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THE SIGNIFICANCE OF SOME BIOMARKERS OF NEUROINFLAMMATION AND ANGIOGENESIS IN STROKES.

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Abstract:

In the recent past, the possibility of neurogenesis in the adult nervous system was denied. It has now been proven that neurogenesis continues throughout a person's life in 2 different areas of the intact brain - the subventricular zone of the lateral ventricles and the subgranular zone in the dentate gyrus of the hippocampus. Some authors also consider these areas as a single neurogenic zone [23]. Neurogenesis is a multistage process of formation of new neurons, astrocytes, oligodendrocytes in the CNS from neuronal stem cells (NSCs), including the proliferation of endogenous NSCs, their migration and differentiation into mature functional neurons. This process underlies the adaptive function of the brain and provides neuroplasticity, which is expressed in the structural and functional reorganization of neural networks. Stroke stimulates neurogenesis in the brain [27].

Keywords: Neuroinflammation, neurogenesis, neurons, astrocytes, oligodendrocytes in the CNS from neuronal stem cells, BDNF, Strokes, brain damage

INTRODUCTION. The transformation of initial progenitor structures into specialized nerve cells under conditions of ischemic damage to brain tissue has been proven in experimental animal models and in patients [16]Not only neurogenesis is responsible for functional recovery after a stroke, but an important role is played by angiogenesis, the process of formation of new microvessels, including the proliferation and germination of endothelial cells (EC), the formation of tubular vascular structures, branches and anastomoses (9). Molecular biomarkers indicating the activation of angiogenesis processes in the nervous tissue have been identified in patients with acute ischemic stroke (10). Neurogenesis and angiogenesis are interrelated processes in acute disorders of cerebral circulation and proceed in parallel.

Inflammation is a complex immune response after injuries of various origins. Under normal conditions, the inflammatory process aids in cleansing and initiates tissue repair. Researchers tend to pay more and more attention to the inflammatory processes in the brain in degenerative diseases, both as a primary cause and as a secondary factor caused by damage to the nervous tissue. Neuroinflammation may be central to the aging process. A number of authors define neuroinflammation as smooth cell processes that cause cell death, dysfunction, or recovery of neurons and oligodendrocytes during a neurodegenerative disease. This definition, which describes the positive and negative sides of neuroinflammation, nevertheless limits the process.

THE PURPOSE OF THE STUDY: to conduct an analytical review of some molecular mechanisms of endogenous regulation of neurogenesis, neuroinflammation and angiogenesis based on the data of scientific research in recent years.

MATERIAL AND METHODS OF RESEARCH: We studied 44 articles from the PubMed database, Google scholar, Scopus. Only new and original articles were selected for the review article. Conclusions and conclusions were made from the selected original reliable articles.

Neuroinflammation is an extremely complex process. It does not show the classic signs of inflammation such as redness, swelling, heat, and pain. However, in neuroinflammation, the molecular and cellular mechanisms are partly the same as in inflammation. In both cases, signaling molecules or cytokines are involved, such as interleukins, chemokines, and tumor necrosis factor. Both processes have positive and negative sides. The key in these processes is the body's attempt to repair damaged tissue in the ways that are available to it. There are also differences. Resident macrophages in brain tissue are microglial cells. They are not found in other body tissues. In place of the usual scar in the nervous tissue, a glial is formed, due to the activation of astrocytes. Inflammation in nervous tissue, especially the nervous system, has far-reaching consequences. Neuroinflammation is involved in aging processes, age-related pathologies, obesity, and some types of dementia Cell adhesion molecules occupy a special

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place in neuroinflammation [3, 15].Cell adhesion molecules are a group of proteins associated with the plasma membrane. These are selectin-adhesive molecules, the lectin-like domain of which ensures the adhesion of leukocytes to endothelial cells, integrins are heterodimeric molecules that function as cell-substrate and intercellular adhesive receptors. Adhesive receptors of the immunoglobulin superfamily that are involved in intercellular adhesion and are especially important in embryogenesis, wound healing and immune response. Cadherins are calcium dependent homophilic intercellular adhesive proteins [4, 19, 22].

