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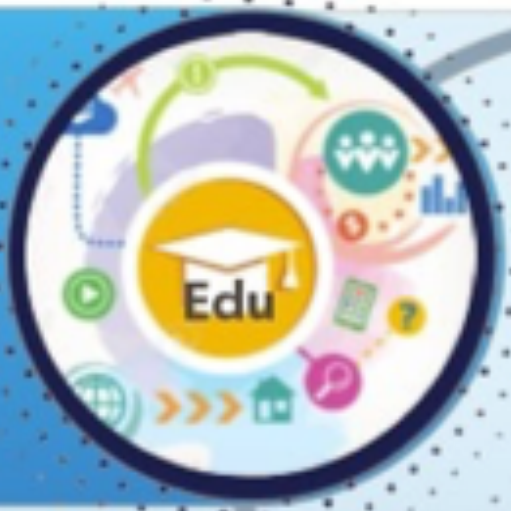

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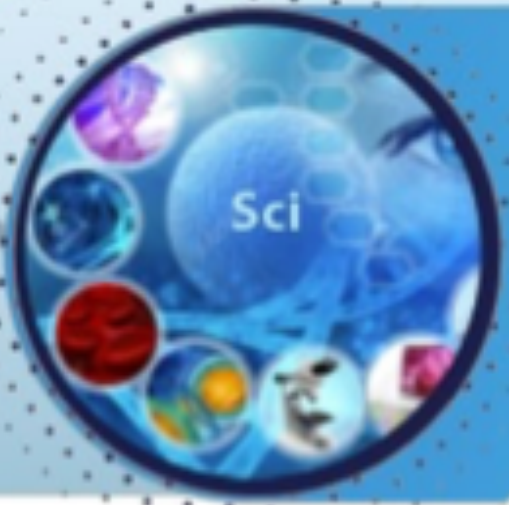

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Review Article

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Neuroinflammatory Mechanisms In Hemorrhagic Stroke: Focus On Background

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ABSTRACT

The scientific review substantiates the role of leukocytes and microglia in the pathogenesis of inflammation in the ischemic brain. Initial neuronal damage occurs within minutes of ischemia, while the inflammatory response that contributes to the progression of the pathology can last from several days to several months. Attention is focused on the fact that the migration of neutrophils into the brain parenchyma and their secretion of proteases is one of the main causes of the death of neurons and glia during reperfusion and delayed brain damage. The role of integrin, CXCR1/2 chemokine receptors, TNF-α, TLR2 and TLR4, Slit1 protein, angiotensin II, adrenaline and serotonin in modulating the functional activity of leukocytes is discussed. Increased blood-brain barrier permeability has been shown to be mediated by G protein-coupled P2Y2 receptors, which cause an increase in intracellular Ca2+ levels, and P2Y1 receptors, which act by inhibiting adenylate cyclase. Interest in lymphocytes is dictated by the presence of lymphopenia after a stroke, which predetermines the possibility of autoimmune inflammation in this group of patients. The data presented by the authors confirm the fact that after cerebral ischemia, monocytes/macrophages are activated through the chemokine receptor CCR2 and act indirectly through TGF-β1, which is necessary to maintain the functional integrity of the neurovascular complex.

Keywords: ischemic stroke, cytokines, leukocytes, microglia

INTRODUCTION

According to international epidemiological studies, in Western countries, hemorrhagic stroke accounts for 10-15% of all strokes and is the second most common type of acute cerebrovascular accident, second only to ischemic stroke in frequency. Estimates of the annual incidence of hemorrhagic stroke range from 16 to 33 cases per 100 thousand population. Uzbekistan ranks among the first in terms of incidence of acute cerebrovascular accidents and mortality from stroke, which negatively affects the healthcare system, social security and society.

Regarding hemorrhagic stroke in the elderly, they are registered quite rarely, their cause is hypertension,

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aneurysms and vascular malformations more often manifest themselves before the age of 60 years. The probable cause is amyloid angiopathy, which is manifested by the accumulation of amyloid in the adventitia of small-diameter arteries. In patients who have suffered a hemorrhagic stroke in under the age of 60 years, this morphological finding appears in 8% of cases, while in patients over 70 years of age - in more than 60%, the formation of microaneurysms and fibrinoid necrosis of the walls of arterioles is associated with the accumulation of amyloid [5].

