BLOOD-SPINAL CORD BARRIER IN SPINAL CORD INJURY: A SCIENTIFIC REVIEW BASED ON OWN EXPERIMENTAL TRIAL

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Objective. To analyze the mechanisms of the blood-spinal cord barrier permeability violation after spinal cord injury and to assess its impact on the development of secondary injuries, including those in the areas significantly remote from the epicenter of injury.
Material and Methods. The article is an analysis of 45 publications supplemented by our own experimental data. The search for articles was conducted in databases such as PubMed, Scopus and Web of Science on the topic under study. Experimental data were obtained using confocal microscopy and bioluminescence detection on a rat spinal cord contusion injury model.
Results. The problem of barrier disintegration in a region remote from the injury epicenter is considered. It is shown that spinal cord injury significantly increases the permeability of the blood-spinal cord barrier, which promotes enhanced transmigration of immune cells and release of cytotoxic molecules. The results of our own studies on a model of dosed contusion injury in the thoracic spinal cord of a rat show that the permeability of the barrier increases not only in the injury epicenter, but also along the entire length of the organ. This circumstance is especially significant for the lumbar spinal cord, where neural networks that are critical for the maintenance and restoration of motor function are localized.
Conclusion. Potential causes of remote barrier disruption have been discussed, including the possible influence of damage biomarker molecules that travel from the injury epicenter to remote regions of the spinal cord via the bloodstream or cerebrospinal fluid. The promising clinical application of effective experimental approaches to contain barrier disruption and restore the blood-spinal cord barrier and the lack of translational research in this direction are highlighted.
Key Words: blood-spinal cord barrier; spinal cord injury; remote injury.
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Damage to the blood-spinal cord barrier (BSCB) significantly worsens the condition of patients with spinal cord injury. Initial mechanical injury to the BSCB results in disruption of its integrity, causing leakage of blood components into the spinal cord and aggravating inflammatory processes, resulting in immediate non-specific vascular changes and extravasation of blood cells and various molecules such as hydrazides and albumins [1]. Further destruction of the barrier enhances secondary injury by oxidative stress and neuroinflammation, causing additional damage to neural tissue [2]. In the first hours and day after injury, a significant increase in the permeability of the BSCB is associated with revascularization and repair of injured vessels, but new vessels are often characterized by abnormal permeability [2].

In spinal cord injury, pathological shifts are found at a considerable distance from the injury epicenter [3–6], impairing recovery of function. The study of the injury and recovery mechanisms of the BSCB is crucial for the development of effective therapeutic approaches to manage the consequences of spinal cord injury. Numerous experimental studies indicate that maintaining the integrity of the BSCB, including in the spinal cord parts remote from the injury epicenter, moderates the development of neurodegenerative manifestations and neurological deficit. The objective is to analyze the mechanisms of the blood-spinal cord barrier permeability violation after spinal cord injury and to assess its impact on the development of secondary injuries, including those in areas significantly remote from the epicenter of injury.

Material and Methods

The article is a scientific review of 45 articles selected in PubMed, Scopus, and Web of Science databases using the keywords: blood-spinal cord barrier, spinal cord injury, and remote injury, including our own unpublished experimental data. The reasons for the impairment of BSCB are discussed, and the prospects for clinical application of experimental techniques to restore its function are considered.

Results and Discussion

Characterization of the blood-tissue barrier in the CNS

The CNS is separated from the body's internal environment by three barriers: the blood-brain barrier (BBB), the BSCB, and a barrier composed of the choroid plexus and arachnoid mater. These barriers control the entry of nutrients into the brain, the removal of metabolic products from the brain, and limit the transport of potentially adverse substances [7]. The BSCB is a physical barrier between the blood and the spinal cord parenchyma that maintains its homeostasis and prevents the entry of toxins, blood cells, and pathogens into the spinal cord. In structural terms, the barrier is represented by non-fenestrated endothelial cells (endotheliocytes) in the wall of capillaries, arterioles, and venules of the brain microvascular network, the basal membrane, pericytes, and the endfeet of astrocytes [8]. The BSCB permeability violation in spinal cord injury is associated with increased immune cell transmigration and secondary injury. Proinflammatory cytokines from immune cells and reactive glia, by directly acting on components of an already incompetent barrier, increase its damage, leading to a vicious cycle.

