Mol Neurobiol (2017) 54:3578–3590
DOI 10.1007/s12035-016-9910-6

Propitious Therapeutic Modulators to Prevent Blood-Spinal Cord Barrier Disruption in Spinal Cord Injury

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Received: 5 December 2015 / Accepted: 3 May 2016 / Published online: 18 May 2016

Abstract The blood-spinal cord barrier (BSCB) is a specialized protective barrier that regulates the movement of molecules between blood vessels and the spinal cord parenchyma. Analogous to the blood-brain barrier (BBB), the BSCB plays a crucial role in maintaining the homeostasis and internal environmental stability of the central nervous system (CNS). After spinal cord injury (SCI), BSCB disruption leads to inflammatory cell invasion such as neutrophils and macrophages, contributing to permanent neurological disability. In this review, we focus on the major proteins mediating the BSCB disruption or BSCB repair after SCI. This review is composed of three parts. Section 1. SCI and the BSCB of the review describes critical events involved in the pathophysiology of SCI and their correlation with BSCB integrity/disruption. Section 2. Major proteins involved in BSCB disruption in SCI focuses on the actions of matrix metalloproteinases (MMPs), tumor necrosis factor alpha (TNF-α), heme oxygenase-1 (HO-1), angiopoietins (Angs), bradykinin, nitric oxide (NO), and endothelins (ETs) in BSCB disruption and repair. Section 3. Therapeutic approaches discusses the major therapeutic compounds utilized to date for the prevention of BSCB disruption in animal model of SCI through modulation of several proteins.

Keywords Blood-spinal cord barrier · Matrix metalloproteinase · Bradykinin · HO-1 · TNF-α · Angiopoietins · Spinal cord injury

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Introduction

The blood-spinal cord barrier (BSCB) is analogous to the blood-brain barrier (BBB) in that both systems are selectively permeable and limit the entry of pathogens, blood-derived products, and cells into the central nervous system (CNS) [1]. The BSCB directs molecular exchanges between the blood and spinal cord to maintain normal functioning and information processing. The BSCB arises from specialized barrier-forming cells and cellular processes, namely, endothelial cells, pericytes, and astrocytic end feet [1]. The orchestrated arrangement of these cellular building blocks provides a specialized capillary microenvironment that controls the entry of molecules into the spinal cord. The morphology and clinical implications of the BSCB are widely discussed in the literature [1].

The regulatory and protective functions of the BSCB stem from a highly evolved, complex network of tight junction (TJ) proteins, including zonula occludens 1 (ZO-1), occludin, and claudin-5 [2, 3] (Fig. 1). Here, we focus on the major target proteins that participate in BSCB disruption/repair following damage to the spinal cord. After spinal cord injury (SCI), the degradation of TJ proteins causes BSCB disruption by increasing BSCB permeability [4], culminating in the development or progression of several CNS diseases, including multiple sclerosis [5], neuromyelitis optica [6], amyotrophic lateral sclerosis [7], post-traumatic syringomyelia [8], neuropathic