An important link in the pathogenesis of stroke is a cascade of inflammatory reactions. According to some authors, chronic inflammation, detected in the form of increased levels of C-reactive protein and fibrinogen, serves as one of the risk factors for cerebrovascular accident [9].

In this regard, attempts to predict the risk of stroke based on the level of inflammatory markers, as well as the introduction of immunomodulatory drugs into the complex treatment of patients are of increasing scientific interest. With hemorrhagic stroke, direct destruction of neurons, astroglia and the blood-brain barrier occurs by iron ions and hemoglobin. Pathobiochemical processes of secondary damage are triggered , that Based on neuroimmunological research in recent years, it has been established that various cells belonging to the nervous, immune or endocrine system synthesize common identical signaling molecules - peptide hormones, biogenic amines, various biologically active substances that are mediators of intercellular interactions and affect the inflammatory process. It has been shown that endocrine cells are present in many organs and tissues, united in the APUD-cell system (Amine Precursor Uptake and Decarboxylation).

THE ROLE OF INDIVIDUAL CYTOKINES IN STROKE AND COGNITIVE IMPAIRMENT

IL-1. Recently, IL-1, a major neurotoxic cytokine, has been identified as a therapeutic target in stroke because inhibition of the production or activity of this cytokine has been shown to significantly reduce lesion size in animal models. IL-1 has a 2-phase expression pattern with a first peak in phase of early reperfusion and the second after 6-24 hours. It has been shown that IL-1 induces apoptosis. It is also interesting that the polymorphism of the IL-1 receptor antagonist gene is a factor in ischemic stroke. The role of IL-1 in the development of Alzheimer's disease is also actively discussed. It has been shown that that polymorphism of the IL-1 gene may play a role in the pathogenesis of the disease. IL-1 can provoke the production of beta-amyloid by modulating the activity of gamma secretase. The cytokine can also induce phosphorylation of tau protein and cause aggregation of neurofilaments. Chronic hyperproduction of IL-1 in the hippocampus, as Both peripheral and intracerebral administration lead to impairment of long-term memory.

THE ROLE OF IL-1 IN LEARNING AND THE FORMATION OF LONG-TERM MEMORY HAS BEEN ESPECIALLY STUDIED

IL-6. Plasma levels of IL-6, a pro-inflammatory cytokine, have been shown to be associated with worse stroke outcome, although it is unclear whether it increases before or after stroke. IL-6 secretion peaks between 6 and 18 hours after infarction On the other hand, animal models do not demonstrate such a clear relationship between elevated cytokine levels and negative disease outcome. This may be due to the fact that IL-6 mediates anti-inflammatory effects in addition to its pro-inflammatory activity. Overall, it is believed that this the cytokine does not directly affect the pathogenesis of ischemia. It has been shown that the level of IL-6 is higher in cardioembolic stroke compared to lacunar stroke. IL-6 may also reflect infectious complications of stroke. Based on data obtained in the North Manhattan study, it is shown that a high level high-sensitivity CP protein is associated with an increased, and IL-6 with a reduced risk of ischemic stroke over 8 years over CRP may indicate greater autoregulation and an anti-inflammatory effect through a feedback mechanism. It has also been shown that the combination of high levels of CP protein and IL-6 leads to a threefold increase in the risk of vascular dementia over 4 years. It is known that polymorphism of the IL-6 gene is associated with the risk of developing AD due to stimulation of microglial synthesis of inflammatory cytokines and phosphorylation of tau.C On the other hand, there is conflicting evidence regarding the role of the cytokine in the development of AD. High serum levels of IL-6 in elderly individuals with cardiovascular disease or CVD are associated with worse cognitive function and graded cognitive decline, and increased levels of the cytokine in middle age are a predictor of KN in the future.

The European Regional Office of the World Health Organization believes that the creation of a modern system of care for patients with stroke will reduce mortality during the first month of the disease to 20% and ensure independence in everyday life 3 months after the onset of

the disease for at least 70% of surviving patients. [2,5,8,13].

