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Mast Cells and Neuroinflammation

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It has been determined that there is extensive communication between the immune system and the central nervous system (CNS). Proinflammatory cytokines play a key role in this communication. There is an emerging realization that glia and microglia, in particular, (which are the brain's resident macrophages), are an important source of inflammatory mediators and may have fundamental roles in CNS disorders. Microglia respond also to proinflammatory signals released from other non-neuronal cells, principally those of immune origin, such as mast cells. Mast cells reside in the CNS and are capable of migrating across the blood-brain barrier (BBB) in situations where the barrier is compromised as a result of CNS pathology. Mast cells are both sensors and effectors in communication among nervous, vascular, and immune systems. In the brain, they reside on the brain side of the BBB, and interact with astrocytes, microglia, and blood vessels via their neuroactive stored and newly synthesized chemicals. They are first responders, acting as catalysts and recruiters to initiate, amplify, and prolong other immune and nervous responses upon activation. Mast cells both promote deleterious outcomes in brain function and contribute to normative behavioral functioning, particularly cognition and emotion. Mast cells may play a key role in treating systemic inflammation or blockade of signaling pathways from the periphery to the brain.

MeSH Keywords:

Blood-Brain Barrier • Inflammation • Mast Cells • Microglia • Neurodegenerative Diseases

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Background

Fundamentally, inflammation is a protective physiologic response to injury and infection and is necessary for removing detrimental stimuli and initiating tissue healing. A similar process that occurs in the CNS in response to injury or disease is termed neuroinflammation. In acute neuroinflammation, microglia become reactive and limit the area of injury through phagocytosing dying cells and releasing pro-inflammatory cytokines [1]. However, when neuroinflammation is prolonged, it overwhelms the bounds of physiological control and produce deleterious effects involving pro-inflammatory signaling pathways, increased oxidative stress, and death of nearby neurons. Neuroinflammation is a common mechanism influencing the severity and progression of neurodegenerative disease and is, therefore, an important target for neuroprotective therapies [2–6].

Central Inflammation

Inflammation and degenerative diseases (AD, PD, HD)

Neurodegeneration, the progressive dysfunction and loss of neurons in the CNS, is the major cause of cognitive and motor dysfunction. Emerging evidence now points to a more active role of neuroinflammation in pathophysiology onset and progression, with glia having key roles in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, and may even contribute to multiple sclerosis, amyotrophic lateral sclerosis, stroke, and neuropsychiatric disorders. The initiation and propagation of neuroinflammation appear to rely very much on the interaction between glia, immune cells, and neurons, although the glia-immune cell connection remained to be fully explored. Microglia are the major resident immune cells in the brain and play a pivotal role in the immune surveillance of the central nervous system (CNS). Consequently, these cells are likely to have an important role in either the development of protective immune responses or the progression of damaging inflammation during CNS disease states. In the steady state, microglia protect the nervous system by acting as scavengers of debris and microbial pathogens and by regulating the innate and adaptive immune responses. Pathological states within the nervous system, including injury, ischemic stroke [7], and infection [8], can lead to activation of microglia. This in turn can cause release of inflammatory molecules that trigger astrocytes and cells of the immune system to respond to the injury [9]. In the disease state, activated microglia mediate neuronal injury and death through production of proinflammatory factors like cytokines and chemokines, glutamate, and reactive oxygen species and help mobilize the adaptive immune response and cell chemotaxis, leading to transendothelial migration of immune cells across the BBB and even perpetuation of neuronal damage [10].

Sustained inflammation resulting in tissue pathology implies persistence of an inflammatory stimulus or a failure in normal resolution mechanisms. A persistent stimulus may result from environmental factors or the formation of endogenous factors that are perceived by the immune system as “stranger” or “danger” signals, such as misfolded protein aggregates, which are present in neurodegenerative diseases (AD, PD, and HD). Inflammatory responses that establish feed-forward loops may overwhelm normal resolution mechanisms. Although some inflammatory stimuli induce beneficial effects (e.g., phagocytosis of debris and apoptotic cells), and inflammation is linked to tissue repair processes, uncontrolled inflammation may result in production of neurotoxic factors that amplify underlying disease states. The cytokines released by necrotic neurons induce further activation of microglia and astrocytes, resulting in positive feedback loops that can become independent of the original inducing molecules that are required to initiate inflammatory responses.