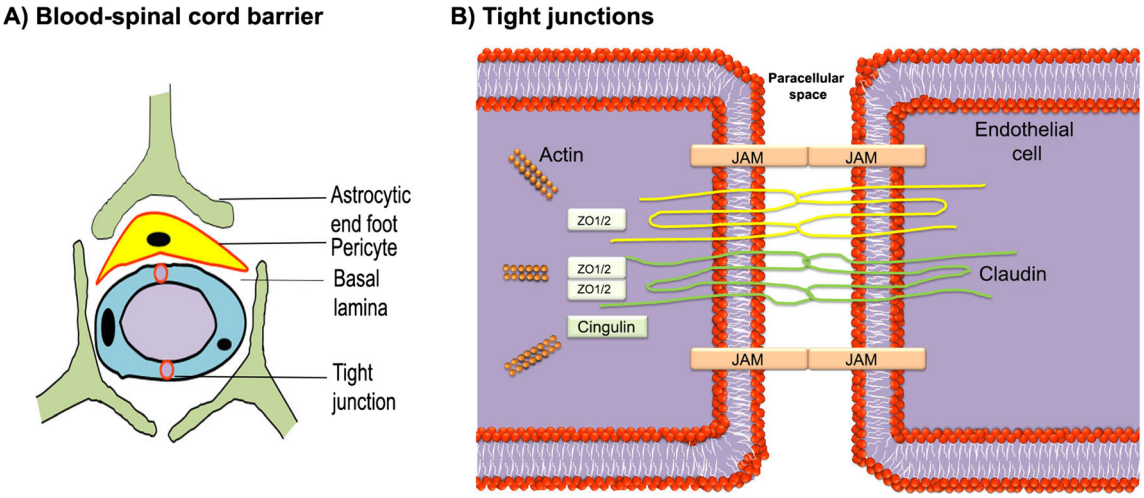

Fig. 1 The blood-spinal cord barrier (BSCB) exists due to the presence of tight junctions (TJs) between endothelial cells and the paucity of transcellular transport mediated by membrane-bound vesicles. Endothelial cells, pericytes, and astrocytic end feet perform the barrier function of the BSCB (**a**). Zonula occludens (ZO) proteins are important for the clustering of claudins and occludin, leading to the formation of TJ strands. ZOs and cingulin provide a direct link to the actin cytoskeleton (**b**)

pain [9], spinal cord ischemia [10], and radiation injury to the spinal cord and the most studied SCI [11–13].

Section 1. SCI and the BSCB

SCI is a clinically devastating condition. From a pathophysiological viewpoint, SCI induces primary and secondary tissue damage, including spinal cord edema and cell death in the injured areas [14]. Initial mechanical damage generates the primary injury, whereas secondary injuries result from progressive cell damage spreading from the gray matter to the white matter. The primary injury leads to axonal and vascular damage and has been considered irreversible. The primary injury is accompanied by a series of strong immune responses characterized by inflammation, synthesis of cytokines and chemokines, and coordinated infiltration of peripheral leukocytes to the site of damage [15–17]. Secondary injuries are characterized by slow and delayed cell death as a consequence of primary injury-induced biochemical changes [18–21]. Scar tissue formed during the process of reactive astrogliosis is a type of secondary injury that is generally regarded as a major obstacle to axonal regeneration [22–25].

BSCB disruption following SCI allows neutrophils and leukocytes to infiltrate the injured parenchyma and contribute to secondary injury [26–28] (Fig. 2). The time course of BSCB disruption and re-establishment of normal BSCB function post-SCI has been studied by a number of investigators. BSCB disruption occurs within 5 min after spinal cord trauma [11], lasts for up to 28 days after the initial injury, and spreads along the entire length of the cord [12, 13, 29]. The BSCB can remain compromised even at 56 days after SCI [30]. The extended time course of barrier breakdown has been confirmed by magnetic resonance imaging analyses [30, 31], but the time course for re-establishment of BSCB function is less clear, with results varying widely among studies [11, 12, 29]. Some reports suggest that SCI generates a biphasic opening of the barrier. The first peak of abnormal leakage occurs within several hours after injury, whereas the second peak is evident between 3 and 7 days post-injury [13].

Significant vascular changes including BSCB disruption occur after SCI and participate in its progressive pathophysiology [32]. Early microvascular reactions and BSCB disruption are instrumental in SCI progression, because, as noted above, the compromised barrier permits neutrophils, lymphocytes, and other immune cells to enter damaged tissue. Lymphocytic infiltration of the injury site [33] increases inflammation, reactive astrogliosis, and the production of scar tissue [34, 35]. Neutrophils mediate the initial events associated with demyelinating neuroinflammatory diseases and are intimately linked with the status of BBB/BSCB integrity [36]. Following the mechanical disruption of capillaries at the moment of primary injury, blood-borne molecules and cells readily cross into the injured parenchyma [29, 37].

Pathophysiological cascades involving various regulatory proteins (discussed in detail in Section 2. Major proteins involved in BSCB disruption in SCI) are initiated after primary SCI and further contribute to spinal cord damage and BSCB dysfunction [38]. These complex secondary pathomechanisms are responsible for extension of damage into the previously uncompromised segments of the spinal cord [12, 29, 39]. BSCB disruption after SCI gives rise to immune cell infiltration and inflammatory injury, eventually triggering various neurological deficits [40–42]. BSCB disruption is associated with increased mortality, whereas improvements in BSCB function can significantly reduce

