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Review

An Overview of the Physiological and Pathological Role of Mast Cells in the Central Nervous System

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ABSTRACT

Neurological disorders present a major group of diseases with the global prevalence of 6.3%. They are responsible for 12% global mortality. Mast cells are one of the most abundantly present cell of the immune system in the connective tissue and the central nervous system is not an exception. In this article is presented a review of studies on mast cells regarding their physiological role in cental nervous system. We also disscuss their role in several conditions like: multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, neuropsychiatric disorders, cerebrovascular disorders and central nervous system trauma, epilepsy, seizures and tumors. Finally, we evaluate whether they can be used as a targed for pharmaceutical treatment.

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1. INTRODUCTION

In the last 25 years, there was a significant increased focus toward nervous and immune system link. This resulted in the development of a new scientific branch called neuroimmunology [1]. The latest data shows that central nervous system (CNS) immune system interactions can be seen in different physiological and pathological conditions. One of the most abundantly present cell of the immune system are mast cells (MC). They are not only widely distributed but also have a great variety of biochemical substances that can alter the function of other cells including in the CNS.

Neurological disorders represent the most common causes of disability-adjusted life years. They account for 12% of global mortality and in lower and middle income countries neurologic disorders constitute 16,8% of the total deaths [2]. With all of this in mind the economic burden of neurological diseases also becomes a major healthcare challenge [3]. Since the global burden of neurological disorders has increased substantially over the past years there will be an increased need in clinicians with expertise in neurological conditions in the following decades [4].

The link between brain pathology and MC is not new and was mentioned by J. Neuman more than 100 years ago in

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1890 [5]. Almost a century later in 1974 Y. Olsson also mentions the presence and role of MC in multiple sclerosis [6]. Now there is a list of conditions where MC may play and important and possibly a key role like: multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, neuropsychiatric disorders, cerebrovascular disorders and central nervous system trauma, epilepsy, seizures and tumors. With all of this in mind, there are new therapies that target immune cells and alter their function within the CNS.

2. HISTAMINE IN THE CENTRAL NERVOUS SYSTEM

Histamine is practically a mast cell marker. Thus, it is important to clearly determine its role in the CNS and different conditions. Histamine is produced by decarboxylation of L-histidine and stored in MC, basophils and some neurons.

The human histaminergic system is located in and around the tuberomamillary nucleus (TMN). These neurons innervate the major parts of the cerebrum, cerebellum, posterior pituitary and the spinal cord [7, 8]. Rat's histaminergic system consists of TMN, supramamillary nucleus, paramamillary and a minor lateral area. Thus the histaminergic neurons occupy a large part of the posterior hypothalamus [9]. Still histaminergic system is relatively different in other animals.

The histaminergic neurons usually are similar between different species and aminergic neurons of the mesencephalon. They have large somata 20 - 30 μm in diameter, 2 - 3 large dendrites with ramifications that connect with dendrites of other histaminergic neurons. Many dendrites have access to cerebrospinal fluid and subarachnoid space. The varicose axons form a dense network in the hypothalamus. It is interesting to note that some of the ventrally located histaminergic neurons may take up L-3,4-dihydroxyphenylalanine (L-DOPA), and produce and release dopamine, making their range of functions a little wider and may partially account for the brains possibility to "regenerate" after injury. Besides that, they also have pacemaker properties. TMN neurons are especially active during waking or attention and completely inactive during sleep. This data led to the suggestion that histamine possibly can be the prime regulator of brain functions as sleep-wake cycles, neuroendocrine responses, suppresses food intake, increases water intake, increases antinociception and other [8-10]. Nevertheless, histaminergic neurons are a heterogeneous group of neurons and are organized into distinct circuits that influence different brain regions, and display selective control mechanisms [11].

Fibers from the TMN consist of two ascending pathways: one lateral, via the medial forebrain bundle and the other periventricular. These pathways combine into the diagonal band of Broca and then continue to many telencephalic areas [10].

Until now, four types of histamine receptors were identified: H1, H2, H3, H4 receptors, named in the order of discovery [9, 10, 12]. Table 1 shows key points on histamine receptors in the CNS.

3. MAST CELLS IN BRAIN'S PHYSIOLOGY

For the first time MC were described by P. Ehrlich in 1877 [13]. They arise from multi-potent hematopoietic progenitor cells and are identified based on expression of the tyrosine kinase receptor c-kit and the Fc receptor for IgE (FcεRI). Unlike basophils, MC live weeks to months and have a potential to proliferate after differentiation [14].