These cells provide mechanical interaction of cells with each other or with components of the extracellular matrix, including participation in the interaction of blood cells with endothelial cells, and also affect the metabolism of the endothelium itself. The course of many physiological and pathological processes in the body depends on the functional state of the vascular endothelium. Activation of endothelial cells in the focus of inflammation, for example, during trauma, affects such processes as the migration of leukocytes from the vascular bed to the surrounding tissues, sequestration and eradication of pathogens and toxins, vascular remodeling, repair, and hemostasis. With excessive activation of the endothelium, hemorrhages, or microthrombi, develop, tissue and cellular hypoxia, excessive vascular permeability and hyperproduction of free radicals develop, which contributes to the progression of inflammation and, as a result, leads to tissue damage [11, 28].

Endothelial dysfunction, which replaces its activation, is one of the key factors in the pathogenesis of sepsis, hemorrhagic fevers, systemic rheumatic and cardiovascular diseases (1,3,8,29,33). Adhesion molecules are considered not only as biomarkers of endothelial activation, but also as important factors influencing the development of the immune response (2).

Cerebral microvascular endothelial cells (CMECs), which form the blood-brain barrier (BBB), are required to maintain homeostasis and limit immune cell access to the CNS. CMECs play an important role in the early stages of brain diseases, including the pathogenesis of MS, by upregulating cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin , which causes them to adhere to inflammatory cells and leads to the migration of inflammatory cells into the brain [9, 14, 31]. Cell adhesion molecules on the surface of cerebral endothelial cells enhance the local inflammatory response in cerebral vessels and brain parenchyma by recruiting and inducing leukocyte transmigration [6, 7, 8]. ICAM-1 and VCAM-1, in particular, are constitutively expressed in CMECs [15].

Various stimuli, such as lipopolysaccharide (LPS), a bacterial component that causes inflammation, activate ICAM-1 and VCAM-1, and changes in the expression of these molecules promote cerebrovascular inflammation, BBB disruption, and vasogenic edema [10].

Numerous studies have shown that VCAM-1 plays a crucial role in the migration of immune cells to the CNS through the BBB [19, 20]. Adhesion of inflammatory cells to the vascular endothelium represents an early stage of cell migration into the brain parenchyma. First, leukocytes are captured and "slow rolling" occurs, keeping leukocytes close to endothelial cells, which leads to chemokine-induced activation of leukocytes and expression of other inflammatory factors on the surface of endothelial cells [34]. Cell adhesion molecules such as VCAM-1, ICAM-1 and selectins then enhance the tight adhesion of leukocytes. In particular, integrin α4β1, expressed on lymphocytes and monocytes, binds to VCAM-1 and induces transendothelial cell migration [22-25]. Due to the interaction between α4β1 integrin on lymphocytes and VCAM-1 endothelial cells, leukocytes attach to the blood vessel wall and then begin the process of diapedesis or "passage" through the blood vessel wall [41].

Although ICAM-1 expression was evident in blood vessels, anti-β2 integrin binding to ICAM-1 did not affect lymphocyte binding [29]. This may be due to differences in the relative levels of VCAM-1 and ICAM-1 in brain endothelial cells. the study showed that VCAM-1 and ICAM-1 contribute differently to the action of leukocytes in brain inflammation, since the expression of adhesion molecules differs depending on tissue type [23.]. VCAM-1 levels in brain endothelial cells have been found to be higher than in other tissues, both in inflamed and non-inflamed brains [31]; however, ICAM-1 was expressed at the same level in many tissues, including the brain. Therefore, the role of VCAM-1 may be more important than ICAM-1 in inflammatory brain diseases.

Recent studies have shown that lipopolysaccharides (LPS) induce the activation of cell adhesion molecules, including ICAM-1, VCAM-1, and E-selectin, in brain endothelial cells, suggesting a mechanism underlying inflammation [32]. Consistent with these reports, LPS has been shown to increase levels of cell adhesion molecules such as ICAM-1, VCAM-1 and E-selectin in CMEC.