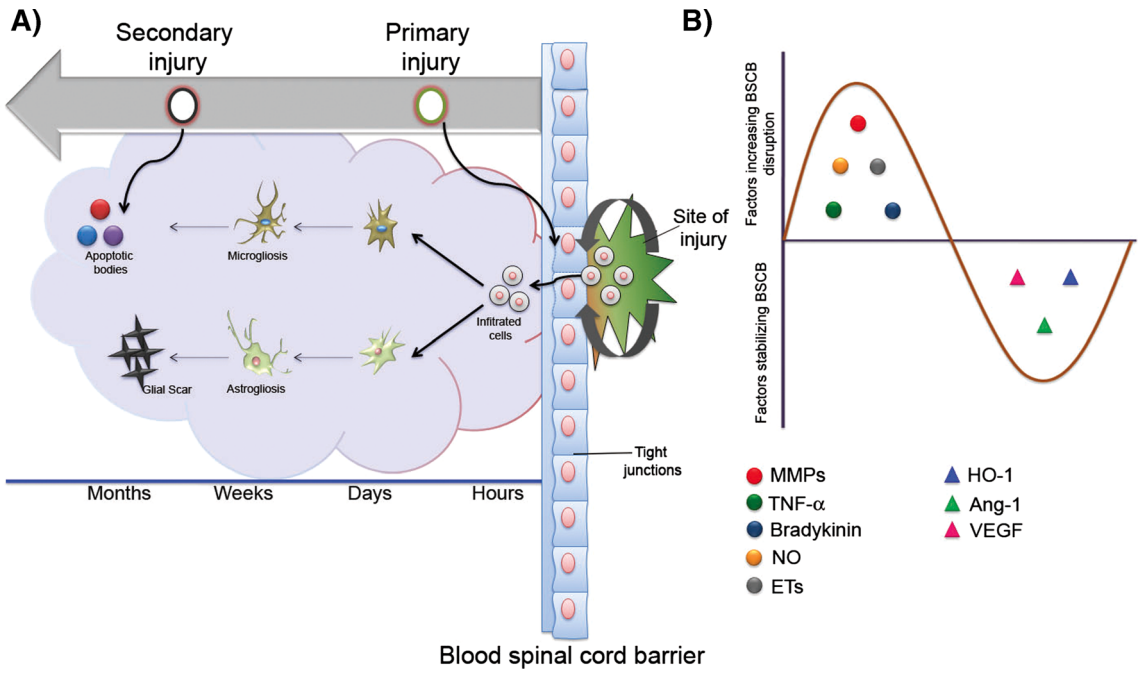

Fig. 2 Spinal cord injury (SCI) causes disruption of the blood-spinal cord barrier (BSCB) and increases BSCB permeability followed by transvascular transport of cytokines, chemokines, leukocytes, and neutrophils. The primary injury phase is characterized by intense inflammation leading to activation of the glial network. The extent of microgliosis and astrogliosis depends on the severity of the injury. In severe injury cases, reactive astrocytes invade neighboring domains, recruit reactive microglia, and increase secretion of extracellular matrix (ECM) molecules. This cascade of events results in the formation of a persistent glial scar that can be impenetrable to regenerating axons. The secondary injury phase includes several mechanisms characterized by numerous cellular, molecular, and biochemical events that significantly contribute to loss of functional recovery (**a**). Assorted active factors (e.g., matrix metalloproteinase (MMP)-3, MMP-9, MMP-12, tumor necrosis factor alpha (TNF-α), bradykinin, nitric oxide (NO), and endothelins (ETs)) participate either directly or indirectly in BSCB disruption to increase barrier permeability. Conversely, heme oxygenase-1 (HO-1), angiopoietin-1 (Ang-1), and vascular endothelial growth factor (VEGF) stabilize the BSCB

secondary nerve injury [43, 44]. This suggests that early BSCB repair is critical for the successful clinical treatment of SCI.

Section 2. Major Proteins Involved in BSCB Disruption in SCI

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of extracellular zinc and calcium-dependent endopeptidases that degrade extracellular matrix (ECM) and other extracellular proteins [45]. MMPs are essential for ECM remodeling, which is clinically relevant in wound healing [46]. However, the excessive proteolytic activity of MMPs can be detrimental and provoke numerous pathological conditions, including BBB/BSCB disruption after injury [40, 47–49]. Experimental models of SCI indicate that leukocytes (mainly neutrophils) are the first cells to migrate across the vascular wall and arrive at the site of parenchymal injury [36, 50, 51]. Next, neutrophils infiltrate the spinal cord within the first hours after injury, peaking at 24 h [50, 51] and remaining at the injury site for up to 10 days [50]. As leukocytes transmigrate, they release MMPs, which degrade TJ proteins (ZO-1 and occludin), ECM components (fibronectin, laminin, heparin sulfate, and others), and the surrounding basal lamina [47, 52, 53].

