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REVIEW ARTICLE

Blood-brain barrier in stroke: Pathophysiological mechanisms and treatment approach

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Abstract

The blood-brain barrier (BBB) is a selective semi-permeable structure in the central nervous system (CNS) and has many structural and functional characteristics. It regulates the transfer of molecules, ions, and cells between blood and CNS. Its components include interneurons, astrocytes, microglia, oligodendrocytes, basal lamina, pericytes, endothelial cells, extracellular matrix, and blood. The BBB plays a critical role protecting the brain parenchyma during the ischemic and hemorrhagic stroke. However, this barrier's integrity is disrupted during ischemic stroke. Pathophysiological mechanisms in stroke induce cerebral edema associated with BBB injury. Many immune reactivations occur in patients with stroke. Especially, neutrophils play a critical role in the BBB disruption. Monocytes have proinflammatory or anti-inflammatory activity related with the type and duration of stroke. In addition, lymphocytes, microglia, astrocytes, pericytes, natural killer (NK) are the other main immune cells in this period. Previous studies reported that some strategies for stabilization of BBB yield positive functional outcome in stroke. Inhibition of neutrophil infiltration with reparixin and junctional adhesion molecule A antagonist peptide (JAM-Ap) is effective treatment approach to reduce infarct volume and neurological deficits. Regulation of neutrophil polarization (all-trans retinoic acid, rosiglitazone, etc.) is another neutrophil-related treatment option. Fingolimod, a S1P receptor agonist, modulates immune homeostasis and reduces hemorrhagic transformation. Microglial regulation, cytokine, and astrocyte inhibition are another BBB-related treatment approach. In conclusion, the severity of BBB' injury is associated with poor functional outcome in ischemic and hemorrhagic stroke. In particular, studies on functional and structural stabilization of BBB may provide significant positive contributions in stroke treatment.

Keywords: Blood-brain barrier, stroke, ischemia, hemorrhage

INTRODUCTION

The blood-brain barrier (BBB) is a selective semi-permeable area and has many structural and functional characteristics in the central nervous system (CNS). The vasculature in the CNS consists of continuous and non-fenestrated capillaries. Moreover, these vasculatures are equipped with specialized structures and mechanisms that tightly regulate the transfer of molecules, ions, and cells between blood and CNS.[1] This highly selective barrier regulates the homeostasis of the CNS and protects cerebral parenchyma from toxic substances, infections, inflammation, and trauma.[2] BBB dysfunction leads to disruptions in ionic homeostasis, regulation of signal transmission, and infiltration of immune cells. Many molecules or immune cells transfer into the CNS as a result of this change. These pathological changes ultimately lead to neuronal dysfunction and neurodegeneration.[3]

The BBB forms between days 10 and 15 in the embryonic life. In the initial phase, a

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continuous layer of endothelial cells is established to prevent paracellular substance passage. Then, endothelial fenestrations and pinocytotic activity are eliminated to restrict transcellular transport. After this period, selective transporter systems become active. The exchange of nutrients and metabolites are facilitated between the brain and peripheral circulation and toxic substances are excreted. In the final stage, the basal membrane and capillary walls interact with pericytes. The structural integrity and functionality of the barrier are increased as a result of this period. This complex developmental process is regulated with growth factors (GF), guidance molecules, micro ribonucleic acids (microRNAs), intracellular signaling pathways, and gene expression.[4]

BBB consists of the glycocalyx layer, endothelial cells, the terminal foot processes of astrocytes, and basal membrane components in pericytes. In addition, microglial cells, pericytes, astrocytes, endothelial cells, and neurons interacting with these cellular components collectively contribute to structure of the neurovascular unit in BBB.[5] The neurovascular unit has a complex cellular network. Components of this structure include interneurons, the terminal foot processes of astrocytes, microglia, oligodendrocytes, basal lamina surrounded by smooth muscle cells, pericytes, endothelial cells, extracellular matrix structures, and blood.[6] The neurovascular unit regulates several fundamental processes, including the control of BBB permeability, the coordination of cerebral blood flow, the modulation of interactions between cells and the extracellular matrix, the uptake and metabolism of neurotransmitters, angiogenesis and neurogenesis.[7]

