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INHIBITION OF THE COMPLEMENT ANAPHYLATOXIN ACTIVITIES IN THE CENTRAL NERVOUS SYSTEM DISORDERS

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The review is devoted to inhibition of the complement anaphylatoxin activities in diseases of the central nervous system. Here we present epidemiological data on the prevalence of cerebrovascular diseases, in particular, ischemic stroke and craniocerebral trauma. The mechanisms of complement activation and complement-mediated pathology in the central nervous system are considered in detail. Clinical data confirming the role of the complement system in the pathogenesis of stroke and of post-traumatic brain injury are presented. We also summarize the results of *in vivo* specific activity studies of the complement anaphylatoxin inhibitors using animal models of stroke and traumatic brain injury. Briefly described is the present state of the art in developing drugs that target the effector compounds of the complement cascade.

Keywords: complement system; anaphylatoxin; C3a; C5a; receptor antagonist; monoclonal antibodies; ischemic stroke; traumatic brain injury.

ИНГИБИРОВАНИЕ ФУНКЦИИ АНАФИЛАТОКСИНОВ КОМПЛЕМЕНТА ПРИ ПАТОЛОГИИ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

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Обзор посвящен ингибированию функции анафилатоксинов комплемента при патологиях центральной нервной системы. Приведены эпидемиологические данные о распространенности цереброваскулярных заболеваний, в частности ишемического инсульта и черепно-мозговых травм. Подробно рассмотрены механизмы активации комплемента и опосредованной комплементом патологии центральной нервной системы. Приведены клинические данные, подтверждающие роль системы комплемента в патогенезе инсульта и вторичных повреждений после черепно-мозговой травмы. Рассмотрены результаты исследований специфической активности ингибиторов функции анафилатоксинов комплемента на моделях инсульта и черепно-мозговой травмы *in vivo*. Кратко описано состояние исследований в области разработки лекарственных препаратов, ингибирующих эффекторную функцию системы комплемента.

Ключевые слова: система комплемента; анафилатоксин; C3a; C5a; рецепторный антагонист; моноклональные антитела; ишемический инсульт; черепно-мозговая травма.

Background

Cerebrovascular diseases remain as the most significant medical and social problem, due to its increased morbidity and mortality, as well as temporary labor losses and primary disability. According to the Ministry of Health of the Russian Federation, in 2016, in Russia, cerebrovascular diseases were diagnosed in 950.9 cases per 100,000 of the population aged 18 years and older, and ischemic stroke was diagnosed in about a quarter of them. In 2016, mortality from cerebrovascular diseases amounted to 190.8 cases

List of abbreviations

BCSB, blood-cerebrospinal barrier; BBB, blood-brain barrier; MCAO, middle cerebral artery occlusion; PNH, paroxysmal nocturnal hemoglobinuria; CNS, central nervous system; TBI, traumatic brain injury; MBL, mannose-binding lectin.

per 100,000 of the population, and mortality from stroke amounted to 123 cases per 100,000 of the population [1]. According to the World Health Organization, about 17 million cases of stroke are registered annually worldwide, and about 50% of patients die later on [2].

Traumatic brain injury (TBI) is one of the main causes of disability and mortality, especially in young people. The incidence of TBI is approximately the same in different countries and amounts to 300–400 cases per 100,000 of the population per year. In Russia, approximately 600,000 people sustain TBI annually, with approximately 50,000 of them dying and the same number becoming disabled. Secondary cerebral damage develops in patients with severe TBI, that is, in about 20% of cases [3].

A common aspect of major diseases affecting the central nervous system (CNS) is inflammation [4]. Acute inflammation begins with the expression of adhesion molecules by the vascular endothelium and the migration of leukocytes from the blood to the brain parenchyma. The cells of the immune system, activated by danger signals, synthesize and release cytokines into the environment. In the CNS, proinflammatory cytokines stimulate the synthesis and secretion of the complement components. The greatest contribution to the etiology of inflammation is made by the complement activation products, especially anaphylatoxins C3a and C5a, which support the inflammatory resource by attracting the migration of leukocytes to the brain, activating brain cells expressing specific C3 and C5a receptors (C3aR and C5aR) on their membranes and additional release of inflammatory molecules [5, 6].