Endothelial cells are key structures of the BSCB. The endothelium comprises several components of the barrier [9]; the most prominent of them is the so-called paracellular component represented by the apical junctional complex that combines tight and adherens junctions (Fig. 1).

The transmembrane proteins such as occludin and claudins, the scaffold proteins ZO-1 and ZO-2, and a number of other associated molecules are involved in the formation of tight junctions. Tight junctions are supported by adherens junctions that involve complexes of transmembrane cadherin proteins with intracellular cytoskeletal proteins (actin) and anchoring proteins catenins, vinculins, and α-actinin (Fig. 1). In studies of permeability violation of the BSCB and its integrity in models of spinal cord injury, expression of the tight junction proteins occludin, claudins, and ZO-1 is most commonly determined.

The transcellular component of the barrier is provided by low levels of pinocytosis and transcytosis. The so-called enzymatic component of the metabolism of bioactive molecules such as neurotransmitters and neuropeptides is also involved in barrier function. The transport of water-soluble substances that cannot penetrate cell membranes is performed by numerous transporters of the solute-like carrier family (SLCs) including transporters of excitatory amino acids, such as ABC (ATP-binding cassette) transporters. The main ones in CNS barriers are SLC2A1/GLUT1, SLC7A5/LAT1, SLC16A1/MCT1, SLC1A3/EAAT1, and SLC1A2/EAAT2 [7].

An essential role in the regulation of the barrier function belongs to the capillary pericytes surrounding the endothelial layer from the outside. The dimension of the area covered by pericytes on the capillary surface differs in white and gray matter and ranges in the spinal cord. This parameter varies when pericytes are analyzed using different markers. In the cervical, thoracic, and lumbar white matter, the surface area of the CD13 capillary covered by immunopositive pericytes is 68, 75, and 68%, respectively, and for pericytes expressing platelet-derived growth factor receptor beta (PDGFRβ), 73, 73, and 68%, respectively [10]. Moreover, it was found that the decrease in the number of pericytes in the BSCB was more pronounced in the spinal cord regions with the greatest presence of perikaryons. Regional variability of pericyte in number and microvessel coverage amount correlates with molecular weight, fluorescent tracer permeability, and expression of occludin and ZO-1 tight junction proteins in the endothelium.

Mutations of the gene encoding PDGFRβ (mouse PDGFRβ (F7/F7)) are expressed by a reduced pericyte population in spinal cord capillaries, resulting in impaired BSCB with abnormal serum protein transport and motoneuron loss due to accumulation of cytotoxic thrombin and fibrin. Barrier disruption in mice deficient in pericytes is combined with a subsequent decrease in occludin and ZO-1 protein expression. These data propose that pericytes maintain the structure and function of the BSCB [10].

During spinal cord injury, disruption of the relationship between endothelial cells and pericytes results in the detachment of pericytes from the capillary surface and reprograms their differentiation into cells expressing the phenotype of fibroblasts (pericyte-fibroblasts), which is mediated by activation of the intracellular PDGF-BB/PDGFRβ signaling pathway and eventually intensifies fibrotic scar formation [11]. Blocking the PDGFBB/PDGFRβ signaling pathway with imatinib didn't affect the amount of capillary coverage by pericytes but inhibited fibrotic scar formation, relieved neuroinflammation, and promoted the recovery of both BSCB and spinal cord function as a whole [11].

One more specialized structure functionally associated with the endothelium of the barrier is the endfeet of perivascular glial astrocytes, which in the BBB cover more than 90% of capillaries. The current understanding indicates that they are involved in the maintenance of barrier structure and function, in providing directional transport, permeability, and tissue revascularization [2, 12, 13]. These structures express the water channel protein, also called aquaporin-4 (AQP4), and Kir4.1 potassium channels that regulate resting potassium ion flux and fluid volume in the spinal cord [12, 14].

It was discovered that both the aforementioned cellular elements and the surrounding extracellular matrix, represented by the basal membrane, contribute to the arrangement and function of the barrier [12]. All BSCB cell types are involved in the formation and support of the basal membrane. The vascular basal membranes contain perlecan protein, which has neuroprotective effects, probably by maintaining the integrity of the microvessel wall. Perlecan is specifically expressed in the basal membranes of the BSCB and is subject to degradation or remodeling during spinal cord injury. Genome editing technology in a spinal cord injury experiment increased the expression of perlecan, significantly

reduced the permeability of the BSCB and neuroinflammatory response, and remarkably improved motor function [15].

