally, it has been suggested that IL-6 has a potential inhibitory role in the modulation of LTP. Although *in vivo* exposure to elevated levels of IL-6 enhanced synaptic transmission in hippocampal neurons, it did not influence LTP (Nelson et al., 2012).

8.3. Excitotoxicity

Excitotoxicity is the neuronal death caused by excessive or prolonged activation of receptors for glutamate, the main excitatory neurotransmitter of the CNS (Pickering et al., 2005; Olmos and Lladó, 2014). Impaired uptake of glutamate by glial cells causes excessive levels of glutamate that may lead to overstimulation of glutamate receptors (Fig. 1C) (Pickering et al., 2005). Cytokines related to neuroinflammation, particularly TNF-α and IL-1β, can influence the glutamatergic response (Viviani et al., 2014). At physiological levels, TNF-α is important for synaptic plasticity due to its influence on ionotropic glutamate receptor trafficking. However, increased levels of TNF-α can inhibit glutamate transporters on astrocytes, resulting in increased glutamate concentrations in the CNS parenchyma (Pickering et al., 2005; Olmos and Lladó, 2014; Zou and Crews, 2005). Several studies have demonstrated that TNF-α is able to enhance glutamate neurotoxicity (Zou and Crews, 2005) and increase excitotoxicity in hippocampal neurons *in vitro* and *in vivo* (Zhu et al., 2010a). Besides TNF-α, IL-1β may also induce glutamate excitotoxicity (Fogal and Hewett, 2008). Histamine, on the contrary, may reduce extracellular glutamate contents, resulting in neuroprotection against excitotoxicity. Fang et al. demonstrated that histamine protected against glutamate-induced neuronal cell death by upregulating glutamate transporter GLT-1 on astrocytes via H1R (Fang et al., 2014). These results are in contrast with results published earlier by Skaper et al., who reported that mast cells, cocultured with hippocampal neurons under conditions of enhanced synaptic transmission, potentiated neurotoxicity likely by the release of histamine (Skaper et al., 2001).

9. BBB permeability

The BBB is a selective and tightly regulated barrier, separating the CNS from the systemic circulation. It creates a stable CNS environment, important for neuronal function, and protects the brain from unwanted molecules, such as pathogens and toxins, which can cause neuronal damage and lead to neuroinflammation and neurodegeneration (Bañuelos Cabrera et al., 2014; Daneman and Prat, 2015; Keaney and Campbell, 2015). The BBB is composed of tight inter-endothelial junctions and has several integral transmembrane proteins (e.g. claudin, occludin) that contribute to its integrity. The basal lamina, a specialized part of the ECM, connects the ECs of the BBB to adjacent cell layers (Strbian et al., 2009). The ECs of the BBB are essential for regulating the movement of molecules, ions and nutrients between the blood and the CNS and have properties distinct from the ECs of other tissues (Daneman and Prat, 2015; Keaney and Campbell, 2015). ECs in the brain express BBB-specific receptors (Mfsd2a) and transport proteins (e.g. glucose transporter GLUT-1), to control the influx and efflux of molecules (Keaney and Campbell, 2015). Furthermore, ECs are held together by tight junctions, which limit paracellular transport (Keaney and Campbell, 2015). Although CNS ECs comprise the main barrier unit of the BBB, it is now recognized that a complex network of different cell types has an important role in BBB development and maintenance. The neurovascular unit (NVU) is a term used to describe the environment of neurons, glial cells, pericytes and other components of the brain parenchyma that communicate with ECs (Bañuelos Cabrera et al., 2014; Ribatti, 2015; Keaney and Campbell, 2015). Infection and inflammation can cause BBB disruption, which results in ion dysregulation, entry of immune cells and plasma molecules, and an instable CNS environment. BBB breakdown has been associated with the initiation and progression of diseases such as MS, stroke and AD (Ribatti, 2015; Daneman and Prat, 2015). Mast cells can interact with several components of the NVU (e.g. glial cells, neurons) and may be involved in the promotion of BBB breakdown (Fig. 1D) (del Zoppo, 2009; Lindsberg et al., 2010). Several mast cell mediators have vasoactive properties (e.g. histamine, TNF-α) and mast cells can release matrix degrading molecules such as proteases. Due to these properties of mast cell-derived mediators, it is hypothesized that they can influence BBB permeability (Strbian et al., 2009).