The complement system, together with various factors of innate and adaptive immunity, helps maintain barrier functions and protect the body from invasion of microorganisms and parasites and the sequelae of traumatic injury [7]. However, it is believed that the same system plays an important role in the development of secondary pathology of the nervous system with the mediated participation of the immune system. The precursors of complement proteins are synthesized mainly by hepatocytes and then released into the bloodstream, ready for activation in various pathways [8, 9]. When the blood-brain barrier (BBB) is impaired, the proteins of the complement system can migrate to the brain and form a potentially effective cytolytic complex on the surface of neurons and glial cells, which, in case of a lack of regulatory proteins, can damage and affect the etiology of neurodegenerative, demyelinating diseases, and ischemic stroke [10].

Thus, uncontrolled pathological activation of the complement plays a significant negative role in the development of CNS diseases, mediating neuronal death, damage to axons, demyelination, and impairment of the BBB and blood-spinal cord barrier (BSB) [11].

Blocking the activation of the complement system has become one of the strategic approaches to the treatment of not only complement-dependent diseases, such as paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome, age-related macular degeneration, and glomerulonephritis, but also a number of other pathological conditions [12].

This review considers pharmacological approaches to the treatment of stroke and brain injury in patients with TBI by inhibiting the effector function of the complement system, namely, the C3a and C5a anaphylatoxins.

Mechanisms of complement activation and complement-mediated pathology of the central nervous system

The complement system, apart from special cases, can be activated by three canonical pathways, namely, classical, lectin, and alternative pathways (Figure), initiated by different inducers, which are risk factors, although it has been revealed over the past 10–15 years that there are noncanonical pathways for complement activation [13, 14]. This indicates the versatility of the mechanisms of action and functions of one of the most evolutionarily ancient systems of innate (nonadaptive) immunity.

The pathways for the activation of the complement system differ in that in the initiation phase, the target inductors recognize different molecules. To launch the classical pathway, a complex subunit protein, C1q, circulating in a calcium-dependent complex with the proenzymes C1r and C1s binds to the Fc fragments of immunoglobulins G or M in the immune complexes fixed on the activating surface (∫). Thereafter, the conversion of the C1s proenzyme into an active protease is initiated, which cleaves the C4 and C2 components in the microenvironment [15].

