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REVIEW

Autoimmunity in acute ischemic stroke and the role of blood–brain barrier: the dark side or the light one?

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Abstract **This article presents a synopsis of the current data on the mechanisms of blood–brain barrier (BBB) alteration and autoimmune response in acute ischemic stroke. Most researchers confirm the relationship between the severity of immunobiochemical changes and clinical outcome of acute ischemic stroke. Ischemic stroke is accompanied by aseptic inflammation, which alters the brain tissue and exposes the co-stimulatory molecules of the immune system and the neuronal antigens. To date, BBB is not considered the border between the immune system and central nervous system, and the local immune subsystems are found within and behind the BBB. BBB disruption contributes to the leakage of brain autoantigens and induction of secondary autoimmune response to neuronal antigens and long-term inflammation. Glymphatic system function is altered and jeopardized both in hemorrhagic and ischemic stroke types. The receptors of innate immunity (toll-like receptor-2 and toll-like receptor-4) are also involved in acute ischemia–reperfusion injury. Immune response is related to the key processes of blood clotting and fibrinolysis. At the same time, the stroke-induced immune activation may promote reparation phenomena in the brain. Subsequent research on the reduction of the acute ischemic brain injury through the target regulation of the immune response is promising.**

Keywords stroke; blood–brain barrier; autoimmunity; innate immunity; inflammation; cell death

Introduction

Stroke incidence has decreased over time but remains one of the global leading causes of death and disability, and as the population ages, the burden of this disease becomes tremendous [1–3]. Ischemic stroke is the most common (83%) type of stroke, and up to 67% of cases result from two main causes, namely, thrombosis and embolism [3,4]. According to the Helsingborg Declaration on European stroke strategies (2006), the priority area for research and development is, among others, the development of the new methods of ischemic stroke treatment. For these purposes, the mechanisms of formation of infarction core and peri-infarction area, including the immune response, need to be studied, because acute ischemia promotes the local and systemic inflammatory reaction and autoreactive immune response [5–8].

Research on the contribution of the immune system to pathogenesis of cerebrovascular disease was initiated by I.V. Gannushkina in the middle of the 20th century [9]. The consequent research on the reduction of the ischemic brain injury through the target regulation of the immune response is also promising [7,10,11].

Blood–brain barrier and immunological privilege of the central nervous system

The immunological privilege of the central nervous system (CNS) implies the isolation of the CNS from the immune system by the blood–brain barrier (BBB) [12]. The brain

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antigens are usually isolated from the immune system. Thus, the autoimmune response to these antigens promotes extensive damage of the brain cells. Patients with stroke have increased levels of circulating antibodies to neurofilaments and components of N-methyl-d-aspartate (NMDA) [13].

The BBB provides structural and immune isolation of the CNS. BBB also consists of three main components, namely, endothelium of microvessels of the brain, pericytes, and processes of astrocytes. The endothelial cells in the brain microcirculatory vessels have specific morphological and functional characteristics (deep interendothelial connections, the absence of pores and fenestrae between endotheliocytes, and solid basal membrane), thereby providing the barrier function and the function of transporting substances through the BBB. The strong interendothelial contacts of intact BBB limit the diffusion of the substances to more than 10–15 nm in diameter into the brain. The BBB structure is preserved in most parts of the brain, except for the hypothalamic-pituitary region, in which the basal membrane has pericapillary spaces; the barrier is abundantly fenestrated [14,15]. Although self-tolerance is facilitated by relative isolation and sequestration of brain antigens, the whole concept of immunologically privileged antigens "behind barriers" should not be overvalued because "no hiding place exists" completely excluding immune influences in the body. All locations are principally accessible for local and/or systemic immune effectors. Studies in the last decades showed that the real amount of cloistered autoantigens is substantially limited, and their isolation is not absolute. Thus, the contribution of the BBB alteration into the pathogenesis of autoimmune disorders has been overestimated. The alteration of blood–tissue barriers and the expression of cell adhesion molecules on the endothelium promote the migration of immune effectors into altered areas and enhance the alteration of the tissues (Fig. 1). According to Dembič [16], the increase of autoreactivity depends not only on barrier violation but also on the presence of tissue disintegration signal (or lack of integrity signals), thereby altering the behavior of antigen-presenting cells. Probably, all autoantigens are prone to immunological surveillance. Thus, the disclosure contribution in autoimmunity response may be not so prominent. The following facts prove this statement (and not recently!).