Mast cells may influence BBB integrity via MMPs. MMPs represent a large family of proteolytic proenzymes, which require removal of a N-terminal pro-peptide to become active (Strbian et al., 2009; Tchougounova et al., 2005). When activated, they can degrade most of the protein components of the ECM, including collagen, elastin, fibronectin and vitronectin (Strbian et al., 2009; Asahi et al., 2001). Therefore, the enzyme activity of MMPs is strictly regulated for example by tissue inhibitors of metalloproteinases (TIMPs) (Asahi et al., 2001). The tight junctions of ECs express tight junction proteins with MMP cleavage sites, such as zona occludens proteins, occludin and claudin. In particular, MMP-9 and MMP-2 have been linked to BBB disruption by mediating the degradation of these tight junction proteins (Strbian et al., 2009; Asahi et al., 2001; Yang et al., 2007). Both MMP-2 and MMP-9 can degrade denatured collagen (gelatin) and are therefore also known as gelatinase A and B, respectively (Tchougounova et al., 2005). It was demonstrated that mast cell activation can influence the activity of gelatinase (Mattila et al., 2011). *In vitro* studies showed that pro-MMP-9 was processed into its active form in the presence of mast cells. The degree of gelatinase activity correlated with the number of mast cells added. In particular, mast cell-derived chymase was shown to regulate the activity of MMP-9 and partially MMP-2 (Tchougounova et al., 2005). Chymase can also influence MMP-9 levels by degrading its inhibitor TIMP-1 (Frank et al., 2001; Rosell et al., 2008; Di Girolamo et al., 2006; Liu et al., 2013; Rochfort et al., 2014; Rochfort and Cummins, 2015; Rochfort et al., 2015; Tang et al., 2011; Dietrich, 2002). Furthermore, mast cells promote the infiltration of neutrophils, which are a source of MMP-9 and may contribute to the MMP-9 levels in the microvasculature of the BBB (Rosell et al., 2008). Moreover, it has been shown that mast cells can produce MMP-9 under the influence of TNF-α (Di Girolamo et al., 2006).

Although results are not always consistent due to different study settings, TNF-α seems to increase BBB permeability (Liu et al., 2013). Recent *in vitro* studies showed that TNF-α induced ROS-mediated downregulation of tight junction proteins occludin, claudin-5 and vascular endothelial-cadherin, resulting in increased paracellular permeability (Rochfort et al., 2014; Rochfort and Cummins, 2015). TNF-α increased IL-6 levels and IL-6 was found to be partly involved in the TNF-α mediated disruption of the endothelial monolayer (Rochfort et al., 2015). Also, TNF-α can upregulate intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 expression on rat brain microvascular endothelial cells *in vitro* (Tang et al., 2011). ICAM-1 is involved in leukocyte adhesion to the endothelium and their entry into the brain. Upregulation of ICAM-1 and leukocyte-mediated breakdown of the BBB are characteristics of various brain inflammatory disorders, such as MS (Liu et al., 2013; Dietrich, 2002). Several reports indicate that brain histamine is involved in the regulation of BBB permeability. *In vitro* research demonstrated that binding of histamine to its receptors on ECs affects cell–cell adhesions of ECs, increasing BBB permeability (Bañuelos Cabrera et al., 2014; Lindsberg et al., 2010). However, Lu et al. demonstrated that H1R overexpression in ECs resulted in decreased BBB permeability *in vivo*, suggesting histamine may be important in maintaining BBB integrity (Lu et al., 2010).

10. Brain disorders

Because of their stored preformed mediators, mast cells can rapidly respond to stimuli. Due to their heterogeneity and their ability to interact with different components of the NVU, mast cells have been considered an important participant in different brain disorders (Skaper et al., 2014b). In this section, we summarize the most recent findings in brain diseases in which mast cells may play a role.

10.1. Traumatic brain injury

In modern society, traumatic brain injury (TBI) is a major cause of death and disability (Okie, 2005; Acosta et al., 2015). Depending on the severity of the injury short- or long-term symptoms such as headache, dizziness, fatigue, and nausea may occur, while in more severe cases cognitive and emotional symptoms may progress (Waxweiler et al., 1995; Lozano et al., 2015).

TBI is the result of mechanical force on the brain leading to disruption of blood vessels, damage to neurons and axons and glial tissue (Maas et al., 2008). These malformations can initiate complex neurochemical, and metabolic alterations. In consequence to these direct responses to brain damage a secondary sequence of ischemia/hypoxia and cerebral swelling may follow, leading to a number of secondary effects such as glutamatergic excitotoxicity, mitochondrial dysfunction, oxidative stress, prolongation of the BBB disruption and neuroinflammation (Acosta et al., 2015; Greve and Zink, 2009; Werner and Engelhard, 2007).