Cells of three types (endothelium, pericytes, and perivascular glia) together with neurons form the neurovascular unit. The functional specificity of CNS parts depends on regional differences in the structure and function of neurovascular units. These differences are evident both between anatomical areas and also between the endothelium of capillaries, arterioles and venules. Though capillaries form the surface for transport to the CNS that is dominant in the microcirculatory network [16], the proposed barrier role of the endothelium of arterioles and venules may also be of significance but is poorly studied.

A number of key proteins regulate the function of BSCB. Among them, matrix metalloproteinases (MMP), tumor necrosis factor α (TNFα), and angiopoietins are of particular relevance. Among the major MMP family members, mainly MMP-3, -9, and -12 mediate a disruption of the BSCB [17]. Tissue infiltration by monocytes/macrophages is not the only consequence of impaired BSCB integrity. Transmigrating immune cells from the blood to the spinal cord tissue themselves act as a source of MMP, worsening the impaired integrity of the BSCB.

Besides MMP, BSCB damaging factor is the action of proinflammatory cytokines that are released by monocytes/macrophages during the first hours after spinal cord injury [17]. Among a large number of proinflammatory cytokines, TNF is the most studied in this regard, increasing barrier permeability and causes a decrease in the expression of occludin and ZO-1 tight junction proteins mediated by activation of the intracellular signaling pathway of nuclear factor kappa B (NF-κB) [17].

Macrophages/microglia produce and secrete molecules that have a damaging effect on the structure of the BSCB, resulting in violation of its permeability. According to Montague-Cardoso et al. [17], the infiltration of the spinal cord by immune cells and disintegration of the BSCB are almost overlapping but independent events, i.e., transmigration of immune cells does not always imply the destruction of the barrier.

While proinflammatory cytokines cause disintegration of the BSCB, some other proteins have the opposite effect, supporting its structure and function. An illustration of such proteins are angiopoietins that have a cytoprotective effect on endothelial cells and stimulate the formation and maturation of microvessels. Decreased expression of angiopoietin results in impaired BSCB. In spinal cord injury, maintenance of angiopoietin-1 level by its intravenous administration recovers vascular integrity and decreases barrier permeability [18].

The BSCB is comprised of the same structural components as the BBB but significantly different in its permeability to various molecules. For example, the BSCB is more permeable to albumin, interferons, TNFα, sucrose, and small molecules such as mannitol and inulin. It is supposed that the reasons for these differences may be associated with lower expression levels of tight junction proteins between endothelial cells in the BSCB. The BBB and BSCB are different, first of all, by the level of expression of proteins of the apical connective complex of endothelial cells, as well as transporter proteins and receptors [19]. Regional differences in the expression of transporters, receptors, and intercellular junction proteins in the CNS barriers provide an estimate of the efficiency of entry of various endogenous and therapeutic molecules into the CNS. One more difference in barrier structure in the spinal cord and brain relates to pericytes, which in the anterior horns of the gray matter of the spinal cord cover a noticeably smaller area of capillaries [10].

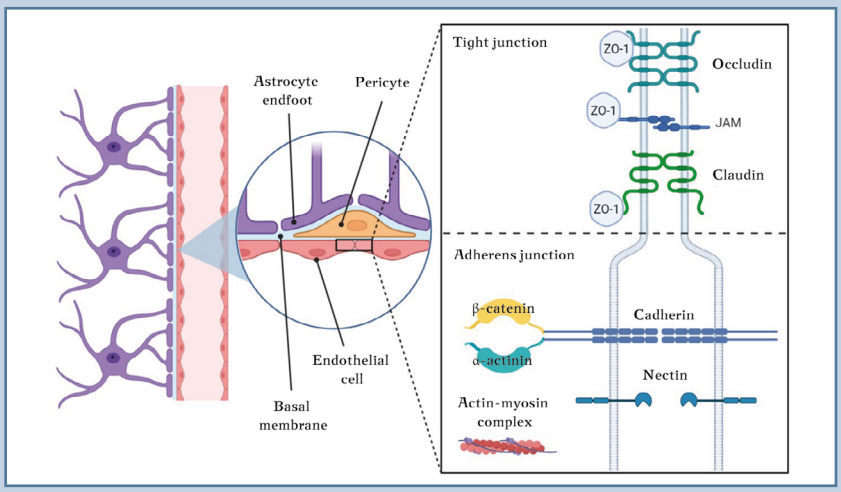

Fig. 1
The apical junctional complex of endothelial cells of the blood-spinal cord barrier includes tight and adherens junctions. The tight junction is formed by transmembrane proteins claudins and occludin, the cytoplasmic domains of which are associated with the ZO-1 protein and other associated proteins. Adhesion junctions include transmembrane proteins cadherins, which interact with catenins in the cytoplasm. Evaluation of the expression level of occludin, claudins and ZO-1 serves as an indicator of the barrier's viability (figure by the authors)