The transfer of substances into the brain depends on many factors such as molecular size, lipid solubility, binding capacity to transporter proteins, and electrical discharge. Small, hydrophobic molecules like oxygen (O_2) and carbon dioxide (CO_2) readily cross plasma membranes via transcellular lipophilic diffusion. In addition, glucose, amino acids, and many small metabolites are transported into brain tissue through facilitated diffusion mediated by specialized transporter proteins. Larger molecules; such as insulin, transferrin, and low-density lipoprotein (LDL); are transferred to the brain via receptor-mediated transcytosis or adsorptive transcytosis mechanisms in BBB.[8] BBB is known to be the main and important structure in patients with stroke associated with all these mechanisms. Identification of these mechanisms is essential to develop new treatment and approach modalities in stroke. This review aims to assess the blood BBB structure, underlying mechanisms and treatment approach in stroke.

ISCHEMIC STROKE

The importance of the blood-brain barrier in ischemic stroke

Ischemic stroke is an acute disease that has many severe neurological symptoms developing after blockage of cerebral blood flow. The BBB maintains cerebral homeostasis and offers protects against toxins and immune infiltration during ischemic stroke. The integrity of BBB barrier deteriorates during and after ischemic stroke. Ischemic period induces cerebral edema, characterized by excessive fluid accumulation in intracellular (cytotoxic edema) and extracellular (vasogenic edema) compartments in the brain. Cerebral edema progresses following ischemia; cytotoxic edema occurs within minutes of ischemia, followed by the relatively delayed onset of vasogenic edema. They are particularly associated with BBB disruption. BBB dysfunction plays a critical role in hemorrhagic transformation and increased mortality after delayed intravenous thrombolytic treatment. Thrombolytic treatment-associated hemorrhage occurs due to severe neuronal injury and disruption of tight junction in BBB.[9]

Early BBB disruption increases the risk of intracerebral hemorrhage (ICH) after intravenous thrombolysis, and it can be predicted by using magnetic resonance imaging (MRI). Intravenous thrombolysis increases matrix metalloproteinases (MMP)-9 levels and connexin 43 phosphorylation. In addition, it leads to increased BBB permeability and hemorrhagic transformation. Disruption in tight junction is a key factor underlying the increased paracellular permeability of the BBB after ischemic stroke. Differential changes, including modifications, translocation, and degradation occur in tight junction proteins. Progression of these processes is associated with higher ischemic damage. BBB dysfunction emerges at the onset of ischemia and deteriorates with progressively. The severity and consequences of BBB disruption vary topographically. The ischemic core progress to severe and irreversible damage. In addition, the salvageable tissue is defined as penumbra. BBB' disruption in the penumbra may be treated with early reperfusion. However, severe parenchymal injury in the

ischemic core may progress to hemorrhagic transformation after vascular reperfusion. The complications of reperfusion treatments are associated with vascular oxidative stress and neuroinflammation in the BBB.[10]

The blood-brain barrier and inflammation

Neutrophils play a critical role in the BBB disruption in ischemic stroke. Both clinical and experimental stroke studies report a strong association between activation of neutrophil and BBB' breakdown. Neutrophils induce activity of reactive oxygen species (ROS), proteases (such as matrix metalloproteinases (MMPs), proteinase 3, and elastase), lipokalin-2 (LCN2), and neutrophil extracellular traps (NETs). All these factors contribute to BBB' breakdown. Excessive ROS generation damages tight junction proteins and reorganizes the endothelial cytoskeleton.[11] MMPs degrade basal membrane components such as the glycocalyx, vascular endothelial (VE)-cadherin, focal adhesion proteins, and collagen type IV. Neutrophils also contribute to BBB' breakdown during acute ischemic stroke with secretion of cytokines and chemokines.[11,12] Moreover, neutrophils exhibit anti-inflammatory properties via Ym1 and CD206 expression.[13]