MICROGLIAL ACTIVATION AND AUTOIMMUNE INFLAMMATION

Inflammation is known to be an important part of the pathophysiology of stroke, especially in the context of reperfusion. Restoring cerebral blood flow is an obvious and priority task. It is known that, along with central neuronal responses, activation of peripheral immune responses occurs (the authors of the article especially focused on this phenomenon) - from several days to several weeks in ischemic tissue. An influx of inflammatory cells begins. There is evidence to support this concept: blocking various phases of the inflammatory cascade prevents the accumulation of destructive immune cells such as neutrophils and T cells.

Microglia play an important role in the sanogenesis of brain function. Microglia are immune cells of the central nervous system (CNS) and serve as sensors and effectors in brain tissue under normal and pathological conditions. Microglia are involved in most pathological processes in the central nervous system and respond to any type of pathological changes, performing the functions of macrophages: phagocytosis, secretion of proinflammatory cytokines and presentation of antigens. Microglia are involved in synaptic remodeling and neurogenesis. Involved in the formation of blood vessels and acts as phagocytes to remove dying cells during the process of programmed cell death.

After ischemic injury, microglia located in and near the injury site are activated within several minutes and accumulate in the affected area and in the penumbra zone. Postischemic microglial proliferation peaks 48–72 hours after focal cerebral ischemia and may continue for several weeks after the initial injury. However, activated microglia can also have a damaging effect in stroke by releasing reactive oxygen species through NADPH oxidase (reduced nicotinamide adenine dinucleotide phosphate), proinflammatory cytokines (for example, tumor necrosis factor, interleukin (IL-Ib)), neurovascular proteases , such as matrix metalloproteinase (MMP9).

Thus, this scientific review showed the role of autoimmune inflammation in the ischemic brain and determined its possible effect on ischemia.

Currently, for the treatment of stroke, it is necessary to search for drugs that could prevent the death of neurons, but also to persistently search for drugs that could restore the functional mutual influence of all cells in the neurovascular unit. The interaction between cells within this unit underlies the remodeling of the fading function of the neuron, and, consequently, the muscle innervated by it.

By taking a truly integrative approach, involving multimodal signaling between different cell types, taking into account the wide variety of mechanisms of both acute stroke injury and delayed recovery after stroke, it is possible to make real progress in the treatment of this difficult disease.

In particular, cell therapy with bone marrow mononuclear cells is one of the treatment options for stroke. Preclinical studies have shown that mononuclear cell therapy can shrink lesions after stroke and improve outcome. Today, the feasibility, safety and clinical outcome of intravenous administration of bone marrow mononuclear cells (on average 80 million CD34+ cells) to patients with ischemic stroke have been assessed. 7 out of 11 patients had a favorable clinical outcome [1.35]. Based on the above, it can be stated that cell therapy should be aimed at increasing the physiological functions of monocytes/macrophages and microglia involved in the repair of the ischemic zone, and not at blocking their renewal, the accumulated experimental and clinical material regarding the role of leukocytes and microglia in the pathogenesis of inflammation Thus in the ischemic brain makes it possible to identify new possibilities for stroke therapy.

APPEARANCE OF AUTOIMMUNE REACTIONS IN THE BRAIN AND CSF AFTER STROKE

Interest in lymphocytes is primarily dictated by the development of lymphopenia after a stroke, which predetermines the development of infectious complications in this group of patients. There is another quite significant reaction - the development of an immune response to brain antigens after a stroke. As experimental studies have shown, the likelihood of developing autoimmune responses to these antigens increases with systemic inflammation accompanying a stroke. It was important to determine whether patients with infections in the post-stroke period are predisposed to the development of autoimmune reactions to nervous tissue antigens. The study conducted by [1,29] was based on an analysis of 114 patients with IS. Patients who had infections, especially pneumonia, were more likely to have a positive Th1 cell response to myelin basic protein and glial fibrillary acidic protein at 15 and 90 days after stroke ($p = 0.019$ and $p = 0.039$, respectively). Moreover, a greater Th1 cell response to myelin basic protein over 90 days was associated with a decreased likelihood of a

good outcome, even after adjusting for stroke severity and patient age (OR 0.477; 95% CI 0.244–0.935, p = 0.031). This study shows that an immune response to brain antigens can occur after stroke. Although these reactions may be an epiphenomenon of ischemic brain injury, the response of lymphocytes to myelin basic protein has clinical implications. The potential role of postischemic autoimmune reactions after stroke merits further study.[23,35,45].