These cells occur mainly in two locations, the pia and the brain parenchyma. The population in the pia reaches a maximum at postnatal day 11 and declines rapidly thereafter, reaching almost zero levels from postnatal day 21. The current hypothesis states that MC enter the pia matter, then access the thalami by traveling along the abluminal wall of penetrating blood vessels. The number of dural mast cells is high from postnatal day 0 but declines from the postnatal day 21 [15, 16].

More than 96% of MC are inside the blood-brain barrier (BBB), with 90% contacting the blood vessel wall or its extracellular matrix. The brains parenchyma vessels have a more prominent role in the control of circulation compared to magisterial or pial vessels and MC may play an important function here. Many authors also mention that MC in the CNS can capture and store excess of neuromediators and then release them when needed. MC expresses α4 integrins - a potential mechanism for adhesion to the vascular wall. They are preferentially located on large diameter vessels (> 16μm; possibly arteries) and contact only those maturing blood vessels that are ensheathed by astroglial processes. MC not only bind to large vessels but also maintain a preferential position at branch points, sites of vessel growth. This observation presents the possibility that MC participate in and/or regulate vasculature growth or differentiation [16].

MC are abundantly present in the CNS, in structures such as circumventricular organs, in the meninges, hypophysis, pineal gland, area postrema, the median eminence and hypothalamus but their main residue area are the thalami

Table 1. Histamine receptors in the CNS

Characteristic	H1	H2	H3	H4
Localization	Hypothalamus, aminergic nuclei brain stem, cerebellum, thalamus, cortex, hippocampus	Cerebral cortex, striatum, nucleus accumbens, hippocampus, amygdala, cortex	Striatum, nucleus accumbens, cerebral cortex, substantia nigra, ventral and dorsal striatum	Hippocampus, cortex, striatum, thalamus, amygdale, spinal cord (but mostly peripheral tissues)
Homology	-	40% homology with H1	22% with H1 and 20% with H2	31 - 43% with H3
Mechanism of action	Stimulates phospholipase C (PLC), PLA2, NF-kB, NOS through Gq	Stimulates cAMP synthesis, PLC, protein kinase C, c-fos through Gs	Inhibits cAMP synthesis through, stimulates MAP kinase Gi	Inhibits cAMP synthesis, stimulates MAP kinase through Gi
Function	Neuroendocrine, behavioral, and nutritional state control, regulator of sleep-wake cycles, reduces seizure activity, production of local vasodilator substances	Postsynaptic histamine action, control of pituitary function, endogenous analgesic response	Behavior, learning, memory, endocrine and inflammatory function	Not clear
Loss of function	Defective locomotor and exploratory behaviors	Selective cognitive deficits along with abnormalities in nociception and gastric and immune functions	Behavioral state abnormalities, reduced locomotion, a metabolic syndrome with hyperphagia, late-onset obesity, increased insulin and leptin levels, and an increased severity of neuroinflammatory diseases	Not clear

CNS: Central nervous system; PLC: Phospholipase C; PLA2: Phospholipase A2; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOS: Nitric oxide synthase; cAMP: Cyclic adenosine monophosphate; MAP kinase: Mitogen-activated protein kinase.

(98%), where they stay in adulthood [17, 18].

The number of MC is not constant and varies between species, sex, time of year, age and behavior state.

Due to their possibility to penetrate blood vessels and blood-brain barrier, MC density can increase in the matter of 1 - 2 hours [19]. Besides their cognitive and behavior role MC also largely participate in endocrine regulation. Their degranulation in dog hypothalamus activates hypothalamic-pituitary-adrenal axis through the release of histamine and results in increased cortisol secretion. This can also be proved by the fact that H1 receptor blockers decrease cortisol secretions. In animal studies, histamine release from brain MC may increase renin and epinephrine secretion (through splanchnic nerves) and antidiuretic hormone secretion (through central nervous system) [20, 21].

They also seem to influence pituitary-thyroid action. Their degranulation leads to elevation of thyroid releasing hormone as well as thyroid stimulating hormone [22].

The level of gonadotropin releasing hormone (GnRH) containing MC in the hypothalamus increase during courtship along with its expression [23]. Their level and activity is increased by testosterone or dihydrotestosterone in males and 17β-estradiol in females [24]. Virgin mice have a decreased level of MC in comparison to postpartum group [25].

