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Review article

Advance in spinal cord ischemia reperfusion injury: Blood–spinal cord barrier and remote ischemic preconditioning

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ABSTRACT

The blood–spinal cord barrier (BSCB) is the physiological and metabolic substance diffusion barrier between blood circulation and spinal cord tissues. This barrier plays a vital role in maintaining the microenvironment stability of the spinal cord. When the spinal cord is subjected to ischemia/reperfusion (I/R) injury, the structure and function of the BSCB is disrupted, further destroying the spinal cord homeostasis and ultimately leading to neurological deficit. Remote ischemic preconditioning (RIPC) is an approach in which interspersed cycles of preconditioning ischemia is followed by reperfusion to tissues/organs to protect the distant target tissues/organs against subsequent lethal ischemic injuries. RIPC is an innovation of the treatment strategies that protect the organ from I/R injury. In this study, we review the morphological structure and function of the BSCB, the injury mechanism of BSCB resulting from spinal cord I/R, and the effect of RIPC on it.

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1. Introduction

Clinically, thoracoabdominal aortic aneurysm repair surgery can lead to spinal cord ischemia reperfusion injury (SCIRI), whose incidence is reported to range from 1% to 32%. However, a main, devastating, and unpredictable complication after spinal cord injury is paraplegia [1–2]. To date, various intervening measures, including hypothermia, improvement of surgical techniques, and pharmacologic adjuncts, have been used to protect the spinal cord from ischemic injury [3]; nonetheless, complications still cannot be prevented completely. Therefore, a

Abbreviations: BSCB, Blood–spinal cord barrier; I/R, Ischemia/reperfusion; RIPC, Remote ischemic preconditioning; SCIRI, Spinal cord ischemia reperfusion injury; BBB, Blood–brain barrier; CNS, Central nervous system; TJ, Tight junction; NVU, Neurovascular unit; JAM, Junction adherence molecular; HO-1, Heme oxygenase-1; BDNF, Brain derived neurotrophic factor; MMPs, Matrix metalloproteinases; TLRs, Toll-like receptors; AQPs, Aquaporins.

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more effective strategy should be developed to protect the spinal cord against ischemia reperfusion (I/R) injury. The pathogenesis of SCIRI includes oxygen-free radical-induced lipid peroxidation, intracellular calcium overload, leukocyte activation, inflammatory response, and neuronal apoptosis. In addition, the disruption of the blood–spinal cord barrier (BSCB) is a major pathological change that can exacerbate spinal cord edema, increase leukocyte infiltration, as well as amplify inflammation and oxidative stress. Therefore, BSCB disruption plays a vital role in the evolution of SCIRI and further damage of neurons [4–6]. BSCB is the physiological and metabolic substance diffusion barrier between blood circulation and spinal cord tissues. This barrier strictly regulates the stability of the spinal cord microenvironment. The repairing of the BSCB should be performed as soon as possible after spinal cord injury because the normal function of neurons is based on the homeostasis of the spinal cord. In recent years, changes of the BSCB after spinal cord I/R and improvement of the neurological function through protecting BSCB integrity have drawn extensive attention from researchers. Clarifying the mechanism responsible for BSCB disruption and further using it as a therapeutic target is greatly significant to alleviate SCIRI.

Remote ischemic preconditioning (RIPC) is an approach in which interspersed cycles of preconditioning ischemia followed by reperfusion to a tissue/organ protect the distant target tissue/organ against subsequent lethal ischemic injuries, and the most convenient method induced by the upper or lower limb. It has a huge development prospect clinically as it is safe, simple, and easily accepted by doctors and patients. Certain studies have shown that RIPC can protect spinal cord against I/R injury [7–9], but the mechanism is not entirely clear yet. In the rat model of brain I/R injury, a researcher has found that remote ischemic postconditioning can alleviate permeability of the blood–brain barrier (BBB) and brain edema after brain ischemia, which reduces infarct volume and improves the neurological outcome as well [10–11]. Meanwhile, the possibility of RIPC alleviating the permeability of the BSCB in the model of spinal cord injury has not been reported. As both BSCB and BBB belong to the central nervous system (CNS) barrier, they are similar not only in structure but also in function, thus it is very likely that RIPC induces spinal cord ischemia tolerance through keeping BSCB intact. The present study will review the morphological structure and function of the BSCB, injury mechanism of BSCB due to spinal cord I/R, and the effect of RIPC on it.