It has been established that after an ischemic stroke, T lymphocytes contribute to brain inflammation, which aggravates the alteration of neurons. Currently, there is an active search for optimal methods for modulating immune responses in the brain after damage to the BBB. It has previously been shown in patients with multiple sclerosis that Fingolimod (a sphingosine 1 phosphate receptor analogue) prevents the release of lymphocytes from primary and secondary lymphoid organs, which suggests that a positive effect in stroke can be achieved with Fingolimod administration [30]. The studies confirmed that this substance, unlike placebo, improved neurological functions and reduced cerebral edema 24 and 72 hours after modeling stroke in CD1 mice ($p < 0.05$). At the same time, significantly fewer lymphocytes accumulated in the brain tissue. In addition, Fingolimod treatment significantly reduced the expression of intercellular adhesion molecule-1 (ICAM-1), interferon (IFN) and interleukin-17 (IL-17) levels in the brain 72 hours after the simulation ($p < 0.05$). Thus, Fingolimod, by reducing T cell infiltration in the brain, may improve short- and long-term outcomes after simulated stroke.

Inflammation is often considered as a new therapeutic target in the subacute stage of stroke. However, in addition to secondary damage, inflammation induces repair and remodeling of the alteration site. At the same time, individual subpopulations of monocytes/macrophages can determine the outcome of lesions associated with inflammation [33]. Within 24 hours after stroke, immature Ly6C monocytes penetrated into the border zone of cerebral ischemia and differentiated into mature Ly6C phagocytes (LO) already in the alteration zone [34]. Tissue infiltration by monocytes/macrophages was CCR2 dependent; there is no evidence for monocyte recruitment via CX3CR1. Depletion of circulating monocytes or selective silencing of CCR2-positive cells delayed clinical deterioration and transformation of the hemorrhage area. Bleeding often occurred around thin-walled, dilated vessels at the ischemic margin and was accompanied by decreased expression of transforming growth factor (TGF-1) and collagen-4 along with decreased Smad2 activation. Thus, monocytes/macrophages were recruited through the chemokine receptor CCR2 and act through TGF¬1, which is necessary to maintain the integrity of the neurovascular complex after cerebral ischemia.

MIGRATION OF NEUTROPHILS INTO THE ISCHEMIZED BRAIN

The migration of leukocytes across the BBB includes several stages: it begins with the rolling of leukocytes along the surface of the endothelium and ends with their passage through the gaps between endothelial cells. Neutrophils are the first to respond to injury and inflammatory diseases of the central nervous system, such as ischemic and hemorrhagic stroke. Research over the past three decades has shown that NFs have mixed effects in stroke. A number of studies support the involvement of NF in stroke outcome. Thus, by reducing the neutrophil infiltration of the brain damage area by influencing CD18+ cells or intercellular adhesion molecules 1 (ICAM1), improved stroke outcomes were noted. A number of researchers point out that activation of neutrophils occurred before the stroke and this could contribute to the progression of the disease. Clinical trials have shown no benefit with NF blockade in stroke patients. It can be assumed that the action of NF is associated with a certain threshold effect. In cases where the amount of NF reaches a critical value in relation to the volume of brain damage, an anti-inflammatory phenotype is formed, which is able to limit alteration. Indeed, if the infiltration of neutrophils is stimulated by introducing the chemokine CXCL1 into the stroke zone, then a decrease in the permeability of the vascular wall is observed. A similar decrease in endothelial monolayer permeability was modeled in tissue culture when NF was added to endothelial cells isolated from brain vessels. Accumulating evidence suggests that NF can be presented in the CNS with both pro-inflammatory (N1) and anti-inflammatory (N2) phenotypes, depending on microenvironmental signals [20]. Moreover, the N2 phenotype can be formed when neutrophil infiltration reaches a certain level. This indicates that the mechanisms that promote the infiltration of neutrophils into the stroke area can be aimed at restoring the architecture in the stroke area.