Blood–brain barrier alteration and immune response

In the absence of the immune response, sensitive immunodiagnostic procedures (such as ELISA and RIA) revealed impactful amounts of autoantigens, which were formerly regarded as covered, for example, myelin basic protein. This finding does not necessarily provoke encephalomyelitis [17]. Notably, BBB permeability for macromolecules is restricted predominantly for the blood to CNS direction, and to a lesser extent, for the CNS to blood [18]. To date, BBB is not considered the border between the immune system and CNS. The local immune subsystems are found within and behind the BBB and consist of local antigen-presenting cells (astrocytes) and effectors (intrathecal lymphocytes) [19]. In the previous century, Pio del Rio-Hortega insisted on the macrophageal origin of microglial cells [20], which is proven today. Microglial cells express the main histocompatibility complex (MHC) I and also MHC II antigens in cytokine or viral stimulation. Microglial cells produce cytokines and

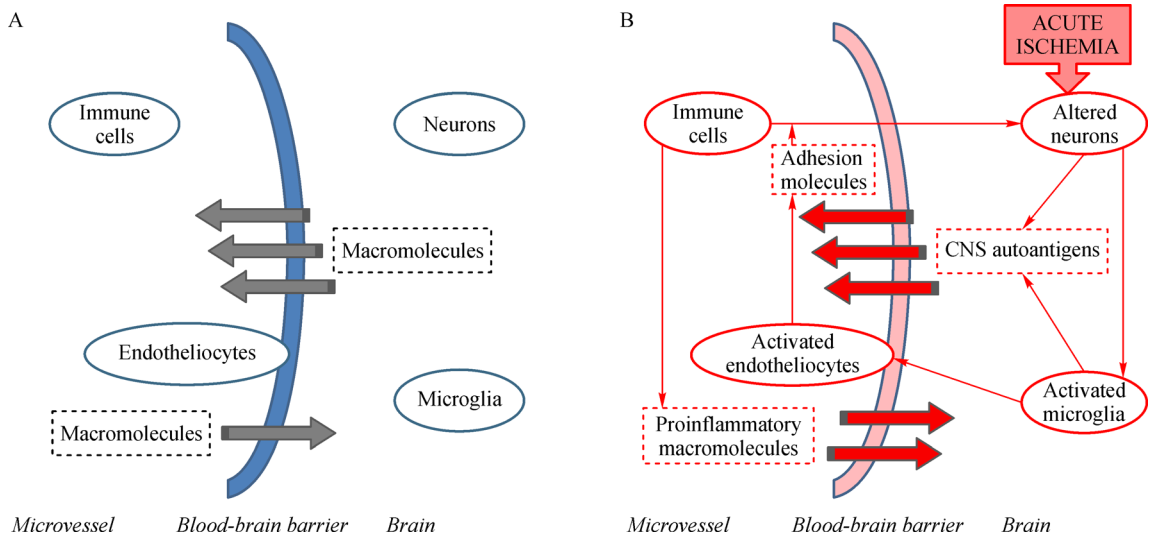

Fig. 1 Cell interaction under intact (A) and altered (B) blood–brain barrier.

can present CNS autoantigens to local effectors (intrathecal lymphocytes). Remarkably, the activation of BBB endotheliocytes by microglial cells promotes the expression of cell adhesion molecules and increases the BBB permeability for lymphocytes [21]. The described local immune mechanisms in the BBB area usually have low activity, but its enhancement can lead to the autoimmune alteration of the CNS. This condition can be clinically relevant, for example, in multiple sclerosis. Immune and phagocytic behavior of microglial cells is sensitive to many factors, such as thyroid hormones, which are essential for the development and function of the brain [22].

