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MAST CELLS AND NEUROINFLAMMATION IN PATHOGENESIS OF NEUROLOGIC AND PSYCHIATRIC DISEASES

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The review summarizes current data on the role of neuroinflammation and mast cells in the pathogenesis of nervous and mental diseases, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, depression, autism, migraine, schizophrenia and some others. The contribution of neuroinflammation to the pathogenesis of many of these diseases has been demonstrated. The involvement of mast cells in the development of the neuroinflammatory process has with varying degrees of evidence been shown for multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease and migraine. There is still no convincing evidence that mast cells contribute to neuroinflammation in Parkinson's disease, depression, schizophrenia and autism spectrum disorder, although it is possible that they play a role in the pathogenesis of these diseases. Data on the causal role of neuroinflammation and mast cells in the development of neuropsychiatric diseases may become the basis for the development of new approaches to their pharmacological treatment. The review provides data on the first clinical trials of anti-inflammatory and mast cell activity-modulating drugs for the treatment of migraine, Alzheimer's disease, multiple sclerosis and amyotrophic lateral sclerosis.

Keywords: mast cells; neuroinflammation; multiple sclerosis; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; depression; autism; migraine; schizophrenia.

ТУЧНЫЕ КЛЕТКИ И НЕЙРОВОСПАЛЕНИЕ В ПАТОГЕНЕЗЕ НЕРВНЫХ И ПСИХИЧЕСКИХ ЗАБОЛЕВАНИЙ

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В обзоре обобщены современные данные о роли нейровоспаления и тучных клеток в патогенезе нервных и психических заболеваний, таких как рассеянный склероз, болезнь Альцгеймера, болезнь Паркинсона, боковой амиотрофический склероз, депрессия, аутизм, мигрень, шизофрения и некоторые другие. Продемонстрирована вовлеченность нейровоспаления в патогенез многих из этих болезней. Участие тучных клеток в развитии нейровоспалительного процесса было показано с разной степенью доказательности для рассеянного склероза, бокового амиотрофического склероза, болезни Альцгеймера и мигрени. Пока не получены убедительные данные об участии тучных клеток в нейровоспалении при болезни Паркинсона, депрессии, шизофрении и расстройстве аутистического спектра, хотя возможно, что они играют определенную роль в патогенезе указанных заболеваний. Данные о влиянии нейровоспаления и тучных клеток на развитие нервно-психических заболеваний могут стать основой для разработки новых подходов к их фармакологическому лечению. В обзоре приведены данные о первых клинических испытаниях противовоспалительных средств и препаратов, модулирующих активность мастоцитов, для лечения мигрени, болезни Альцгеймера, рассеянного склероза и бокового амиотрофического склероза.

Ключевые слова: тучные клетки; нейровоспаление; рассеянный склероз; болезнь Альцгеймера; болезнь Паркинсона; боковой амиотрофический склероз; депрессия; аутизм; мигрень; шизофрения.

In the last two decades, massive evidence has accumulated, which indicated an important, if not decisive, role of inflammatory processes in the pathogenesis of many nervous and mental diseases. In this regard, interest in the cells of the first line of defense against pathogens acting in the nervous system, which regulate the inflammatory process in the brain, has sharply

Abbreviations

CNS, central nervous system; IL, interleukins.

increased. Microglia is the focus, while mast cells, or mastocytes, another group of immunocompetent resident brain cells, are in the background. This review presents the information obtained to date on the role of mast cells and neuroinflammatory response in the pathogenesis of some socially significant nervous and mental diseases.