Increased brain infiltration by neutrophils occurs early after stroke, plays an important role in the acute inflammatory response of the brain and modulates neurological recovery after stroke. Based on the results of many experimental studies, a paradigm has emerged in

the literature that moderate infiltration of brain neutrophils occurs 24 hours after simulating cerebral ischemia, with NFs being localized predominantly around arterial vessels at the periphery of the stroke zone [21]. The absence of NF infiltration in the ischemic zone was confirmed in 25 people with stroke in the initial period [22]. Nevertheless, the migration of NF into the brain parenchyma and their secretion of proteases are considered the main causes of neuronal death during reperfusion (delayed) injury after ischemia. Therapy aimed at limiting the release of NP from the vascular bed after a stroke turned out to be ineffective [22]. Moreover, mortality in the group of patients with acute ischemic stroke with blockade of the adhesion molecules ICAM¬1 (Enlimomab) was significantly higher than in the control group. Suppression of integrin expression can be achieved by reducing the stimulation of P2X7 nucleotide receptors during the destruction of ATP by CD39. It must be emphasized that integrin blockade abolished the appearance of the post-ischemic pro-inflammatory phenotype of leukocytes. These data are consistent with the results of in vitro studies demonstrating that ischemia of the vascular endothelium does not promote migration of NP from the blood into the tissue. It is likely that a rethinking of the causes of this phenomenon and the targets of therapy aimed at reducing reperfusion damage to the brain after stroke is required.

REACTION OF PERIPHERAL BLOOD LEUKOCYTES DURING THE DEVELOPMENT OF STROKE

A number of studies have shown that inflammation plays a significant role in the pathogenesis of hemorrhagic stroke. Indeed, in patients with hemorrhagic (HI) and ischemic (IS) stroke, high leukocytosis was detected, and in the case of rupture of the vessel wall, the number of leukocytes in the blood exceeded 10109/l [1]. For comparison, in IS associated with atherosclerosis of large cranial arteries, the number of leukocytes reached 8.7±2.3 109/l; cardioembolism - 8.2±2.8 109/l; embolism of small vessels - 8.4 ± 2.4 109/l ($p = 0.022$). After adjusting for age, gender, stroke severity, and the presence of vascular risk factors, a multiple regression model found that an increased white blood cell count was a factor independently associated with arterial wall alteration in stroke patients (odds ratio (OR) 2.56, 95 % CI 1.60–4.11; $p < 0.001$). It is likely that leukocytosis reflects the presence of preexisting inflammation inducing alteration of the arterial wall. Leukocytosis can be maintained for a long time (for 18 months) after a stroke [2]. At the same time, the preservation of the functional activity of polymorphonuclear leukocytes (PMNL) plays an important role in maintaining the inflammatory response after ischemic stroke. However, in the current literature there are only a few studies regarding the activation process and the role of PMN. There is an opinion [3] that PMN activation in peripheral blood should be attributed to a systemic inflammatory reaction in response to ischemic stroke, but this does not reflect PMN activity in the area of the ischemic brain. In this context, inhibition of PMN functional activity is considered as a promising therapeutic strategy for the treatment of stroke patients. Lower leukocytosis during hospitalization of patients with stroke is a predictor of good or satisfactory functional status of the patient 1 year after acute cerebrovascular accident [4].

As for the reasons for changes in leukocytopoiesis during stroke, there is no generally accepted point of view. It is known that the markers of stroke-induced immunosuppression syndrome are: lymphocytopenia, dysfunction of T helper cells and monocytes. It has been proven that the volume of the brain damage zone (penumbra) is the main factor causing lymphocytopenia on the 1st and 4th days after a stroke [5]. The number of killer cells decreased after stroke, while monocytes increased in parallel with the development of neurological deficits. A decrease in T helper cells, DR monocyte antigen expression, and TNF production by monocytes is associated with the development of infections. However, only volume of brain damage prevailed as an early independent predictor of respiratory infections (OR 1.03; CI 1.01 to 1.04)! There was no difference in the peripheral inflammatory response (i.e., increased white blood cell count) in transient ischemic attack (TIA) and stroke patients at the time of hospitalization [6]. In both groups, the percentage of neutrophils and monocytes was significantly higher than in healthy individuals (in the case of TIA: neutrophils - 67.9%, monocytes - 8.2%; in stroke: neutrophils - 64.9%, monocytes - 7.7% ; $p < 0.001$). The absolute number of neutrophils was also significantly higher than in the control. The percentage and absolute number of lymphocytes in both groups were significantly lower than in the control (TIA and stroke, respectively, 21.7 and 24.7%; $p < 0.001$).