Several MMPs, including MMP-2, MMP-3, MMP-9, and MMP-12, contribute to SCI pathogenesis [54–58]. The presence of these proteinases has been reported as both beneficial and detrimental. For example, MMP-2 facilitates wound healing events that promote functional recovery after SCI [54], whereas MMP-3, MMP-9, and MMP-12 trigger BSCB disruption after SCI, promote inflammation, and contribute to early development of secondary pathogenesis [40, 55, 57]. The role of MMP-3, also known as stromelysin-1, has recently been established in BSCB permeability and blood-borne inflammatory cell infiltration after SCI. BSCB permeability and cell infiltration are significantly lower in MMP-3 knockout (KO) than in wild-type (WT) mice, and the expression levels of certain TJ proteins (e.g., occludin and ZO-1) are higher in MMP-3 KO mice than in WT mice. Furthermore, exogenous MMP-3 injection into the normal spinal cord induces BSCB permeability [57].

MMP-9, also termed type IV collagenase, is a gelatinase/gelatinase B secreted by infiltrating neutrophils [59] and a key

mediator of early pathogenesis in SCI [58]. MMP-9 contributes to abnormal vascular permeability and inflammation within the first 3 days after SCI, while MMP blockade during the initial injury period mitigates deleterious vascular events and improves locomotor recovery. MMP-9 KO mice exhibit significantly less BSCB disruption after SCI than WT mice. Similar findings were observed in mice treated with an MMP inhibitor from 3 h to 3 days after injury relative to vehicle control animals [40]. On the other hand, oxidative stress post-SCI promotes MMP-9 upregulation, BSCB disruption, and apoptosis, whereas overexpression of superoxide dismutase1 in transgenic rats decreases oxidative stress and offsets MMP-9-mediated BSCB disruption [58].

MMP-12, or macrophage metalloelastase, is critical for the migration of blood-borne macrophages across the endothelial basement membrane into inflammatory sites [60]. Spinal cord-injured MMP-12 null mice show attenuated BSCB disruption and a lower density of microglia and macrophages than WT controls [55]. Clearly, spinal cord-injured mice with a genetic null mutation in MMP-3, MMP-9, or MMP-12 exhibit stabilization of the BSCB, reduced infiltration of neutrophils, microglia, and macrophages, and significant improvements in locomotor recovery relative to spinal cord-injured WT mice [40, 55, 57].

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine involved in systemic inflammation and is a major component of the acute phase injury reaction. Serum levels of TNF-α and other proinflammatory cytokines are higher in patients with SCI than in uninjured individuals [61]. TNF-α is produced both in the spinal cord and in the periphery as a consequence of tissue damage, and its transport after SCI is time-, region-, and lesion type-specific [62, 63]. TNF-α can be detected at 1 h post-injury in resident neurons and glial cells, as well as in infiltrating monocytes and macrophages, and its expression can persist for upto 1 week after SCI [64, 65]. Once BSCB permeability returns to normal, TNF-α levels secreted from the initially infiltrating inflammatory cells generally decrease.

The effects of TNF-α after SCI are somewhat controversial. Accumulating experimental evidence now supports a dual role for the cytokine [66, 67]. On the one hand, axonal regeneration after compressive SCI in the rat is facilitated by transplantation of macrophages, which secrete TNF-α [68]. On the other hand, TNF-α overproduction after SCI may be directly toxic and lead to cellular apoptosis [69]; the cytokine also augments inflammatory/immune responses [70, 71]. Furthermore, TNF-α increases BBB/BSCB permeability while decreasing the expression of TJ proteins through activation of nuclear factor-kappa B (NF-κB) signaling [72, 73]. TNF-α can additionally modulate barrier permeability via other mechanisms [74–76]. For example, increased transport of TNF-α across the BSCB (rather than cellular leakage) is primarily responsible for the increased entry of TNF-α into the spinal cord [65]. TNF-α receptors (p55 and p75) critically facilitate TNF-α transport and thus, p55 and p75 TNF-α receptor double-KO mice do not transport the cytokine [77].

Elevated p55 receptor expression is observed during early SCI (between 12 h and 1 week), whereas p75 expression is upregulated at later time points [78]. Transport systems for TNF-α at the BSCB are upregulated between 3 and 5 days after SCI in WT CD1/ICR mice with functional p55 and p75 receptors [79], whereas transcytosis of ^{125}I-TNF-α across an endothelial cell monolayer composing the BBB/BSCB is significantly reduced in the absence of functional p55 and p75 receptors. Interestingly, p75 receptor single-KO mice showed a reduced increase in ^{125}I-TNF-α uptake after SCI relative to WT controls, while p55 receptor KO mice showed no significant increase in ^{125}I-TNF-α uptake [78]. Furthermore, histological and behavioral studies showed that deletion of the p55 receptor yielded enhanced rates of cell apoptosis, larger lesion sizes, and delayed functional recovery compared with deletion of the p75 receptor. These findings indicate that the p55 receptor plays a greater role in mediating the increased uptake of TNF-α into the spinal cord after SCI than the p75 receptor [80].

