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Review article

Targeting the blood-spinal cord barrier: A therapeutic approach to spinal cord protection against ischemia-reperfusion injury

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ABSTRACT

One of the principal functions of physical barriers between the blood and central nervous system protects system (i.e., blood brain barrier and blood-spinal cord barrier) is the protection from toxic and pathogenic agents in the blood. Disruption of blood-spinal cord barrier (BSCB) plays a key role in spinal cord ischemia-reperfusion injury (SCIRI). Following SCIRI, the permeability of the BSCB increases. Maintaining the integrity of the BSCB alleviates the spinal cord injury after spinal cord ischemia. This review summarizes current knowledge of the structure and function of the BSCB and its changes following SCIRI, as well as the prevention and cure of SCIRI and the role of the BSCB.

Contents

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1. Introduction

Spinal cord ischemia-reperfusion injury (SCIRI) is a devastating event that induces a series of complex cellular and molecular cascade events, sometimes converging to paralysis that physically and socially affects individuals. This condition is a serious complication of numerous pathophysiological states, such as hypotension, thoracoabdominal aortic aneurysm surgery, and thoracoabdominal aortic repair surgery [1,2]. Blocking of the aorta for a certain period of time is often necessary in order to reduce bleeding and easily perform operations, especially in thoracoabdominal aortic aneurysm surgery and spinal operation. This procedure can cause spinal cord injury and even paralysis after restoring blood flow. The incidence of spinal cord injury after thoracic and thoracoabdominal aortic repair surgery is up to 32% [3]. With the development of medical technologies, the incidence rate of paraplegia following spinal cord injury decreased, while the incidence of paraplegia was still 5.1% following open thoracoabdominal aortic aneurysm repair surgery [4]. Reducing the SCIRI occurrence, as well as preventing and effectively taking care of patients with SCIRI, are key points that have attracted increasing research interests. Blood-spinal cord barrier (BSCB) is the diffusion barrier of physiological and metabolic molecules between the microvascular and surrounding tissues, which plays an important role in maintaining the stability of the central nervous system environment. Recently, several studies have demonstrated that the BSCB plays a vital role in SCIRI [5–7]. In fact maintaining the integrity of the BSCB can attenuate the spinal cord ischemia injury. Thus, the protection of the integrity of the BSCB is a promising tool to relieve spinal cord ischemia-reperfusion injury.

2. Morphological structure and physiological function of BSCB

Similarly to the blood-brain barrier (BBB), the BSCB composition is based on specialized nonfenestrated endothelial cells, pericytes, end feet of astrocytic processes, and include some accessory structures, such as the tight junctions (TJs) and basal lamina (Fig. 1). TJs consist of several proteins, including occludin, claudins (claudin-1, claudin-3, and claudin-5), zonula occludens proteins (ZO-1, ZO-2, and ZO-3), and junctional adhesion molecules (JAMs) (Fig. 2). The orchestrated interaction of these building blocks makes possible the regulatory and protective functions of the BSCB [8,9]. One of the principal functions of the BSCB is to keep the homeostasis of the central nervous system. The barrier can selectively regulate the passage of water, ions, inflammatory factors, toxic metabolic substances, and inflammatory cells in the spinal cord tissue from the blood. Thus, the BSCB effectively protects the spinal cord [8]. The disruption of the barrier integrity leads to an increase in its permeability. As a consequence, many toxic substances can penetrate into the spinal cord, causing spinal cord edema, neurons apoptosis, and death.

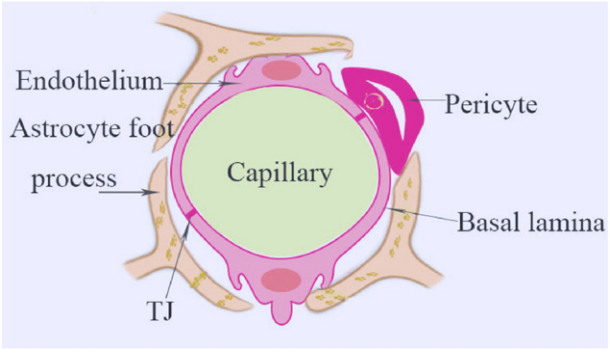

Fig. 1. Schematic representation of the principal building blocks of the blood-spinal cord barrier (BSCB). A representative spinal cord capillary consists of nonfenestrated endothelial cells linked with tight junctions (TJs), basal lamina, pericytes, and astrocyte foot processes. The barrier provides a specialized mircroenviroment for the cellular constituents of the spinal cord.