The number of leukocytes and their ratio are considered as a prognostic criterion for outcome in patients with stroke and TIA. The most significant study in this regard was conducted on 868 patients: IS was 75%, HI was 14.3%, TIA was 10.7% [7]. It turned out that the

neutrophil-lymphocyte ratio (NLR) was significantly higher in patients who died ($p < 0.001$). The value of the indicator in TIA was significantly lower than in patients with IS and HI ($p < 0.001$). In the group with IS, the NLO value was significantly higher in the group with atherosclerosis or thrombosis of large arteries ($p < 0.001$). It is proposed to use NLO as a simple criterion for predicting hospital mortality in ischemic and hemorrhagic stroke.

ACTIVATION OF BIOGENIC AMINES IN STROKE

The literature discusses the role of humoral factors, in particular angiotensin II (AT II), adrenaline, serotonin and other biologically active substances in modulating the functional activity of leukocytes. The participation of AT II in the pathogenesis of stroke is considered, firstly, in connection with the presence of AT1 receptors for AT II on segmented NFs and endothelial cells of brain vessels [8, 9]. Secondly, angiotensin II circulating in the blood and produced locally regulates cerebral circulation by stimulating AT1 receptors expressed on endothelial cells of cerebrovascular vessels and in brain centers that control cerebral blood flow. Increased expression of AT1 receptors is the main factor in reducing the distensibility of the vascular wall, as well as changes in the eNOS/iNOS synthase ratio and the inflammatory response of brain blood vessels in genetically determined hypertension. These factors may predetermine increased sensitivity of the brain to ischemia and stroke. Third, inflammation (adhesion phase of blood cells) and damage to the BBB (permeability, stroke volume) increase in AT II-induced hypertension [9]. The effect was significantly less with long-term administration of AT II in mice lacking AT1 receptors (AT1 aR–/– mouse line). Inflammation of the vessel wall is accompanied by the adhesion of neutrophils to the vascular endothelium, which can contribute to ischemic brain damage. In this context, it was important to answer the question: does the AT1 receptor antagonist affect the adhesion of neutrophils to endothelial cells in patients with stroke. To answer this question, the authors [10] conducted an in vitro study with brains removed within 48 hours after death from 12 patients with ischemic stroke. Neutrophils added to a monolayer of human endothelial cells (ECV-304) were incubated with candesartan (AT1 receptor blocker). Candesartan, like dipyridamole (an antiplatelet agent), significantly suppressed the attachment of neutrophils to the endothelium due to a decrease in the expression of the adhesion molecule Mac¬1. The effect was not reproduced when using NF in stroke patients or healthy controls. The authors [11] presented evidence that one of the mechanisms mediating inflammation in brain microvessels under the influence of AT II is oxidative stress. The results of intravital microscopy of the vessels of the pia mater indicate a 4.2-fold increase ($p < 0.05$) in leukocyte adhesion already on the 4th day of AT II infusion; at the same time, the permeability of the BBB increased by 3.8 times ($p < 0.05$). The use of an antioxidant (Tempol) significantly weakened the interaction of leukocytes and endothelium and preserved the barrier functions of the BBB. Fourth, an experimental model of stroke showed that blockade of AT1 receptors reduced the functional activity of NF, the expression of adhesion molecules on them, and increased permeability of cerebral microvessels [8]. The phenomenon of increased BBB permeability at high levels of AT II continues to be studied. Some researchers [12] confirmed in an experiment on mice that long-term administration of AT II leads to an increase in blood pressure and is accompanied by increased BBB permeability, a high density of leukocytes and platelets attached to the endothelium. Immunodeficient mice (Rag¬1(–/–)) showed a decrease in leukocyte recruitment and no changes in BBB permeability when administered AT II. Similar protection was observed in mice deficient in RANTES (–/–) and P-selectin (–/–) molecules, which made it possible to consider these molecules as effectors of signaling upon stimulation of AT1 receptors. Fifth, AT1 receptor blockers are effective for the prevention and treatment of stroke [13]. The SCOPE clinical trial analyzed the effect of the AT1 receptor blocker to angiotensin II, candesartan, on the development of complications of hypertension in elderly patients. It was found that mortality from fatal stroke and myocardial infarction occurred significantly less frequently with the use of candesartan. The ACCESS study was conducted to evaluate the safety of moderate BP lowering with candesartan early in stroke treatment. The study showed that even in the absence of a decrease in blood pressure, the administration of candesartan for 7 days, starting from the first day after the onset of stroke, reduced 12-month mortality (7.2 and 2.9% in the placebo and candesartan group, respectively). Stable blockade of AT1 receptors reduces the severity of cerebrovascular pathology and inflammation in the brain, maintains blood flow in the penumbra zone and significantly limits neuronal damage. Interestingly, protection against ischemia is associated with inhibition of the renin-angiotensin system and is not directly related to a decrease in blood pressure, since a similar decrease in blood pres-