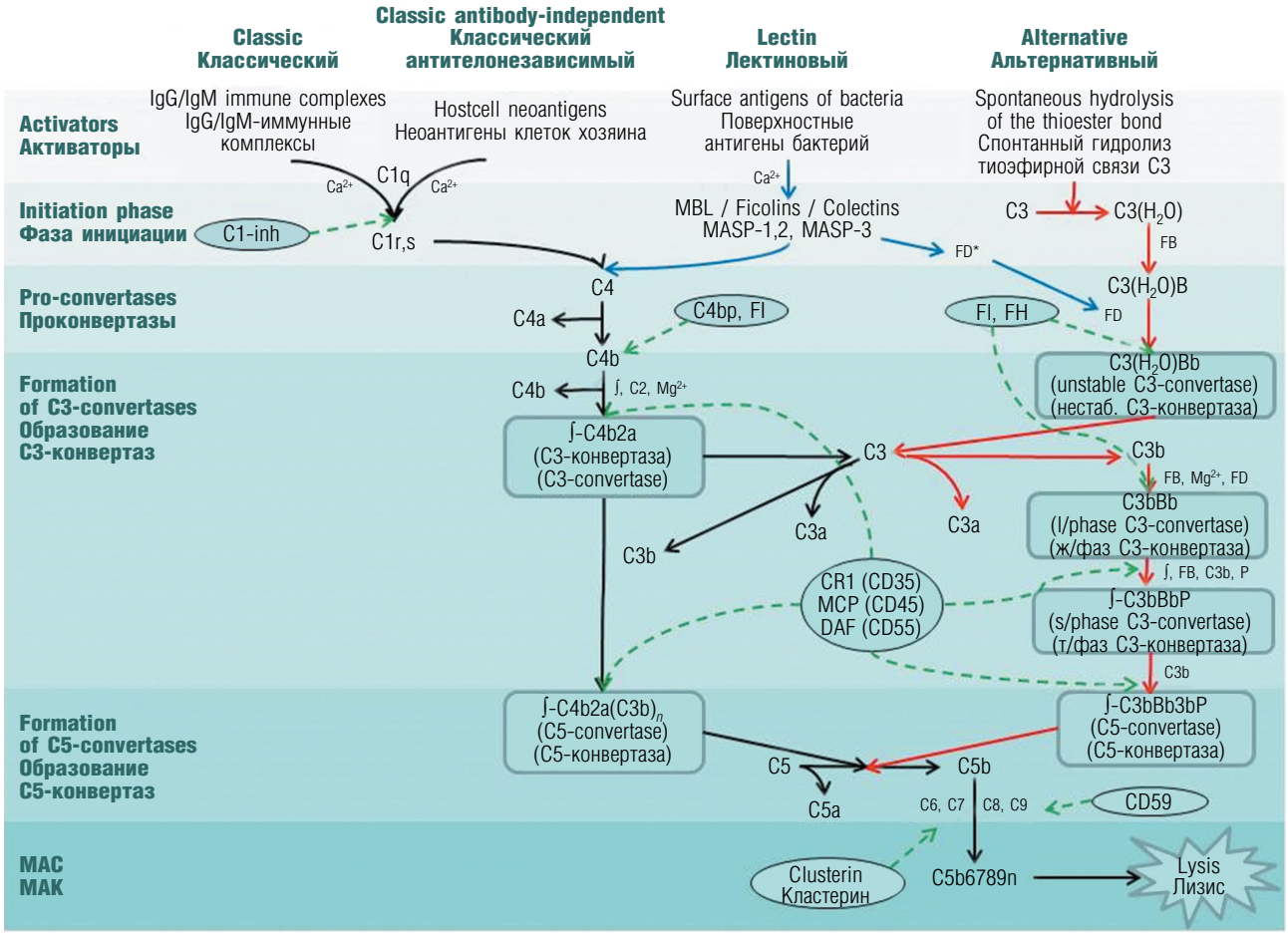

Figure. Mechanisms of activation of the complement system. Continuous arrows — the pathways of complement activation, brocken arrows — negative regulation of convertases and membrane attack complex (MAC) assembly, ovals — regulatory proteins, ∫ — activating surface, FD* — precursor of factor D, l/phase — liquid-phase, s/phase — solid-phase

Рисунок. Механизмы активации системы комплемента. Непрерывные стрелки — пути активации комплемента, пунктирные стрелки — отрицательная регуляция конвертаз и сборки мембраноатакующего комплекса (МАК), овалы — регуляторные белки, ∫ — активирующая поверхность, FD* — предшественник фактора D, ж/фаз — жидкофазная, т/фаз — твердофазная

The lectin pathway is launched due to the interaction of structural elements of bacterial surfaces with mannose-binding lectin (MBL), collectins (CL-K1 and CL-L1), or ficolins, which circulate in a complex with serine proteases, zymogens MASP-1, MASP-2, and MASP-3. After interaction with the complementary target surface, bound zymogens are activated and initiate a proteolytic cascade system, resulting in MASP-2, like C1s, cleaving C4 and C2 into large (C4b, C2a) and small (C4a and C2b) fragments [16].

As a result of a chain of successive interactions, a complex enzyme, C3 convertase, of the classical pathway (C4b2a) is formed, which also cleaves the C3 protein into large (C3b) and small (C3a) fragments. After adherence of additional C3b molecules to the complex, a new enzyme, C5 convertase, of the classical pathway (∫-C4b2aC3b$_n$) is formed, which cleaves the C5 component into C5b and C5a [17].

Concurrently, in plasma under normal physiological conditions, the alternative pathway is the dominant pathway of complement activation. It is activated due to the slow spontaneous hydrolysis of the thioester bond of C3 constantly circulating in the bloodstream. As soon as the thioether bond breaks, C3 takes on a special conformational form, C3(H_2O), and as a result of its interaction with factor B (FB) and factor D (FD), C3(H_2O)Bb, a C3 convertase, is formed, which cleaves native C3 into C3b and C3a fragments. The formation of this unstable C3 convertase is called a tick-over process and is a constantly functioning mechanism for triggering an alternative pathway activation

cascade [18]. The C3b fragment is converted by FB and FD into the liquid-phase C3 convertase (C3bBb). Additionally, this enzyme is stabilized due to covalent binding to the activating surface with the formation of the solid-phase C3 convertase (∫-C3bBb) and/or due to the interaction with the protein properdin (P) [19].

