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REVIEW

Ischemia Reperfusion Injury Induced Blood Brain Barrier Dysfunction and the Involved Molecular Mechanism

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Abstract

Stroke is characterized by the abrupt failure of blood flow to a specific brain region, resulting in insufficient supply of oxygen and glucose to the ischemic tissues. Timely reperfusion of blood flow can rescue dying tissue but can also lead to secondary damage to both the infarcted tissues and the blood–brain barrier, known as ischemia/reperfusion injury. Both primary and secondary damage result in biphasic opening of the blood–brain barrier, leading to blood–brain barrier dysfunction and vasogenic edema. Importantly, blood–brain barrier dysfunction, inflammation, and microglial activation are critical factors that worsen stroke outcomes. Activated microglia secrete numerous cytokines, chemokines, and inflammatory factors during neuroinflammation, contributing to the second opening of the blood–brain barrier and worsening the outcome of ischemic stroke. TNF-α, IL-1β, IL-6, and other microglia-derived molecules have been shown to be involved in the breakdown of blood–brain barrier. Additionally, other non-microglia-derived molecules such as RNA, HSPs, and transporter proteins also participate in the blood–brain barrier breakdown process after ischemic stroke, either in the primary damage stage directly influencing tight junction proteins and endothelial cells, or in the secondary damage stage participating in the following neuroinflammation. This review summarizes the cellular and molecular components of the blood–brain barrier and concludes the association of microglia-derived and non-microglia-derived molecules with blood–brain barrier dysfunction and its underlying mechanisms.

Keywords Ischemic stroke · Blood–brain barrier · Microglia · Cytokines · Transporters · Ion channels

Introduction

According to the different etiology, there are two types of stroke: hemorrhagic stroke and ischemic stroke. Hemorrhagic stroke is characterized by the rupture of blood vessels in the brain, leading to bleeding into the brain. However, the pathophysiology of ischemic stroke features an abrupt failure of blood flow supply to a specific brain region, which leads to insufficient oxygen and glucose in the ischemic brain tissue [1]. Notably, ischemic stroke brings about magnificent changes in the morphology of cells in the brain. After the organelles' swell and the cell contents' leak into the extracellular space, necrosis occurs, eventually resulting in the loss of neuronal function. Additionally, lactic acid production increases due to the transition to anaerobic metabolism, leading to tissue acidosis. Consequently, excess tissue acidosis and insufficient ATP production cause membrane transporter dysfunction and also compromise cellular Ca^{2+} buffering, which then initiates the cascade of phosphorylation and neuronal damage [2, 3]. Importantly, blood–brain barrier dysfunction, inflammation, and activation of glial cells, among other pathophysiologies accompanying ischemic stroke, are critical factors that worsen the stroke outcome.

The blood–brain barrier (BBB) is a hallmark of the mature central nervous system (CNS), which functions as a diffusive barrier selectively ruling out most blood-borne substances from getting into the brain. The BBB is formed by an

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endothelial layer wrapped with pericytes (PCs), which share the same basement membrane with endothelial cells (ECs), and the astrocyte (AC) end-feet continuously surround this layer. Likewise, neurons form innervation on the surface with the AC end-feet [4]. Simultaneously, these cells are components of the neurovascular unit (NVU) as well. As an integral part of BBB, tight junctions (TJs) present between the cerebral ECs and contribute to the diffusive function of the BBB. In the setting of ischemic stroke, insufficient oxygen and glucose significantly influence BBB function, altering its TJs expression and distribution, the morphology of its cellular parts, transporter functions, and so on. Most of the TJ proteins get degraded while the expression of transporters may increase or decrease depending on their location in the infarcted tissues. This BBB breakdown can lead to edema, ionic homeostasis disruption, and immune infiltration [5]. Importantly, the neuroinflammation following ischemic stroke contributes to the biphasic opening of the BBB, during which cytokines and inflammatory factors secreted by glial cells and neurons play a key role. In the present review, we will discuss the cellular and molecular dysfunction of the BBB after ischemia and its underlying mechanisms. Furthermore, we will discuss the implications of these mechanisms which give insight into clinical diseases and treatment.

Basic Components of BBB and Their Dysfunction Following Ischemia/Reperfusion Injury

The components of the BBB involve unique cells, such as AC end-feet, PCs, ECs, and neuronal innervation. ECs contact with PCs by "peg-and-socket" junctions in a shared basal lamina with AC end-feet that form the ensheathment of brain capillaries [6], and the main components of BBB are shown in Fig. 1. Additionally, interneurons and perivascular microglia contact with ECs, PCs, and ACs to form the construction of the NVU [7]. Rather than looking at each cell type separately, these cells interact intimately and reciprocally. Furthermore, TJs seal adjacent endothelial cells along with ACs and PCs to form a selective barrier that regulates solute movement, maintaining normal BBB function.

Ischemia can rapidly elicit cerebral edema, developing stepwise from cytotoxic edema to vasogenic edema [8]. This is partly due to the BBB's increased permeability, resulting from cellular components' dysfunction and disruption of TJ proteins. And the degradation of TJ proteins is the hallmark of BBB dysfunction. Here we concluded the changes in different components of the BBB caused by ischemia/reperfusion(I/R) injury and their final influence on BBB.