Exploration of the neuroinflammatory aspect might lead to the discovery of new therapeutic targets for preventing secondary cell death and symptom progression (Lozano et al., 2015). The initial inflammation following TBI is in first instance a protective process, separating damaged tissue from healthy tissue (Kumar and Loane, 2012; Loane and Kumar, 2016). The continuation of the inflammatory process however, seems to lead to enhanced neurodegeneration. In rat models for TBI mast cells are activated and infiltrate the brain after initial injury (Lozada et al., 2005; Shimada et al., 2012), leading to enhanced release of histamine (Stokely and Orr, 2008). The nature of the role of mast cells in this process is rather controversial. On the one hand, mast cells seem to mediate protection against neuroinflammation via mast cell specific chymase mCP-4 in a mouse TBI model (Stokely and Orr, 2008). On the other hand, palmitoylethanolamide (PEA) induced attenuation of mast cell numbers and chymase and tryptase in the brain of experimental TBI mice coincided with beneficial effects on edema, infarct volume and behavioral effects (Ahmad et al., 2012). Also, in a model for spinal cord injury PEA has shown to limit neuronal damage, decreased activation of microglia and reduced mast cell infiltration and activation (Esposito et al., 2011). In another study using a model of pediatric TBI, inhibition of mast cells with chromoglycate did not show an effect on cell loss or microglia density, suggesting a subtler role for MCs in TBI (Moretti et al., 2016). While these results seem contradictory, we must keep in mind that the effect of inflammation in TBI can be, depending on the time after the injury and the stage of the TBI, either beneficial or malicious. In this light, it seems logical that the role of mast cells during these different stages is also dual.

10.2. Cerebral ischemia

Cerebral ischemia is defined as a decrease in cerebral blood flow to a critical threshold that results in brain damage involving the entire brain or a selective region (Hu, 2012). Early damaging events of the ischemic cascade include vasogenic brain edema, haemorrhage formation and initiation of inflammation. These events are associated with the disruption of the BBB and are important determinants for survival and recovery in stroke (McKittrick et al., 2015; Strbian et al., 2009). Mast cells have been hypothesized to play a role in the initiation of the early phase of ischemic damage and may be a potential important factor influencing stroke severity (McKittrick et al., 2015; Lindsberg et al., 2010). Being resident in the brain, in the perivasculature, and present already at the onset of ischemia, mast cells may induce the initial inflammatory response and subsequent BBB disruption in stroke (Strbian et al., 2009; Lindsberg et al., 2010). Treatment of adult Wistar rats with compound 48/80 after middle cerebral artery occlusion showed a 70% increase in edema, while treatment with the mast cell stabilizer cromoglycate reduced edema by 40% compared with control values. Genetically mast cell-deficient rats even showed a 60% reduction in brain swelling compared to the wild-type controls (Strbian et al., 2006). Furthermore, cromoglycate treatment and mast cell-deficiency significantly reduced the density of neutrophils in the ischemic hemisphere (Strbian et al., 2006). Also, mast cell-deficiency was associated with a 50% reduction in BBB leakage to molecules the size of albumin compared with controls (Lindsberg et al., 2010; Strbian et al., 2006). Moreover, it was shown that cerebral mast cells can regulate acute microvascular gelatinase activity, leading to BBB degradation and vasogenic edema following transient ischemia (Mattila et al., 2011).

Most of the results supporting a role for mast cells in ischemia are obtained from rat models for stroke. However, recently, McKittric et al. investigated the role of mast cells in the acute post-ischemic phase in a murine model of stroke (McKittrick et al., 2015). Similar to studies using rats, they compared wild-type mice and W^{sh}/W^{sh} mice after transient middle cerebral artery occlusion. Additionally, a group of wild-type mice were treated with cromoglycate. Mast cells increased in numbers in the ischemic hemisphere and promoted neutrophil infiltration, BBB breakdown and edema within 4 h, but not at 72 h after occlusion. Although TNF-α is thought to be a major player in enhanced BBB permeability, mast cell-derived TNF-α was not found to be associated with the observed effects. However, endothelin-1, endoglin and MMP-9 levels were elevated, suggesting the effect may be induced via these mediators. Still, neutrophils are also a source of these factors, so it remains unclear whether BBB breakdown is caused by mast cells, neutrophils or both (McKittrick et al., 2015). Interestingly, the role of mast cells seems less important after 72 h of recovery. Possibly, after the acute response of mast cells, the population is depleted due to excessive degranulation and is no longer able to influence the BBB.

In addition, mast cell-derived mediators were shown to protect against neuronal death induced by oxygen-glucose deprivation, which is an *in vitro* model of ischemia. This protection was found to be dependent on histamine in cooperation with other unidentified mediators (Hu et al., 2007). Also, H3-knockout mice showed less impairment of neurological function and a reduced infarct area after middle cerebral artery occlusion. Several mechanisms behind this protection have been hypothesized, such as the protective effect of histamine on excitotoxicity and a reduction in the infiltration of leukocytes through the H2-receptor (Hu, 2012). Mast cells account for a large portion of the brain histamine, so the protective effect of histamine is somewhat conflicting. However, histamine is not considered to play a pivotal role in the pathogenic cascade, but is suggested as a potential target due to its multi-directed interactions with glia, neurons and immune cells (Hu, 2012).

