HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Stroke. 2020 April ; 51(4): 1344–1352. doi:10.1161/STROKEAHA.120.028928.

Basement membrane changes in ischemic stroke

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Keywords

Ischemic stroke; blood-brain barrier; basement membrane; pericytes; endothelial cells

Introduction

Ischemic stroke, the most common type of stroke, causes high rate of long-term disability and significant economic burden.[1] Current therapeutic options for ischemic stroke include thrombolysis and thrombectomy, which only help less than 10% of patients due to the relatively narrow therapeutic windows.[2] Additionally, these treatments are associated with severe complications, such as secondary hemorrhage.[2] One important pathology of ischemic stroke is blood-brain barrier (BBB) breakdown.

The BBB is a physical barrier that separates the central nervous system (CNS) and systemic circulation. By preventing the entry of blood components and toxic macromolecules into the brain, the BBB maintains the homeostasis of the CNS. Accumulating evidence suggests that BBB disruption is a common pathology in a variety of neurological disorders,[3–5] including stroke. More importantly, BBB breakdown also plays a causal role in some diseases. For example, it has been shown that BBB disruption induces secondary brain injury and actively contributes to the pathogenesis of ischemic stroke.[5–7] Over the past century, we have made substantial progress on the cellular constituents of the BBB, including endothelial cells (ECs), pericytes, and astrocytes. The non-cellular component of the BBB–the basement membrane (BM), on the other hand, is understudied and its importance in BBB function has just started to be elucidated.

Here, we first introduce the structure and function of the BM in detail. Next, we summarize how the BM and its individual components change in ischemic stroke. Furthermore, we discuss potential therapeutic targets at the BBB and critical questions that need future research with a focus on the BM. Our goals are to provide a comprehensive review on BM alterations in ischemic stroke, stimulate novel hypotheses in the field, and promote the development of innovative therapies for ischemic stroke.

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Disclosures

None.

Structure and Function of the BM

The BBB is a dynamic structure composed of specialized ECs, pericytes, astrocytes, and the BM (Figure 1). These components play important roles in maintaining BBB integrity. Since the cellular constituents of the BBB are well-studied and many excellent reviews already exist, we predominantly focus on the BM in this article.

Basement membrane—The BM is a sheet-like extracellular matrix (ECM) complex beneath epithelium and endothelium.[8] At the BBB, the BM encircles the abluminal side of blood vessels and is located at the interface of the circulation system and CNS. Brain BM consists of five major proteins: collagen IV, laminin, nidogen, perlecan, and agrin. The critical roles of these components in BBB integrity are discussed below in detail.

Collagen IV: Collagens are triple-helix proteins composed of three polyproline α-chains. Among 29 different collagen isoforms found so far, collagen IV is the major one that makes up the BM.[9, 10] A recent single cell-RNAseq analysis shows that Col4a1 and Col4a2, which make α1-α1-α2 collagen IV, are synthesized by brain endothelial cells, mural cells (pericytes and vascular smooth muscle cells [vSMCs]), and astrocytes.[11] Consistent with this finding, Col4a1 and Col4a2 were detected in both endothelial cells and pericytes at mRNA and protein levels *in vitro*.[12]

It has been reported that Col4a1/Col4a2-deficient mice show embryonic lethality at E10.5–11.5.[13] Interestingly, structural defects of BM are observed in the mutants at E10.5–11.5 but not before E9.5,[13] strongly suggesting that collagen IV is not required for initial BM formation but contributes to its stabilization. Similarly, the Col4a1$^{\Delta ex41/+}$ mutants that skip Col4a1 exon 41 show disorganized vascular BM and brain hemorrhage due to increased intracellular accumulation of mutant collagen IV.[14–16] Further studies demonstrate that deletion of Col4a1 exon 41 in endothelial cells and pericytes, but not astrocytes, leads to brain hemorrhage,[14] highlighting a critical role of endothelium- and pericyte-derived collagen IV in cerebrovascular function. In addition, mice with various point-mutations in Col4a1 and Col4a2 also develop brain hemorrhage, although not as severe as the Col4a1$^{\Delta ex41/+}$ mice.[16, 17] More importantly, Col4a1/Col4a2 mutations result in BM defects and are associated with diverse disorders in humans, including stroke (hemorrhagic and ischemic) and small vessel disease.[16, 18, 19] Genome-wide association studies have linked Col4a1[20, 21] and Col4a2[21, 22] with stroke. These results highlight an important role of collagen IV in the pathogenesis of stroke.

Laminin: Laminins are large glycoproteins that consist of one α chain, one β chain, and one γ chain. There are five, four, and three isoforms for α, β, and γ chains, respectively.[17, 23, 24] Various combinations of these isoforms generate many different laminin isoforms. Interestingly, different cells synthesize distinct laminin isoforms. For example, astrocytes predominantly make laminin-211,[25, 26] pericytes mainly express α4/α5- and γ1-containing laminins,[12, 27] and ECs synthesize laminin-411 and −511.[25, 28] There are also reports showing that astrocytes make laminin-α5 and pericytes produce laminin-α2. For example, immunohistochemistry revealed laminin-α5 expression in retinal astrocytes.[29] Single cell-RNAseq analysis found laminin-α2 expression in brain pericytes[11] and laminin-α2 level

was significantly reduced in mice with decreased pericyte density.[30] Additionally, there is also evidence suggesting the existence of laminin-β2 and -γ3 in the BM. Laminin-β2[31–33] and laminin-γ3[31, 32, 34] display a similar expression profile: in the pial membrane, a subset of cerebrovascular BM, and retinal BM. Compared to laminin-β1 or -γ1, laminin-β2 and -γ3 show a much restricted distribution pattern.[34] Further studies demonstrate that these isoforms are mainly synthesized by retinal astrocytes and possibly endothelial cells.[32, 35, 36]