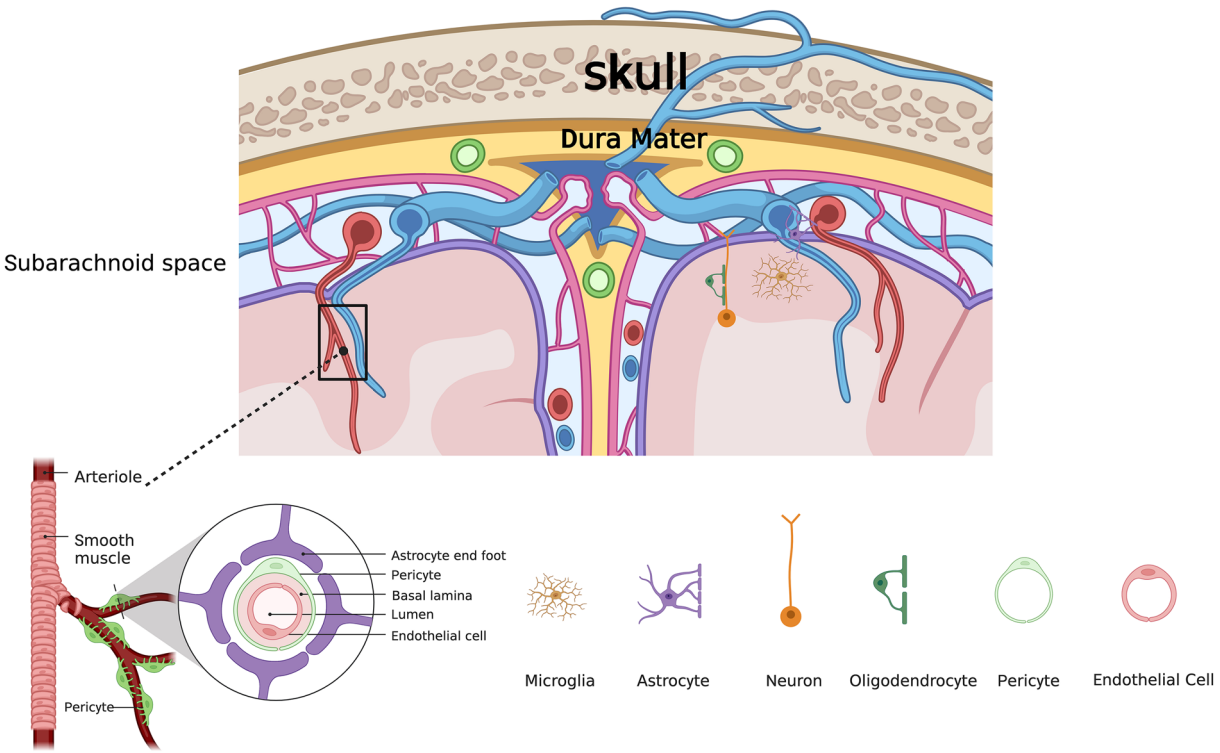

Fig. 1 The components of BBB. The constitution of the BBB involves astrocytes end-feet, pericytes, and endothelial cells. These cells interact intimately and reciprocally with each other and together maintain the integrity of the BBB

Endothelial Cell and Tight Junction Proteins

Endothelial cells (ECs), composing the BBB, are equipped with specialized TJ structures, shaping a selective barrier that effluxes potential toxins and delivers specific nutrients into the brain [9]. Subtle changes can result in the significant alteration in BBB permeability. Although more attention has been paid to TJ protein degradation during BBB dysfunction induced by ischemic stroke, an increasing focus has shifted to the dysfunction of the cerebral endothelium directly [10]. Consequently, ischemic stroke impairs normal endothelial morphology and function. As investigated, the vessels in the ischemic penumbra showed signs of swelling and edema of the endothelium [11], and vasodilation and vasoconstriction function gets compromised [12, 13], which ruins the restoration of cerebral blood flow. Furthermore, I/R injury also elicits endothelial apoptosis and necroptosis [14, 15], leading to the impaired function of the BBB, thereby limiting substrates to pass the selective barrier.

In the CNS, TJs are part of the ECs, which confer ECs to their CNS phenotype. TJs are critical to sustaining functional BBB integrity, enabling the BBB to restrict the free flow of water and solutes. Three integral proteins form TJs on the cell membrane–claudin, occludin, and JAM, and many cytoplasmic accessory proteins including ZO-1, ZO-2, ZO-3, cingulin, and others [16], and the main components of TJs and their arrangement are shown in Fig. 2. The zonula occludens proteins (ZO-1, ZO-2, and ZO-3) are members of the MAGUK family [17]. Adherens junctions (AJs) recruit ZO-1 and ZO-2 to nascent adhesion sites to accomplish their formation [18]. Additionally, the assembly of TJ proteins induces claudin polymerization and conjugation of an incessant TJ belt [19]. Claudin proteins are the most abundant transmembrane proteins of the TJs and play a determining role in paracellular ion conductance [20]. By regulating the degradation and distribution of Claudin 5, autophagy could mitigate the hypoxic injury to the BBB induced by ischemic stroke [21]. Claudin proteins are also substrates of diverse kinases, including protein kinase C (PKC), protein kinase A (PKA), and mitogen-activated protein kinase (MAPK), so they serve as a modulator to regulate TJs [22]. Moreover, Occludin interacts with many other TJ-associated proteins. Notably, ZO-1 and ZO-2 were initially found to directly interplay with occluding [23]. Likewise, VE-cadherin is one of the adherens junction proteins regulating adhesion between ECs. In the CNS, VE-cadherin is exclusive to ECs, assisting them to interact with other same type cells. Therefore, VE-cadherin plays an important role in the maintenance of the BBB [24]. Evidence demonstrates that recycling endocytosed VE-cadherin increased the