Heme Oxygenase-1

The heme oxygenase (HO) system efficiently degrades heme into equimolar quantities of biliverdin, carbon monoxide, and free iron (Fe^{3+}) [81]. To date, three HO isoenzymes (HO-1, HO-2, and HO-3) have been reported. HO-1 and HO-2 are fully characterized, catalytically active forms, whereas HO-3 possesses marginal activity [82–84]. HO-1 and HO-2 function differently in the defense mechanism of the injured CNS. HO-1 protects against further damage by contributing to controlled death of injured cells through an intrinsic suicide program, while HO-2 suppresses inflammatory responses mediated by nitric oxide (NO)-derived radicals after SCI [85].

HO-1 is an inducible enzyme found at low levels in the uninjured spinal cord [86] but is upregulated post-injury [86–88]. Administration of an HO-1 inhibitor in vivo delayed motor function recovery in the damaged spinal cord, suggesting a protective effect of the enzyme in SCI [87]. After SCI, activated neutrophils in the damaged tissue express HO-1 [87], stabilize the BSCB, and limit infiltration of additional neutrophils. Barrier permeability and neutrophil infiltration are significantly higher in spinal cord-injured HO-1$^{+/-}$ mice than in WT mice [89], whereas vascular induction of HO-1 by systemic administration of hemin modulates neutrophil infiltration and lessens barrier disruption in the acutely injured spinal cord [90]. Experiments conducted in HO-1 KO mice, as well as studies of HO-1 deficiency in humans, support the

hypothesis that HO-1 modulates early inflammatory responses and exerts potent anti-inflammatory actions [91, 92].

Indirect observations also demonstrate the beneficial impact of HO-1 in SCI. For instance, HO-1 decreases the expression of intracellular adhesion molecule 1, which arbitrates neutrophil adhesion to the endothelial surface and is required for the transmigration of neutrophils into the parenchyma [93, 94]. Additionally, HO-1 may stabilize the BSCB by modulating interleukin-10 and TNF-α expression levels [95]. Notably, hypoxia, oxidative stress, and exposure to endothelin 1 (ET-1) all result in the induction of the enzyme [50, 88, 96]. Recently, numerous studies have shown that HO-1 induction is an important cellular protective mechanism against oxidative injury [97].

Angiopoietins

Angiopoietins (Angs) are vascular growth factors involved in blood vessel formation/maturation and endothelial cell survival through interactions with the endothelial tyrosine kinase (Tie-2) receptor [98, 99]. Angs are essential for normal vascular functions in the brain [100, 101] and spinal cord [102–104]. The Ang family has four members: Ang1 through Ang4. Ang-1, Ang-2, and Ang-4 are found in humans, while Ang-3 is a mouse ortholog of human Ang-4 [99, 105].

Ang-1 and Ang-2 exert opposite actions on blood vessels by competing with similar affinity for the same receptor, Tie-2. Ang-2 exerts autocrine and paracrine effects on the Tie-2 receptor, thereby antagonizing the effects of Ang-1. SCI produces a lasting decrease in Ang-1 levels, which further contributes to pronounced vascular dysfunction and functional impairment [103, 104]. Contrarily, SCI promotes a marked and persistent increase in Ang-2 levels [106]. Ang-1 reduces vascular leakage in uninjured tissue by strengthening platelet endothelial cell adhesion molecule- and vascular endothelial cadherin-regulated inter-endothelial adhesions [100, 107], whereas Ang-2 contributes to beneficial pro-angiogenic and/or gliogenic processes underlying recovery processes after SCI [106].

Downregulated Ang-1 and upregulated Ang-2 expression coincide with marked BBB breakdown after brain injury [108]. Ang-1 combats vascular endothelial growth factor (VEGF)-induced BBB permeability, which is linked with a decrease in MMP-9 activity [109]. In a similar manner, Ang-1 can prevent VEGF-induced retinal vascular permeability [110]. Of note, transplantation of bone marrow stromal cells reduced BBB permeability by increasing the expression of Ang1/Tie2 [100]. Along the same lines, Ang-1 treatment reduced BSCB permeability in an animal model of SCI [102]. Administration of an αvβ3 integrin-binding peptide (C16) or an Ang-1-mimetic agent following SCI rescued blood vessels at the injury epicenter, prevented white matter degeneration, improved locomotor function, and reduced inflammation [102]. Meanwhile, combined treatment with adenoma-associated virus (AAV)-VEGF and AAV-Ang-1 improved BSCB integrity and functional recovery after SCI [104].