2. Morphological structure and function of the BSCB

2.1. Morphological structure of the BSCB

Similar to BBB, the basal components of BSCB include endothelial cells between spinal cord capillaries and tight junction (TJ) proteins, basal lamina, pericytes, and astrocytic end feet processes [12]. Endothelial cells, pericytes, astrocytes, neurons, and extracellular matrix are collectively known as the neurovascular unit (NVU) [13]. Endothelial cells of spinal cord capillaries, which are characterized by the absence of cell membrane fenestrations unlike those of peripheral circulation, contain a high number of cytosolic mitochondria, lack pinocytic vacuoles, and include a very weak activity of the pinocytosis [14]. TJs between endothelial cells are composed of some specific transmembrane proteins such as claudins (claudin-1, claudin-3, claudin-5, etc.), occludin, and junction adherence molecular (JAM). These transmembrane proteins are linked to cytoskeletal filaments by interactions with accessory proteins (ZO-1, ZO-2, ZO-3, etc.). The basal lamina surrounds capillary endothelial cells and engulfs pericytes. The major components of the basal lamina include collagen, fibronectin, laminin, and proteoglycans [16]. Astrocytes, which are one of the most numerous types of cells in the CNS, projects end feet processes to surround neural synapses, ranvier nodes, and blood vessels [17].

2.2. Function of each component element of BSCB

Endothelial cells of spinal cord capillaries, as the most important part of BSCB, strictly restrict free transcellular flow of blood-borne molecules, and a high number of cytosolic mitochondria provides high energy for selective active transport and calcium homeostasis. In addition, heme oxygenase-1 (HO-1) and brain derived neurotrophic factor (BDNF) can be expressed and secreted by endothelial cells, which contribute to recovery of the neural function [18–19]. The paracellular diffusion pathway is severely restricted by TJs between individual endothelial cells. Claudin-5, occludin, and ZO-1 are the main proteins of TJs, which are also considered as the sensitive markers no matter when the CNS barrier is normal or damaged. Moreover, ZO proteins can not only act as the scaffold for multiple signal pathways within cells but also involve in the regulating function of TJs [15,20]. Pericytes are small-vessel wall-associated cells that are separated from endothelial cells by the basal lamina. Capillary pericytes and endothelial cells communicate with each other in several ways, including gap junctions and soluble factors. Furthermore, pericytes play a significant regulatory role in endothelial cell proliferation, migration, and differentiation [21]. Astrocytes can be stimulated by neuronal activity and can regulate vascular function, thus further adjusting blood flow to neuronal activity in specific regions [22–23]. In addition, astrocytic end feet processes express a high concentration of water channel aquaporin 4 (AQP-4), which is involved in the volume regulation of CNS [24].

3. Injury mechanism of BSCB due to spinal cord I/R

3.1. Disruption of BSCB induced by MMPs

Matrix metalloproteinases (MMPs) comprise a large family of extracellular zinc endopeptidases that can degrade and remodel basal lamina proteins, tight junction proteins, and many other extracellular matrices [25]. MMPs can be expressed by various cells in the brain, including endothelial cells, microglia, neurons, astrocytes, and infiltrating inflammatory cells during cerebral ischemia [26]. MMPs are secreted as inactive zymogens, and their expression and activation can be strongly promoted by the overproduction of reactive oxygen species and proinflammatory cytokines (TNF-α, IL-1β, etc.) during the I/R process [27]. MMP-9 is the most widely researched among all types of MMPs, and has been demonstrated to play a critical role in regulating BBB during cerebral ischemia. A considerable number of studies have shown that MMP-9 can degrade claudin-5, occludin, and ZO-1 in cultured brain endothelial cells in vitro and in vivo ischemia model. Moreover, knockout mice that lack MMP-9 have shown a significant protective effect on BBB [28–30]. In the SCIRI model, Fang Bo et al. found that the permeability of the BSCB was increased and the expression of MMP-9 was up-regulated in microglia, neuron, and astrocyte. In addition, MMP-9 was also involved in the infiltration and migration of microglia and in the increased production of proinflammatory cytokines and chemokine, which amplified the inflammation and further exacerbated BSCB disruption and neuronal apoptosis [31–32]. Some studies have indicated that dexmedetomidine or sevoflurane preconditioning or intrathecal transplantation of bone marrow stromal cells can down-regulated MMP-9 expression after spinal cord I/R, thus maintaining the integrity of the BSCB and improving the neurological outcome [31–33]. The above-mentioned research results indicate that MMP-9 could destroy the BSCB, and play an important part in the development and progression of inflammatory reaction. Consequently, taking some interventions to inhibit MMP-9 expression will contribute to the stability of the BSCB structure and alleviation of SCIRI.

3.2. Disruption of BSCB induced by inflammatory reaction

Inflammatory cytokines are one of the most pivotal factors for BSCB disruption in SCIRI; they lead to the dissociation of ZO-1 from the