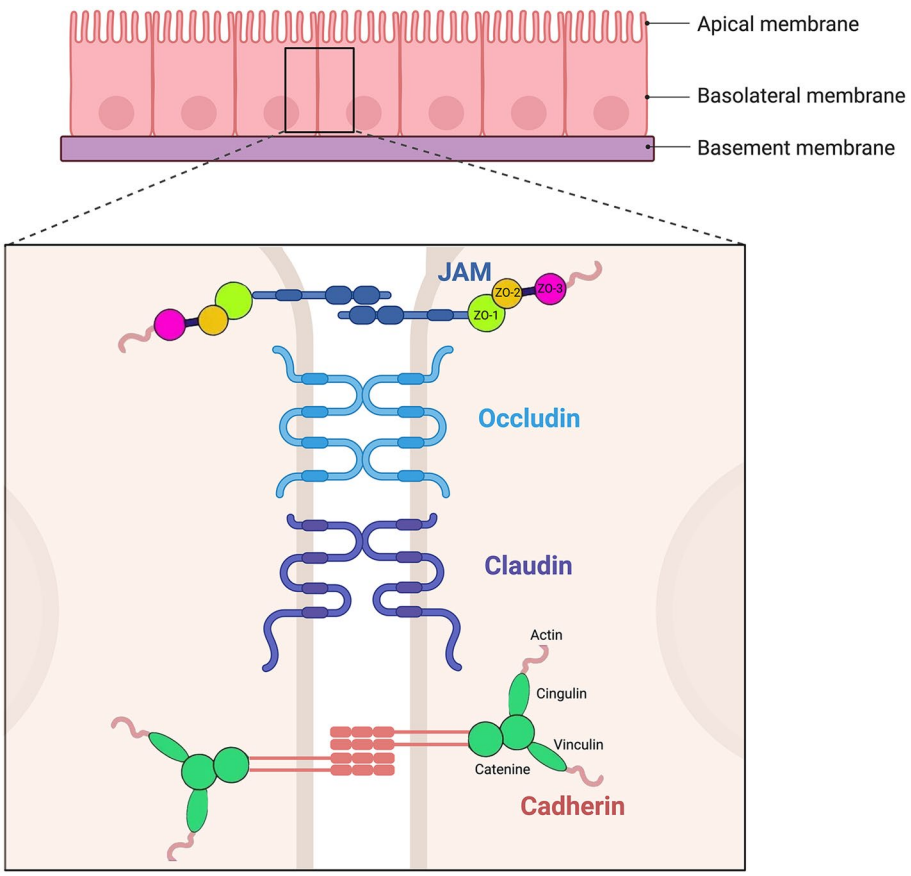

Fig. 2 The organization of tight junction proteins (TJs). The primary constituents of an integral TJ, including proteins on the membrane—claudin, occludin, and junction adhesion molecules (JAM), and accessory proteins in the cytoplasm—ZO-1, ZO-2, ZO-3, cingulin, etc.

integrity of the vascular system following BBB dysfunction [25]. Ischemic injury arouses various forms of pathological dysfunction in the brain and its insult in the BBB is mainly due to the degradation, disintegration, and redistribution of the TJ proteins, such as VE-cadherin, occludin and ZO-1 [26–28]. TJs breaking down compromises BBB integrity, and its permselectivity becomes damaged as a result of this.

Pericytes

Pericytes (PCs) are the NVU's perivascular cells inserted into the basement membrane (BM), surrounding ECs and acting as a roundabout target for small molecules to regulate BBB function [29]. Its contractile ability contributes to the normal function of the cerebral vasculature. Pericytes enhance angiogenesis in leptomeninges and infarct brain regions, contributing to the recovery of cerebral blood flow in the affected areas thus improving tissue repair [30]. By trapping blood cells, pericytes could inhibit the occluded vessels from reperfusion after ischemic stroke, thus functioning as a potential therapeutic target [31]. Previous studies have shown that pericytes are vulnerable to ischemic injury, and they could die a few minutes after insufficient blood flow and therefore constrict the microcirculation [32]. In the setting of chronic cerebral hypoperfusion, neurotoxic molecules pass through the BBB via endothelial transcytosis, which leads to the loss of pericytes and ultimately, the dysfunction of the BBB [33].

Astrocyte

Astrocytes (ACs) exist around cerebral microvessels and mediate BBB function via AC-derived factors and astrocytic terminal processes (end-feet) [34]. Under ischemic conditions, the number of activated astrocytes increased, most of which are not perivascular astrocytes, indicating that the activated astrocytes mainly got involved in neurological inflammation instead of restoring and regulating the impaired vasculature. Additionally, ischemic insult activates perivascular astrocytes, develops swollen end-feet, and retracts processes from blood vessels, leading to the opening of gap junctions and disassembly of TJ proteins [35]. Further studies showed that under OGD/R condition (oxygen glucose deprivation/reperfusion, the I/R condition for cultured cells), the level of apoptosis of astrocytes increases and neurological inflammation is elicited [36]. Notably, the crosstalk between ECs and perivascular ACs is critical to maintaining the function of the selective barrier and its completeness [37]. Furthermore, the changes in reactivated perivascular astrocytes insulted by ischemic injury ruined the astrocyte-endothelium interaction, leading to morphological alterations in BBB and its dysfunction [38].

Microglia

Microglia are the resident immune cells in the CNS, whose role in maintaining and regulating the structural and functional completeness of the BBB is yet to be elucidated [39]. In the setting of ischemic stroke, microglia are activated, which initiates following neuroinflammation. As a part of the NVU, microglia can secrete numerous inflammatory factors, such as TNF-α, IL-1 and IL-6, to affect the permeability of the BBB [40]. Microglia could also phagocytize cell debris to suppress the inflammatory response, consequently assisting recovery of the BBB. The dual function of microglia relates to its different phenotypes which are M1 (pro-inflammatory type) and M2 (anti-inflammatory type) [41]. Notably, activated microglia contribute to BBB leakage via the downregulation of endothelial junctional proteins such as claudin-5 and occluding [42]. Furthermore, M1 microglia secrete TNF-α to elicit necroptosis in endothelial cells, resulting in compromised BBB integrity and function during the pathological condition of I/R [43]. Simultaneously, microglia also polarizes into the M2 phenotype in acute ischemic stroke, limiting poststroke inflammation progression in the early phase of ischemic stroke [44].