The scientific data about the effect of monocytes in BBB' breakdown are still insufficient. M1-type monocytes secrete cytokines and chemokines; they can degrade tight junctions. Many monocyte subgroups play various roles in BBB' integrity.[11] After stroke, the monocytes phenotype shifts from M1 (proinflammatory) dominance to M2 (anti-inflammatory) profile within approximately 7 days. Previous studies reported the dual roles of monocytes as pro-inflammatory and anti-inflammatory activity.[14]

Clinical studies reported that T lymphocyte differentiation shifts proinflammatory features after acute ischemic stroke. T lymphocyte immune cells contribute directly to BBB' breakdown with cytokine secretion. Specifically, interferon-gamma (IFNγ), interleukin (IL)-17, and IL-21 destroy tight junctions and BBB' integrity. γδ T cells exhibit proinflammatory effects via IL-17 production. In addition, the regulatory T cells (Tregs) and Th2 immune cells protect the ischemic area by suppressing immune hyperactivation. Tregs suppress hyperactivation of microglia and proinflammatory T cells, primarily by upregulating IL-10 and transforming growth factor-β (TGF-β). These factors reduce the levels of proinflammatory mediators.[2] IL-10 is a potent anti-inflammatory cytokine that inhibits the secretion of IL-1β, TNF-α, and IL-17. Other sources of IL-10 include B cells, microglia, and astrocytes.[15]

The microglia are the main in cells in in the ischemic brain area. Activated intracellular signaling pathways lead to polarization of microglia as M1pro-inflammatory and M2-anti-inflammatory immune cells. M1 microglia contribute to BBB' breakdown through secretion of proinflammatory mediators (IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, C-C motif ligand 2 (CCL2)), MMP-9, vascular endothelial growth factor (VEGF), and ROS. On the other hand, M2 microglia have an anti-inflammatory effect and support BBB' integrity with the secretion of IL-4, IL-10, and TGF-β.[11]

The A1/A2 astrocyte classification like to M1/M2 microglia classification in CNS. Astrocytes (particularly A1 astrocytes) contribute to BBB' breakdown by secretion of VEGF; cytokines such as IL-1β, IL-6, TNF-α, IL-15, chemokines including CCL2, CCL5, ROS, MMPs, and LCN-2. A2 astrocytes secrete anti-inflammatory mediators such as IL-2, IL-10, and TGF-β.[11]

Recently, the immunological role of pericytes in BBB' disruption during ischemic stroke has drawn interest. A study reported that toll-like receptors (TLRs) are constitutively expressed on the surface of pericytes. In addition, ischemia-induced damage-associated molecular patterns (DAMPs) induce nuclear factor-κB (NF-κB) and proinflammatory mediators in pericytes.[16] Furthermore, IL-1β was demonstrated to induce the expression of monocyte chemoattractant protein (MCP)-1, IL-8, and intercellular adhesion molecule (ICAM)-1 in pericytes. This process is inhibited via activation of the transcription factor CCAAT/enhancer-binding protein delta (CEBPD). These results indicate that pericytes have a biphasic phenotype during ischemic stroke.[11,17]

Considering all stroke data, immune cells have a dual effect in the inflammatory activity in ischemic stroke. Inflammation, particularly hyperinflammation, has a destructive effect in the acute phase. However, inflammation has a positive effect on neuronal stabilization in the subacute and chronic phases.[15]

BBB disruption and its consequences

Hypoxia, inflammatory processes, and oxidative stress have a destructive effect on BBB associated with increased hyperpermeability during ischemic stroke. In particular, the activation of enzymatic reactions, such as MMPs, has a destructive effect

on the structural integrity of endothelial cells. This process leads to BBB disruption, cerebral parenchymal edema, inflammation, and secondary neuronal injury. As reported in a previous study, hyper-activation of inflammation contributes to the cytokine- and chemokine-associated disruption of barrier integrity.[10] It leads to the leakage of plasma proteins and toxic substances into the cerebral parenchyma. This process is associated with increased neuronal parenchymal injury.