In recent years, these classical data on routine brain–immune interaction have been supported by newly discovered brain lymphatic vessels [23] and description of so-called glymphatic system of the brain and communication between the cerebrospinal and intracerebral interstitial fluids and the key role of astrocyte aquaporins in brain glymphodynamics [24]. Lymph drainage from the brain to cervical lymph nodes has been recently proven [25]. Glymphatic system function is altered and jeopardized both in hemorrhagic and ischemic cerebral circulatory disorders. Remarkably, all these data considerably modified the BBB concept compared with its classical version.

BBB dysfunction is specific for severe neurological diseases, such as multiple sclerosis, brain tumors, and hemorrhagic and ischemic stroke. To date, most researchers focus on the study of the neurons during acute damage to the CNS, whereas relatively less attention is provided to the BBB changes. The brain areas, which were subjected to ischemia and subsequent reperfusion, usually have massive microcirculatory disorders with relevant clinical implications [26]. In acute cerebral ischemia, capillarostasis, diapedesis, and BBB disruption are found both in the affected basin and at a considerable distance from the zone of vascular catastrophe due to hypoxic alteration of cerebral structures [14]. The early damage of the BBB may also be the cause but not the result of brain parenchyma cell alteration [27]. O'Connell *et al.* [28] studied 16 candidate genes that may be predictive for the BBB disruption. *ITGA3* gene encodes the adhesion molecule integrin α-3. The overexpression of *AKAP7* gene, which is co-expressed with *ITGA3*, showed the highest prognostic value as a biomarker for BBB alteration after the stroke.

Blood–brain barrier alteration in stroke

Within hours after a stroke, the microvacuoles, eosinophilic cytoplasm, pyknotic nuclei in the neurons, and the first signs of the BBB alteration can be found. These conditions can be divided into three stages. In stage I, the leukocytes begin to penetrate into the damaged area. In stage II, macrophages come through the BBB, and the astrocyte activity remains, and in stage III, a pseudocyst is formed [7]. The damage to the BBB after the stroke onset also has two phases. The first starts within a few hours, and the second begins in 24–48 h after the stroke onset. Matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, are involved in both early and late phases of the BBB damage, but early damage is largely due to MMP-2 activity. Accordingly, an MMP-9 increase, which is considered one of the main factors of BBB disintegration in ischemic stroke, begins in 4 h after the stroke onset and lasts up to 4 days. At this time, the degradation of the dense connective proteins (occludin, claudine-5, and adhesion molecules) starts, naturally constituting the actin–myosin skeleton and are distributed in the form of short filaments and diffuse monomers between the endothelial cells. However, in ischemia, the actin filaments polarize into linear stress fibers, leading to complete BBB destruction and subsequent brain swelling [36].

BBB disruption in ischemic stroke contributes to the tissue disintegration and leakage of brain autoantigens, including the myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein (MOG). The leakage of brain autoantigens is followed by the activation of the immune system and migration of immunocytes to the CNS, promoting the local inflammation. MOG-reactive splenocytes secrete neurotoxic Th1-cytokines, tumor necrosis factor-α (TNF-α), and interferon-γ and exacerbate brain damage in ischemic stroke. The MOG-reactive splenocytes can promote neuronal death or injury directly or indirectly through the augmentation of the BBB permeability and enhancing of transendothelial transport and infiltration of immune cells into the brain [12].

Many authors believe that immune cell activation promotes the production of antibodies to the myelin basic protein. The growth of the serum levels of antibodies to myelin basic protein at the end of acute period of ischemic stroke correlates with the severity of the post-stroke period. By contrast, the patients with good clinical outcome have the decreased level of the organ-specific antibodies at the end of the acute period of stroke [29]. However, whether several active autoimmune cells responding to myelin basic protein contributing to worse recovery of neurological functions or an inability to recover the lost function provokes an autoimmune response to increase neuroplasticity during continuous recovery remains to be elucidated [30]. Recently, Jin *et al.* [31] have demonstrated that brain ischemia induces T cell responses, which are specific to the neuroantigens and enhance brain injury. Using a mouse strain that harbors a transgenic T cell receptor to MOG, the anatomic location and involvement of antigen-presenting cells in the development of T cell reactivity after brain ischemia were determined [31].