Neuron

As a part of the neurovascular unit, neurons interact with ECs [45] and their activities impact cerebral blood flow [46]. Studies show that experience-dependent neuronal activity alterations could influence endothelial function [47]. Additionally, neuronal activity mediates brain endothelial gene expression and is inversely correlated with the expression of BBB ABC (ATP-binding cassette) efflux transporters in the BBB [46]. Following I/R injury, transient autophagy activation in neurons occurs, leading to lysosomal dysfunction during the later phase and contributing to the compromised synaptic plasticity in the reperfusion phase [48]. Moreso dysfunction of the BBB exacerbates neuronal injury as CLEC14A deficiency increases leakage in the endothelial barrier, which leads to larger infarct areas of affected brain tissue and severe neurological defects following I/R injury [49] (The changes in cells following I/R injury are summerized in Fig. 3).

Mechanisms Underlying BBB Dysfunction Following I/R Injury

Microglia-Derived Molecules Involved in BBB Breakdown

During ischemia stroke, high levels of cytokines and chemokines produced by microglia, such as TNF-α, IL-1β,

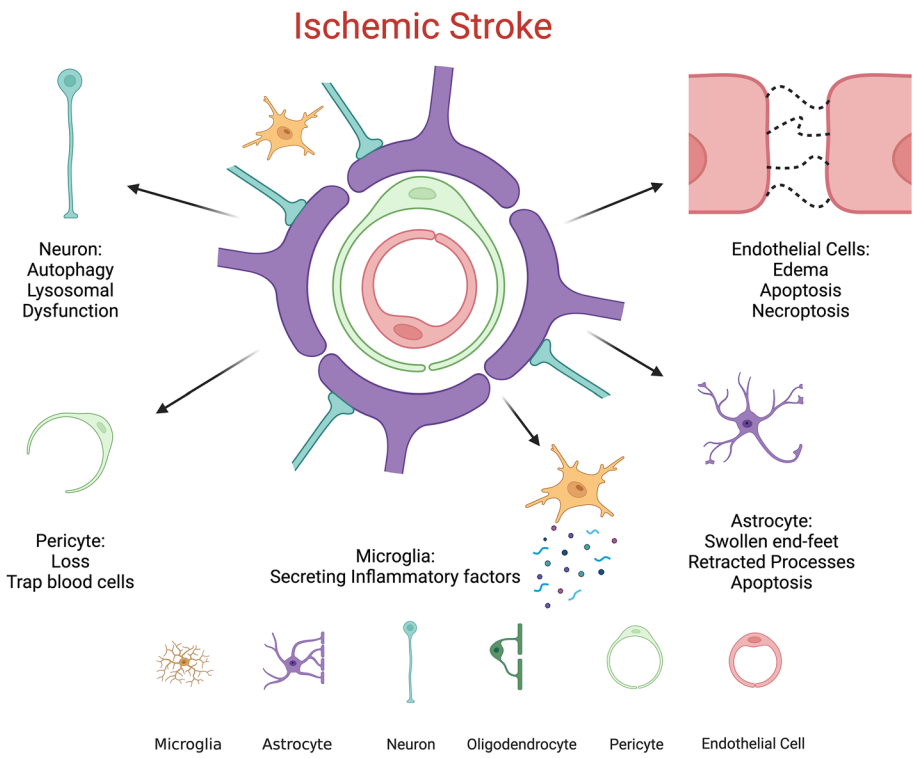

Fig. 3 I/R insult induces alterations in the cellular composition of BBB and the involved molecules. They ultimately cause TJs degradation and breakdown of the endothelial belt

and IL-6, upregulate EC adhesion molecules and speed up the infiltration of leukocytes, contributing to the impairment of the BBB [50]. Importantly, different inflammatory factors and chemokines secreted by microglia exert different function phenotypes. Here, we concluded common cytokines and chemokines that function on TJ proteins and ECs, ultimately affecting the integrity and function of the BBB.

Cytokines

Tumor necrosis factor (TNF)-α, an inflammatory factor released from M1 phenotype-activated microglia, is a pleiotropic molecule that regulates cell proliferation, death, immunity, and metabolism [51]. Upon injury, TNF-α increases as early as 6–24 h following permanent middle cerebral artery occlusion (pMCAO) [52]. A. Q. Chen et al. found that M1 microglia-derived TNF-α could bond to its receptors on EC to initiate the necroptosis process, leading to endothelial necroptosis and destroying the completeness of the endothelial barrier [14]. Notably, ZO-1 is a downstream target of TNF-α signaling, and its level drops in cerebral I/R injury [53]. However, the intercellular ZO-1 distribution and its expression got improved when inhibiting the TNF-α receptor with its antagonist, R-7050. Simultaneously, R-7050 also increases TEER (trans-endothelial electrical resistance) and lowers the permeability of the BBB [54].

IL-1 is mainly produced by resident microglia in the brain [55], and its concentration increases up to 40 to 60-fold during the first 24 h after the MCAO condition [56]. Importantly, systemically infusing IL-1β antibody ameliorates parenchymal brain injury and attenuates apoptosis and caspase-3 activity in non-neurons [57]. R. Wong et al. found that deleting cerebral ECs IL-1R1 greatly decreased both ischemic lesions and IgG leakage. However, there's no significant impact on neurons [58]. Another isoform of IL-1, IL-1α, is widely known as a direct regulator of angiogenesis after ischemic injury [59]. Furthermore, it exerts an identical function as IL-1β via IL-1RI [60]. However, further explorations are necessary to determine the exact mechanisms underlying the functions.