McKittrick et al. reported a mortality of 25% due to brain edema in wild-type mice within the first 24 h of recovery after transient occlusion, while there was no mortality in the group of mast cell-deficient mice. Mast cells may be causal to this increased mortality by mediating the development of brain edema (McKittrick et al., 2015). Recently, masitinib, an oral tyrosine kinase inhibitor, has shown potential in the treatment of ischemia (Kocic et al., 2015). By combined targeting of c-kit and Lyn, masitinib can control the survival, differentiation and degranulation of mast cells. In this way, it can indirectly control the release of proinflammatory and vasoactive molecules by mast cells (Piette et al., 2011). Masitinib showed to reduce infarct size in rats after permanent artery occlusion when used in combination with standard therapy. Standard therapy after stroke is thrombolysis using recombinant tissue plasminogen activator and is associated with a risk of haemorrhage formation (Kocic et al., 2015). It is not likely that masitinib can pass the BBB, so its actions may be directed towards mast cells localized at the BBB and those migrating towards the brain, thereby reducing BBB permeability (Piette et al., 2011). There is substantial evidence that mast cells are involved in the acute ischemic response and potentially initiate neuroinflammation and BBB breakdown. However, the exact mechanisms by which they influence ischemia remain unclear.

10.3. Neuropathic pain

Neuropathic pain can be the result of neural damage leading to malfunction of the somatosensory system. Neuronal cell death or compromised signal transduction by axonal damage or terminal atrophy may in first instance lead to negative symptoms; loss of sensory information, numbness or elevated threshold for heat sensitivity. Some patients however, experience positive symptoms like increased pain sensitivity or spontaneous activation of the nociceptive pathway (Jensen et al., 2011). While initiated by neural damage and subsequent changes in the sensory neurons, the immune system also plays a role in the pathogenesis of neuropathic pain (von Hehn et al., 2012). A complex interplay between mast cells and glia leads to an inflammatory process that affects both neuronal tissue as the BBB (Skaper, 2016). Inflammatory mediators, such as cytokines, induce heightened pain sensitivity by increasing nociceptive neuronal firing, via phosphorylation of transient receptor potential channels (TRPV1 or TRPA1) or modification of voltage-gated sodium channels (e.g., Nav1.7, Nav1.8, and Nav1.9) (von Hehn et al., 2012; Pinho-Ribeiro et al., 2017).

Here we will focus on the contribution of mast cells to neuropathic pain. Mast cells can stimulate the nociceptive pathway with the release of a plethora of well-known mediators such as cytokines (IL-5, TNFα, IL-6, and IL-1b), 5-HT, histamine, and nerve growth factor (NGF), leading to pain sensitization (Aich et al., 2015; Chatterjea and Martinov, 2015; Woolf et al., 1997). Moreover, mast cells are a potent source for IL17, which via its receptor can activate nociceptor neurons directly hereby adding to neuropathic pain (Murphy et al., 2015; Noordenbos et al., 2012). TNFα mediates hyperalgesia via both TRPV1 and prostaglandins (Cunha et al., 1992; Cunha et al., 2005). TNFα also reduces GABAergic interneuron activity via p38, in dorsal horn neurons of the spinal cord leading to reduced GABA release (Kim et al., 2008; Yowtak et al., 2011; Zhang et al., 2010b). This decrease of GABAergic inhibition leads to increased excitatory transmission (Baba et al., 2003) and produces pain sensitization (Sivilotti and Woolf, 1994).

Elucidation of the role of mast cells and glia in neuroinflammation identified them as new putative therapeutic targets for neuropathic pain (Skaper et al., 2014a; Facci et al., 1995). Studies using palmitoylethanolamide (PEA) to downplay mast cell and glia activity showed a significantly reduced pain sensation in patients treated with PEA (Paladini et al., 2016).

Management of chronic pain is still a challenging task for the clinician. In approximately 50 percent of patients no clinically relevant pain relief can be accomplished (Dworkin et al., 2010). Further research on the role of neuroinflammation hopefully leads to new therapeutic targets. Remarkably, pain and inflammation seem to form a two-way street. Inflammation contributes to the pain sensation, but activation of the nociceptive pathway can also stimulate the immune system. Nociceptive neurons releasing substance P (SP), calcitonin gene-related peptide (CGRP) or vasoactive intestinal peptide (VIP) for instance can activate mast cells either directly on mast cells) or indirectly via dendritic cells and T-cells that subsequently release several mediators that can stimulate mast cells such TNFα, IL-13, IL5 and IL17 (Pinho-Ribeiro et al., 2017; Corrigan et al., 2016). In addition to this SP and CGRP facilitates neuroinflammation directly via vascular endothelial cells acting as potent vasodilators and modulators of the contraction of lymphatic tissue (Brain and Williams, 1985; Davis et al., 2008). Taken together this means that neuroinflammation plays a significant role in neuropathic pain and mast cells seem to be all-round players in this process.