The BSCB in spinal cord injury

Mechanical abnormality in spinal cord injury, combined with shear stress caused by vascular compression or dilation, disrupts the structure of neurovascular units and the BSCB [11, 20]. Increased permeability of the BSCB in spinal cord injury (Fig. 2) results in tis-

sue oedema, neuroinflammation, and impaired function.

The disruption of the BSCB in spinal cord injury aggravates the primary injury, resulting in the development of a secondary injury. After injury, the structure of the BSCB is disrupted, and the permeability of the barrier becomes higher, which directly results in the release of blood components into the tissue [21, 22]. For this reason, it is suggested that correction of BSCB disruption may reduce neuroinflammation and improve structural and functional recovery in spinal cord injury.

In a model of spinal cord injury, a meta-analysis of 28 studies of the status of the BSCB as indicated by a permeability index determined using the fluorescent Evans blue dye suggests a positive association for recovery of function between a decrease in this index and an increase in the expression of the tight junction proteins occludin, claudin-5, and ZO-1, as well as the adhesion junction proteins P120 and β-catenin [22].

The disruption of the barrier is evident as early as 15 min after spinal cord injury [23] and rapidly increases in the first hours [22]. Within 30 minutes of injury, white blood cells begin to cross the BSCB, contributing aggressively to the formation of ruptures and leaks. There are pathological hemodynamic abnormalities in the low-tension circulation that cause disintegration of the barrier and increased leakage [23].

Vascular permeability in response to injury is enhanced by vasoactive substances such as histamine, NO, reactive oxygen species, and proinflammatory cytokines TNFα and interleukin IL-1β [24]. Subsequently, despite the activation of angiogenesis, which continues for 3–7 days after injury, the abnormal permeability of the BSCB persists [2]. Hyperpermeability of the BSCB intensifies the destruction of blood vessels in the injury epicenter. At the same time, lymphocytes, neutrophils, and monocytes infiltrate into the focus of injury, resulting in a neuroinflammatory response, and increased calcium, excitatory amino acids, free radicals, and inflammatory mediators increase secondary injury [25].

Understanding the mechanisms of chronic pain, in the occurrence of which impaired BSCB permeability and neuroimmune communication are of decisive importance, is essential for the identification of new potential therapeutic targets in spinal cord injury. These factors have recently been the focus of preclinical studies of chronic pain [17, 26]. Dorsal horn neurons in the spinal cord not only interact with resident immune cells such as microglia but may also participate in bidirectional cross-coupling with immune cells (monocytes/macrophages) that infiltrate the spinal cord under pathological conditions. Infiltration of spinal cord tissue by immune cells may be partially regulated by changes in the permeability of the BSCB. Current literature on the subject discusses *pro et contra* the importance of barrier disruption factor and associated shifts in neuroimmune responses in chronic pain [17].

The BSCB in an area remote from the traumatic injury epicenter

Focal lesions in the CNS trigger metabolic and structural changes in areas remote from the site of primary injury (Fig. 3).

In a strategy to restore motor function, these pathological shifts are particularly relevant to consider in the region of the lumbar spine remote from the injury epicenter. It contains neural circuitry critical for the maintenance and post-injury recovery of locomotion. Remote injury is a multifactorial phenomenon in which components such as neuroinflammation, oxidative damage, and cell death are activated at specific times (Fig. 4). The interactions between these components have various effects on neural cell survival and functional outcomes.

Secondary changes in the remote area are characterized by induction of expression of proinflammatory cytokines such as TNFα and IL-1β factor and neuroinflammatory responses that are activated by macroglia and astrocytes [3, 4, 27]. Almost all the main cell types are implicated in the processes of neuroinflammation and neurodegeneration: neurons, astrocytes, microglia/macrophages, and even the extracellular matrix.