After the addition of supplementary C3b molecules to this complex, the specificity of the formed complex enzyme is changed. The enzyme ∫-C3bBbC3bP is a C5 convertase of the alternative pathway, which, acting similarly to the classical pathway C5 convertase, causes the conversion of C5 into C5b fragments and a potent biologically active C5a. C5b interacts with the C6 component, and the final assembly cascade of the membrane attack complex commences from it. After interaction with the C7 component, the formed C5b67 complex is incorporated into the surface membrane of the target cell and then supplemented with the C8 components, providing polymerization of the C9 component on the target cell surface, which leads to the formation of a pore (C5b6789n) in the membrane [20], disruption of the lipid bilayer integrity, and cell death due to osmotic lysis [8].

The complement system is strictly balanced. Activation processes at almost every site are controlled by regulatory soluble and membrane-bound proteins. In solution, at the initiation stages of the classical pathway, activation is interrupted by an inhibitor of the C1 complex (C1-Inh). At the formation stage of C3 convertases of the classical and lectin pathways, the C4b-binding protein (C4bp) functions, which immobilizes C4b, and the course of the alternative pathway is controlled by factor H (FH). Both C4bp and FH proteins serve as cofactors for factor I serine protease, which causes the conversion of C3b and C4b to inactive forms C3bi and C4bi. In addition to the aforementioned circulating C4bp and FH, regulatory proteins CR1 CR1(CD35), MCP(CD46), and DAF(CD55) are expressed on the membranes of many host cells, which prevent the assembly of convertases or their rapid dissociation. Two proteins, clusterin and membrane-bound glycoprotein CD59, control the assembly of the membrane attack complex on the host cell, protecting it from attack by its own complement [21]. Due to regulatory proteins, negative regulation of convertases and assembly of the membrane attack complex develop. The imbalance of the complement system due to a genetic deficiency of a number of regulatory proteins is the main cause of very serious diseases that lead to the destruction of their own cells and, ultimately, to lethal outcomes [22].

Normally, the BBB/BSB separates the CNS from plasma complement proteins; however, disruption of the integrity of astrocytes, pericytes, or endothelium that support this barrier enables circulating complement components to enter the CNS. In addition, it is now recognized that resident cells of the CNS can synthesize a functional set of complement proteins under conditions of homeostasis [23]. In addition to immune surveillance, physiological functions of complement components in the CNS include the elimination of excess neurotransmitters, old and glycated proteins, as well as maintenance of neuronal viability, removal of excess synapses, and neurogenesis in adults [24]. However, in a disease, synthesis and/or an increase in the expression of complement proteins by neurons and glia contributes to complement-associated neuropathology, including in the early stages of neurodegenerative diseases, when the BBB/BSB is not impaired yet.

In the state of CNS homeostasis, the balance of the complement system is shifted toward inhibition of activation due to its own regulatory proteins, and spontaneous activation of the complement usually does not occur. In particular, microglia and astrocytes express the surface of C1-Inh [23]. Astrocytes regulate an alternative pathway by expressing FH and CR1/CD35 [25]. Astrocytes and microglia produce the CD59 protein [26]. Unlike astrocytes and microglia, neurons only weakly express regulatory proteins CR1, C1-Inh, FH, MCP, and CD59 and do not express DAF [23]. Oligodendrocytes also produce only small amounts of CD59, C4bp, and CR1 [25]. Finally, apoptosis in neurons decreases the expression of surface molecules that inhibit the complement, which enhances the vicious cycle triggered by the complement activation in neurodegenerative diseases.

Complement activation products, anaphylatoxins C3a and C5a, being chemoattractants, activate powerful inflammatory mechanisms targeting a wide range of immune and nonimmune cells. C3a acts on the C3aR receptor, which

is found in most myeloid cells. In the CNS, C3aR is expressed on astrocytes and microglia [27]. The immunomodulatory effects of this axis include the regulation of oxidative burst in macrophages [28], neutrophils [29], and eosinophils and the production of proinflammatory cytokines, although several other physiological functions of C3aR stimulation are becoming known [30]. C5a activity is implemented through two types of specific receptors, C5aR1 and C5aR2, which are often co-expressed [31]. In the CNS, the C5aR1 receptor is detected on most cells of the myeloid line, as well as microglia, astrocytes, and some neurons of the CNS. C5aR1 signaling promotes inflammation, which can lead to devastating consequences for the CNS, since it includes the activation of phagocytosis, oxidative burst, the production of proinflammatory cytokines, and an increase in the content of integrins [32]. The neuroprotective physiological effect of C5a is also known [33], which may result from interaction with the C5aR2 receptor, which include both anti- and proinflammatory effects.