Inflammation and anesthesia

Some anesthetic agents have been shown to have anti-inflammation and immune-modulatory properties. Propofol, an intravenous anesthetic agent, was demonstrated that have neuroprotective effects. It is reported that propofol could inhibit LPS-induced microglial activation [11,12]. Propofol also exerted neuroprotection against ischemic brain damage through inhibited COX-2 and TNF- α expression and NF- κ B activation in rat [13]. Volatile anesthetics have organ-protective effects against ischemia-reperfusion injury. Sevoflurane has protective action against cerebral ischemia reperfusion-induced brain injury by regulating cerebral antioxidant enzymes activities, Bcl-2, Bax, c-Fos, and Caspase-3 protein positive expression levels, and Bcl-2, Bax, TNF- α , and Caspase-3 mRNA expression [14].

Mast Cells

Mast cells were first characterized in 1878 by the Nobel-prize winning immunologist Paul Ehrlich, who described the histochemical properties and distinct morphological phenotypes of these small (6–12 μ m) cells [15]. Mast cells originate in the bone marrow arising, in humans, from CD34⁺/CD117⁺ pluripotent progenitor cells [16]. Mast cells circulate in the blood as committed precursors and complete their differentiation in tissues where they reside. They are infamous and well-studied for their role in immunoglobulin type E (IgE)-associated allergic and inflammatory disorders. Efficient activation of MCs is via IgE binding to Fc ϵ RI (high-affinity surface receptors for the Fc region of IgE), although MC activation can also occur through ligand binding to other receptors, including Fc γ RIIa, TrkA, complement component receptors, Toll-like receptors (TLRs), and interleukin (IL) receptors [17,18].

Mast cells and inflammation

General inflammation of mast cells activation

Mast cells are effector cells of the innate immune system. They are distributed in virtually all organs and vascularized tissues [19]. They are present in the skin, the gastrointestinal tract, and the airways, where they are in close contact with the outside environment. Mast cells are also normal residents of the peritoneum, synovium, hair follicles, and many other organs.

Mast cells produce a plethora of mediators, including biogenic amines (histamine and serotonin), cytokines [interleukin (IL)-1 to IL-6, leukemia inhibitory factor, tumor necrosis factor (TNF) α , interferon- γ , transforming growth factor- β , and granulocyte-macrophage colony-stimulating factor], enzymes (acid hydrolyases, chymase, phospholipases, rat mast-cell protease I and II, and tryptase), lipid metabolites (prostaglandins, leukotrienes, and platelet-activating factor), ATP, neuropeptides (vasoactive intestinal peptide), growth factors [nerve growth factor (NGF)], nitric oxide, and heparin [20]. It should be kept in mind that while mediator release via degranulation is a very rapid process, longer lasting activation results in the release of *de novo* formed mediators [21]. Mast cells as a class are heterogeneous, and no single mast cell makes all of these substances. Their immune regulatory role includes participation in switching of IgE by B cells [22] and the release of chemoattractants that recruit eosinophils [23] and monocytes [24].

Mast cells and central inflammation

Mast cells are also found in the brain, on the brain side of the blood-brain barrier (BBB) and in the leptomeninges [25,26]. Almost 97% of mast cells reside on the abluminal (brain) side of the blood vessels, thus, they are able to communicate with neurons, astrocytes, microglia, extra cellular matrix, and blood vessels. Under baseline conditions, in the absence of stress, disease, or trauma, the numbers of mast cells is considerably smaller than that of neurons, microglia, and other brain-resident cells. Despite their small numbers, activated mast cells can impact the BBB, neurons, microglia, and astrocytes (Figure 1). The multiphasic response pattern of mast cells, wherein they release preformed granular material within minutes and newly synthesized mediators for the next several hours, enables their actions as catalysts that amplify and prolong numerous vasoactive, neuroactive, and immunoactive cellular and molecular response.