On the other hand, MC are also susceptible to hormones. Their quantity increases after administration of 6-n-propyl-2-thiouracil to frogs while T3 and T4 seems to have no significantly visible effect on them [26]. Somatostatin has inhibitory function on them, reducing histamine and other mediator synthesis and release [27].

One of the most significant proteins synthesized and stored by MC is the nerve grow factor (NGF) [28]. NGF reduces neurological deficit after trauma in experiments and clinical trials. It plays a trophic role during development and in adulthood, by maintaining phenotypical and functional characteristic of several populations of neurons and immune cells. NGF can change and reverse the neurotoxic lesions. This raises the question rather MC may act as information carriers between nervous and immune systems [13].

4. MAST CELLS IN BRAIN'S PATHOLOGY

For many years, the CNS was considered to be immune privileged. The link between brain pathology and MC is not new and was mentioned by J. Neuman more than 100 years ago in 1890 [5]. Almost a century later in 1974 Y. Olsson also mentions the presence and role of MC in multiple sclerosis [6].

4.1. MULTIPLE SCLEROSIS

Polymerase chain reaction analyses of patients with MS reveals an up-regulation of mast cell-associated genes such as tryptase, chymase and FcεRI chains [14]. The elevated levels of tryptase can also be found in cerebrospinal fluid of patients with MS [29]. They are abundantly present in MS plaques and in experimental autoimmune encephalomyelitis (murine model for MS) are actively recruited into the CNS from the bone marrow. MC can affect the course of the disease outside the CNS probably by recruiting other cells [30, 31]. They also can enhance astrocyte pro-inflammatory function thus causing development of neurodegenerative disease including demyelization [32]. In a model of relapsing-remitting MS, MC-deficient mice were shown to have significantly reduced disease severity but retain the relapsing-remitting course [33, 34]. Meningeal mast cells are activated within 24 hours of disease induction and begin to produce *tumor necrosis factor* (TNF) thus providing neutrophil influx in the area. Thus inflammation in the meninges actually may precede the CNS inflammation in MS [35]. Therefore, meninges may very well be a sort of a "gateway" for later CNS inflammation [36].

Several other studies also have shown that MC-deficient c-Kit mutant mice have some degree of protection or a milder form of the disease [37].

MC function depletion can result in better outcomes in patients with autoimmune brain pathologies. Several drugs can be used such as degranulation inhibitors (proxicromil) or a depletor of vasoactive amines in MC granules (reserpine) [38]. Masitinib has also shown therapeutical benefits, ameliorating clinical presentation and progression of the disease [39]. Dimethyl fumarate was shown to have positive results in MS treatment and was demonstrated to induce apoptosis of human MC, primarily via the mitochondrial apoptotic pathway [40]. Natalizumab which is currently a potent drug used in MS patients treatment may also target MC [41].

4.2. AMYOTROPHIC LATERAL SCLEROSIS

Current data suggests that inflammation in amyotrophic lateral sclerosis (ALS) affected spinal cord and cortex is based on innate immune responses by macrophages, and MC and adaptive immune responses by T cells [42]. It is well known that IL-17 and IL-6 positive MC play an important role in ALS progression and are more often present in the CNS of ALS patients in comparison with control subjects. Serum and spinal fluid levels of these ILs are also increased [43]. M. Fiala et al. report that ALS patients have increased levels of serum IL-17A. Spinal cord was infiltrated with IL-1b and TNF-a positive macrophages, IL-17A positive CD8 cells and MC [43]. The use of several drugs that decrease inflammation have been shown to be useful, possibly by suppressing some of the MC functions as well [44]. Clemastine, for instance, is associated with reduced microgliosis, modulation of microglia-related inflammatory genes and enhanced motor neuron survival [45]. In a case report by S. Clemente, palmitoylethanolamide was used to improve clinical course of ALS patient, presumably by inhibiting microglia and MC function [46]. Since immune system has a role in the development of ALS, several methods such as intravenous immunoglobulins, vaccinations, antibodies and other modalities may prove to be useful in its treatment.

4.3. ALZHEIMER'S DISEASE

A group of researchers found that in postmortem brains of Alzheimer patients there is a decrease in histamine levels: in the frontal (45% of control value), temporal (20%), and occipital cortices (38%) and in the caudate nucleus (25%). Histidine levels were decreased in the frontal (15%), temporal (21%), and occipital cortices (30%) and in the caudate nucleus (25%); the decrease was statistically significant in the last two brain regions. The data indicates that brain histamine regulation is altered in Alzheimer's disease [13]. Another group of scientists found significantly reduced histamine levels in the hypothalamus (42%), hippocampus (43%) and temporal cortex (53%) of Alzheimer patient brains [47]. Histaminergic neurons enhance cognition and memory, suggesting that their degeneration may contribute to the cognitive decline of Alzheimer's disease [48].