Overview of mast cells

Mast cells are found in all organs and are derived from hematopoietic stem cells in the bone marrow. They are characterized by numerous secretory granules in the cytoplasm. Granules contain many (over two hundred) different components, including biogenic amines (such as histamine, catecholamines, and polyamines), proteases (tryptase, chymase, and many other proteases specific and nonspecific for mast cells), lysosomal and other enzymes (cathepsins, β-hexosaminidase, β-glucuronidase, heparanase, peroxidase, etc.), cytokines (interleukins [IL]-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-16, tumor necrosis factor (TNF)-α, etc.), growth factors (such as nerve growth factor, stem cell factor, and vascular endothelial growth factor), proteoglycans (serglycin), mucopolysaccharides (heparin and chondroitin sulfate), peptides and hormones (such as vasoactive intestinal peptide, substance P, endorphin, antimicrobial peptide cathelicidin LL-37, and vasoconstricting peptide endothelin-1), and many other substances [1, 2]. Mast cell mediators are grouped into those permanently stored and synthesized *de novo* after mast cell activation. Mast cell mediators include both proinflammatory cytokines (such as IL-1, IL-2, IL-6, IL-12, and TNF-α), and anti-inflammatory cytokines (IL-4, IL-10, and IL-13). The presence and release of these modulators of inflammation allows mast cells, after stimulation with certain substances, to initiate and control inflammation in the central nervous system (CNS), which in this case is called neuroinflammation.

Distribution of mast cells in the CNS

Histochemical staining, primarily with aniline dyes, is used to stain selectively and detect mast cells on histological specimens. These cells are detected immunohistochemically even more efficiently, using antibodies to enzymes tryptase and chymase, which are found almost exclusively in mast cells. These imaging techniques have detected mast cells in various organs, including the CNS of humans and animals. In the human brain, mast cells were discovered at the end of the nineteenth century in the affected area in stroke, progressive paralysis, and multiple sclerosis [3]. Over the past several decades, mast cells have been identified in the *area postrema*, pineal gland, choroid plexus, as well as dura mater and pia mater [4]. Some data indicate the presence of mast cells also in the subfornical organ, vascular organ of the terminal plate, midbrain (without specifying the specific structure), pituitary gland, spinal cord, and neoencephalon parietal cortex [5, 6].

In all publications, attention is drawn to the predominant location of mast cells near the blood vessels and brain structures washed by the cerebrospinal fluid of the ventricles, that is, at the boundaries of the brain (and, apparently, the spinal medulla) and fluids washing it, namely, blood and cerebrospinal fluid. The presence of mast cells in the structures of the blood–brain, cerebrospinal fluid–brain, and blood–cerebrospinal fluid barriers indicates their importance for the normal functioning of brain barriers and corresponds to their role as first line cells of the CNS immune defense.

Relationship of mast cells with cells of the nervous system

Numerous receptors are located on mast cells, including those that determine their sensitivity to pathogenic microorganisms, helminths, and allergens. These include receptors for immunoglobulins E and G (FcεRI and FcγRI), various complement receptors, Toll-like and Nod-like receptors, as well as receptors for some type C lectins. Activation of mast cells by pathogens, mediated by these receptors, causes the release of a certain set of mediators that affect the surrounding nerve, glial cells, and endothelial cells in the CNS.

Mast cell tryptase binds to the protease-activated receptor 2 and the Toll-like receptor localized on neurons, astroglial cells, and microglial cells and triggers the MAPK, AKT, and NF-κB signaling pathways on these cells [6–8]. Mast cells also influence astroglial and microglial cells

through histamine, activating histamine receptors H_1 and H_4 [7, 8].

Mast cells are located near vessels, often in direct contact with them and have various vasoactive compounds, such as histamine, serotonin, nitric oxide, endothelin-1, vascular endothelial growth factor, tryptase, proinflammatory cytokines IL-6, IL-8, TNF-α, etc. Consequently, the activation of mast cells has a pronounced effect on the functional activity of the endothelium of cerebral vessels, changing their permeability and, consequently, the permeability of the blood–brain barrier [9, 10]. Since the impairment of the blood–brain barrier is characteristic of almost all nervous and mental diseases, mast cells are probably, and in some cases proven, involved in this process.