Secondary neural cell damage in remote parts of the CNS is associated with antero- and retrograde degeneration. Anterograde degeneration is characterized by a later expression of neuronal cytokines. In retrograde degeneration, the earlier expression of cytokines is more associated with the response of astrocytes [27]. Pharmacological correction directed at reducing TNFα expression restrains secondary neuronal damage. These data suggest that inflammatory responses in remote areas are involved in the pathogenesis of secondary neuronal injury.

In focal traumatic injury in the CNS, signs of secondary injury, such as inflammation, oxidative stress, and excitotoxicity, aggravate the severity and consequences of the primary injury and spread not only to adjacent areas but are also detected at a considerable distance from the injury epicenter [3–6, 27, 28]. The cellular and especially molecular mechanisms of pathological shifts in the region remote from the epicenter are poorly studied, although a general idea of the importance of this component in the general pathological picture of spinal cord injury has already been formed.

Pathological shifts in the remote area can result from a variety of factors. If in spinal cord injury the primary injury epicenter is anatomically associated with a remote region, the most likely reason for pathological shifts in it is the degeneration of axons of the ascending and descending tracts. In this case, synaptic contacts in the remote region partially collapse or are rearranged, and patterns of functional connections are disrupted or blocked. These shifts are accompanied by known responses from astrocytes and microglia/macrophages.

Another suspected reason for the cellular response and changes in the structural and molecular arrangement of the matrix in the remote region may be the influence of cytotoxic molecules transported by the bloodstream or through the cerebrospinal fluid from the primary site. They can be alarmins and endogenous molecular damage signals (Damage-Associated Molecular Pattern, DAMP) such as High mobility group

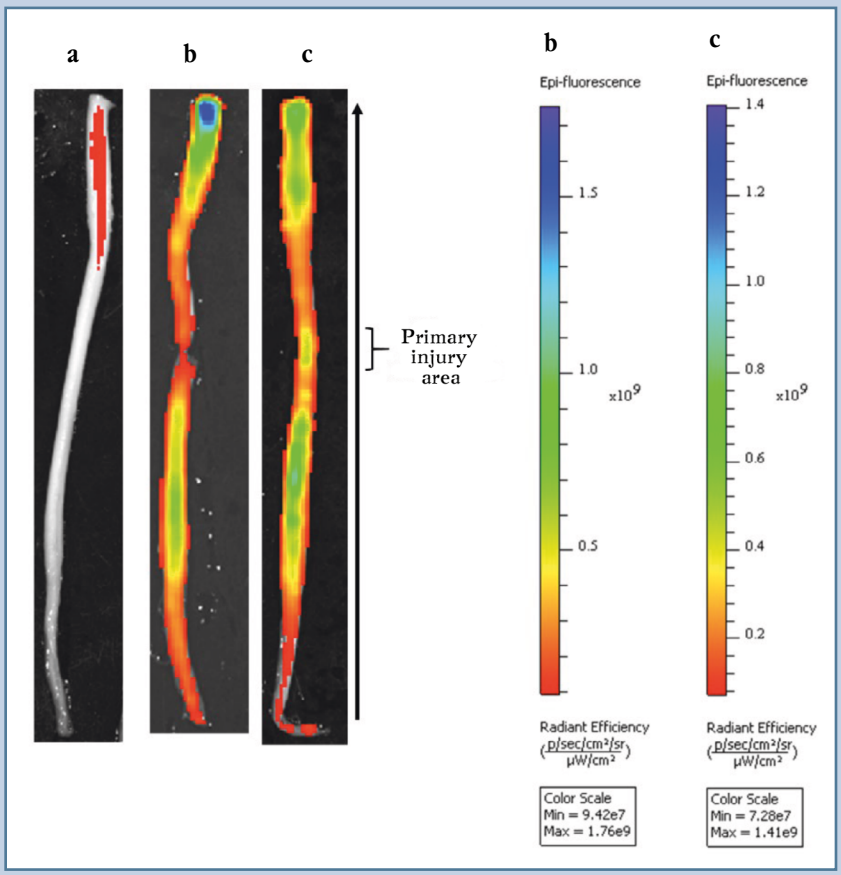

Fig. 2
Increased permeability of the blood-spinal cord barrier on rats with dosed contusion injury of the spinal cord at the T8 level. The presence of the fluorescent Evans blue dye, introduced into the blood 30 minutes before euthanasia, was detected by the bioluminescence method (IVIS Spectrum bioluminescence imaging system, USA) along the entire length of the spinal cord, indicating an increase in barrier permeability not only at the epicenter of injury, but also in remote areas of the spinal cord, located both caudally and rostrally: a – intact group; b and c – 3 and 7 days after injury, respectively (data from own experiment, protocol No. 2 dated 05.05.2015 of the local ethics committee of the Kazan (Volga Region) Federal University)

box-1 (HMGB1), heat shock proteins (HSPs), S100 proteins, DNA, etc. [29]. These molecules, regarded as biomarkers of injury, enter the blood and cerebrospinal fluid from the area of primary injury and reach a remote region in the spinal cord.