Blood-brain barrier

There is substantial evidence that mast cells can penetrate the BBB and break its integrity. Mature mast cells themselves can migrate from blood to brain [28]. Intramuscular injection of the mast cell degranulator, compound 48/80, results in vastly

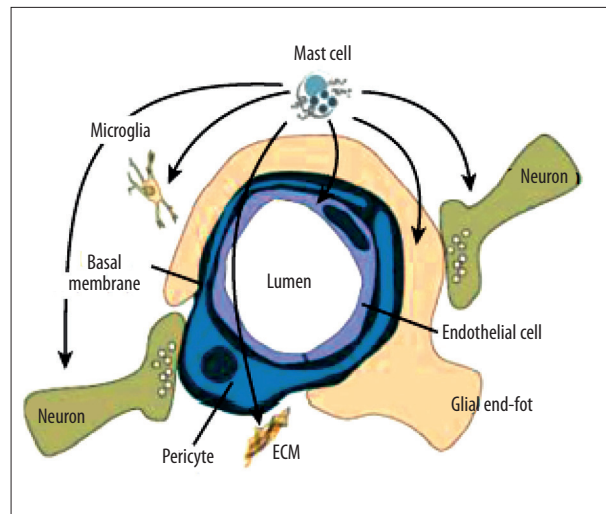


Figure 1. The picture shows the close proximity of the mast cells to other cellular elements in nerve tissue, and points to its ability to signal blood vessel components, neurons, glia, and microglia. Abbreviation: ECM, extracellular matrix. Reproduced from Silver and Curley [27].

increased Evans Blue tracer leakage in mast cell-rich, but not mast cell-lacking brain regions bearing fenestrated capillaries. These findings have been confirmed with various techniques in several species [29,30]. Mast cell effects on vascular permeability are blocked by mast cell stabilizers and are absent in mast cell-deficient W/W^v mice [31]. The mechanism of mast cell disruption of the BBB and basal lamina degradation may involve the vasoactive and matrix degrading components of mast cells, such as heparin, histamine, serotonin, nitric oxide, vasoactive intestinal peptide, calcitonin gene-related peptide (CGRP), vascular endothelial growth factor, and cytokines, including TNF- α , which in turn induces the expression of intercellular adhesion molecule-1 (ICAM-1) and permits leukocytes to enter the affected tissues [32–34]. Although other resident cells in the CNS produce TNF- α , most notably microglia/macrophages and endothelial cells, the presence and release of TNF- α from mast cells precedes its detection in other cells [35]. Proteolytic gelatinase enzymes, most importantly matrix metalloproteinases (MMP)-2 and MMP-9, are considered to be central mediators of ischemic BBB disruption; this is because of their ability to degrade components of microvascular basal lamina, especially collagen type IV [36,37], and to disrupt tight junction proteins [38]. A recent study demonstrated that cerebral mast cells participate in regulation of acute microvascular MMP-2 and -9 activation and consequent BBB disruption following transient cerebral ischemia [39]. Notably, mast cells can contribute approximately 90% of thalamic histamine and up to 50% of total brain histamine in rats [40]. Several reports indicate that BBB permeability is regulated by brain histamine. Infusion of histamine into the carotid artery enhances the penetration of albumin through the capillary and increases

Table 1. Mast cells and degenerative diseases.