In the acute phase of stroke, activated microglia would secrete IL-6 to contribute to post-stroke inflammation [61]. Previous studies showed that the expression and bioactivity of IL-6 were induced in the infarcted hemisphere in the pMCAO rat model [62]. Additionally, after 24 h exposure to IL-6, BBB permeability was compromised [63]. Likewise, the TJ protein expression decreased after treatment with IL-6, IL-17, or TNF-α. However, their study showed that IL-6 reduced ischemic damage by activating the STAT3 transcription factor singling pathway [64, 65]. Notably, oncostatin M (OSM) is the most powerful molecule among the IL-6 family to impair BBB function [66]. Its expression peaked at 12 h post-stroke and remained stable until 72 h [67]. Recent evidence demonstrates its close relationship with the integrity of BBB. OSM was found to downregulate TJs thus impairing the endothelial integrity of BBB under both normal and inflammatory conditions via prolonged activation of the JAK/STAT3 signaling pathway

[68]. Additionally, OSM also stimulates brain cells to produce prostaglandins and cytokines, thus decreasing TEER of in vitro BBB model [69]. The above findings illustrate that IL-6 family closely associates with BBB function and may be a vital regulator to maintain an intact BBB.

Chemokines

Chemokines are a big group of small proteins secreted by resident microglia in post-stroke inflammation and signal via G protein-coupled heptahelical chemokine receptors on the cell surface, attracting and activating leukocytes further [70]. Chemokine (C–C motif) ligand 2 (CCL2) participates in the inflammatory response and modulates monocytes migrating into tissues and the subsequent differentiation of monocytes into macrophages [71]. CCL2/CCR2 increased its expression on brain ECs and ACs in the ipsilateral hemisphere, and the highest expression of CCL2 was observed 24 h after stroke. Additionally, CCL2 regulates BBB permeability via the interaction with CCR2 on brain endothelial cells [72]. When mesenchymal stromal cells overexpressing CCR2 were transplanted into animal and cell models, ischemic lesions, BBB permeability, and neurological function improved. Furthermore, MSC^{CCR2} (mesenchymal stromal cells expressing CCR2 on the cell surface) partially restored BBB integrity in a PRDX4-mediated antioxidant manner after stroke [73]. Overall, CCL2 is one chemokine that links tightly to ECs tightly and is therefore relevant to the integrity of the BBB. Notwithstanding, more chemokines may take part in the mediation of BBB during physiological and pathophysiological conditions, which requires more research to illustrate.

Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are members of the endopeptidase's family. They function to degrade and remodel the extracellular matrix (ECM) proteins [74]. Studies demonstrated that MMP-2/-9 released from activated microglia could induce TJs degradation BBB dysfunction [75]. Besides microglia, astrocytes and some cortical and cerebellum neurons also express MMPs in the brain [76, 77]. MMP-9 (gelatinase B), a member of MMPs, are well known for its regulation of I/R-induced BBB breakdown via the degradation of TJ proteins and the basal lamina of capillaries and infiltration of immune cells [78]. Furthermore, the activation of endothelial MMP-9 was observed when endothelial cells were exposed to astrocytes, indicating a relationship between endothelial MMP-9 activity and astrocytic influence. At the same time, ACs could release soluble factors to mediate BBB function via the activation of endothelial MMP-9 [79]. Recent findings showed that ICS II, which is derived from Herbal Epimediiand, could bind to and inhibit MMP2/9 by attenuating the MMP/TIMP1 balance to improve BBB dysfunction and suppress the death of hipponeurons [80]. Besides, pretreatment with CB2R agonist JWH-133 prevented activating MMP9 and upregulated perivascular expression of STLR4/MMP9 after cerebral I/R injury [81]. However, MMPs are emerging in research and demonstrate regulatory functions on the BBB, and more research is required to elucidate their underlying mechanisms.

Non-Microglia Derived Molecules Mediate BBB Permeability

Micro-RNAs

Micro-RNAs(miRNAs) that are small non-coding RNAs have emerged as a kind of gene expression regulator by inhibiting or degrading target mRNAs [82]. During the last decade, accumulating research has emerged to prove the therapeutic function of miRNAs on experimental I/R murine models. Many miRNAs are abundant in endothelial cells, which resist the I/R insult by targeting TJ proteins or cellular components of ECs. The miRNA function in the I/R condition is listed in the following Table 1.

Circular RNAs

Circular RNAs (circRNAs) are a particular kind of RNA with a circular structure rather than a linear structure formed by a back-splicing mechanism that joins 30 and 50 methyl guanosine caps together [112]. They can specifically combine with miRNAs to regulate the expression of relevant genes by acting as miRNA sponges [113]. Circ-Foxo3 is highly expressed in normal tissues and its expression is usually downregulated in some pathological conditions [114]. Recently, studies proved that circ-Foxo3 expression was elevated following tMCAO with autophagy activation. Moreover, short-FoxO3 exacerbated the TJ deformation, which can be attenuated by circ-FoxO3 overexpression, suggesting circ-FoxO3 is needed for the integrity of the BBB following ischemic stroke in an autophagy-dependent manner [115]. With more focus on gene modifications via non-coding RNAs, miRNA and circRNAs may be a potential therapy for I/R injury.