Most studied is the effect on the BSCB of pathological molecules of HMGB1, a highly conserved non-histone protein that interacts with DNA. HMGB1 is passively released from degenerating neurons or secreted by microglia and astrocytes during spinal cord injury. It takes on enormous importance in the immune response, exhibiting cytokine properties: it boosts autophagy, regulates mitochondrial function, and inhibits apoptosis [22]. During spinal cord injury, inhibition of HMGB1 by antibodies, ethyl pyruvate, and the plant inhibitors such as shikonin or glycyrrhizin restrains the disruption of the BSCB, resulting in reduced oedema and inflammatory response [22].

The use of plant-derived molecules like carotenoids in spinal cord injury decreases tissue oedema due to the lower expression of AQP4 and MMP-9, the severity of the neuroinflammatory response, and improves motor function, which correlates with the maintenance of BSCB integrity on the background of HMGB1 reduction. These data confirm the universal role of molecular biomarkers of injury in the direct negative impact on BSCB structures. It is logical to assume that in regions remote from the primary spinal cord epicenter, the detected pathological shifts may be the consequence of the action of molecules-biomarkers of injury.

It would appear that other cytotoxic molecules entering the blood or cerebrospinal fluid from the area of primary injury may also have a negative and, perhaps, more pronounced effect on the condition of the BSCB in the area of the spinal cord remote from the injury epicenter, aggravating the pathological picture and depressing functions. A conspicuous example of this can be exemplified by the data of Sharma et al. [30], which demonstrated an increase in β-amyloid peptide (AβP), phosphorylated form of tau protein (p-tau), and TNFα after spinal cord injury in the thoracic spinal cord in the adjacent segments as well as in different parts of the brain, that was followed by microglia activation, oedema, and cell damage and resulted in disruption of both the BSCB and BBB.

Potential clinical applications of forward-thinking experimental approaches for the maintenance and restoration of the BSCB

It is known that restoration of the integrity of the BSCB in spinal cord injury is one of the core factors in the containment of neurodegeneration and functional deficit. Nevertheless, despite considerable advances in basic preclinical research in understanding the cellular and molecular mechanisms of BSCB impairment in spinal cord injury, clinical guidelines based on these BSCB-specific advances are practically unavailable. Prominent non-specific ways of maintaining the BSCB, such as anti-inflammatory, anti-apoptotic, and