Disease species	Manipulation used	Findings
MS	EAE	Mast cell stabilizer reduced the severity of EAE
		Mast cell-deficient mice develop a less severe EAE
Stroke	Hypoxic-ischemic brain damage	Rapid increase in cerebral mast cell number and activation
		Significant neuroprotection by inhibition of the early mast cell response
		Mast cell-degranulating increased the ischemic brain edema
AD		Fibrillar amyloid beta peptides trigger concentration-dependent exocytosis and histamine secretion from mast cells
		Tryptase-containing mast cells have been infiltrated in the brains of AD patients
		Masitinib slowed the cognitive decline in AD patients in phase II clinical trial

the cortical water content by activating H2 receptors [41,42]. Furthermore, serine proteases such as the mast cell-specific protease cause not only microvascular leakage, but also neuronal hyperexcitability and inflammation through protease-activated receptors [43–46].

Microglia and astrocytes

Besides releasing proinflammatory mediators, microglia also responds to proinflammatory signals released from other non-neuronal cells of immune origin. In this context, mast cells are of particular relevance. Several molecular mechanisms for potential interactions between mast cells and microglia have been determined *in vitro* [47]. For instance, activation of P2 receptors on microglia by ATP stimulates the release of IL-33, which binds to mast cell receptors, triggering the release of IL-6, IL-13, and monocyte chemo-attractant protein 1, which in turn may regulate microglia activity. Similarly, mast cell tryptase activates microglial-activated receptor 2 (PAR2) receptors, facilitating the release of pro-inflammatory mediators such as TNF- α , IL-6, and reactive oxygen species (ROS), which consequently upregulate the expression of PAR2 receptors on mast cells [48,49]. Mast cell activation leads to the upregulation of purinergic receptor P2X, ligand-gated ion, 4 (PR2X4) receptors on microglia, resulting in the release of brain-derived neurotrophic factor (BDNF) [50]. Furthermore, a new study now demonstrates that microglia can constitutively express all 4 histamine receptors (H1R, H2R, H3R, and H4R) and the expression of H1R and H4R can be selectively upregulated in primary cultured microglia in a dose-dependent manner by histamine. Histamine can also dose-dependently stimulate microglia activation and, subsequently, production of pro-inflammatory factors TNF-alpha and IL-6. The antagonists of H1R and H4R, but not H2R and H3R, reduced histamine-induced TNF-alpha and IL-6 production and MAPK and PI3K/AKT pathway activation, and mitochondrial membrane

potential loss in microglia, suggesting that the actions of histamine are via H1R and H4R [51]. Numerous other molecules and receptors such as complement component 5a receptor (C5aR), chemokine (C-X-C motif) receptor 4/12 (CXCR4 and CXCL12) and TLRs provide even more opportunities for microglia-MC interaction [47], suggesting that MCs have a large role in the normative functioning of microglia, as well as modulating host responses to infection, inflammation, trauma, and stress.

Besides microglia, mast cells also have a dynamic relationship with astrocytes. Mast cells and astrocytes are co-localized in the perivascular and thalamus [52]. *In vitro*, astrocytes can be activated by mast cells via activation of CD40-CD40 ligand interactions, and mast cells also are stimulated to release histamine, leukotrienes, and cytokines [53]. Interestingly, astrocytes also have histamine receptors (H1R and H2R) [54], and cytokines released from astrocytes can induce mast cell degranulation [55].

Mast cells and degenerative diseases

For their heterogeneity, first-responder capability, and positioning to impact on each of the elements of brain, it is perhaps not surprising that mast cells have been considered as a participant in almost all major CNS disease states, including MS, cerebral ischemia, AD, and PD (Table 1) [56,57]. In this section we summarize findings in 3 diseases from among the many that have been implicated in mast cell function: multiple sclerosis (MS), cerebral ischemia, and AD.