Long Non-coding RNAs

Long non-coding RNAs (LncRNAs) are non-coding RNAs that are longer than 200 nucleotides (nt), they can function in a regulatory role at post-transcriptional, epigenetic, translational, and post-translational levels. Unlike miRNAs, lncRNAs are highly cell-specific [116]. Of the many lncRNAs expressed in ECs, some are exclusively related to

Table 1 miRNAs tightly associated with BBB damage in I/R conditions

miRNA	Locations	Changes in I/R condition	Treatment in experiments	Function on I/R	Reference
miRNA-98	Xp11.22	↓	Overexpression	Improve neurological outcomes; Attenuate post-stroke inflammation; Reduce BBB disruption	[83]
miRNA-126	9q34.3	↓	Knockdown	Impair angiogenesis and vessel integrity;	[84, 85]
			Overexpression	Suppress inflammation; Reduce infarct and edema volume; Elevate BBB leakage;	
miRNA-30a	6q13	↓	Inhibition	Reduce the permeability; Block the loss of TJ proteins Decrease zinc accumulation and the loss of ZnT4 in the microvessels of the ischemic brain	[86]
miRNA-182	7q32.2	↑	Knockdown Inhibition	Target endothelial cells Reduce infarction volume; Preserve BBB integrity preserved; Attenuate degradation of TJ proteins	[87, 88]
miRNA-130a	11q12.1	↑	Inhibition	Regulate occludin via HoxA5; Reduce the size of cerebral infarct; Suppressed OGD-induced increase of paracellular permeability	[89]
miRNA-15a and miRNA-16–1	13q14.2 13q14.2	↑	Deletion	Upregulate Claudin-5; Inhibited M1-type microglia/macrophage polarization in the peri-infarct area; Enhanced angiogenesis; Improved long-term functional recovery	[90]
miRNA-132/212	17p13.3 11; 11 B5	↑	Overexpression	Attenuates cerebral injury via repressing MMP; Target TJ proteins including Cldn1, Jam3, and Tjap1; Attenuate the decline in TEER values after OGD	[91, 92]
			Downregulation	Aggravate ischemic brain injury; Aggravate neuronal damage via RBFox-1; Suppress vascular bed; Destabilize tight junction protein expression	
miRNA-34a	1p36.22	↑	Knockout	Participate in the opening of BBB during the early phase of ischemic reperfusion; Ameliorate stroke infarction; Reduce BBB permeability; Alleviates disruption of tight junctions; Improves stroke outcomes	[93]
miRNA-92b	1q22	↓	Overexpression	Maintain the BBB integrity; Raise the viability and lessen the permeability of OGD-induced BMECs;	[94]
miRNA-668	14q32.31		Inhibition	Attenuate infarction volume and BBB leakage; Attenuate neurological functions; Attenuate BBB permeability; Attenuate increase in cytokine levels; Attenuate neuronal cell apoptosis	[95]
miRNA-149–5	2q37.3	↓	Overexpression	Regulate pericyte migration, N-cadherin expression; Regulate BBB permeability via targeting S1PR2; Improved the outcome of transient middle cerebral artery occlusion (tMCAO) rats	[96, 97]
miRNA-29b	7q32.3	↓	Overexpression	Attenuate BBB dysfunction; Inhibit Aquaporin 4; Reduce infarct volume and edema; Decrease apoptosis of neurons and hCMEC/D3 cells	[98, 99]
miRNA-150	19q13.33	↓	Overexpression	Increase BBB permeability in vivo and in vitro; Decrease BMEC survival; Decrease claudin-5 expression	[100]

Table 1 (continued)

miRNA	Locations	Changes in I/R condition	Treatment in experiments	Function on I/R	Reference
miRNA-122	18q21.31	↓	Overexpression	Promote proliferation; Inhibit apoptosis and autophagy; Decrease the infarct area	[101, 102]
miRNA-210	11p15.5	↑	Overexpression	Decrease infarct volume and hemispheric swelling	[103, 104]
miRN-21	17q23.1	↑	Inhibition	Downregulate MMP-9; Improve BBB permeation	[105, 106]
miRNA-539	14q32.31	↓	Overexpression	Inhibit OGD/R-induced BBB disruption; Suppress the expression of MMP-9 mRNA and protein	[107]
miRNA-155	21q21.3	↑	Deletion	Protect I/R-induced brain injury and neurological deficits;	[108]
miRNA-149-5p	2q37.3	↓	Overexpression	Attenuate pericytes migration; Increase N-cadherin in pericytes; Increase BBB integrity; Promote neurological recovery after stroke	[97]
miRNA-1	20q13.33	↑	Inhibition	Reduce infarct volume; Reduce brain edema; Decrease BBB permeability	[109]
miRNA-503	Xq26.3	↑	Inhibition	Reduce infarct volume; Improve BBB dysfunction; Increase cerebral blood flow (CBF); Decrease apoptosis and the production of ROS and NO in ECs; Increase permeability of HBMECs	[110]
miRNA-141-3p	12p13.31	↓	Inhibition	Higher cell apoptosis rate Increase ROS level in PC 12 cells	[111]

BBB function via influencing the TJs dynamics. LncRNA HOTAIR also modifies the levels of occludin, claudin-5 and ZO-1 by interacting with upstream stimulatory factor 1 (USF1) [117]. Some lncRNAs interact with miRNAs to mediate TJs, primarily functioning as miRNA sponges or competing endogenous RNAs (ceRNAs) to suspend the target genes of miRNAs. As reported, lnc00462717 could bind to polypyrimidine tract binding protein (PTBP1) to downregulate miR-186-5p, thus regulating occludin levels in an in vitro blood-tumor barrier model [33]. Additionally, Linc00174 and FOS like 2 (FOSL2) bind to miR-138-5p and miR150-5p to exert TJs regulator function [51]. Moreover, lncRNA MIAT competes with miR-140-3p to adjust TJs expression [95]. Under the I/R condition, XIST was downregulated, leading to the decreased expression of ZO-1 and claudin-5 [118]. Besides, inhibiting lncRNA H19 neuron exosomes significantly reduced the permeability of the EC monolayer in in vitro OGD/R conditions [119]. Reported as the most upregulated lncRNA, the upregulation of Malat1 was found to contribute to the survival of brain microvascular endothelial cells (BMECs) by promoting the autophagy of BMECs [120]. Meanwhile, You at el. found that MEG3 expression of BMECs increased in OGD/R condition and inhibiting its expression could relieve the hyperpermeability of the BBB [121]. Several signaling pathways are known to be involved, including the Wnt/β-catenin signaling pathway and Notch pathway, as well as some molecules like STAT3, HIF-1α, P53, NOX4 and VEGF [121, 122].