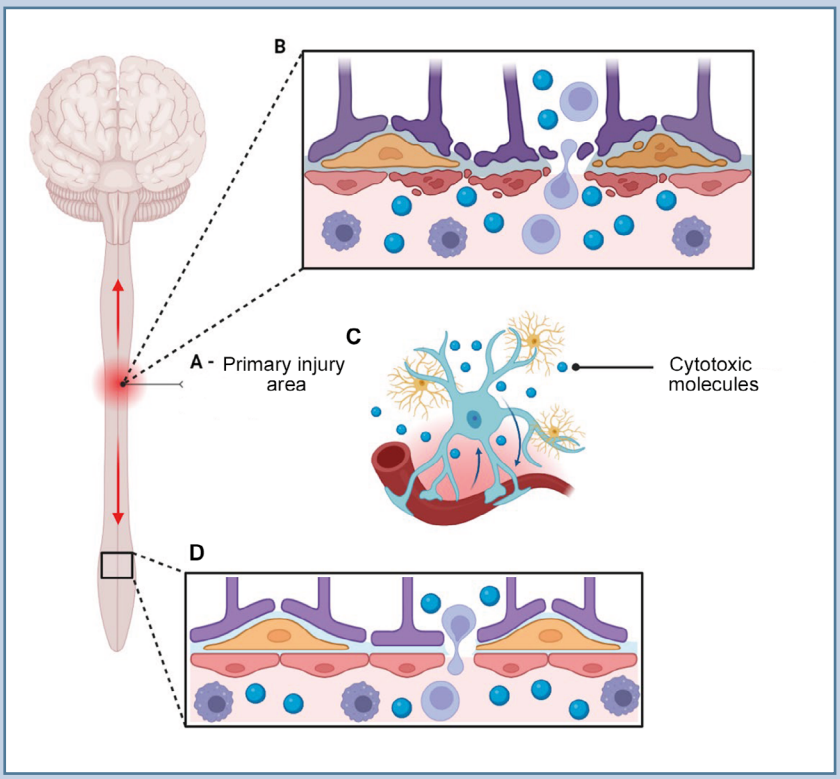

Fig. 3
Involvement of the blood-spinal cord barrier in remote damage in spinal cord injury. There is the barrier permeability violation at the injury epicenter (*A*), as the result of cell death, tissue destruction, and development of neuroinflammation. From the area of destruction, proinflammatory cytokines, DAMP, and damage markers enter the blood and cerebrospinal fluid (*B*) and reach remote areas in the CNS (red arrows; *D*). These cytotoxic molecules disrupt the barrier permeability that is most pronounced at the injury epicenter, but also manifests itself in remote areas (*C*). This leads to transmigration of immune cells into the spinal cord tissue along its entire length and the development of neuroinflammation (figure by the authors)

antioxidant therapy, prove to be ineffective in restoring the integrity of the BSCB, although they generally retain their value by positively influencing other points of application in the spinal cord structures. Whatever it may seem paradoxical, clinical trials of the latest experimentally based approaches have not yet been performed. Consequently, pathologically and physiologically based specific ways and guidelines to restrain BSCB abnormalities in spinal cord injury are currently not available in the clinic. Hopefully, given the experimentally proven efficacy of new therapeutic approaches to overcome the effects of spinal cord injury, they will be integrated into clinical trials.

Most relevant to practical medicine today are the new effective ways to restore the BSCB identified by experiments in models of spinal cord injury and including data on inhibition of MMP, heme oxygenase-1, angiopoietins, bradykinin, nitric oxide, and endothelin. For instance, the use of protocatechuic acid, folic acid, and flufenamic acid, as well as fluoxetine, the selective serotonin reuptake inhibitor, results in reduced MMP expression and restoration of the BSCB, decreasing the content of proinflammatory cytokines and infiltration by neutrophils and monocytes/macrophages in the injury site [31–35]. Some interesting data have been obtained with an enzyme in the intracellular protein degradation cascade, UCHL1 deubiquitinase, maintaining angiogenesis and restoration of barrier function by stabilizing the Sox17 transcription factor [36].

The use of plasmids or viral vectors encoding genes for neurotrophic and angiogenic factors to stimulate neuroregeneration in spinal cord injury is not novel and has been widely used in recent decades. It was found that epidermal growth factor and fibroblast growth factor prevent disintegration of the BSCB, improving functional outcomes in spinal cord injury [37–39]. The source of neurotrophic factors and molecules stimulating neuroregeneration are stem and progenitor cells, the transplantation of which is being actively implemented in clinical practice in spinal cord injury. Conclusive evidence has been obtained for stabilization of the BSCB associated with the indirect/paracrine influence (via secreted factors) of transplanted mesenchymal stem cells [40].

Nanoparticles of synthetic and biological (stem cell vesicles) origin provide the restoration of tight junctions, preventing the destruction of BSCBs, and also have great potential as carriers of biologically active molecules with neuroprotective properties [41–45]. Recently, a meta-analysis of experimental treatment options aimed at reducing destruction of the BSCB in the early stage of spinal cord injury found that exosomes obtained from mesenchymal stem cells were the most efficient therapeutic agent to repair the BSCB through regulation of MMP synthesis, the Akt signaling pathway, and the endoplasmic reticulum stress [22]. Given the active release of this treatment option to the stage of clinical trials for a number of neurological diseases, it is worth expecting the implementation of this technological platform for spinal cord injury.