Bradykinin

Bradykinin is an endogenous nonapeptide produced by enzymatic cleavage of precursor kininogens and acts on B_1 and B_2 receptors [111]. Bradykinin is a potent endothelium-dependent vasodilator that increases vascular permeability, participates in inflammatory reactions, and contributes to BSCB disruption in SCI. The bradykinin B_1 receptor is induced by chronic infection or tissue injury, while the B_2 receptor is constitutively present at the BSCB [112, 113]. Bradykinin can promote nerve damage and potentiate disturbances in BBB/BSCB function through activation of B_2 receptors [114].

Following SCI, bradykinin increases TNF-α production at the site of injury and induces other inflammatory mediators, raises intracellular calcium levels, and provokes glutamate release [111, 114]. Bradykinin antagonists attenuate BSCB permeability following SCI [115, 116]; clinically, these agents also reduce neurological impairment after closed head injury, suggesting that bradykinin inhibition is a key mechanism for neuroprotection [112, 113]. An interesting clinical use of the nonapeptide concerns pharmacological preconditioning to induce bradykinin tolerance in nerve tissue. Bradykinin preconditioning 15 min before ischemia decreases BSCB permeability and protects the rat spinal cord against ischemic injury; this therapeutic action is reversed by the bradykinin B2 receptor antagonist, B9430 [117]. Similarly, bradykinin preconditioning can provide mitochondrial preconditioning, increase antioxidant enzyme levels, and promote neuronal survival in rabbits with spinal cord ischemia [118].

Nitric Oxide

Nitric oxide (NO) is a gaseous biomolecule involved in a variety of physiological processes in the CNS. NO can have both beneficial [119] and detrimental [120] effects in neurological disease states. NO is produced by nearly all tissues; however, the highest content of NO is reported in the CNS [121]. NO synthase (NOS) is responsible for the production of NO and exists in three isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). The first two isoforms are constitutively expressed, while iNOS is expressed under pathological conditions [122]. Uncontrolled NO production can lead to tissue injury and cellular damage in the spinal cord through the generation of assorted reactive oxygen species (ROS), including peroxynitrite [123, 124]. Increased NOS expression is found in the dorsal horn following spinal cord ischemia or peripheral nerve injury [125, 126], whereas NOS-positive interneurons are upregulated following

more severe spinal cord hemisection or impact injury, especially rostral to a lesion [127].

NO concentrations and NOS activity in the injured spinal cord have been measured in animal models during the immediate post-injury period. Direct measurement of peroxynitrite via microdialysis in the spinal cord revealed increased NO levels within the injured tissue [128]. Another study reported that NO levels in injured spinal cord were approximately three times higher than those in the uninjured cord at 30 min after SCI, as determined by an electron spin resonance spin-trapping technique [129]. Some investigators have suggested that the initial maximal increase in NO production in SCI is caused by nNOS and that the second wave of increased NO generation is mainly due to iNOS [130]. Notably, immunohistochemical findings showed a marked upsurge in the number of nNOS-expressing cells immediately after an injury; however, the cell count returned to control levels by 24 h post-SCI [129].

Brain-derived neurotrophic factor and insulin-like growth factor-1 can defend against upregulation of nNOS, thereby reducing BSCB damage, spinal cord edema, and cell injury [131]. Likewise, topical application of TNF-α antiserum for 10 min after SCI followed by NOS antiserum for 20 min significantly improved functional recovery and BSCB integrity, inhibited edema formation, and diminished spinal cord pathology, suggesting that early blockade of both TNF-α and nNOS is beneficial [132]. Furthermore, acute inhibition of iNOS by antisense and pharmacological agents mitigated several pathological processes in SCI, including BSCB disruption [133]; acute molecular perturbation of iNOS via the antisense approach also enhanced neuronal preservation and functional recovery after SCI [134].

Endothelins

The endothelins (ETs) are a family of peptides consisting of three isoforms: ET-1, ET-2, and ET-3. ETs exert their biological effects by activating three receptor subtypes: ET_A, ET_{B1}, and ET_{B2} [50, 135]. ETs are the most potent known vasoconstrictors and have essential functions in embryonic development, vascular remodeling, and wound healing [136, 137]. Conversely, several reports suggest that BSCB disruption by traumatic SCI can generate ETs [138, 139]. Excessive activation of the ET system can be detrimental, leading to multidimensional pathological conditions, including prolonged vasospasm, ischemic damage, and BBB or BSCB disruption following brain injury or SCI [50, 136, 140, 141].