10.4. MS and EAE

MS is a chronic inflammatory disease of the CNS and is characterised by demyelination, immune cell infiltration and axonal damage, primarily located in the white matter. The disease can occur in genetically predisposed individuals after exposure to a, so far unidentified, environmental trigger (Costanza et al., 2012; Russi and Brown, 2015). This trigger activates myelin-specific T cells in the peripheral lymphoid organs, which would normally reside within the periphery in tolerant state (Russi and Brown, 2015). If these cells are able to enter the CNS via the BBB, they are reactivated by myelin antigen presenting cells. These autoreactive T cells then induce a localized inflammatory response leading to myelin and axonal damage, inefficient propagation of action potentials and, consequently, neurological deficits (Costanza et al., 2012; Russi and Brown, 2015). Experimental autoimmune encephalomyelitis (EAE) is the most widely used murine model for MS. Similar to MS, EAE is characterised by the infiltration of immune cells, loss of BBB integrity and subsequently neuronal damage (Russi and Brown, 2015).

A large amount of research has been directed towards the potential involvement of mast cells in EAE and MS (reviewed by (Costanza et al., 2012)). Mast cells have been found in demyelinated lesions within perivascular areas associated with immune cell infiltrates, but also in the CNS parenchyma and the leptomeninges of MS patients (Ibrahim et al., 1996; Toms et al., 1990). Moreover, elevated levels of histamine and tryptase were present in the cerebrospinal fluid of MS patients (Russi and Brown, 2015; Kallweit et al., 2013). These findings suggest that mast cells are actively present in tissues involved in disease pathology. It was hypothesized that mast cells might be play a role MS and EAE by modulating trafficking of inflammatory cells through the BBB. However, studies in mast cell-deficient mice have yielded conflicting results with some claiming mast cells reduced EAE severity (Li et al., 2011; Secor et al., 2000), some claiming mast cells worsened EAE severity (Piconese et al., 2011; Sayed et al., 2010), and some studies not finding any influence (Bennett et al., 2009; Feyerabend Thorsten et al., 2011). These discrepancies may be explained by the differences in the dose of immunization and/or the murine model that was used (Costanza et al., 2012; Piconese et al., 2011). Also, the artificial induction of EAE via active immunization likely bypasses the natural initiation steps that take place during disease progression. These are all complications that make it difficult to define the exact impact of mast cells on the pathogenesis of MS.

Recently, the role of the meninges in MS has gained interest. The meninges cover the brain and spinal cord, and interface with the grey matter of the cerebral cortex. Although plaques of demyelination are mainly observed in the white matter and are considered a hallmark of MS, plaques in the cortical grey matter also contribute to the disease pathogenesis (Russi and Brown, 2015). Interestingly, cortical demyelination is characterised by inflammation in the meninges (Russi and Brown, 2015). Post mortem analysis of tissue samples from MS patients revealed that a greater degree of meningeal inflammation was associated with more extensive cortical demyelination and neurite loss in primary progressive MS. Also, increased meningeal inflammation correlated with a younger age of death and shorter disease duration, suggesting that meningeal inflammation plays a role in MS pathology (Choi et al., 2012). Mast cells are resident cells of the meninges and may be involved in meningeal inflammation in EAE. A study by Christy et al. (2013) showed that the meninges are site of high immune activity and that MC activation occurred very early post immunization (Christy et al., 2013). Mast cells were found to promote drastic neutrophil influx but were not required for neutrophil infiltration itself. Furthermore, it was demonstrated that mast cell-derived TNF directly influenced meningeal neutrophil influx and alterations in BBB permeability (Christy et al., 2013). Injection of wild-type mice with compound 48/80 resulted in meningeal mast cell degranulation. However, BBB permeability was not affected. This indicates mast cells are not acting directly to compromise BBB integrity (Christy et al., 2013).

10.5. Alzheimer's disease

There is some evidence, although limited, which suggests a possible role for mast cells in the pathology of AD. One of the hallmarks of AD is

the extracellular deposition of β-amyloid plaques. Autopsy of brains of AD patients showed infiltration of numerous tryptase-containing mast cells that were found close to the amyloid plaque lesions in different brain regions. Brains of controls had only few numbers of tryptase-containing mast cells. Recent *in vitro* studies by Harcha et al. showed that amyloid peptides can induce degranulation via membrane hemichannels on mast cells. They suggest mast cells are one of the first brain cells that sense amyloid peptides and, therefore, may have a crucial role in the onset of the pathology and possibly also the progression of AD (Harcha et al., 2015). A randomized, placebo-controlled phase 2 trial with masitinib as an add-on therapy to standard care showed masitinib might have benefits in patients with mild-to-moderate AD. The mechanisms underlying this response are not known since passage of the BBB of orally administered masitinib is very unlikely. A possible scenario that has been suggested is that inhibition of release of mediators by mast cells localized at the BBB reduces permeability and −in turn- the influx of proinflammatory molecules released from peripheral mast cells. This leads to decreased neuroinflammation and migration of mast cells into the brain (Piette et al., 2011).