Thus, in case of CNS damage due to opsonization of necrotized cells, recruitment of leukocytes, increased C3a and C5a generation, and lower expression of regulatory proteins, the balance in the complement system is shifted toward uncontrolled activation, which makes the CNS more vulnerable to its own local and plasma-derived complement, compared to other organs. In this regard, the search for therapeutic agents, namely, inhibitors of the complement system, for the treatment of the CNS pathology becomes especially important.

Following the mechanisms of complement system activation, a few sites for potential inhibition can be selected. The most effective means of complement blocking is neutralizing antibodies against key molecules of the activation cascade. The classical and lectin pathways can be blocked using antibodies to the C1s and MASP-2 proteases, respectively. To block the alternative pathway, antibodies to FB and FD, as well as chimeric recombinant molecules of regulatory proteins that enhance their activity, can be used. However, the search for agents blocking the functional domains of the complex C3 molecule, which is central in the activation of the complement system by any of the three pathways, is of particular interest.

Inhibition of complement anaphylatoxins in ischemic stroke

More than 70% of stroke cases occur as a result of ischemia/reperfusion due to thrombotic or embolic occlusion of cerebral vessels [34]. Reperfusion of the injured area of the brain causes further damage due to oxidative stress, BBB dysfunction, inflammation, and apoptosis, which results in the formation of an ischemic nucleus surrounded by a weakly perfused penumbra area with a subsequent loss of the functional capacity of this entire area [35].

The development of stroke is consistently correlated with the complement activation [35]. Components of the complement system and products of its activation—C1q, MBL, C3, C3a, C3c, C4d, C5a, and C9—are always present in areas of ischemic brain damage [6, 36]. Patients with a history of stroke also have elevated levels of a number of complement proteins (C3, C3a, C4, C4d, C5, C5a, C5b-9, FB, MBL, MASP-1/2) and the membrane attack complex in blood plasma, with reduced ficolin levels [37, 38]. The degree of increase in the blood serum concentrations of C3, C3c, C4, and MBL is associated with the severity of stroke, and the increase in MBL and C3 levels correlates with each other and is associated with a worse stroke outcome [39].

Anaphylatoxins C3a and C5a, as well as the membrane attack complex, can potentially be involved in tissue damage caused by reperfusion in stroke. However, most researchers suggest that immediately after reperfusion, tissue damage is mediated mainly by C3a and, to a lesser extent, by C5a, whereas the membrane attack complex is only a marker of the complement cascade activation [40, 41]. In this regard, the possibility of its influence in stroke on later mediators of activation of the complement system, namely, on anaphylatoxins, is of great interest.

Studies have demonstrated that C3aR antagonists mitigate ischemic brain damage mainly by reducing neutrophil infiltration and inflammatory response in the acute stage of ischemic stroke [40, 41]. Exposure to the C3aR by an antagonist (SB290157) decreases the stroke area, decreases the expression of ICAM-1 cell adhesion molecules on endothelial cells, and decreases the count of C3aR-positive granulocytes in mice with middle cerebral artery occlusion

(MCAO) within 30 min, but not with constant MCAO [41].

However, there is still debate concerning the effect of C3aR antagonists on neurogenesis after ischemic stroke. In a study of transient ischemic stroke in adult male C57BL/6 mice, when using a low dose of the C3aR antagonist (1 mg/kg) for 3 days after ischemia, the proliferation of DCX^+ neuroblasts in the subventricular zone increased 7 days after ischemia, whereas a high dose of the C3aR antagonist (40 mg/kg) inhibited the proliferation of neural progenitor cells [42]. According to Ducruet et al. (2012), during ischemia, slow infiltration of the brain with T-lymphocytes expressing C3aR occurs, and the use of a C3aR antagonist 72 h after injury significantly reduces the subcortical damage. This suggests that activated T cells may interfere with endogenous neurogenesis, although the mechanism of this effect is unknown.

In a model of permanent ischemia in mice, it was shown that injection of a C3aR antagonist twice daily for 10 days after surgery suppressed the proliferation of neuroblasts in the subgranular zone of the hippocampus and in the granular cell layer of the dentate gyrus from day 7 to day 21 after ischemia [43].