MS

Large numbers of mast cells are found at sites of inflammatory demyelination in the brain and spinal cord of MS patients [58,59], and mast cell tryptase is elevated in their cerebrospinal fluid [60]. Experimental autoimmune encephalomyelitis (EAE) is a widely

studied rodent model of MS. As in MS, significant destruction of myelin and oligodendrocytes, the myelin-producing cells, occurs due to T cell-mediated autoimmune response against proteins in the myelin sheath following an influx of immune cells into the CNS through the BBB [61]. Rodents with EAE exhibit increased degranulation of their brain mast cells [62] and elevated levels of the demyelinating mast cell protease [63]. Perivascular mast cells are among the earliest participants in MS, which produce TNF and other cytokines, break down the BBB, and elicit an early influx of neutrophils into myelin [64]. The proinflammatory mediators released from mast cells also aggravate the development of MS. Treatment is with the mast cell stabilizer picroximil, the H1 receptor antagonist hydroxyzine, or intracisternal administration of c48/80 [32]. The most direct evidence for mast cell action in EAE comes from studies utilizing W/W^v mice in a model of primary progressive (PP) MS [65]. This model disease is induced by immunization with MOG35–55 in CFA along with pertussis toxin. Mast cell deficiency leads to significantly less clinical disease that is associated with loss of BBB permeability and inflammatory cell infiltration into the parenchyma of the CNS [65,66].

Cerebral ischemia

The function of mast cells in ischemic brain injury is well documented and amply reviewed in both the adult and the immature brain [57]. In brief, the inflammatory response triggered by stroke is associated with the influx of many inflammatory cells, including leukocytes, neutrophils, and macrophages [67]. Mast cells differ from other hematopoietic cells in that they are resident in the brain and meninges and are first responders, even before microglia [68]. They can act rapidly on the cerebral vessels and other CNS compartments during the very earliest phase of acute cerebral ischemia and hemorrhage by releasing their preformed cytoplasmic granules containing a host of readily available vasoactive and neuroactive mediators. Mast cells act on the basal membrane, promoting BBB damage, brain edema, prolonged extravasation, and hemorrhage. Indeed, mast cell stabilization inhibits hypoxic ischemic-induced brain damage [69]. Furthermore, following even acute ischemic brain injury, cerebral mast cells amplify and prolong the endothelial expression of adhesion molecules and the continued breakdown of the BBB, thereby enabling the infiltration of other blood-borne cells and signals [57,70].

AD

The role of mast cells in AD remains elusive, but there have been studies suggesting the linkage between mast cells and

AD. In this respect, fibrillar amyloid beta peptides trigger concentration-dependent exocytosis and histamine secretion from mast cells [71]. It was demonstrated that tryptase-containing mast cells have been infiltrated in the brains of AD patients, and these mast cells are colocalized with amyloid plaques [72]. Recently, a study showed that administration of masitinib mesylate, a selective tyrosine kinase inhibitor efficient in controlling the survival, differentiation, and degranulation of mast cells, slowed the cognitive decline in AD patients in a phase II clinical trial [73].

Conclusions

Neuroinflammatory disorders are conditions in which components of the nervous system are damaged by inflammatory effectors derived from the innate and adaptive immune systems, as well as glia within the CNS. Microglia, in particular, act as sensor cells for disturbed brain tissue homeostasis and accumulate locally in response to neuron injury [74]. Few studies until now have focused on resident cell types capable of mounting immediate host responses in the brain. Mast cells are effector cells of the innate immune system, and represent the 'first responders' to injury rather than microglia. Potent preformed mediators of mast cell release are very rapid, while *de novo*-formed mediators are slower in activating [75].

The puzzling differences in the findings between distinct mast cell-deficient mouse models, as well as those between different laboratories, indicate that the role of mast cells in inflammatory CNS diseases is far from clear. Systematic analyses should include strictly controlled parameters such as sex and age of the animals, different immunization protocols, and EAE type (ie, onset and disease course). The development of new mast cell-deficient mouse models [76,77] and comparison of those with existing models such as KitW-sh/W-sh mice and KitW/W-v mice will help to unravel the true mast cell functions and distinguish them from other mechanisms resulting from mast cell-independent c-kit effects or CRE toxicity. A key role of mast cells in neuroinflammation can be expected from the known pro- and anti-inflammatory activities in the periphery. However, because of the contradictory results from experiments in rodents, very little is actually known about the exact role of mast cells in neuroinflammation.

Conflict of interests

The authors declare that they have no competing interests.

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