By activating astroglia and microglia, mast cells, together with them, regulate the neuroinflammatory process in response to incoming signals about pathogens and organize later the interrelated work of brain cells to restore the nerve tissue [11, 12]. Inflammation is a complex process caused by infection or mechanical damage to counteract antigens and repair subsequently the damaged structures. However, if the inflammatory process in the CNS becomes out of control and chronic, it can become a damaging factor and cause the death of nerve cells. Data obtained in recent years indicate that neuroinflammation plays a significant role in the pathogenesis of several CNS diseases.

Multiple sclerosis is one of the most common neurodegenerative diseases and has an autoimmune nature. Although its etiology is unknown, multiple sclerosis is believed to be initiated by myelin-specific $CD4^+$ T lymphocytes activated at the periphery. When entering the CNS, these cells cause a neuroinflammatory response aimed at myelin-producing oligodendrocytes, as well as neurons, resulting in myelin breakdown and local impairment of nerve conduction, which leads to neurological disorders. In patients with multiple sclerosis, mast cell count in the brain and spinal cord increases significantly (several times), and they were found in the foci of demyelination (so-called plaques of multiple sclerosis) [3, 13, 14]. Concentrations of histamine and tryptase (compounds characteristic of mast cells) in the cerebrospinal fluid of patients with multiple sclerosis also increase [15, 16]. Increased count and activity of mast cells were also revealed in the brain and spinal cord of rats with experimental allergic encephalomyelitis (a model of multiple sclerosis) [17, 18]. In patients with mastocytosis (a disease characterized by activation and increased mast cell count in body tissues), the incidence of multiple sclerosis increased [19, 20]. By contrast, experimental allergic encephalomyelitis develops in a milder form in transgenic mice without mast cells ($Kit^{W/Wv}$) [21]. Opposite results were also obtained in mice without mast cells of a different line ($Kit\ W^{-sh}/W^{-sh}$) [22], which may be associated with various responses of animals of two different lines to the induction of experimental allergic encephalomyelitis.

The abovementioned findings reveal the participation of mast cells in the development of multiple sclerosis; however, research results do not give an unambiguous answer whether mast cells are a pathogenic factor or they counteract the disease development. Animal experiments have shown that mast cells can induce apoptosis of oligodendrocytes and demyelination because of proteases they secreted [23, 24]. Multiple sclerosis is also accompanied by infiltration of type 1 T-helpers into the brain through the blood–brain barrier, which leads to inflammation and neurodegeneration [25]. Impairment of the blood–brain barrier integrity is characteristic of multiple sclerosis and even precedes its clinical manifestations [21, 26], and mast cell mediators can disrupt (increase) the permeability of the blood–brain barrier and thereby facilitate infiltration of type 1 T-helpers and other immunocompetent cells into the brain [27]. These data indicate the possible involvement of mast cells as a pathogenic factor. Based on this, drugs were tested, which inhibit (through various mechanisms) the activity of mast cells for the treatment of multiple sclerosis. Preclinical and clinical trials of this kind of drugs, namely, imatinib, masitinib, cladribine, or tyrphostin AG126, gave moderately positive results [28–31]; evobrutinib had no effect on improvement [32]. In addition, a model of experimental allergic encephalomyelitis demonstrated that antagonists of histamine, one of the main products of mast cells, slow down disease development and severity (but do not prevent it) [11, 33], and in patients taking antihistamines, multiple sclerosis is less common [34].

A study of the brain of patients with multiple sclerosis revealed that mast cells in demyelination foci appear because of inflammation, and not

vice versa [13]. However, this finding does not indicate that mast cells migrate to the inflammation focus to perform a protective function, and they can also contribute to neurodegeneration.

Thus, by now, mast cells are clearly involved in the development of multiple sclerosis, and most of the evidence confirms that they are a pathogenic factor causing demyelination and neurodegeneration. Thus, the blockade of their activity (particularly inhibition of the action of their mediators) can contribute to the treatment of multiple sclerosis. However, the original reason why mast cells migrate to the focus of inflammation are activated and become a pathogenic factor has not been established yet.