Heat Shock Proteins

Heat shock proteins (HSPs) are a group of proteins binding to DNA to regulate gene expression [123]. An early study reported that the expression of HSPB8 was upregulated to attenuate cell death induced by OGD/R injury [124]. Likewise, Li et al. found that HSPB8 significantly alleviated brain injury during I/R. However, they also observed aggravated mitophagy and TJs degradation following HSPB8 overexpression, which boosted autophagic flux and weakened its protective effect on BBB after MCAO/R [124, 125]. Additionally, HSP70 overexpression facilitated neuronal repair and improved recovery of neurological function after stroke as well. Moreover, Jiang found that Pla-Exo inherited HSP70, and it reduced I/R injury by reducing ROS generation and maintaining the integral mitochondria. Notably, it also protects BBB from dysfunction by elevating the integrity of TJ proteins [126]. Furthermore, recent studies show that endothelial HSP70 induction by GGA could inhibit inflammation BBB leakage following stroke [127].

Transporters and Ion Channels Participate in BBB Breakdown

Ion disturbance occurs early during I/R injury, contributing to hypoxic injury. Several ion channels and transporters are suggested to be involved in the regulation of ionic homeostasis during I/R, which is essential for BBB function, such as Na^+/H^+ exchanger isoform 1 (NHE1), Na^+/Ca^{2+} exchanger (NCX), Na^+/Ca^{2+} cotransporters (NBCs), voltage-gated Na^+ channel (Navs), ATP-sensitive K^+ channel (K_{ATP} channel), Na^+-K^+-ATP pump, and so on [128–131]. Here we try to give insights into the updates of these channel's roles in the setting of I/R injury.

NHE1

NHE1 mainly functions in astrocytes as a pathway for H^+ efflux in exchange for Na^+ influx [132]. Recently, evidence demonstrated that infarction and neurological function both are improved in *Nhe1* null mice. Simultaneously, microvessel damage and BBB integrity were improved in *Nhe1* null mice in the setting of ischemic stroke [133]. Moreover, in the astrocyte OGD/R model, NHE1 was activated, leading to Na^+ overloading and swelling at the end feet [134]. Knockout of *Nhe1* in astrocytes resulted in reduced paracellular permeability and enhanced cerebral perfusion and angiogenesis. Additionally, the endothelial Wnt/β-catenin signaling pathways play a vital role in this process [135]. Furthermore, NHE1 also exists at the abluminal side of endothelial cells in the brain capillaries, which regulates Li^+ influx in brain endothelium and is critical to maintaining Li^+-Na^+ homeostasis [136]. Thus, the close association between NHE1 and astrocytes and its role in ionic homeostasis contributes to BBB regulation during I/R condition.

NCX

To sustain normal Ca^{2+}-Na^+ homeostasis, NCX plays an indispensable part. NCX1-3 is selectively expressed in the brain tissues, such as pyramidal neurons in the cortex and dentate gyrus within the hippocampus [137, 138]. During ischemic stroke, NCX is downregulated in the core but upregulated in the penumbra [139]. Moreso, recent evidence shows that the expression of NCX1 and NCX3 are reduced in the hippocampus of neonatal mice subjected to hypoxic-ischemic. In contrast, the activation of NCX significantly reduced hippocampal injury and improved short-term memory and motor performance [140]. BBB dysfunction is closely related to intracellular calcium levels and calcium-mediated signaling, such as C3a/C3aR signaling, which functions as a second messenger to mediate endothelial pMLC activity and endothelial VE-cadherin homeostasis [141].

NBCs

NBCs are widely expressed in the neurons and astrocytes [142, 143], and play a significant part in intracellular pH regulation and ionic homeostasis. It was found to increase within 12 h after I/R and it began to decrease 2 days after I/R and reached the lowest level at 2 days following I/R. Notably, neuronal death was improved with the application of an inorganic anion exchanger blocker DIDs [144]. Another study showed that NBCn and NBCe1 were upregulated both in RNA and protein levels in experimental I/R conditions, which induced astrocytic death. However, NBC inhibition with S0859 aggravated astrocytic death [145]. Conversely, S0859 attenuates neuronal death in the gerbil hippocampus [130]. Considering its significant impact on astrocytes and neurons, two crucial components of the BBB, there's much potential for NBCs to play a part in BBB regulation following I/R insult. Furthermore, more studies are needed to elucidate its role in that function.

Other Molecules Involved in Post-stroke BBB Permeability Modulation

Peroxiredoxin 4 (Prx4), belonging to the antioxidant enzyme family (Prx1–6), has been identified as an efficient scavenger for H_2O_2 [146]. It likely also plays a direct role in protecting ECs from ROS and functions as a peroxidase that is associated with the membrane in ECs [147]. Therefore, Prx4 may prevent endothelial dysfunction and alleviate BBB breakdown. However, more evidence is needed to illustrate the role Prx4 plays in BBB integrity and its underlying mechanism.