In addition, in models of thromboembolic stroke, which are more consistent with stroke in humans, it has been demonstrated that 6 h after injury, plasma levels of C3a, as well as the cerebrovascular expression of C3aR, increase, which persists for up to 4 weeks. In the photothrombotic stroke model in mice with rapid spontaneous reperfusion, when SB290157 was administered 1 h after injury, an improvement in neurofunction and a decrease in infarction were observed after 48 h. In the embolic stroke model, when SB290157 was administered 2 h after the injury, an improvement in histological and functional parameters was noted, and when using SB290157 in conjunction with intravenous thrombolysis, bleeding and edema decreased and the indicators improved, in contrast to the use of thrombolysis only 4.5 h after injury [44].

It is noteworthy that SB290157 functions as an antagonist in cell lines with low receptor density and as a partial agonist in cell lines expressing higher levels of C3aR [45].

In contrast to the studies described above, which confirmed the positive role of inhibition of C3aR in stroke, there is evidence that C3a regulates the migration and differentiation of neuronal progenitor cells and increases astrocyte survival [43, 46].

In a model of neonatal hypoxic-ischemic encephalopathy, a decrease in memory impairment after injury was registered in transgenic mice expressing C3a and in wild-type mice injected with exogenous peptide C3a [47].

In another study, the lack of C3aR reduced the penetration and plasticity of axons in the peri-infarction zone after stroke, which can be restored by intranasal administration of C3a [46].

The foregoing enables to conclude that to efficiently characterize the role of C3a and C3aR in stroke and to optimize therapeutic strategies, the development of more specific C3aR antagonists and further research on C3aR agonists are required.

Compared to C3a, anaphylatoxin C5a, when bound to its canonical receptor C5aR1, is an active agent in many complement-mediated inflammatory diseases, including arthritis, myocardial ischemia, and ischemic stroke [48, 49]. It is believed that inhibition of C5a prevents brain damage during ischemia or reperfusion [50, 51].

In all the pharmacological inhibitors of C5a, the antagonist of C5aR1, which is the orally administered cyclic peptide AcF-[OPdChaWR] (PMX53), is greatly studied [52, 53]. In mice injected with PMX53 30 min before ischemia, moderate improvement in outcomes was registered after MCAO for 60 min [54]. Administration of PMX53 even at a lower dose 45 min before ischemia also led to a decrease in the volume of cerebral infarction in mice 24 h after injury [55].

A monoclonal antibody to C5, which specifically blocks the formation of C5a and C5b-9, was studied in a rat model of ischemic stroke [50, 56]. Administration of monoclonal antibodies to C5 (18A10.62) caused a decrease in motor impairment and development of the stroke zone (by 40% when administered before ischemia and by 30% thereafter), edema, and brain infiltration in rats with 90-min MCAO [50].

In addition, it was demonstrated in the mouse MCAO model that C5a is activated one day after ischemic injury and is predominantly produced by brain neurons [40, 57]. Blocking the C5a signaling by genetic C5aR1 knockout in mice improved neurologic parameters and decreased the infarction size one day after ischemic stroke. Apoptosis of neurons was noted in the model of

oxygen-glucose deprivation using C5a, whereas neurons with C5aR1 deficiency were protected from apoptosis, which indicates a neuroprotective effect by inhibiting the interaction between C5a and C5aR1 in the acute phase of ischemic stroke [57]. Although there is some evidence that C5a activation is deleterious in the early stages of ischemic stroke, C5a has been shown to exhibit neuroprotective properties in glutamate-induced neurotoxicity in mice [58]. This is why C5a can probably act as a protective factor, inhibiting tissue damage in the late stage of ischemic stroke.

The studies described above confirm that modulation of C5a/C5aR signaling has potential at the early stage of ischemic stroke. However, the effect of anti-C5 monoclonal antibodies and C5aR1 antagonists in ischemic stroke is limited.

Inhibition of complement anaphylatoxins in traumatic brain injury

Secondary brain injury after TBI is closely related to the activation of the inflammatory response. The complement system is the main coordinator of posttraumatic neuroinflammation and secondary neuropathology [59, 60]. After activation, proteins of the complement system increase the BBB permeability through C3a and C5a, promote the infiltration of leukocytes into the damaged brain and the subsequent formation of free radicals, induce apoptosis of neurons and glia by binding C3a and C5a to their receptors, and cause lysis of neurons through the membrane attack complex [11, 24]. Thus, therapeutic strategies aimed at blocking the complement activation can potentially reduce neuroinflammation and neurodegeneration in TBI patients [61–63].