Massive evidence suggests that **Alzheimer's disease**, another neurodegenerative disease, is also associated with neuroinflammation. Alzheimer's disease, which leads to profound memory impairment, is morphologically characterized by the appearance of amyloid plaques and neurofibrillary tangles in brain structures, as well as the development of an inflammatory reaction. The neuroinflammatory process is accompanied by the infiltration of immune cells from the blood into the brain and the activation of intracerebral mast, microglial, and astroglial cells.

The role of mast cells in the neuroinflammatory process in Alzheimer's disease is poorly investigated. Studies have revealed that the mast cell count increases significantly in the brain and spinal cord of patients with Alzheimer's disease [5, 35]; moreover, in the autopsy material, if their confinement to places of accumulation of amyloid plaques was not noted, in the mouse model of Alzheimer's disease, mast cells were detected near the amyloid plaques [36]. In addition, the concentrations of histamine, IL-1β, and IL-6 as proinflammatory mediators' characteristic of mast cells, increase significantly in the blood serum and cerebrospinal fluid of the patients [37]. Some mast cell mediators (IL-1β, IL-6, TNF-α, and prostaglandins) are known to interfere with the process of memory consolidation [38, 39], which indicates a possible mechanism by which mast cell dysfunction may contribute to memory impairment in Alzheimer's disease.

Based on data on the involvement of neuroinflammation and mast cells in the development of Alzheimer's disease, researchers have attempted to use nonsteroidal and other anti-inflammatory drugs to treat and prevent this disease; however, studies have yielded conflicting results [40, 41]. Since 2015, clinical trials of cromolyn, which inhibits the activity of mast cells, have been performed in the USA for the treatment of Alzheimer's disease [42]. By inhibiting mast cells, this drug was believed to stop the neuroinflammation-induced neurodegeneration and thereby slow down or even stop the progression of Alzheimer's disease, especially in the early stages. Similarly, a preclinical and clinical study of masitinib, which is another drug that inhibits mast cell activity, has noted some improvement in the condition and the slowdown in the development of Alzheimer's disease [29]. Thus, the data indicate the participation of mast cells in the pathogenesis of Alzheimer's disease, as they can contribute to the development of neuroinflammation and disruption of the blood–brain barrier in this disease and possibly affect the metabolism of amyloid proteins.

Amyotrophic lateral sclerosis is a neurodegenerative disease that is accompanied by the degeneration of the spinal and cortical motor neurons. The causes of this disease have not been established, but obtained evidence revealed that the inflammatory response in different areas of the CNS, which is implemented by immunocompetent cells, including mast cells, plays an important role in disease development [43, 44]. In this disease, the blood–brain barrier is disrupted, including at the spinal cord level [45]; as already noted, the permeability and integrity of the barrier can change significantly under the influence of vasoactive mediators of mast cells. Consequently, mast cells (or their precursors) can enter the spinal cord from the bloodstream and release various mediators there, some of which can cause local inflammation and impairment of neuronal function [46]. This assumption is based on the detection of mast cell infiltration into the gray matter of the spinal cord and muscle tissue (including around neuromuscular synapses) in both patients with amyotrophic lateral sclerosis and experimental disease models [5, 43, 47]. In addition, a significant increase was found in the concentration of proinflammatory cytokines IL-6, IL-8, IL-12, and IL-15 in the cerebrospinal fluid, at least some of which originated from mast cells [48–50]. In this regard, TNF-α and specific mast cell proteases can participate in demyelination [23, 24], and this indicates

directly the possible involvement of mast cells in the degeneration of motor neuron axons, neuromuscular synapses, and muscle fibers.