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Previous studies have shown that the NF-κB signaling pathway regulates VCAM-1 expression in the CMEC [6, 35] and is activated by various inflammatory stimuli such as LPS. In addition, p38MAPK and JNK pathways have been found to mediate inflammatory signaling stimulated by LPS, cytokines, and stress factors such as oxidation and other shocks, while p44/42MAPK activation mediates cell proliferation in response to growth factors and mitogens [36- 38]. In this study, VCAM-1 expression was partially suppressed by inhibition of NF-κB, p38MAPK or JNK (SN50, SB202190 or SP600125), respectively, but not p44/42MAPK, in LPS-exposed CMECs. These data suggest that induction of VCAM-1 expression by LPS may depend on activation of NF-κB and p38MAPK/JNK signaling. NF-κB and p38MAPK/JNK signaling may participate in the same signaling when VCAM-1 is active, or may be synchronized by running both in parallel. However, some results presented by Kempe et al. indicate that synergistic activation of NF-κB and p38MAPK/JNK is required for VCAM-1 expression, and that both pathways are required for this expression. Phosphorylation of p38MAPK/JNK has been reported to activate transcription factors such as Elk-1, AP-1 and CREB [38]. In addition, cross-talk between transcription factors NF-κB and AP-1 in LPS-induced inflammatory cells was investigated [40]. In the present study, VCAM-1 expression could allow NF-κB in cooperation with p38MAPK/JNK to elicit a transcriptional response in LPS-activated cells, and chrysin treatment could repress VCAM-1 expression by inhibiting NF-κB and p38MAPK/JNK signaling.Type 1 adhesion molecules ICAM-1 and vascular endothelial adhesion molecules type 1 VCAM-1 belong to the immunoglobulin superfamily. Under physiological conditions, ICAM-1 is poorly detected on the resting endothelium, and VCAM-1 is simply absent. Upon activation of the endothelium, the expression of these molecules is enhanced under the influence of free radicals, complement components, nitric oxide, lipopolysaccharides, pro-inflammatory cytokines, leukotrienes, histamine, and many other mediators. In addition to endothelial cells, ICAM-1 expresses lymphocytes, monocytes, cells of the broncho-alveolar epithelium, and VCAM-1 - tissue macrophages, dendritic cells, bone marrow stromal cells. In the process of transmigration of leukocytes, ICAM-1 and VCAM-1 provide strong adherence of these cells to the endothelium. ICAM-1 is involved in the formation of the immunological synapse by binding to integrin, it promotes the formation of contact between the antigen-presenting cell and T-lymphocyte. (27). VCAM-1 is involved in the processes of angiogenesis and leukocyte adhesion outside the vascular bed (14). A certain role of VCAM-1 in the development of atherosclerosis, vasculitis, autoimmune diseases, and in an increased risk of hemorrhage into an atherosclerotic plaque has been shown (2-3). A number of authors found that a high level of VCAM-1 is a sign of a severe course of coronary heart disease. The vascular cell adhesion molecule VCAM-1 is a molecule that promotes the localization of immune cells at the site of inflammation and its expression is regulated by microRNA (35). This group of molecules differs from ordinary RNAs in that they are not involved in the process of protein synthesis, but are involved in the regulation of the expression of other genes in cells. The cell can secrete miRNAs in special exosome containers, which has been experimentally proven. MicroRNAs are small non-coding RNA molecules of 18-22 nucleotides that function as post-transcriptional regulators of gene expression in mammalian cells. Their action is carried out through pairwise conjugation with 3-untranslated regions (3-UTR) in messenger RNA molecules, leading to the suppression of gene activity through translational repression. MicroRNAs are involved in most fundamental biological processes such as cell cycle control, cell metabolism, apoptosis, cell proliferation and differentiation (3) Studies show that microRNA dysregulation in both brain cells and body fluids with effects on certain target genes can lead to hemorrhagic strokes.