In TBI, the levels of C5b-9 in the ventricular fluid are 1,800 times higher than the control levels and correlate well with the degree of BBB impairment [61]. Examination of the tissues of the frontal and temporal lobes of the brain of TBI patients, operated on due to a persistent increase in intracranial pressure, revealed increased levels of C1q, C3, C3b, C3d, and the membrane attack complex in the penumbra region [59]. These data are supported by the fact that the content of a number of complement components, for example, C3, C1q, and FB, was increased in the cerebrospinal fluid of TBI patients compared to controls [64].

Similarly, the levels of the membrane attack complex were significantly increased in the cerebrospinal fluid of TBI patients compared with that in controls [61]. The role of the membrane attack complex in acute neuronal loss after TBI was confirmed in a model of controlled cortical damage in adult male mice; nevertheless, it was revealed that the upstream products of complement activation, formed predominantly through an alternative pathway, aggravate chronic neuroinflammation [65].

Evidence for the involvement of the complement system in the pathogenesis of TBI was obtained using various *in vivo* models, in particular, a model of intracerebral hemorrhage simulating a hemorrhagic stroke, a model of cold injury, and a model of the weight-drop injury model [66]. All of these models differ in their ability to simulate different aspects of TBI. Thus, a cold injury is accompanied by cerebral edema and impaired BBB, which are typical for TBI [11], but this injury is not mechanical. In contrast, standardized weight-drop models simulate mechanical trauma more accurately, but they have the disadvantage of low reproducibility [67]; therefore, the results obtained using such models should be interpreted with great caution in the context of human TBI.

The animal models listed were used to study the role of anaphylatoxins C3a and C5a in TBI. In a model of intracerebral hemorrhage in mice, it was shown that when the C3aR antagonist (SB290157) was administered 45 min before the intracerebral hemorrhage, neurological disorders, edema, and granulocyte infiltration decreased for up to 3 days after the injury, and disorders were also weakened when the drug was administered 6 h after hemorrhage [68]. Although this strongly suggests a negative role of C3aR signaling in TBI, interpretation of the results is complicated by the fact that SB290157 can function as an agonist [45].

In addition, using the weight-drop injury model in rats, it was demonstrated that the administration of high-affinity monoclonal antibodies to experimental animals with TBI, blocking the activation of rat complement via an alternative pathway at the stages of formation of liquid-phase and solid-phase C3 convertases, preventing the formation of the C5 convertase, and thus inhibiting pointwise the functions of the complement system, in particular the formation

of anaphylatoxins C3a and C5a, led to a pronounced positive effect manifested in the preservation of the cognitive functions of animals, as well as in improvement of the histological pattern of the brain tissue of animals [69].

Dysfunction of C5a, for example, using $C5^{-/-}$ knockout mice or administration of a C5aR antagonist, caused a decrease in secondary damage in a cold injury model [70]. More compelling evidence for the general damaging role of complement anaphylatoxins was obtained when a C5aR1-specific antagonist (PMX53) was administered to mice with cerebral hemorrhage. PMX53 significantly improved neurological function as measured by spatial memory retention and decreased edema and granulocyte count [51]. When a C5aR antagonist was used in combination with a C3aR antagonist (SB290157), a synergistic neuroprotective effect was registered [51]. In a model of intracerebral hemorrhage, it was also illustrated that PMX53 in combination with a thrombin antagonist worked better than either drug individually [71].

These studies confirm that the therapeutic inhibition of C3a and C5a and their interaction with receptors can be considered as a component of the comprehensive treatment of TBI.

Development of drugs that inhibit the effector function of the complement system

At the moment, there are several complement-targeted drugs approved. The drug eculizumab, based on therapeutic antibodies to C5, named Soliris®, is manufactured by Alexion Pharmaceuticals and is approved for the treatment of PNH and atypical hemolytic uremic syndrome [72, 73]. The mechanism of action of the drug consists in inhibiting the cleavage of the C5 component and preventing the assembly of the membrane attack complex C5b-C8 on erythrocyte membranes in the case of PNH and the destruction of platelets in atypical hemolytic uremic syndrome.