MC increase amyloid plaques formation in the CNS by the secretion of chymases and immune factors [49, 50]. Thus, the use of alpha 1-antichymotrypsin may play a role in Alzheimer's disease treatment [51].

Masitinib, which has a variety of indications, is studied for the treatment of malignant melanoma, mastocytosis,

multiple myeloma, MS, gastrointestinal, and pancreatic cancers and rheumatoid arthritis, may be used in Alzheimer's disease [52]. Masitinib administered as add-on therapy to standard care during 24 weeks was associated with slower cognitive decline in Alzheimer's disease [53].

4.4. NEUROPSYCHIATRIC DISORDERS

MC can also be involved in a wide range of neuropsychiatric disorders. Patients with mastocytosis often suffer from depression. The use of mastinib results in 67% decrease of depression in these patients along with symptoms of anxiety [54].

There is an increase of neurotensin level in serum of autistic children which can stimulate MC and microglia, resulting in focal brain inflammation and neurotoxicity which can result in autism-like disorder (ASD) [55].

Children with mastocytosis sometimes have learning disabilities, hyperactivity and difficulty focusing. Additionally, they have 10 times higher chance for autism spectrum disorder. Mastocytosis patients have high IL-6 levels and sometimes develop seizures. Some patients with mastocytomas have seizure-like symptoms. Increased serum IL-6 was linked to the expression of an autistic phenotype in mice. Twenty-five percent of ASD children have "allergic-like" symptoms suggesting MC activation by non-allergic triggers [56-58].

On the other hand, the level of histamine in cerebrospinal fluid in patients with narcolepsy is significantly decreased which may account for the symptomatology of the disease [59]. There is evidence linking MC to migraine and other hyperalgesia conditions [60].

4.5. CEREBROVASCULAR DISORDERS AND CNS TRAUMA

MC have been shown to degranulate during hypoxia and stress, two key components of a cerebrovascular disorder. From 2% to 20% of the total mast cell population crosses the blood-brain barrier during 1 hour, changing permeability and causing perivascular edema [61].

Several authors report that MC stabilization with sodium cromoglycate reduces ischemic brain swelling, blood-brain barrier leakage, whereas the stimulation of MC degranulation causes their increase [62-64]. In one of the experiments, involving a model of middle cerebral artery occlusion MC-deficient mice showed 58% less brain swelling, 47% lower BBB damage, 47% neutrophil infiltration in comparison with normal mice. Which may be important in case of an after stroke brain swelling [64]. MC increase infiltration of granulocytes, activation of macrophages, brain swelling, and infarct size by multiple mechanisms that involve IL-6 and other substances synthesized by them [65]. MC stabilization with sodium cromoglycate provides up to 48 hours of protection from ischemia in immature rat brains [66]. MC stabilization in rats with Intracerebral hemorrhage results in better neurologic scores, decreased mortality, less brain swelling and smaller hematoma volume growth compared with saline or compound 48/80 [67].

M. B. Abrams et al. in an experimental imatinib treatment of rat spinal cord injury report significant positive effects. Oral treatment with imatinib for 5 days, 30 minutes after the injury enhanced blood-spinal cord barrier integrity, sensory and motor function. It also decreased astrogliosis and deposition of chondroitin sulfate proteoglycans, preserving nervous tissue. Thus, imatinib can have beneficial neuroprotective effects in case of trauma [68]. It was shown that MC-deficient Kit mice display significantly increased astrogliosis and T cell infiltration as well as significantly reduced functional recovery after spinal cord injury compared to wildtype mice [69]. Similar data was shown in case of mouse MC protease 4 or MC-deficient Kit mice in brain injury [70].

Interestingly, a variety of manipulations can increase the MC activation. For instance, dural mast cells subjacent to the craniectomy degranulate, causing reduced histamine in dura mater subjacent to the craniectomy, increased histamine in the subjacent cerebral cortex and, finally, cause breakdown of the blood-brain barrier. Similar results were observed in mice after scoring the bone surface. Pretreatment with the zolantadine (H2-receptor antagonist) inhibited the breakdown of the blood-brain barrier [71]. Administration of tissue plasminogen activator in vitro also causes MC degranulation. In vivo experiments, in a focal cerebral ischemia model in rats showed a 70-100-fold increase in hemorrhagic formation after postischemic tissue plasminogen activator administration [62].