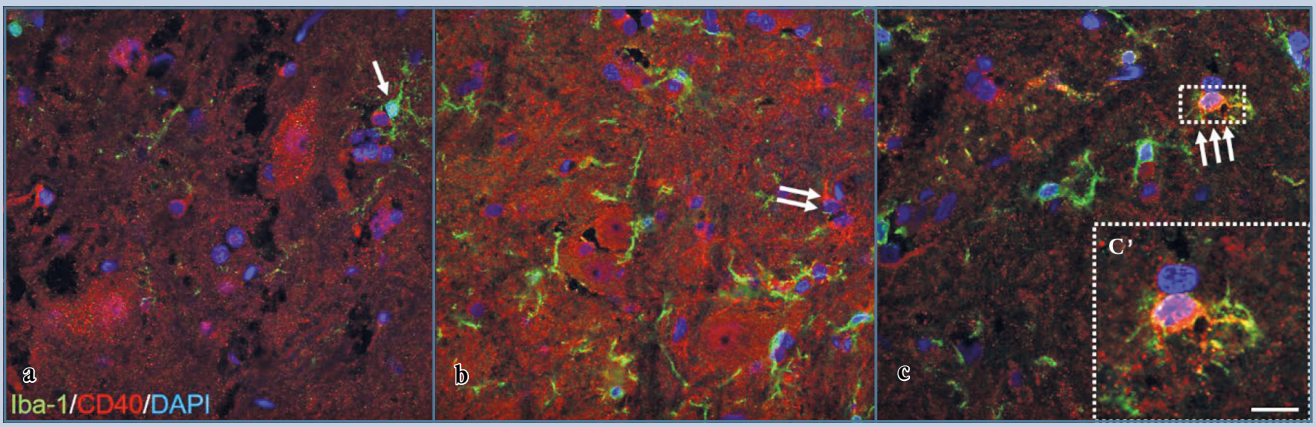

Fig. 4
Immunohistochemical analysis of the ventral horns of the intact **(a)** and injured rat lumbar spinal cord on day 7 **(b)** and 60 **(c)** after injury; **c'** – a magnified view of the dotted area in **c**. Iba-1$^+$ cells (green) are indicated by a single arrow, CD40$^+$ cells (red) – by a double arrow, and Iba1$^+$/CD40$^+$ cells – by a triple arrow. All images were obtained using identical settings of a confocal laser scanning microscope (LSM 700, Carl Zeiss, Germany). Nuclei are stained with DAPI (4',6-diamidino-2-phenylindole, blue). Magnification: 20 μm **(c)**; 10 μm **(c')**. An increase in the number of Iba-1/CD40 immunopositive microglial/macrophage cells in the lumbar spinal cord on day 60 after injury indicates the development of neuroinflammation in a spinal cord region remote from the epicenter of injury (data from own experimental studies)

Conclusion

The BSCB provides a specific functionally prominent structure, the disruption of which is crucial in spinal cord injury. At its early stage, disintegration of tight junctions is the major manifestation of BSCB disruption that is already aggravated in the acute stage by hemodynamic changes and white blood cell transmigration. Massive disruption of the BSCB and its propagation from the area of the primary lesion in rostral and caudal directions is manifested at a later stage simultaneously with the development of secondary injury, which is reinforced by barrier damage. The time span between the early stage and the stage of secondary injury indicates a therapeutic window for clinical interventions to restrain focal BSCB permeability violations and their propagation along the spinal cord length. During the late period of spinal cord injury, there may be an over-reduction of BSCB permeability, which retards the elimination of oedema and inhibits the transport of metabolites essential for reparative processes.

During spinal cord injury, disruption of BSCB permeability and transmigration of immune cells is the reason for neuroinflammation in spinal cord segments remote from the injury epicenter that considerably aggravates the clinical outcome. The complexity of cellular and molecular mechanisms, as well as the clinical relevance of the resulting damage, encourages the active study of factors of remote degeneration. These processes development in several days or months after the injury indicates the presence of a therapeutic window and the necessity of prolonged correction of remote pathological shifts.

In regard to the BSCB, the participation of both capillaries and other vessels of the microvascular network of the spinal cord in proper functioning and in cases of barrier disruption remains practically unstudied. It is essential to examine the role of pericytes as a cambial reserve for the repair of vascular wall cells, astrocytic glia, and the molecular arrangement of the extracellular matrix of the barrier not only under physiological conditions but also when its permeability is disturbed at different phases of spinal cord injury. In this regard, success in the treatment of patients with BSCB pathology will be grounded on new data on the cellular and molecular mechanisms of barrier function and on the challenging pathological and physiological mechanisms of its disintegration.

Figures 1 and 3 given in this article are drawn by authors.

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The authors declare that they have no conflict of interest.

The study was approved by the local ethics committees of the institutions.

All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

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