The Hippo/YAP kinase cascade induces the phosphorylation of YAP and TAZ which are crucial downstream effectors and co-activators of transcription. Activation of YAP or TAZ protected the brain tissue from cerebral edema elicited by I/R insult. Additionally, YAP could reduce the infarction volume and maintain TJ protein integrity, consequently, attenuating BBB dysfunction [148]. However, some evidence shows that inhibition of YAP ameliorated I/R-induced damage and preserved the BBB integrity [149]. Thus, the contradictory effects of YAP on BBB function require added investigations for clarity.

Insights for Treatment

In the setting of I/R, many molecules are involved in the pathological process exacerbating or attenuating the injury, which provides targets for adjuvant treatment for ischemic stroke accompanying thrombolytic therapy with tPA. Microglia mainly participate in post-stroke inflammation, and the strategy to suppress inflammation can remarkably reduce the secretion of microglia-derived molecules, thus attenuating

I/R injury. TPCD NPs are bioactive nanoparticle-derived multifunctional nanoparticles whose effectiveness in treating ischemic stroke has been tested in vivo and in vitro. Notably, studies show that TPCD NPs could significantly reduce the production of intracellular ROS, alleviate oxidative stress, and suppress inflammation in OGD conditions. Simultaneously, TPCD NPs also mitigated neuronal death that was induced by activated microglia [150]. Furthermore, cottonseed oil can also suppress microglial and astrocytic activation via inhibiting TLR4/NF-κB, thus reducing brain edema induced by ischemic injury [151]. Moreover, a neutralized antibody targeting MMP-9 could attenuate BBB dysfunction. Furthermore, it even could neutralize MMP-9 in stroke patients' serum and brain tissue samples, providing strong evidence to support its clinical potential for acute stroke treatment [152]. Liposomes are widely used to enhance the efficiency of treatment for cerebral vascular disease because of their ability to cross the BBB. Ginkgolide B (GB) is one ingredient of G. biloba leaf extract, which possesses the strongest effect in cerebral vascular disease treatment. Recent studies showed that a GB-DHA complex, which can be integrated into the lipid bilayer, thus crossing the BBB was beneficial to I/R injury [153]. Evidence has shown the efficiency of Baicalin (BA), an extract from Radix Scodelario, for I/R injury treatment. And Yu Long et al. found that the complex of Borneo and BA was highly lipid-soluble and could enhance its efficiency and could reduce BBB hyperpermeability induced by I/R injury[154]. However, most of the efficiency of these treatments is still at the basic experimental stage. Therefore, more evidence and trials are needed to explore whether they are qualified for clinical use.

Conclusion

The normal function of BBB is maintained by its essential cellular components, TJ proteins, and extracellular matrix (ECM). However, insufficient oxygen and glucose condition-the core of stroke pathology induces BBB dysfunction, resulting in its dysfunction. Simultaneously, the primary damage also causes neuroinflammation, which worsens BBB dysfunction, leading to the second opening of BBB. Microglia are activated following I/R injury, which is the hallmark of neuroinflammation. Once microglia are activated, they polarize into either the M1 phenotype to promote neuroinflammation, or the M2 phenotype to suppress neuroinflammation. M1 phenotype-activated microglia occur in the early phase of stroke and secretes inflammatory factors to exert its proinflammatory function, which would deteriorate the prognosis of ischemic stroke. However, M2 phenotype-activated microglia emerge in the relatively later phase of ischemic stroke, suppressing the inflammation and counteracting the tissue damage induced by M1 phenotype microglia. Notably, TNF-α, IL-1β, and IL-6, which are secreted by M1 phenotype microglia and increased upon I/R injury, can destroy TJs or influence the function of ECs via receptors on their membrane, aggravating BBB dysfunction. Importantly, suppressing TNF-α and Il-1β expression are reported to attenuate BBB damage induced by I/R injury. However, IL-6 is proven to play a protective role in I/R damage. Activated microglia are one of the MMPs resources which also play a part in BBB breakdown following ischemia/reperfusion injury. For instance, MMP-2 and MMP-9 have been proven to influence either TJs, ACs, or ECs. Besides, non-microglia-derived molecules also contribute to BBB breakdown following I/R either in the primary damage stage or the secondary damage stage. miRNAs and circ-FoxO3 have been discovered to maintain BBB integrity during stroke. Additionally, HSPs, peroxiredoxin 4, and YAP participate in the disease progression of stroke, and they are involved in the autophagy process or/and inflammatory process. The same goes for the ion channels and transporters responsible for the regulation of BBB function, which play a large part in maintaining the ion balance and homeostasis. Perturbations in the ion balance may lead to cascades that trigger microglial activation, inflammation, autophagy, or necroptosis in cells, which eventually causes EC dysfunction, TJs degradation, and BBB breakdown. However, the precise mechanism of how these molecules protect BBB and brain tissues against stroke damage or aggravate its outcome is yet to be illustrated, which would give more clinical insight into treating ischemic stroke and improving its prognosis.

Numerous studies have highlighted the importance of microglia during ischemic stroke, as well as the role of microglia-derived and non-microglia-derived molecules in the progression of I/R injury. Microglia-derived molecules are mainly involved in the secondary damage to the central nervous system (CNS) and BBB dysfunction, whereas non-microglia-derived molecules can contribute to either primary or secondary damage, resulting in biphasic opening of the BBB. However, there are still several unanswered questions: How do these molecules contribute to primary damage? Do they only function in a neuroinflammatory manner? Do non-microglia-derived and microglia-derived molecules interact with each other to worsen disease progression, given that they may both engage in inflammatory and non-inflammatory processes? If so, how do they interact? To shed light on the role of microglia and its secreted molecules, as well as non-microglia-derived molecules, in I/R injury, particularly BBB breakdown, more studies are needed.

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content of the review. MJ and QW checked the grammar of the review. JW made critical revisions and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Declarations

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