4.6. EPILEPSY AND SEIZURES

During the status epilepticus, rats that received saline showed an enhanced release of histamine, GABA and glutamate, even after diazepam administration. One day after the status epilepticus, there was an increased number of mast cells and neuronal damage in the hippocampus. In contrast, the group which was pretreated with sodium cromoglycate showed increased latency to the establishment of the status epilepticus, absence of "wet-dog" shakes, reduced histamine release, lower number of mast cells and reduced neuronal damage in the hippocampus [72].

The opposite results can be seen in case of compound 48/80 administration. After administration of the compound 48/80 there was a significant increase in rates of seizure at 60th and 120th minutes. After mast-cell depletion the rate of seizure tended to decrease [73].
There are also data that administration of such drugs as fexofenadine, cetirizine, sodium cromoglycate and ketotifen attenuated the seizurogenic activity that tramadol exerted on pentylenetetrazole-treated mice [74]. On the opposite, a H1 antagonist astemizole seems to have a potential to induce seizures [75]. This underlines the role of different receptors in the pathogenesis of the diseases. As seen in several studies H1 agonists decrease the seizure activity, whereas in case of H3-receptor antagonists decrease convulsions [76, 77].

4.7. CNS TUMORS

A promising field where MC function alteration can prove to be useful is oncology.
Tumors often produce stem cell factors which induce proliferation and recruitment of mast cells. The presence of MC near the tumors was linked to poor and better outcomes in patients. Thus, the presence or absence of MC in tumors is still controversial. MC accumulate in gliomas, which express stem cell factors present only in vessels, close to the tumor but not outside of it. Besides that, the level of MC presence correlates with macrophage migration inhibitory factor, which has been reported to be pro-inflammatory and pro-tumorigenic [78, 79].
It is hypothesized that Nf1–/– Schwann cells secrete soluble factors to activate signaling pathways in Nf1+/– MC to promote their migration to Nf1–/– Schwann cells. Nf1+/– MC, in turn, may secrete soluble factors into the tumor microenvironment [80].
MC promote angiogenesis and tissue remodeling in tumors such as neurofibromas. A group of authors in 2010 used imatinib in experimental treatment of neurofibroma in a 3-year old girl. The tumor compressed her airway, leading to drooling, sleeplessness and anorexia. After 3 months of treatment, magnetic resonance imaging showed a 70% reduction in tumor volume [81, 82].
Microscopic examination of 19 cases of subependymal giant cell astrocytomas showed an admixture of MC and T lymphocytes in these tumors the role of which was not clear [83]. In astrocytic tumors they were observed in the collagen matrix around larger vessels in the leptomeninges but not adjacent to malignant tumor vessels, thus their role in these tumors is also debatable [84].
In capillary hemangioblastomas of the cerebellum MC are numerous, mostly in the tumor mass and only occasionally found in adjacent areas of the cerebellum. At periphery of hemangioblastomas some MC could be degenerated and calcified. Most of these cells are tryptase/chymase phenotype [85].
MC as well may play a role in meningiomas development. The expression of tryptase was observed in 32 - 40.4% of low grade meningiomas and 86 - 90% of high grade meningiomas. Therefore, the number of MC might be a significant prognostic factor for the recurrence or bad prognosis of meningiomas [86, 87]. There is statistically significant correlation between hypoxia inducible factor-1, tryptase expression, peritumoral brain edema, which leads to surgical complications and worse recovery [87]. Also, the secretory meningiomas were characterized by a significantly increased number of MC as compared with non-secretory [88].
There are also some data that link brain metastasis with MC secretory function and their possibility to alternate blood-brain barrier and thus facilitate cancer migration to the CNS [89, 90].

5. CONCLUSION

For many years CNS was considered a «privileged» zone, to which immune system had no access. This concept was significantly altered during the last years. This gives new therapeutical possibilities for treatment of different nervous disorders. Among the cells that may be targeted by pharmacological substances are the MC. Their role in different pathologies was realized long ago and with every year, this concept grows stronger. Centering the treatment specifically on MCs with different drugs (ex.: imatinib) may result in a better life expectancy rate, lower pathological symptoms of the disease as well as possible cure for the disease or at least its slower progression.

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