sure as a result of administration of an adrenoreceptor and Ca2+ channel blocker does not protect against cerebral ischemia [14].

Inhibition of AT1 receptors also increases the expression of AT2 receptors, which are associated with high eNOS activity and subsequent increased vasodilation. Direct inhibition of AT1 receptors and indirect stimulation of AT2 receptors help normalize the distensibility (wall elasticity) of cerebral vessels, reduce inflammation in the ischemic zone and reduce the sensitivity of the brain to ischemia. These results show that inhibition of AT1 receptors should be considered as a preventive therapeutic measure to protect the brain from ischemia and possible therapy for inflammatory diseases of the brain.

The facts regarding the influence of adrenaline on the function of leukocytes during the development of stroke are interesting. Experimental and clinical evidence suggests that excessive activation of the sympathetic nervous system (SNS) is an important pathogenetic factor in increasing the patient's susceptibility to infection after stroke. Thus, in the PANTHERIS study, the authors [15] examined the effect of SNS activation on immunosuppression and the incidence of post-stroke infections. In univariate analysis, it was found that a larger volume of the stroke area, cortical damage in various regions of the middle cerebral artery (MCA) cortex and activation of the SNS (increased levels of norepinephrine in the blood) are associated with impaired immune system function (decreased expression of mHLA¬DR on monocytes) and higher susceptibility to infections. Multivariate analysis confirmed that increased norepinephrine levels and ischemia of the cortex in the area of the cerebral artery are independent risk factors for the development of post-stroke infections. Others hold a similar point of view [16]. A number of researchers believe that post-stroke immunosuppression is associated with the volume of brain stroke, but not with the specific location of the lesion. Clinical laboratory parameters and brain imaging data were analyzed in 384 patients (174 women, mean age 70.8 ± 12.9 years) within 24 hours after the onset of acute ischemic stroke in the areas of vascularization of the CMA. Patients with lesions covering >33% of the MCA territory had higher serum levels of metanephrine and normetanephrine, as well as neutrophycytosis, while the number of eosinophils, T helper cells and cytotoxic T lymphocytes was reduced compared with patients with lesions of less than 33% of the territory , supplied by the CMA. In patients with a significant amount of cerebral ischemia, the incidence of infections within 14 days after stroke, especially pulmonary infections, increased. Thus, we can assume a specific role for hyperactivation of the sympathetic division of the autonomic nervous system in the pathogenesis of inflammation and immunosuppression induced by stroke.

CONCLUSION

1.The role of integrin, CXCR1/2 chemokine receptors, TNF-α, TLR2 and TLR4, Slit1 protein, angiotensin II, adrenaline and serotonin in modulating the functional activity of leukocytes is discussed.

2.Increased blood-brain barrier permeability has been shown to be mediated by G protein-coupled P2Y2 receptors, which cause an increase in intracellular Ca2+ levels, and P2Y1 receptors, which act by inhibiting adenylate cyclase was determined.

3.The data presented by the authors confirm the fact that after cerebral ischemia, monocytes/macrophages are activated through the chemokine receptor CCR2 and act indirectly through TGF-β1, which is necessary to maintain the functional integrity of the neurovascular complex.