As a result of hemorrhage from a pathologically altered artery, a number of pathophysiological processes are activated - the death of nerve cells, inflammation, oxidative stress, impaired BBB, cerebral edema. MicroRNAs regulate target genes in these processes by binding to 3-UTR mRNA to suppress gene expression. The mechanisms leading to changes in the content of molecular biomarkers in the blood serum in hemorrhagic stroke remain poorly understood. Understanding the mechanisms of microRNA involvement in the pathogenesis of hemorrhagic stroke and their further study will help to create new biomarkers and therapeutic targets. The dynamics of the content of candidate molecular markers in the blood serum of patients with hemorrhagic stroke may reflect the processes of alteration and regeneration corresponding to the stages of the disease. The use of these candidate molecular biomarkers may be promising for complex diagnostics, monitoring of treatment and rehabilitation measures in patients with stroke.

Brain-derived neurotrophic factor (BDNF) is a protein with the highest expression in the brain from

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the neutrophin family, secreted by the postsynaptic membrane in response to excitation of neurons, freely penetrating the blood-brain barrier and playing a crucial role in neurogenesis, neuroplasticity and neuronal survival BDNF is synthesized in the endoplasmic retuculum as a precursor (pro BDNF) and is converted into a mature form during protealytic processes involving propretin convertase PC7. By binding to tropomyosin-dependent kinase B receptors on the cell surface, BDNF promotes the survival and differentiation of neurons and is involved in the regulation of the phenomenon of long-term potentiation and synaptic plasticity (40). BDNF can be secreted by neurons from axons also from dendrites in response to neuronal activity [25, 42]. When bound to the p75 neurotrophin receptor, BDNF activates a cascade of intracellular signaling pathways that inhibit axonal regeneration and lead to apoptosis. BDNF promotes the proliferation and differentiation of oligodendrocyte progenitor cells and myelination, prostocyclin biosynthesis in the arteries of the brain [27]. Endogenous BDNF is a key mediator of CNS cell survival and recovery after stroke. The mechanisms of inhibition of spatial learning and memory ability in rats with cerebral hemorrhage may be associated with a decrease in brain expression of BDNF [22]. This is supported by experimental studies showing that BDNF secreted by transplanted stem cells is one of the paracrine factors that plays a major role in alleviating severe brain damage caused by cerebral hemorrhage in neonatal rats [35, 38]. The mechanism of regulation of BDNF expression mediated by ECs and neurons is largely unclear. In recent years, the relationship between the level of BDNF and the risk of stroke, functional outcome and mortality in patients with stroke has been actively studied [19]

All stages of neurogenesis are regulated by signaling growth factor molecules that mediate changes in apoptosis, inflammation, angiogenesis, cell differentiation and proliferation. One of them is vascular endothelial growth factor (VEGF) - a group of angiogenic proteins involved in the processes of arteriogenesis, neuroprotection, neurogenesis, angiogenesis in strokes. In the area of ischemia bordering the nucleus, it induces angiogenesis, which is necessary for the survival of resident and newly generated neurons. VEGF and its receptors play a central role in initiating angiogenesis in the CNS by promoting survival, proliferation, and migration of epithelial cells. Increased expression of VEGF was detected during the first 24 hours after occlusion in the peri-infarct brain tissues of rats with ischemia of the middle cerebral artery (MCA) and persisted for several days. Comparison of transient and permanent cerebral occlusion in rats showed an increase in VEGF-A levels (in neurons and endothelial cells). VEGFR-1 (in neurons, ECs and astrocytes) and VEGFR-2 (in ECs and astrocytes) on days 1-3 in the ipsilateral hemisphere of the brain. High expression of VEGF-A, VEGFR-1, and VEGFR-2 was also shown in hippocampal and cerebral cortex neurons for several hours and days after transient global cerebral ischemia in rats [50]. Ischemia contributed to the survival of neurons during glucose-oxygen deprivation, which models hypoxia-ischemia in cell cultures in experiments. Topical application of VEGF-A on the oral surface reduced infarct volume in rats. It has been shown that VEGF-A and VEGF-B enhance neurogenesis not only in normal, but also in ischemic brain tissue [49,51-53]. At the same time, the effects of VEGF in the CNS are opposite. On the one hand, VEGFR-2 activation induces intracellular pathways associated with neuroprotection. VGEF-2-PIZK-Akt signaling has been associated with neuronal survival and reduction in infarct core size in mice subjected to 90 min MCA occlusion, on the other hand, VEGFR-2 mediated PIZK-Akt signaling induces blood-brain barrier permeability, and VEGFR-1 is involved in modulation of inflammatory responses 54,55 Angiogenic activity has been found to occur 3-4 days after stroke, but how long it persists is not fully understood [28]. During development, vascular and neural networks form similar mechanisms of growth and maturation. The functional correspondence between nerve and vascular cells is provided by the relationship between them, therefore, changes in neuronal activity are associated with changes in cerebral blood flow - neurovascular communication, implying a balanced secretion of vasoconstrictor and vasodilator molecules, including nitric oxide (NO) and prostaglandin E [34].Vascular remodulation, a process initiated by fluid shear stress rather than hypoxia. The dynamics of molecular factors and collateral circulation is not yet clear. The study showed that collateral vessels have different phenotypes of ECs and smooth muscle cells of blood vessels, which also potentiates the interest of scientists in the study of angiogenesis (62). In the stroke zone, VGEF induces angiogenesis, which is necessary for the survival of resident and newly generated neurons. VEGF and its receptors play a central role in initiating angiogenesis in the CNS by stimulating EC survival, proliferation, and migration. Increased expression of VEGF was detected during the first 24 hours after occlusion in the peri-infarct brain tissues of rats and persisted for several days. After 48 and 72 hours of ischemia, there was a sharp increase