With the above background information, we studied the effect of mast cell blockade on neurological status and pathomorphological and biochemical parameters in experimental models of amyotrophic lateral sclerosis and in clinical practice. A model of amyotrophic lateral sclerosis demonstrated that inhibition of mast cells with cromolyn or the flavonoid tetramethoxy luteolin led to a slight but significant improvement in neurological manifestations and a decrease in the expression of proinflammatory cytokines and chemokines (particularly IL-6 and TNF-α) in the spinal cord and blood plasma of mice [51, 52]. A similar rat model demonstrated that tyrosine kinase inhibition by masitinib blocked the tyrosine kinase receptor c-kit and present abundantly on mast cells as well as on neutrophils, thereby preventing mast cell and neutrophil infiltration into the muscles, axonal damage, demyelination, and loss of myofibrils in rats [47]. The first two phases of clinical trials of masitinib (in combination with riluzole) in the treatment of patients with amyotrophic lateral sclerosis revealed slowing down of the progression of motor symptoms and an elongation of the life of patients [53]. Thus, the data indicate the involvement of mast cells in the pathogenesis of amyotrophic lateral sclerosis, even if their role in disease development has yet to be established more precisely.

Parkinson's disease ranks first as the most common movement disorder worldwide and ranks second among the most common neurodegenerative diseases. Its development is associated with the degeneration of the *substantia nigra* dopaminergic neurons. Recent studies have indicated that the pathogenesis of this disease is also associated with a neuroinflammatory process [16, 54, 55].

Data on the possible involvement of mast cells in neuroinflammation in Parkinson's disease are limited. To our knowledge, only one study reported increased amount and activity of mast cells in the midbrain of patients with Parkinson's disease [6]. Nowadays, no other data on the possible localization of mast cells in the human *substantia nigra* in norm or pathology. Moreover, we managed to find only one work in which mast cells were demonstrated in the *substantia nigra* of experimental animals (mice) in the norm [56].

Under the action of the selective dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP^+), which is widely used to model Parkinson's disease, the mast cell count in the substantia nigra of mice increased several times simultaneously with increased concentration of inflammatory histamine mediators in the *substantia nigra* and blood serum, as well as leukotrienes, various cytokines, including IL-1β, IL-2, IL-6, CCL2, TNF-α and transforming growth factor-β, and synthesized in mast cells [6, 57, 58]. This reveals the participation of mast cells in the inflammation process.

Moreover, some of the mediators secreted by mast cells, for example, histamine, CCL2 chemokine, transglutaminase-2, matrix metalloproteinase-3, and murine mast cell protease-6 and -7, can induce directly selective degeneration of nigral dopaminergic neurons or contribute to its development [56, 57]. Accordingly, the experimentally induced decrease in mast cell count leads to a decrease in the number of neurons degenerating under the influence of the MPP^+ neurotoxin [59]. These data indicate that the increased activity of mast cells can enhance the neurodegeneration process in the *substantia nigra*, caused by selective dopaminergic neurotoxin in the experiment, or even directly cause neuronal degeneration. However, so far, this is only a hypothesis that is based on a few experimental data and has serious controversial points, the main one of which is that mast cells were not detected in the *substantia nigra* of humans and were extremely rarely found in experimental animals. As a result, the possible role of mast cells in the pathogenesis of Parkinson's disease requires further investigation.

The minimal amount of data indicates the probable involvement of neuroinflammation in the pathogenesis of **Huntington's chorea** and the involvement of mast cells in this process [60, 61].