Aseptic inflammation that occurs in the CNS in ischemic stroke alters the brain tissue and exposes CNS antigens. The experimental study showed the upregulation of autoreactive $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cells at 4 days after the stroke onset. The mice with large infarct volume showed early lymph nodes (but not the spleen) and T- and B-cell autoreactivity for the subunit of the NMDA receptor NR2A. If the volume of the brain infarct was low, consequently, MAP-2 and myelin-derived peptide autoreactivity was elevated. Moreover, these autoimmune reactions were present during 10 days after the stroke onset. Thus, ischemic stroke induces secondary autoimmune response to neuronal antigens and long-term inflammation [30]. Wang *et al.* [32] also showed the important role of invariant natural killer T cells in brain alteration and brain edema in the model of focal permanent cerebral ischemia. Propagation of $CD8^+$ T cell-mediated and natural killer-cell-mediated immunity in acute brain ischemia can be promoted by astrocytic interleukin (IL)-15 [33]. Future research on T cell activity in acute stroke may be the key for the new strategies for the treatment of the long-term degenerative consequences of stroke [34].

Other evidence proved the expression of the MHC antigens and cell adhesion molecules by the BBB endothelial cells. The loss of the BBB integrity leads to the endothelial and glial cell activation, followed by inflammatory process. During inflammation, the complex interaction of the cytokines and adhesion molecules provokes attraction and invasion of leukocytes, increasing the damage to the brain tissue [12,14,35].

Notably, the immune response is related to blood clotting and fibrinolysis. This dependence is largely due to the presence of active compounds possessing the properties of procoagulants, anticoagulants, and activators of fibrinolysis in T- and B-cells. Proinflammatory cytokines affecting the endothelial cells and macrophages increase the production and secretion of procoagulants but decrease the formation of anticoagulants. The acute focal ischemia of the brain turns the monocytes (macrophages) into a hyperactive state, thereby increasing the IL-1α synthesis. The degree and duration of the increase of IL-1α level are of prognostic importance for the course and outcome of stroke [29].

MMP-9 is mainly secreted by neutrophils, which infiltrate BBB, and endothelium of microvessels [27]. Polymorphonuclear granulocytes are the first subset of leukocytes that appear in ischemic brain tissue. Thus, they were previously suspected to alter neurons. However, recently, during the acute phase of ischemic damage, this type of cells is not found in the brain parenchyma. At this time, they remain trapped within the neurovascular units and leptomeningeal spaces. Therefore, the neutrophil-mediated neuronal death may not require the presence of neutrophils near the target brain cells. The observation of the absence of active migration of polymorphonuclear neutrophils through the BBB during the early stage of reperfusion is not only limited to the experimental studies but also is confirmed by postmortem studies in patients with stroke [7]. Chronic cerebral ischemia is accompanied by the increase of granular leukocytes with azurophilic granules, containing elastase, myeloperoxidase, cathepsin G, and acid hydrolases. The movement of inflammatory cells into the perivascular space is promoted by the disruption of the connective proteins in the BBB. Involvement of perivascular areas activates resident macrophages and mast cells, thereby promoting the release of proinflammatory cytokines, vasoactive mediators, and the infiltration of leukocytes [37]. The experimental stroke models show that circulating leukocytes penetrate the brain by diapedesis and accumulate in the injury area within a few hours after stroke. $CD4^+$ T cells are activated when the peptide antigens are present on the surface of MHC II cells, including dendritic cells, macrophages, and B cells. $CD8^+$ T cells react to antigenic peptides of the MHC I, which are present on most types of cells [30].

The cytokines promote the leukocyte infiltration of the ischemic core, activation of microglial cells, inducible form of cyclooxygenase-2, and nitric oxide synthase in ischemic stroke [38]. Brain alteration elevates the serum levels of heat shock proteins-70, i.e., endogenous ligands for the toll-like receptor-4 (TLR4), which is the key receptor of innate immunity. Toll-like receptors (TLRs) initiate the synthesis of pro-inflammatory cytokines by activating the nuclear factor and are capable of triggering the immune response in both infectious and non-infectious diseases [39]. By the structure, TLRs belong to the IL-1 receptor family. IL-1 is a mediator of microglial neuroimmune functions and is secreted locally in response to cerebral ischemia.