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in proliferating ECs in the peri-infarction zone and on the pial surface. It has been proven that the expression of VEGF and its receptor VEGFR-2 increase after a stroke and have a pro-angiogenic effect. An increase in the expression of VEGF-A, a key mediator of arteriogenesis in the penumbra zone, leads to an increase in the density of microvessels in this area and predetermines the clinical outcome of a stroke. In patients with ischemic stroke, the peak concentration of serum VEGF was registered on the 7th day of acute cerebrovascular accident (ACV) and persisted up to 14 days [37].

DISCUSSION: Cerebral stroke is the driving force behind angiogenesis in the acute phase of the disease and is mediated by VEGF and its receptors. There is evidence of an increase in VEGF in the blood plasma of patients within 3 months in all stroke subtypes [19]. The adverse effects of endogenous VEGF expression in the acute period of stroke are associated with astrocytic glia activation, disruption of the endothelial barrier, development of cerebral edema, and risk of hemorrhage 34,49,56.

Vascular endothelial growth factor (VEGF) is a signal protein produced by cells to stimulate angiogenesis (30-31). It increases vascular permeability, increases the antithrombotic and anti-inflammatory properties of the endothelium, reduces the risk of its alteration when exposed to damaging factors, and has a neurotrophic and neuroprotective effect on neurons and glial cells of the CNS [32]. Vascular endothelial growth factor proteins bind to cell surface receptors with tyraninase activity, which are activated as a result of transphosphorylation. During hypoxia, under the influence of a factor induced by hypoxia, proteins are released that bind to VEGF receptors on the surface of the endothelium, activate tyrosine kinase, triggering angiogenesis. The content of VEGF in the blood serum of patients with hemorrhagic stroke increases and correlates with indicators of neurological deficit [33].

The regulation of angiogenesis in the neurogenic niche determines the behavior of resident NSCs. VEGF plays a key role in stimulating vasculogenesis in the infarcted area. BDNF is a key regulator of stem and progenitor cells in SVZ [69].

The mechanisms leading to changes in the content of molecular biomarkers in the blood serum in hemorrhagic stroke remain poorly understood. MicroRNAs, which are a flexible network of gene expression regulators, play an important role in these processes. Particular attention is paid to several miRNA clusters involved in neuroprotection [21]. Micro-RNA is considered as a promising target for future stroke therapy [42].

CONCLUSIONS:

1. The dynamics of the content of candidate molecular markers in the blood serum of patients with hemorrhagic stroke probably reflects the processes of alteration and regeneration corresponding to the stages of the disease.
2. The use of these candidate molecular biomarkers, after appropriate validation, is promising for complex diagnostics, monitoring of treatment and rehabilitation measures in this category of patients.

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