In 1993, it was first shown and later confirmed that **depression** is accompanied by activation of the immune system. This is manifested as increased levels of inflammatory markers [62]. Then, a study hypothesized that inflammation underlies the pathogenesis of depressive disorders, including major depressive disorder (according to the DSM-5 classification), and their

immediate cause is an increase in the amount of proinflammatory cytokines. These claims are based on several arrays of data. First, with depression, the concentration of inflammatory markers (IL-1, IL-6, IL-10, IL-17A, TNF-α, as well as C-reactive protein) increases significantly in the blood and cerebrospinal fluid [63–68], and in one-third of patients with major depressive disorder, abnormalities in the chemical and cellular composition of the cerebrospinal fluid characteristic of inflammation are observed [69]. Increased level of TNF was also noted in the prefrontal cortex of patients with depression [70]. These data are consistent with reports that the intake of anti-inflammatory drugs leads to a decrease in the risk of depression and can be used for its treatment [71–73], while antidepressant drugs are effective in the treatment of atopic dermatitis, which development is closely associated with increased activity of mast cells [74].

Second, many chronic inflammatory diseases are accompanied by a depressive state [75, 76], and activation of the human immune system by injecting a low dose of Salmonella endotoxin increased the blood concentrations of proinflammatory cytokines and is accompanied by symptoms of depression such as depressed mood, anxiety, and cognitive impairment [77].

Third, symptoms of depression are noted in patients after the administration of interferon-α or IL-2 for the treatment of hepatitis C and cancer [78, 79]. Typically, depression caused by proinflammatory cytokines in humans is arrested by antidepressants [80], just as in "classical" depression, which suggests that both types of depression have a common pathogenic mechanism associated with the inflammatory process in the body as a whole and in particular in the CNS. Antidepressants used in clinical practice have a pronounced anti-inflammatory effect; as a result, when remission is achieved, the blood concentration of proinflammatory cytokines decreases [66], while in the absence of a therapeutic effect the level of inflammatory markers in the blood does not decrease [81].

These findings indicate the involvement of neuroinflammation caused by proinflammatory cytokines in the pathogenesis of depression. Mast cells, along with other immunocompetent cells, produce and secrete proinflammatory cytokines that cause depression. However, the real contribution of mast cells in general and in particular that of intracerebral mast cells to the induction of neuroinflammation and development of depression is not clear yet. The involvement of mast cells in the pathogenesis of depression is revealed by clinical data on two diseases associated with mast cells, namely, mastocytosis, characterized by activation and increased count of mast cells in body tissues, and mast cell activation syndrome, in which the count of mast cells does not increase; however, their functional activity (release of mediators) increases sharply. Both diseases, in addition to somatic disorders, are accompanied by depression, which is noted in up to 70% of patients, while the same biochemical changes are registered in the blood as in major depressive disorder, and magnetic resonance imaging identifies structural abnormalities in the brain characteristic of depression [82, 83].

Some other circumstantial evidence also points to the possible involvement of intracerebral mast cells in the pathogenesis of depression. In the brain of patients with depression, the binding of ligands to histamine receptors is reduced, and histamine is mainly involved in the regulation of neuroinflammation. In addition, endogenous histamine has antidepressant properties (in experimental models), and the effect of antidepressants is partially implemented by binding to histamine H_1 and H_2 receptors [84, 85]. These data indicate the involvement of the brain histaminergic system in both neuroinflammation and development of depression. Since brain mast cells contain a significant portion of histamine, it is reasonable to assume that intracerebral mast cell histamine is significant in the neuroinflammatory process and development of depression.

Thus, the pathogenesis of depression is closely related or, which is quite possibly, caused by body and brain inflammation with the direct participation of immunocompetent cells, including intracerebral mast cells.

Similar data can be cited about the role of neuroinflammation and mast cells in the pathogenesis of **schizophrenia**. Schizophrenia is known to be based on an inflammatory process, which is accompanied by increased concentrations of proinflammatory cytokines in the blood serum. In the acute phase of schizophrenia (as in depression), blood concentrations of proinflammatory cytokines IL-1β, IL-6, IL-8, as well as TNF-α, C-reactive protein, and transforming

growth factor-β are increased [67, 86], and successful antipsychotic therapy normalizes the concentrations of at least IL-1β, IL-6, and transforming growth factor-β [65]. In addition, increased concentrations of IL-1β, IL-6, and IL-8 were revealed in the cerebrospinal fluid [68]. Based on these data, attempts were made to treat schizophrenia with anti-inflammatory (primarily nonsteroidal anti-inflammatory) drugs, which gave moderately beneficial effects [87].