All TLRs are integral transmembrane proteins with the same structure. At rest, unactivated TLRs are present on the cell membrane in the monomeric state. Most receptors form homodimers, whereas TLR2 forms heterodimers with TLR1 or TLR6 depending on the ligand. When activated by exogenous or endogenous ligands, the receptors dimerize and lead to subsequent signal transmission inside the cell and activation of cytokine synthesis. TLR2 and TLR4 are involved in ischemia–reperfusion injury. TLR4 mediates immune response to systemic bacterial infection and brain alteration. TLR2 expression rapidly increases after the stroke onset long before the microglial activation. TLR4 activation is accompanied by the expression of cytokines and other signal peptides, including MMP-9 and TNF-α. In ischemic stroke, the effector receptors of TNF-α (type 1 TNF-receptor and Fas-receptor) regulate apoptosis in neurons and non-neural cells involving caspase-dependent and caspase-independent pathways [40–42]. Thus, inflammation is regarded as the key mechanism of

ischemia–reperfusion injury, and the anti-inflammatory treatment is promising in acute stroke [43–46]. In particular, lymphocytes are regarded as the target for the neuroprotection in acute ischemia [47]. Li *et al.* [48] showed that C-C chemokine receptor type 5 is a critical molecule for T cell-mediated BBB protection and is a potential target to optimize acute ischemic stroke therapy. Nalamolu *et al.* [49] showed that attenuation of TLR2- and TLR4-mediated inflammation after the stroke prevents ischemic brain damage. At the same time, some TLRs exert a neuroprotective effect after ischemic stroke [50].

The infarct core becomes a source of MMPs, various proteins, and molecules that initiate an autoimmune response accompanied by the production of immunoglobulins with abnormal temperature solubility and immune complexes with cryoproperties. The cerebrospinal fluid level of nerve growth factor autoantibodies in patients with ischemic stroke is 180%–190% as compared with the reference values. The decrease of the nerve growth factor level diminishes neurotrophic support. As for the S100-β protein, on the 1st day after the stroke onset, the concentration of S100-β protein antibodies is also increased by 25%–50% [29]. Notably, all these processes are not a sequence of events but a complex network of intertwining cascades [6].

Altered brain cells can promote the activation of immune system. Numerous intracellular components, which vacate destroyed cells, can activate TLRs on various cells, followed by upregulation of proinflammatory molecules and presentation of antigens by dendritic cells. Escalation of cell death reduces the anti-inflammatory effect of neurons and neurotransmitters on the microglia [37]. Some researchers suggest that autoimmune reactions promote chronic inflammation and can be a risk factor of dementia. They are also associated with the phenomenon of "anamnestic recall," which results from autoreactive T cell activation and comprises the temporary reoccurrence of stroke symptoms that have been regressed in this patient usually in systemic infection [13].

Blood–brain barrier alteration: the light side

The protective role of autoimmunity was previously shown in experimental CNS trauma in rats [51] and can be boosted by immunizing with neural constituents or neural-derived peptides, promoting motor recovery in experimental moderate spinal cord contusion or incomplete spinal cord transection [52]. Copolymer-1, also known as glatiramer acetate, stimulates protective autoimmunity and has been approved in the treatment of multiple sclerosis. Cruz *et al.* demonstrated enhancing of neuroprotection and neurogenesis by copolymer-1 in acute cerebral ischemia models [53,54].

Summary and perspectives

Most researchers confirm the relationship between the severity of immunobiochemical changes and clinical outcome of ischemic stroke. Ischemic stroke is accompanied by aseptic inflammation that exposes co-stimulatory molecules of the immune system and neuronal antigens. The increase of autoreactivity in ischemic stroke depends predominantly not on BBB violation but on the presence of tissue disintegration signal, activation of innate immunity, and probably alteration of glymphodynamics.

Despite the large number of studies on immune-inflammatory status in patients with ischemic stroke, many questions remain. First is the role of stroke-induced immune activation in neuroreparation. A study on immune response and inflammatory reaction in pathogenesis of ischemic stroke and its influence on the clinical outcome is also important for the new approaches to diagnostics and searching for the new molecular therapeutic targets.

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Compliance with ethics guidelines

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