10.6. Mast cell involvement in migraine pathology

Migraine headache is a throbbing, incapacitating, episodic headache often associated with vomiting, nausea and photophobia which affects around 15% of the Western population (Pietrobon and Striessnig, 2003; Lipton et al., 2007). It is classified by the World Health Organization as one of the most incapacitating chronic conditions (Goadsby et al., 2002). It is the most common neurological disorder (Pietrobon and Striessnig, 2003). Though there is still speculation about the mechanisms behind migraine, it is now generally believed that the migraine headache is mediated by nociceptive afferent neurons close to the cerebral meninges and large meningeal blood vessels, causing activation and sensitization of the trigeminal nerve (Goadsby et al., 2002; Pietrobon and Moskowitz, 2013).

The neurovascular theory that is constructed upon this assumption connects headache with (vascular) inflammation (Tietjen, 2007). This theory consists of two parts. Heightened levels of inflammatory factors in the brain circulation lead to vascular inflammation. This causes dilation in the intracranial meninges leading to activation of the meningeal nociceptive neurons during a migraine attack (Goadsby and Edvinsson, 1993; Sarchielli et al., 2006). In the second part of the neurovascular theory, meningeal inflammation arises as a result of cortical spreading depression (CSD). CSD is a front of intense neuroglial depolarization, which slowly spreads like a wave throughout the rest of the brain (Pietrobon and Moskowitz, 2013; Bogdanov et al., 2011). Mediators, such as potassium-ions and glutamate, released during CSD can cause the activation of nociceptors on meningeal sensory neurons. In response, these neurons can locally release proinflammatory neuropeptides, such as SP and calcitonin gene-related peptide (CGRP) (Colonna et al., 1994), which could facilitate inflammation by direct stimulation of meningeal blood vessels, or indirectly via activation of local mast cells, causing the release of other inflammatory mediators (Waeber and Moskowitz, 2005; Vargas et al., 2005) that can result in vasodilation of meningeal vessels (mostly due to CGRP) and elevated endothelial permeability (Pietrobon and Moskowitz, 2013; Vargas et al., 2005). The local inflammation could be responsible for maintaining a continuous activation of meningeal nociceptors.

Another take on the aetiology of migraine involves a role for stress response, which is a presumed migraine inducer. Corticotropin releasing factor (CRF) regulates the stress response via the hypothalamic–pituitary adrenal (HPA) axis (Smith and Vale, 2006). Mast cells are located close to CHR-positive neurons in the rat median eminence (Theoharides et al., 1995) and are positive for CRF receptors that can be activated by CRH or urocortin (Singh et al., 1999; Theoharides and Cochrane, 2004; Cao et al., 2005). This may result in secretion of inflammatory cytokines inducing vasodilation of meningeal vessels and activation of meningeal nociceptors (Waeber and Moskowitz, 2005; Levy, 2009). Although the precise role of mast cells in migraine is still not elucidated, there are several links that point towards mast cell involvement in the migraine pathophysiology.

10.7. Autism spectrum disorders (ASD)

In the majority of the patients suffering from ASD, the cause is unknown. However, it is now recognized that autism is associated with some immune dysfunction, aspects of autoimmunity and neuroimmune responses (Theoharides et al., 2013). It is hypothesized that brain mast cells may be involved in the pathogenesis of ASD (Theoharides et al., 2013). Elevated serum levels of neuropeptide NT were found in young ASD patients and NT, also present in the brain, can trigger mast cell activation (Alysandratos et al., 2012; Carraway et al., 1982; Tsilioni et al., 2014). Stimulation of mast cells by neuropeptides can result in the release of extracellular mitochondrial DNA and ATP, which can maintain neuroinflammation by stimulating mast cells to release inflammatory cytokines (Theoharides et al., 2013; Zhang et al., 2012b; Theoharides et al., 2016). Indeed, extracellular mitochondrial components were significantly elevated in the serum of autistic children compared to controls (Zhang et al., 2010d). Proinflammatory cytokines TNF-α, IL-6 and granulocyte macrophage colony-stimulating factor were significantly increased in brain tissue of autistic patients compared with controls (Li et al., 2009) and also high levels of MCP-1, a strong mast cell chemoattractant, in brain tissues and in the cerebrospinal fluid of autistic patients were reported (Vargas et al., 2005).