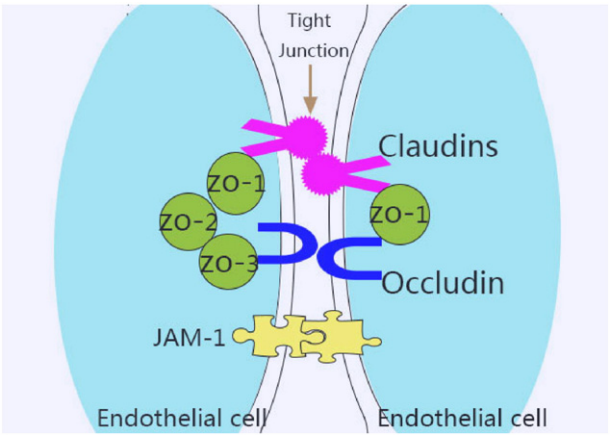

Fig. 2. Endothelial cells are linked by tight junctions (TJs). A typical TJ consists of occludin, claudins, zona occludens (ZO-1, ZO-2, and ZO-3) proteins, and junctional adhesion molecules (JAMs). The paracellular diffusion pathway is severely restricted by TJs between individual endothelial cells.

3. Morphological and functional changes in BSCB following SCIRI

3.1. Morphological changes

The morphological structure of the BSCB is disrupted when spinal cord injury occurs. Matsushita et al. [7] showed ound that pericytes dissociate from endothelial cells after spinal cord injury and rapidly recover following intravenous infusion of bone marrow mesenchymal stem cells. Moreover, the matrix metalloproteinase-9(MMP-9) was found as increased in endothelial cells following spinal cord injury, while occludin and ZO-1 decreased in endothelial cells following hypoxia treatment [10]. Lee et al. [11] demonstrated that the expression of matrix metalloproteinase-3 (MMP-3) increased in endothelium after spinal cord injury and this result was related to the BSCB disruption. The expression of caveolin-1, the major structural protein required for the formation of caveolae, was detected as significantly increased in microvascular endothelial cell following SCIRI. In addition, the down-regulation of caveolin-1 expression could decrease the permeability of the BSCB [12]. Taken together, it is clear that changes in MMP-9, MMP-3 and caveolin-1 expression may affect the integrity of the BSCB following spinal cord injury. A study conducted in rats by Nordal and Wong [13] showed that the overexpression of the intercellular adhesion molecule-1 (ICAM-1) in the endothelium and astrocytes of the spinal cord induced the BSCB disruption after radiation injury. However, whether ICAM-1 expression increases in endothelium cells and astrocytes following SCIRI it is not clear and needs further investigation. Fang et al. [14,15] reported that the expression of MMP-9 was increased even in the astrocytes, along with the decrease in the expression of ZO-1 in endothelium cells; Moreover, they observed that the distribution of ZO-1 along microvasculatures became discontinuous. Among morphological changes occurring in BSCB, claudin-5, occludin, and ZO-1 levels increases after cerebral ischemia injury [16,17]. APQ-4 is a molecular water channel present in the brain and spinal cord, predominantly expressed in astrocytes and astrocytic end-feet processes and astrocytes. Similar changes have been observed after spinal cord injury [14,18]. In summary, principal changes occurring in BSCB following spinal cord injury comprise the dissociation of the pericytes from endothelial cells, the increase of the expression of AQP-4, MMP-9, MMP-3 and caveolin-1 and the increase of claudin-5, occludin, and ZO-1 levels. The variation of basilemma after spinal cord injury and changes in ICAM-1 expression following SCIRI have not been elucidated and need further investigation.