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GEMMORAGIK INSULTDA NEYROINFLAMATOR MEXANIZMLAR

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ABSTRAKT

Ilmiy ish ishemik miyada yallig'lanish patogenezida leykotsitlar va mikrogliyalarning rolini asoslaydi. Neyronlarning dastlabki shikastlanishi ishemiyadan bir necha daqiqa o'tgach sodir bo'ladi, patologiyaning rivojlanishiga hissa qo'shadigan yallig'lanish reaksiyasi bir necha kundan bir necha oygacha davom etishi mumkin. Neytrofillarning miya parenximasiga migratsiyasi va ularning proteazalarni sekretsiyasi reperfuziya va kechiktirilgan miya shikastlanishi paytida neyronlar va glialarning o'limining asosiy sabablaridan biri ekanligiga e'tibor qaratiladi. Integrin, CXCR1/2 xemokin retseptorlari, TNF-a, TLR2 va TLR4, Slit-1 oqsili, angiotenzin II, adrenalin va serotoninning leykotsitlarning funksional faolligini modulyatsiya qilishdagi roli muhokama qilinadi. Qon-miya to'sig'ining o'tkazuvchanligi oshishiga hujayra ichidagi Ca2 + darajasining oshishiga olib keladigan G oqsili bilan bog'langan P2Y2 retseptorlari va adenilat siklazasini ingibitsiya qiluvchi P2Y1 retseptorlari vositachiligi ko'rsatilgan. Limfotsitlarga bo'lgan qiziqish qon tomiridan keyin limfopeniya mavjudligi bilan belgilanadi, bu bemorlarning ushbu guruhida autoimmun yallig'lanish ehtimolini oldindan belgilaydi. Mualliflar tomonidan taqdim etilgan ma'lumotlar miya ishemiyasidan so'ng monositlar / makrofaglar CCR2 kimyokin retseptorlari orqali faollashishi va neyrovaskulyar kompleksning funktsional yaxlitligini saqlash uchun zarur bo'lgan TGF-b1 orqali bilvosita ta'sir qilishini tasdiqlaydi.

Kalit so'zlar: ishemik insult, sitokinlar, leykotsitlar, mikrogliya, yallig'lanish mexanizmlari.

НЕЙРОВОСПАЛИТЕЛЬНЫЕ МЕХАНИЗМЫ ПРИ ГЕМОРРАГИЧЕСКОМ ИНСУЛЬТЕ: АКЦЕНТ НА ПРЕДПОСЫЛКАХ.

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ТАШКЕНТСКАЯ МЕДИЦИНСКАЯ АКАДЕМИЯ

АБСТРАКТ

В научном обзоре обосновывается роль лейкоцитов и микроглии в патогенезе воспаления ишемизированного мозга. Первоначальное повреждение нейронов возникает в течение нескольких минут после ишемии, тогда как воспалительная реакция, способствующая прогрессированию патологии, может продолжаться от нескольких дней до нескольких месяцев. Акцентировано внимание на том, что миграция нейтрофилов в паренхиму мозга и секреция ими протеаз — одна из основных причин гибели нейронов и глии при реперфузионном и отсроченном повреждении мозга. Обсуждается роль интегрина, CXCR1/2-рецепторов хемокинов, ФНО-α, TLR2 и TLR4, Slit1-белка, ангиотензина II, адреналина и серотонина в модуляции функциональной активности лейкоцитов. Показано, что повышение проницаемости гематоэнцефалического барьера опосредуется P2Y2-рецепторами, связанными с G-белком, вызывающим увеличение уровня внутриклеточного Ca2+, и P2Y1-рецепторами, действующими путем ингибирования аденилатциклазы. Интерес к лимфоцитам продиктован наличием лимфопении после инсульта, что предопределяет возможность аутоиммунного воспаления у данного контингента больных. Приведенные авторами данные подтверждают тот факт, что после ишемии головного мозга моноциты/макрофаги активируются через хемокиновый рецептор CCR2 и действуют опосредованно через TGF-β1, необходимый для поддержания функциональной целостности нейрососудистого комплекса.

Ключевые слова: ишемический инсульт, цитокины, лейкоциты, микроглия.