These findings indicate that the inflammatory process is characteristic of schizophrenia, and changes are noted not only in the blood but also in the cerebrospinal fluid, which indicates a functional impairment of immunocompetent cells in the CNS. A set of proinflammatory cytokines, which concentration is altered in this disease, is characteristic of mast cells. They are assumed to be involved in neuroinflammation that occurs in schizophrenia.

Autism (DSM-5 autistic spectrum disorder) is associated with impaired functioning of the immune system and is characterized by pronounced signs of neuroinflammation. It is reasonable to suppose that autistic spectrum disorder develops during the embryonic period and is associated with the immune system hyper function of the expectant mother. For example, women suffering from diseases associated with impaired immune system, such as asthma, atopic dermatitis, hay fever, mastocytosis, and others, during pregnancy, have a significantly increased risk of having a child with autism [88]. In the blood serum of pregnant women whose children were later diagnosed with autistic disorder, increased concentrations of IL-4 and IL-5 were noted at weeks 15–19 of gestation, and the levels of IL-4, IL-10, and TNF-α and -β were increased in the amniotic fluid [89, 90]. These findings are consistent with the hypotheses about the possible role of perinatal stress in the pathogenesis of autism. Since maternal cytokines pass through the blood–placental barrier, they can enter the fetal brain in excess amounts and have both a direct effect on the development of the fetal nervous system and an indirect effect by changing the activity of microglia and mast cells and stimulating the release of proinflammatory and neurotoxic mediators, which increased concentration leads to the abnormal development of the fetal nervous system and may contribute to the development of autism [88, 89, 91].

Children with autistic spectrum disorder also have elevated serum levels of IL-1β, IL-4, IL-6, IL-8, IL-16, and IL-17A, and their concentration correlates with disease severity [92, 93]. Levels of proinflammatory cytokines IL-6, IL-8, and TNF-α are increased not only in the blood but also in the cerebrospinal fluid of pediatric patients [94, 95], which indicates the activation of immune cells in the CNS. Moreover, levels of IL-6, IL-8, and TNF-α were increased in the frontal cortex [96] and those of IL-6 and IL-10 were increased in the anterior callosal gyrus [94]. The expression of IL-6 was also increased found in the cerebellum [97], which indicates the presence of neuroinflammation in autistic disorder and suggests its involvement in the pathogenesis of this disease.

The majority of proteins, which are markers of inflammation and which concentration is increased in autistic disorder, is synthesized in mast cells (as well as in some other cells involved in immune reactions) and indicates their possible involvement in disease pathogenesis. This is supported by the finding that autism occurs many times more often in children with mastocytosis [98]; conversely, autistic children suffer from allergies much more often, and mast cells were found to play a primary role in the pathogenesis [99]. These findings, together with data on the changes in the levels of proinflammatory cytokines that can be synthesized by mast cells, suggested that “autism is a brain allergy,” which was caused by (like any allergy) excessive activation of mast cells [100, 101]. However, this hypothesis has not been sufficiently substantiated yet to become a generally accepted theory.

Few data support the finding that **attention-deficit hyperactivity disorder** is also associated with the development of neuroinflammation with the participation of mast cells [102].