ET-1 and ET-3 are expressed in vascular endothelial cells within the intact spinal cord [142]. In the normal, uninjured spinal cord, the ET_A receptor is found mainly in vascular smooth muscle cells and primary afferent nerve fibers, while the ET_B receptor is abundantly expressed in endothelial cells, radial glia, a small population of astrocytes, and epithelial tissues [143]. ETs are injury-dependent peptides, and their synthesis is initially increased in neuronal and endothelial cells [140, 144], followed by delayed synthesis in reactive astrocytes [144, 145], infiltrating leukocytes [146], and activated microglia and macrophages [144, 147]. ET-1 contributes to the axial pattern of BSCB breakdown after SCI [140] and intrathecal ET-1 administration reduces spinal cord blood flow and results in prolonged BSCB disruption [141]. Moreover, intrathecal administration of ET (48 ng) results in moderate to severe locomotor deficits, whereas higher ET doses produce more pronounced locomotor deficits characteristic of severe SCI [148]. Notably, the ET antagonist, bosentan, can significantly diminish BSCB disruption [140] and SB209670, a potent nonselective ET receptor antagonist, can prevent or delay axonal degeneration after SCI [149].

An additional function of ET-1 is to mediate oxidative stress by modulating blood flow to the spinal cord [150]. ET-1 employs three routes of entry into the damaged spinal cord: (i) through the disrupted barrier; (ii) via softening of the spinal cord, a pathological condition termed myelomalacia; and (iii) through erythrocytes [50]. After SCI, ET_BR expression is markedly upregulated in glial cells, but vascular ET_AR/ET_BR expression remains unaltered [143]. Accordingly, therapeutic strategies that employ ET-1 antagonists to impede ET-1-mediated vasoconstriction are beneficial in terminating SCI progression. ET receptor antagonists likewise prevent or delay axonal degeneration after SCI [149], and blockade of ET_AR and/or ET_BR reduces inflammatory responses and oxidative stress, overturns MMP-9 activation, and enhances long-term neurological function post-injury [151]. Following spinal cord trauma, vascular ET_AR/ET_BR activation plays a critical role in post-traumatic ischemia, whereas astrocyte-only ET_BR activation is associated with reactive gliosis [143]. These studies suggest that BSCB disruption facilitated by ET activation is a crucial event leading to leukocyte infiltration, inflammation, and ROS-induced damage to the spinal cord.

Section 3. Therapeutic Approaches

Therapeutic approaches to improve BSCB integrity focus on restoring BSCB function to alleviate spinal cord tissue damage. Numerous drugs have been investigated for their capacity to target specific proteins that are involved in BSCB disruption after SCI (Table 1). Many reports suggest that hypoxic conditions [165] and certain drugs (e.g., methamphetamine) [166], like traumatic SCI, strongly increase the permeability of the BSCB. Recently, pretreatment with highly purified rat growth hormone in an animal model significantly attenuated edema formation and BSCB permeability following SCI [167]. Intravenously delivered mesenchymal stem cells also reduced BSCB leakage and the permeation of Evans blue, a marker of barrier permeability [168]. Therefore, future