Protective mechanisms associated with blood-brain barrier

The integrity of BBB is very important to prevent secondary neuronal damage after ischemic stroke. Anti-inflammatory agents contribute to the protection of BBB' integrity. MMP inhibitors and free radical scavengers support cellular repair mechanisms associated with BBB. In addition, neuroprotective agents and strategies aim the stabilization of BBB, decreased cerebral parenchymal edema and inflammation.[18]

Current researchers report that some pharmacological strategies on BBB have a positive result for neurological and functional outcome in ischemic stroke. Targeted drug delivery systems may help protection the structural integrity and functionality of the BBB by modulating the inflammation. These approaches aim to inhibition of neuroinflammation, and the main aim is reduction of secondary neuronal injury as a result of this period.[10,18]

The preservation of the BBB after ischemic stroke is a critical factor in determining the long-term prognosis in patients with stroke. Current researches aim to detect novel therapeutic strategies associated with BBB for peri and post-stroke period.

HEMORRHAGIC STROKE

The importance of the blood-brain barrier

Hemorrhagic stroke constitutes approximately 20% of all strokes, with ICH being the most common subtype.[19] It is an acute and severe neurological disease with high mortality and morbidity rates. During this process, the function of the BBB is altered with different mechanisms associated with uncontrolled hemorrhage and inflammation. ICH develops when a cerebral blood vessel ruptures, which leads to hematoma. Primary effect of hematoma is associated with the mechanical compression, which leads to increased intracranial pressure, and brain herniation. Inflammation, cerebral edema, and BBB' disruption are main factors for increasing the secondary brain injury.[20]

The blood-brain barrier and inflammation

Microglial cells play a significant role in neuronal inflammation after hemorrhagic stroke. They are activated and transformed phenotypic and functional changes.[20,21] Activated microglia polarize into either a proinflammatory M1 or anti-inflammatory M2 phenotype. M1 microglia induce brain injury by increasing proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. All these cytokines damage BBB integrity.[20,22] On the other hand, M2 microglia have neuroprotective and anti-inflammatory features.[23]

Astrocytes have dual phenotypic characteristics like microglia.[20] A1 astrocytes are proinflammatory in a hemorrhagic stroke. Hemoglobin and iron in the hematoma induce oxidative stress and reactive astrocyte-induced MMP-9. They lead to increased BBB breakdown and cerebral edema.[24] Furthermore, A2 astrocytes have many neuroprotective functions.[20]

After microglial activation, neutrophils infiltrate into the cerebral parenchyma and induce inflammation.[25] In addition, NK cells contribute to focal inflammation with cytotoxic effects on brain endothelial cells and BBB.[20]

There are many studies on the role of T lymphocytes in ischemic stroke. However, their roles in hemorrhagic stroke have not been comprehensively studied.[20] CD8+ and CD4+ T cells contribute to inflammation in post-hemorrhagic stroke.[26] However, previous studies reported that Tregs have neuroprotective effects in hemorrhagic stroke.[23]

BBB disruption process

In contrast to ischemic stroke, hemorrhagic stroke involves the direct infiltration of blood components into cerebral tissue, induces endothelial damage and BBB disruption. The extravasation of blood and the accumulation of erythrocytes and plasma proteins in the brain induce a cascade of neuroinflammation.[27] Anormal neuropathological injury occurs as a result of hyperinflammation. Peripheral immune cells contribute to the inflammation in the perihematomal area. During the acute phase, hemoglobin and iron extravasation induces microglial activation, proinflammatory signaling, neurodegenerative processes, and secondary brain injury.[20] In hemorrhagic stroke, BBB' treatment strategies primarily focus on

limiting the hemorrhage and suppressing the inflammation. Osmotic diuretics, iron chelators, and anti-inflammatory agents decrease BBB' disruption.[28]

Hemorrhagic stroke is a neurological disorder that damages the BBB. This period is associated with many immune and structural mechanisms. Cytotoxic effects of blood components and inflammation are associated with BBB disruption. Next-generation antioxidant therapies are promising regarding BBB protection. Future studies should focus on targeted drug delivery systems to prevent secondary cerebral injury. Pathophysiological mechanisms associated with BBB in ischemic and hemorrhagic stroke were summarized in Table 1.