Currently, phase III clinical studies of the eculizumab biosimilar, BCD-148, developed by BIOKAD, are being performed in PNH patients [74].

Ravulizumab (Ultomiris®, Alexion Pharmaceuticals), which is a second-generation C5 inhibitor, a humanized monoclonal antibody that binds specifically to complement protein C5, was approved by the US Food and Drug Administration for the treatment of PNH patients [75].

By analogy with Soliris, a strategy of interrupting the activation cascade is being developed by blocking the cleavage of the C5 component through the C5 convertase. The phase II clinical trials of fully human antibodies LFG316 (Tesidolumab, Novartis Pharmaceuticals), obtained by combinatorial approaches for the treatment of age-related macular degeneration, have been completed [76].

Studies are underway on several molecules that block the cleavage by C5 convertase and prevent the formation of inflammatory molecules C5a and C5b and the lytic attack complex. They include a small OmCI protein from the lipocalin family, Coversin (Coversin, AKARI Therapeutics). The drug Coversin has passed phase II clinical trials for the treatment of PNH [77].

Clinical trials are being conducted for several aptamer-based drugs, namely, large nucleotides and peptides that bind to the target molecule C5 and neutralize complement activation cascades [78].

Phase I–II clinical studies to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of Cemdisiran (Alnylam Pharmaceuticals), which inhibits the C5 expression in the liver, in healthy volunteers and PNH patients, have been completed [79].

Phase III clinical studies of Avacopan (ChemoCentryx) therapeutic, a novel highly selective orally-administered human C5aR1 antagonist, are being conducted for ANCA-associated vasculitis [80]. Avacopan does not interfere with the formation of C5b or membrane attack complex and does not block the binding of C5a to the C5L2 receptor (C5aR2).

It should be noted that C5-inhibiting drugs block complement cascades following any of the three known activation pathways (classical, lectin, and alternative).

In addition to C5 inhibition, the strategy of blocking complement activation at earlier stages is being actively investigated. In this case, C3 is the most obvious target for blocking.

One of the approaches to neutralizing C3 is associated with the use of the drug compstatin and its derivatives belonging to the compstatin family [81]. Compstatin is a cyclic peptide that

binds selectively to the native C3 component and its C3b fragment. Clinical trials of various compstatin derivatives are currently performed [82–86].

The problem of C3 neutralization with therapeutic antibodies is the most difficult, since C3 is a large multidomain protein with a concentration of approximately 1 mg/mL in blood plasma, which hinders the search of neutralizing antibodies and requires high therapeutic doses. Nevertheless, the development of neutralizing antibodies to C3 has been intensively performed and is being conducted by various researchers and companies, as evidenced by a significant number of publications and patents [87, 88].

Monoclonal antibodies to C3 H17 have been obtained, which recognize fragments of activated C3, C3b/iC3b, and effectively block the alternative pathway of activation, interrupting the formation of C3 convertase [89, 90]. Currently, the American company Elusys Therapeutics is conducting preclinical studies of H17 antibodies for the treatment of diseases associated with renal failure.

These antibodies represent the closest analog of the hC34 antibodies developed at the State Research Institute of Highly Pure Biopreparations, but they differ significantly in specificity, recognize other C3 domains, and are inferior in efficiency to the hC34 antibodies. Humanized antibodies hC34 [91] are original and, unlike many other complement inhibitors, selectively block the activation of the alternative pathway only and do not affect the cascades of the classical and lectin pathways, preserving antiinfectious activity and other useful functions of the complement system.

To date, complement inhibition strategies have not been studied in clinical stroke patients. Based on the data presented above, it can be assumed that in the treatment of stroke, inhibition of an alternative pathway, as well as inhibition of C3 convertase or anaphylatoxins C3a and C5a, may be beneficial. For example, eculizumab is well studied and has proven useful in a variety of diseases both in the CNS and beyond; however, its inability to block C3a binding to C3aR and its extremely long half-life make its use in ischemic stroke less attractive. The most promising complement system inhibitors are compstatin analogs that mechanically block the formation of C3a and C5a. They showed safety in a series of human diseases and short half-lives, resulting in protection against ischemia [92].

In secondary injuries after TBI in humans, inhibitors of the complement system have not been studied either, but many of them, particularly the inhibitors of complement anaphylatoxins described above, have been tested in animal models of TBI with promising results. Thus, there are prerequisites for the use of these drugs in clinical practice.

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