Migraine is manifested as periodic attacks of severe throbbing, usually unilateral headache, and refers to primary headaches according to the international classification of headache. For more than a century of research, many hypotheses have been put forward to explain the occurrence of migraine, but its pathogenesis remains unclear. Nevertheless, to date, researchers have created a general scheme of the occurrence of migraine, which is associated with the excitation (for an unknown reason) of neurons of the trigeminal nerve, extending their processes

to various parts of the head, including the dura mater, and activation of mast cells, which are predominantly located in the dura mater of the human brain [103]. In the dura mater, the terminals of trigeminal fibers (C-fibers) secrete several neuropeptides, namely, the substance P, CGRP, neurokinin A, vasointestinal peptide, pituitary adenylate cyclase-activating peptide, as well as histamine, nitric oxide, and adenosine triphosphate, which lead to local vasodilation and activation of numerous dural mast cells [103, 104]. Activated mast cells degranulate, releasing many mediators that, together with peptides released from the terminals of trigeminal fibers, cause inflammation of the dura mater and its vessels and excite the terminals of nociceptive afferent fibers (Aδ fibers) [105, 106]. This general pattern is supported and supplemented by the results of different studies conducted using various approaches and methods. Thus, study of brain biopsies of patients with headaches showed that, on the side of pain, degranulating mast cells accumulated around the temporal artery [107], and degranulation of mast cells increased the activity and sensitivity of meningeal nociceptors and caused migraine-type headache [108]. A characteristic symptom of mast cell dysfunction is headaches, as up to 2/3 of patients with mastocytosis and mast cell activation syndrome suffer from them, and in every third case, the pain can be defined as migraine [20, 83]. Pharmacological inhibition of dural mast cell degranulation prevents migraine development [109].

Migraine attacks and primary headaches are also known to be accompanied by a significant increase in the level of proinflammatory cytokines IL-1β, IL-10, and TNF-α, as well as histamine and endothelin-1 in the blood and cerebrospinal fluid [110–112], which indicates the presence of an inflammatory process in migraine. The information that nonsteroidal anti-inflammatory drugs help combat migraine is also consistent with these data [113, 114]. If these cytokines are characteristic not only for mast cells but also for other immune competent and protective cells, then histamine is the main mediator of mast cells. Moreover, in pediatric patients with migraine, the level of tryptase, an enzyme that is a marker of mast cells, was increased in the urine. Therapeutic relaxation, which soothes the headache, also lowered the urinary tryptase concentration [115]. These data, which are in good agreement with each other, indicate the activation of meningeal mast cells in migraine and primary headaches, and the intensity of the headaches correlates with the level of mast cell activity.

Which mediators of mast cells can cause algogenic effects? Histamine is well known to cause headache [112, 116, 117], and its action is mediated through histamine H_1 receptors; therefore, H_1 antagonists can arrest migraine attacks [118]. IL-1β and TNF also increase the activity and sensitivity of meningeal nociceptors [119]. Degranulation of dural mast cells can be induced by various factors such as stress hormones, certain foods, nitric oxide donors, oxidative stress, and strong sensory stimuli, all of which are well known to induce migraine attacks [120]. A recent study revealed that the algogenic effect of mast cell degranulation of the dura mater is mediated by PAR2, a receptor expressed on dural afferents of neurons of the trigeminal nerve nucleus and specifically activated by serine proteases tryptase, trypsin, and elastase, which are secreted by mast cells [108]. These findings open up new perspectives for the pharmacological suppression of migraine headaches.

Conclusion

Increasing evidence indicates that CNS inflammation is a key pathophysiological component in the development of nervous and mental diseases. Brain mast cells are the most important group of cells that regulate neuroinflammation. They perceive signals about pathogens through various receptors and, together with microgliocytes, initiate an inflammatory response in the brain and spinal cord. In some cases, for an unknown reason, neuroinflammation gets out of control, becomes chronic, and can cause neurodegeneration. This general pathogenic mechanism may be characteristic of multiple and amyotrophic lateral sclerosis, Alzheimer's disease, migraine, depression, schizophrenia, autistic spectrum disorder, and Parkinson's disease. Mast cells are proven to play a role in neuroinflammation in multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, and migraine. Data on the importance of neuroinflammation and mast cells in the development of neuropsychic diseases provide reference for the development of new approaches to their pharmacological treatment and prevention.

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