THERAPEUTIC MODALITIES TARGETING THE BLOOD-BRAIN BARRIER IN STROKE

Recent experimental studies targeting neutrophils in the treatment of ischemic stroke made a significant progress.[11] It was reported that reparixin, an inhibitor of C-X-C chemokine receptor type (CXCR) 1 and CXCR2, significantly reduced neutrophil extravasation and infarct volume. In addition, this treatment has a positive effect on functional outcomes after ischemia-reperfusion injury.[29] Neutralization bioactivity of C-X-C motif Chemokine Ligand 1 (CXCL1) and CXCL2 with evasin-3 reduced neutrophil infiltration; however, it did not affect infarct volume, neurological deficits, or BBB permeability.[30] Inhibition of receptor function for platelet glycoprotein Ib (GPIb) was reported to reduce ischemia-induced BBB' hyperpermeability through the mechanism of inactivation and downregulation of MAC-1 and P-selectin.[31] In addition, blocking neutrophil-endothelial interactions via junctional adhesion molecule A (JAM-A) antagonist decreased the expression of inflammatory mediators, BBB disruption, and infarct volume.[32] Neutrophil polarization also presents a current treatment approach for ischemic injury. All-trans-retinoic acid significantly reduced BBB disruption and infarct volume by suppressing STAT1 and increasing N2 neutrophil subgroup.[33]

Shifting monocyte-derived macrophages toward the M2 phenotype is an effective and current treatment strategy in acute ischemic stroke. Treatment with P2X purinoceptor 4 (P2X4R) antagonist significantly reduced BBB disruption, infarct size, and neurological deficits.[34] Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) agonism, such as rosiglitazone, significantly preserved tight junctions in BBB integrity. This treatment leads to decreased infarct volume and better neurological scores.[35]

Targeting T lymphocytes is another therapeutic pathway in acute ischemic stroke. One treatment approach is inhibition of T cell infiltration. Fingolimod, a S1P receptor agonist, is an important treatment for ischemic stroke due to its capacity to inhibit lymphocyte transport from lymph nodes into circulation. Fingolimod was reported to improve BBB integrity, reduced infarct-related damage, and enhanced good functional outcomes.[36] Another approach is modulation the balance between pro-inflammatory and anti-inflammatory T cell. Lymphocyte subgroup modulation is a treatment for inhibition of BBB permeability during ischemic process.

Table 1: Pathophysiological mechanisms related to the blood-brain barrier in ischemic and hemorrhagic stroke

	Ischemic Stroke	Hemorrhagic Stroke
Pathophysiological mechanisms	Decreased CBF leads to hypoxia, which damages the structural integrity of tight junctions and leads to increased BBB' permeability.	Hemorrhage-induced structural damage occurs and that leads to endothelial damage.
	Hypoxia and inflammation induce MMP and cytokines. They initiate the disruption of the BBB.	Blood extravasation, iron toxicity, and free radical formation contribute to disruption of the BBB.
	Cerebral edema, inflammation, and secondary neuronal injury contribute to progressive neurological dysfunction.	The extravasation of blood into cerebral parenchyma induces BBB' disruption associated with hyperinflammation and oxidative stress.