10.8. Depression

The prevalence of major depression in patients suffering from chronic infections like rheumatoid arthritis or inflammatory bowel disease led to the idea that chronic inflammation can increase the risk for major depression (Isik et al., 2007; Dantzer et al., 2008; Hauser et al., 2011; Benros et al., 2013). This hypothesis is further supported by the observations that on the one hand, treatments with different immunological mediators like interferon α (IFN-α) and IL-2 lead to higher incidences of depression and on the other hand, therapies with TNF-α antibodies decrease symptoms of major depression (Tyring et al., 2006; Uguz et al., 2009; Hoyo-Becerra et al., 2014)

Inflammation may induce depression via several different pathways like the proinflammatory attenuation of brain-derived neurotrophic factor(Guan and Fang, 2006; Kenis et al., 2011; Patas et al., 2014) which is associated with depression (Karege et al., 2002; Duman and Monteggia, 2006). But also, the increased activity of monoamine transporters by proinflammatory cytokines leading to lower dopamine, noradrenalin and serotonin levels is associated with anhedonia (Mossner and Lesch, 1998; Zhu et al., 2006; Tsao et al., 2008; Zhu et al., 2010b; van Heesch et al., 2014). An important process in the context of inflammation induced depression is the tryptophan catabolism (Fig. 3). Proinflammatory cytokines in the brain can induce the enzyme indoleamine 2,3-dioxygenase (IDO) (Stone and Darlington, 2002; Kwidzinski et al., 2005; Maes et al., 2011). IDO is the rate limiting enzyme in the kynurenine pathway, responsible for the catabolism of tryptophan to kynurenine, known to induce depressive-like behaviour in the forced swim test (O'Connor et al., 2009). Furthermore, higher levels of kynurenine are associated with symptoms of depression in humans (Eisenberger et al., 2010; Gabbay et al., 2012). Kynurenine enhanced IgE-mediated responses of mast cells, including degranulation, LTC_4 release, and IL-13 production via activation of PLC-γ1, Akt, MAPK p38, and release of intracellular calcium in an aryl hydrocarbon receptor-dependent manner (Kawasaki et al., 2014). In this way changes in the tryptophan metabolism, leading to enhanced levels kynurenine, are possibly modulating mast cell responses. Kynurenine is further metabolized into the metabolites quinolinic acid and kynurenic acid (for an overview see (Campbell et al., 2014)).

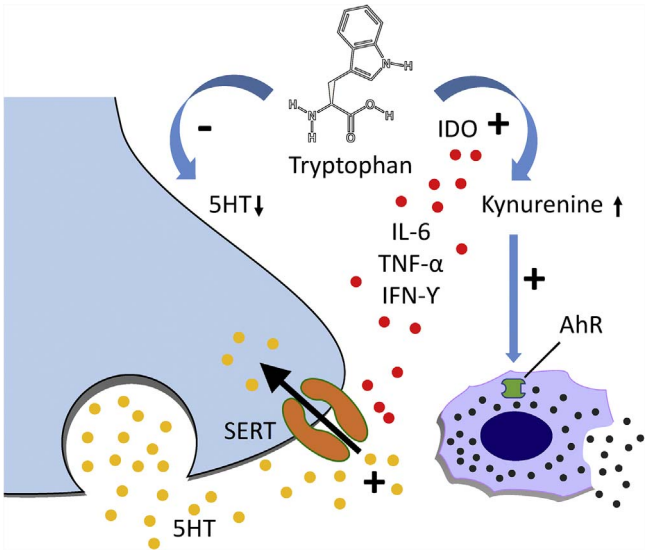

Fig. 3. Possible role for mast cells in depression.
Mediators released by mast cells can influence the IDO pathway leading to an imbalance between kynurenine and serotonin. Levels of serotonin can also be decreased as a result of increased activity of monoamine transporters induced by proinflammatory cytokines.
Abbreviations: 5HT, 5-hydroxytryptamine; AhR, Aryl hydrocarbon receptor; IDO, Indoleamine-pyrrole 2,3-dioxygenase; IFN-γ, interferon-γ; IL-6, interleukin-6; SERT, serotonin transporter; TNF-α, tumor necrosis factor-α.

Quinolinic acid, produced by microglia, acts as a NMDA agonist and has neurotoxic effects while kynurenic acid, produced by astrocytes, inhibits alpha7 Nicotinic receptor activity, acts as a NMDA antagonist and has neuroprotective effects (Stone and Perkins, 1981; Hilmas et al., 2001; Raison et al., 2010). Increased levels of quinolinic acid and kynurenic acid are associated in several studies with depressive symptoms (Hoyo-Becerra et al., 2014; Raison et al., 2010; Baranyi et al., 2015; Georgin-Lavialle et al., 2016; Savitz, 2016; Erhardt et al., 2013; Bay-Richter et al., 2015).