Table 1 Modulators of blood-spinal cord barrier permeability

Therapeutic approach	Class	BSCB permeability	Ref
Valproic acid	Histone deacetylase inhibitor	Valproic acid improves functional recovery by attenuating BSCB disruption via inhibition of MMP-9 activity after SCI.	[152]
Vascular endothelial growth factor and Angiopectin-1	Angiogenic response and vascular stability proteins	Sustained delivery of both $VEGF_{165}$ and Ang-1 using adeno-associated virus vector immediately after injury improves BSCB integrity and functional recovery after SCI.	[104]
B9430	Bradykinin antagonist	B9430 decreased the BSCB disruption immediately after SCI but failed to affect delayed opening of BSCB observed 72 h after SCI.	[116]
Fluoxetine	Selective serotonin reuptake inhibitor	Fluoxetine prevented BSCB disruption via inhibition of MMP activation after SCI.	[4]
Dexmedetomidine	α_2-adrenergic receptor agonist	Dexmedetomidine preconditioning stabilized the BSCB integrity against spinal cord I/R injury by inhibition of MMP-9 and enhancing the Ang1-Tie2 system.	[153]
L-N^G-Nitroarginine (L-NNA)	nNOS inhibitor	Long-term treatment with L-NNA attenuated SCI-induced NOS upregulation, BSCB breakdown, edema formation, and cell injury.	[154]
Ghrelin	Neuropeptide	Ghrelin inhibits BSCB disruption/hemorrhage by attenuating MMP-9 and SUR1/TrpM4 expression and activation after SCI.	[155]
Tamoxifen	Estrogen receptor antagonist	Tamoxifen attenuates BSCB permeability, tissue edema formation, microglial activation, neuronal cell death, and myelin loss in rats subjected to SCI significantly decreased interleukin-1beta production.	[156]
D-JNKI1	Specific inhibitor of JNK pathway	D-JNKI1 treated animals show a lower increase of erythrocyte extravasation and BSCB permeability in a mouse model of SCI.	[157]
iNOS antisense oligonucleotides, N-[3(Aminomethyl) benzyl] acetamidine or aminoguanidine	iNOS inhibition	All of iNOS inhibitors reduced the degree of BSCB disruption and neutrophil accumulation within the injury site in a rat model of SCI.	[133]
ONO-5046	Neutrophil elastase inhibitor	Pretreatment of ONO-5046 significantly reduced the increase of neutrophil accumulation or infiltration and the extent of BSCB permeability.	[158]
Aminoguanidine	Nitric oxide synthase inhibitor	Aminoguanidine injection at 150 mg/kg after SCI significantly decrease BSCB permeability in a rat model of SCI.	[159]
Bone marrow stromal cells (BMSC)	Stem cells	Intrathecal transplantation of BMSC stabilized BSCB integrity through inhibiting the upregulation of MMP-9 and TNF-α induced by spinal cord I/R injury in rabbits.	[160]
Ischemic preconditioning	Preconditioning	Ischemic preconditioning attenuates the increase in BSCB permeability due to spinal cord I-R injury in rabbits by the preservation of tight junction protein ZO-1 and reducing MMP-9 and TNF-α expression.	[161]
MiR-27a	MicroRNAs	MiR-27a ameliorates inflammatory damage to the BSCB after spinal cord I/R injury in rats by downregulating TICAM-2 of the TLR4 signaling pathway.	[10]
17β-Estradiol (E2)	Estrogen steroids	E2 (300 μg/kg) administration immediately after SCI inhibits MMP-9 and SUR1/TrpM4 expression and thereby attenuates BSCB disruption/hemorrhage in a rat model of SCI.	[162]
Melatonin	Hormone	Melatonin (50 mg/kg) exhibited significantly reduced BSCB permeability in a mice model of SCI through reducing MMP3/AQP4/HIF-1α/VEGF/VEGFR2 expression after SCI.	[163]
Sevoflurane	Anesthetic	Preconditioning with 2.4 % sevoflurane attenuated spinal cord IR injury by inhibiting recruitment of microglia and secretion of MMP-9; thus inhibiting downstream effects on inflammatory damage to BSCB integrity and neuronal apoptosis.	[164]

TICAM-2 Toll-like receptor adaptor molecule 2, *TLR4* Toll-like receptor 4, *I/R* ischemia-reperfusion, *JNK* c-Jun N-terminal kinases, *ZO-1* zonula occludens, *BMSC* Bone marrow stromal cells, *BSCB* blood-spinal cord barrier, *VPA* valproic acid, *TNF-α* tumor necrosis factor alpha, *SCI* spinal cord injury

approaches to prevent barrier breakdown after SCI might be directed toward developing proteins or drugs or combinations thereof to synergistically target different aspects of BSCB pathophysiology.

Conclusions

SCI and other spinal cord disorders significantly impair the normal function of the BSCB. The BSCB represents the first line of defense against injuries to the spinal cord, and BSCB dysfunction is well documented in SCI. Vascular damage and barrier breakdown are universal consequences of SCI, both clinically and in animal models. BSCB disruption after SCI generates harmful levels of various bioactive factors, including MMPs, TNF-α, ETs, bradykinin, inflammatory cytokines, and ROS. TJ proteins represent the major protein component of the BSCB and, therefore, interference with TJ content and function can impact BSCB permeability. Inflammatory factors also increase BSCB permeability by time-dependently modulating the expression and distribution of TJ proteins. Finally, strategies to improve barrier integrity may delay the progression of SCI or related disorders, and target proteins involved in maintaining BSCB integrity may provide an attractive strategy to arrest or impede SCI progression.

Acknowledgments This work was supported by a grant of the National Research Foundation of Korea (NRF) (NRF-2014R1A1A2059118) and the Ministry of Science, ICT and Future Planning (NRF-2013R1A2A1A09013980).

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