MMP: matrix metalloproteinase, BBB: blood brain barrier, CBF: cerebral blood flow

In a previous study, the poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor significantly preserved tight junctions in BBB. Brain edema, intracranial hypertension, cerebral infarct volume, and functional disability were decreased treated with PARP-1 inhibitors in stroke.[37] Moreover, targeting the gut microbiota to protect the BBB in ischemic injury was demonstrated as a strong potential treatment option in experimental animal models. Resveratrol, a microbiota composition, plays an important role in preserving BBB structure by modulating the gut flora. This treatment reduces inflammation-related damage in cerebral parenchyma.[38]

Previous studies focused on inhibition microglial activation and regulation microglial polarization in treatment of acute ischemic stroke.[11] Ticagrelor, a reversible antagonist of purinergic receptor P2Y12, significantly reduced BBB damage by decreasing microglia activation, IL-1β, CCL2, MCP-1, and induced nitric oxide synthases (iNOS) levels.[39] Furthermore, statin significantly reduced BBB disruption by suppressing microglial activation.[40] Metformin, an antidiabetic drug, activates AMP-activated protein kinase (AMPK). In addition, metformin also has a positive effect on angiogenesis and microglial M2 polarization in stroke.[41]

Treatment with an IL-1 receptor antagonist in an experimental study reduced inflammation-induced BBB disruption, infarct volume, and neurological deficits.[42] Anti-TNF-α therapy (infliximab) was reported to stabilize BBB integrity in experimental stroke models.[43]

Inhibition of astrocytes prevent BBB disruption in ischemic stroke. Therefore, immunosuppressive therapies based on astrocytes were hypothesized to have therapeutic effects.[11] Toll-like receptor-mediated NF-κB (TLR-NF-κB) activation is the main pathway for astrocyte activation. Gossypol and Ginkgoaceae extracts, inhibitor TLR and NF-κB expression, reduce the number of reactive astrocytes and decrease IL-1β, IL-6, and TNF-α levels. These pathophysiological mechanisms prevent BBB disruption and brain edema.[44,45] The NLR family pyrin domain containing 3 (NLRP3) inflammasome is an important signaling mechanism associated with activation of A1 astrocytes. Telmisartan, an inhibitor of NLRP3, prevent A1 astrocyte-mediated BBB damage and neurological deficits.[46]

In the literature review, there are many researches associated with immune cells in acute stroke. Microglia are among the main immune cells in hemorrhagic stroke.[44] IL-4 was reported to reduce hematoma volume after hemorrhagic stroke.[47] Several treatment options, including the NLRP3 inhibitors and triggering receptors expressed on myeloid cells 1 (TREM-1) modulators, were shown to inhibit microglial activation.[48,49] Astrocytes also play a significant role in CNS immunity, and various treatment strategies addressed these immune cells. IL-15 plays a main role astrocyte-microglia interaction after stroke. This process increases neuroinflammation-related neuronal damage. As a result of this study, IL-15 modulation is a current treatment strategy for stroke.[50]

Treatment strategies related to peripheral immune cells in stroke were also investigated. Inhibition of T cell and NK cell infiltration into the CNS is an effective treatment option in stroke.[51] In patients with stroke, a negative correlation was detected between neutrophils, BBB disruption, and neuroinflammation.[52] Several interleukins that inhibit neutrophil activity were reported to improve outcomes in hemorrhagic stroke. Rapamycin, a mechanistic target of rapamycin (mTOR) inhibitor, significantly improved neurological deficits after ICH by increasing Treg cell, IL-10 and IFN- γ.[53] Current treatment options and immune targets in stroke were demonstrated in table 2.

CONCLUSION

Stroke is one of the main causes of mortality and disability worldwide. Therefore, studies have been carried out on current and effective treatment options. BBB plays an important role in patients with stroke, especially in inflammatory cell transport and cerebral parenchymal edema. Therefore, BBB-specific treatments in stroke are promising. Many treatment options were reported in experimental studies on this subject.