Thus, deviation in the tryptophan catabolism towards the kynurenine pathway my lead to attenuated serotonin synthesis and serotonin concentration, higher kynurenine, kynurenic acid and quinolinic acid levels, that possibly in concert contribute to the development of depression.

While the role of inflammation in the pathophysiology of depression is highlighted in recent literature, the part for mast cells in this process is still an underexplored territory. However, there are some indications that mast cells are involved in the pathology of depression. The prevalence of depression among patients with mastocytosis, a rare disease characterised by mast cell accumulation and activation, ranges from 40% to 70% (Rogers et al., 1986; Hermine et al., 2008). Treatment with masitinib, a tyrosine kinase inhibitor with a specific action on mast cells (Dubreuil et al., 2009), led to a significant improvement of depression in patients with mastocytosis (Moura et al., 2011), suggesting a role for the mast cells in the pathophysiology of depression seen in these patients.

Georgin-Lavialle et al. proposed, in a study with fifty-four patients with mastocytosis, a role for mast cells in the tryptophan catabolism pathway leading to depression. Mastocytosis patients showed significantly lower levels of tryptophan and serotonin, higher IDO1 activity, and higher levels of kynurinic acid and quinolinic acid, with a shifted ratio towards the latter (Georgin-Lavialle et al., 2016). Moreover, higher depression scores correlated with lower levels of tryptophan and higher activity of IDO1. Moreover, it has been shown that mast cells can be activated by kynurenine catabolites (Kawasaki et al., 2014; Sibilano et al., 2012). This might lead, under specific circumstances like in mastocytosis, but maybe also during other situations of enhanced mast cells activation, to a vicious circle of activating more mast cells, which in turn leads to the release of more proinflammatory cytokines and subsequently results in further IDO activation. The role of mast cells might be direct as illustrated above in the special case of mastocytosis, but could in non-mastocytosis patients also be indirect, via microglia. Brain mast cells can activate microglia, leading to the release of inflammatory mediators. Moreover, suppression of mast cell degranulation inhibits the activation of microglia and subsequent release of inflammatory mediators (Dong et al., 2016).

In addition to the presumed role in the tryptophan catabolism, mast cell function might possibly be linked to other pathways leading to depression. In a study with mice, histamine release from brain mast cells decreased the amount of sleep. In this same experiment mast cell deficient mice showed higher levels of anxiety (Chikahisa et al., 2013). Mast cells can contribute significantly to serotonin levels in the hippocampus of mice. Serotonin is involved in hippocampal functioning and neurogenesis and associated with depression. Mast cell deficient mice have a disrupted hippocampal dependent cognitive functioning and lower levels of neurogenesis. These deficits were reversed by enhancing the levels of serotonin with a serotonin reuptake inhibitor (Nautiyal et al., 2012b).

It is likely that mast cells play a role, directly or indirectly, in proinflammatory cytokine-induced depression. But also, other routes leading to depression are linked to mast cell function. Their precise role and contribution to depression is however, still to be elucidated.

11. Concluding remarks

There is a growing interest in the role of mast cells in the brain and their role in neuroinflammation. This review discussed the mast cell interactions within the brain and the influence of their mediators on neurogenesis, neurodegeneration and BBB permeability (Fig. 1). Immune responses do take place in the CNS and are essential to combat infections and repair any damage caused by harmful stimuli. Interactions between mast cells, glial cells and neurons result in the release of different inflammatory signalling molecules. While a lot of research has focused on the negative effects of these mediators, it is important to keep in mind that many of these neuroimmune actions are beneficial. Physiological levels of inflammatory mediators released by mast cells and/or glial cells do not only have an immune function, but also have a role in the CNS promoting neurogenesis (e.g. serotonin, IL-6), providing neuroprotection (e.g. IL-1β) and maintaining BBB integrity (e.g. histamine). However, excessive levels of these mediators have detrimental effects on neurons and BBB integrity, linking mast cells to a variety of brain disorders (Fig. 1). Mast cells are considered first responders due to their ability to release preformed mediators within seconds after activation. The role of mast cells in the disease pathogenesis of brain disorders, such as cerebral ischemia and MS, may be caused by their negative influence on BBB permeability, allowing an increased influx of peripheral immune cells such as neutrophils and T cells. Clearly, much remains to be learned about the impact of mast cells and future studies should focus on the interactions that take place between mast cells and the different components of the NVU. Their ability to interact with the resident cells of the brain − glial cells, neurons and ECs − suggests that mast cells also play a role in the communication within the healthy brain.

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