The most effective treatments for acute ischemic stroke are tissue plasminogen activator (tPA) and mechanical thrombectomy. However, patients need to be treated for limited periods of time. In hemorrhagic stroke, stabilization of the hemorrhage and prevention of progression are important. Many neuroprotective treatments were investigated for the treatment of stroke. However, these treatments have not positive results to be used in routine clinical practice. Therefore, it is important to identify new approaches for the treatment of stroke. Disruption of the BBB is associated with poor functional outcome and mortality in stroke. Immunotherapy targeting the BBB in stroke is a recent and popular

Table 2: Current treatment options and immune targets in patients with stroke

Immune targets	Mechanism	Drug	Molecular target	Results and outcomes
Neutrophils	Inhibition of neutrophil infiltration	Reparixin	CXCR1 CXCR2	Reduced infarct volume, improved functional outcomes
		Evasin-3	CXCL1 CXCL2	No improvement in BBB permeability, infarct volume, or functional outcome
		JAM-Ap	JAM-A	Decreased BBB permeability, infarct volume, and neurological deficits
	Regulation of neutrophil polarization	All-trans retinoic acid	STAT-1	Reduced infarct volume and neurological deficits
		5-BDBD	P2X4R	Decreased BBB leakage, infarct size, and neurological deficits
		Rosiglitazone	PPARγ	Reduced BBB permeability and hemorrhagic transformation
	mechanistic target of rapamycin (mTOR) inhibition	Rapamycin	mTOR	Improved neurological deficits associated with Treg cell, IL-10 and IFN-γ
T cells	Inhibition of T cell infiltration	Fingolimod	S1P R	Reduced hemorrhagic transformation
	Modulation of immune homeostasis	JPI-289	PARP-1	Decreased BBB permeability, infarct size, and neurological deficits
Microglia	Regulation of microglial activation and polarization	Ticagrelor	P2Y12R	Reduced BBB disruption and infarct volume, improved functional outcomes
		Statin	HMG-CoA reductase	Reduced BBB disruption and infarct volume, improved functional outcomes
		Metformin	AMPK	Reduced BBB disruption and infarct volume, improved functional outcomes
Cytokines	Cytokine inhibition	IL-1Ra	IL-1	Reduced BBB disruption and infarct volume, improved functional
Astrocytes	Inhibition of astrocyte activation	Cottonseed oil	TLR	Decreased BBB damage, infarct size, and improved functional impairment
		Ginkgo species	TLR	Decreased BBB damage, infarct size, and improved functional impairment
		Telmisartan	NLRP3	Reduced GFAP-positive astrocytes

CXCR: C-X-C chemokine receptor, CXCL: C-X-C motif chemokine ligand, JAM: Junctional adhesion molecule, JAM-Ap: JAM-A antagonist peptide, BBB: Blood-brain barrier, STAT: Signal transducers and activators of transcription, 5-BDBD: 5-(3-bromophenyl)-1,3-dihydro-2H-benzofuro[3,2-e]-1,4-diazepin-2-one, P2X4R: P2X purinoceptor 4, PPAR-γ: Peroxisome proliferator-activated receptor γ, S1P R: S1P receptor, PARP-1: Poly (ADP-ribose) polymerase-1, P2Y12R: purinergic receptor P2Y12, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A, AMPK: AMP-activated protein kinase, IL-1Ra: Interleukin-1 receptor antagonist, IL: Interleukin, TLR: Toll-like receptor, NLRP3: NLR family pyrin domain containing 3, GFAP: Glial fibrillary acidic protein

research area. Immune cells migrate from the peripheral circulation via the BBB to the cerebral parenchymal area after stroke. Neutrophils are the immune cells that play the main role in this process. Monocytes can differentiate into M1 or M2 macrophages. They play a dual role on BBB and cerebral parenchyma in stroke. Lymphocytes have a proinflammatory effect and induce damage to the BBB. Therefore, T lymphocyte-related treatments contribute to the stabilization of the BBB. Microglia-related treatments draw significant interest in stroke. Astrocytes are innate immune cells that regulate the structure of the blood-brain barrier. Recent studies have demonstrated that pericytes are also important immune cells in the post-stroke period. The immune system is integrated with all other systems with a complex mechanism after stroke. Post-stroke immune system is associated with stroke subtype, time of stroke, severity of stroke and many individual characteristics. Therefore, it is very important to develop specific treatment options through clinical and randomized studies on immune system and BBB in stroke.

DISCLOSURE

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