Using the Cre-Lox system, we have shown that ablation of astrocytic laminin-γ1 (laminin-211) leads to severe BBB disruption and age-dependent intracerebral hemorrhage.[37] Consistent with our finding, laminin-α2 knockout mice display BBB breakdown,[38] strongly indicating an indispensable role of astrocyte-derived γ1-containing laminins in BBB maintenance. Similarly, we also generated mice with laminin-γ1 deficiency in mural cells by using PDGFRβ-driven Cre. In C57Bl6 dominant background, these mutants are grossly normal at young age but start to show mild BBB compromise at old age.[39] Given that BBB compromise is not observed in vSMC-specific laminin conditional knockout mice,[27] we concluded that pericyte-derived γ1-containing laminins also contributes to BBB integrity but to a lesser extent compared to astrocytic laminin. In addition, we and others have demonstrated that deletion of laminin-α5 in ECs fails to affect BBB integrity,[40–42] suggesting a dispensable role of endothelial laminin-α5 (laminin-511) in BBB maintenance and possible compensation by laminin-411. Laminin-α4 knockout mice, however, fail to show BBB disruption in adulthood (after laminin-511 expression[43]), although vascular leakage is observed at perinatal stage (before laminin-511 expression).[44] This data suggests that loss of laminin-411 may be compensated by laminin-511. Due to this mutual compensation between laminin-411 and −511, the role of endothelium-derived γ1-containing laminins in BBB integrity remains unknown. We are currently investigating the function of endothelium-derived γ1-containing using mutants with simultaneous deletion of laminin-411 and −511. Unlike laminin-α2, -α4, -α5, and -γ1, the roles of laminin-β2 and -γ3 in BBB maintenance remain largely unknown. Although laminin-β2$^{-/-}$ mice die at P15-P30 due to defects in the kidney/retina/neuromuscular junctions[45–49] and laminin-γ3$^{-/-}$ mice have a normal lifespan with minor abnormalities in the cerebellum and retina,[34–36, 50] BBB integrity in these mutants has not been examined. Future research should answer this important question. Altogether, these findings suggest that laminin plays an important role in BBB maintenance under homeostatic condition.

Nidogen: Nidogens, glycoproteins with three globular domains, function as a bridge to connect laminins and collagen IV.[51] Two nidogen isoforms (nidogen-1 and −2) have been identified in mammals.[52] Single-cell RNAseq analysis demonstrates that nidogen-1 and −2 are mainly produced by mural cells and endothelial cells, and possibly by astrocytes.[11] Consistent with this report, nidogen-1 and −2 are found in both endothelial cells and pericytes at the mRNA level *in vitro*, although they are detected in endothelial cells but not pericytes at the protein level.[12]

Genetic ablation of nidogen 1 fails to induce obvious abnormalities: the mutant mice are fertile and have normal BM structures in the kidney, skeletal muscle, and heart.[53] Interestingly, abnormal movement of the hind legs and a thinner BM in brain capillaries are observed in a different nidogen 1 knockout mouse line.[54] Like nidogen 1 mutants, mice

lacking nidogen 2 fail to show obvious abnormalities, are fertile, and have normal BM structure.[55] In sharp contrast to these single knockout mice, mutants with simultaneous abrogation of both nidogen isoforms die within a day after birth with disorganized BM structure and reduced BM deposition.[56, 57] Based on these results, it is reasonable to hypothesize that functional compensation exists between the two isoforms of nidogen. Unfortunately, BBB integrity was not examined in neither the single mutants nor the double knockout mice. Future studies should address the functional significance of nidogen in BBB integrity.

Perlecan: Perlecan is a large heparan sulfate proteoglycan with five domains and three glycosaminoglycan chains in the N-terminus.[58] Its expression is substantially increased in cerebrovasculature during embryogenesis,[59–61] suggesting an important role of perlecan in brain development. Single cell-RNAseq analysis reveals that perlecan is mainly synthesized by endothelial and mural cells at the BBB.[11] *In vitro* studies show that perlecan is predominantly generated by endothelial cells rather than pericytes, although co-culture of endothelial cells with pericytes induces perlecan expression in pericytes.[12, 62] Furthermore, perlecan expression predominantly colocalizes with endothelial cells but not pericytes in the brain,[62] indicating that perlecan is mainly synthesized by endothelial cells.

Echoed with the expression data, loss-of-function studies show that perlecan$^{-/-}$ mice die either at E10.5 (40%) or right after birth (60%) due to respiratory failure caused by cartilage defects.[59, 63] These perlecan$^{-/-}$ mice display impaired brain development with normal BM structure.[64] To avoid lethality and enable investigation of BBB integrity, conditional perlecan-deficient mice, which express perlecan in cartilage, were generated. These mutants have no detectable expression of perlecan in the brain, are grossly normal, and fail to show BBB or BM damage under homeostatic conditions,[62] indicating a dispensable role of perlecan in BM formation and BBB maintenance. Similarly, the perlecan hypomorphic mutants (C1532Yneo), which produce approximately 10% of total perlecan, are viable with normal BM structure, although they have a smaller body size, show enhanced susceptibility to exencephaly, and develop skeletal muscle defects.[65] BBB integrity in these hypomorphs, however, was not examined. It should be noted that an *in vitro* study suggests that perlecan may support BBB function via promoting basic fibroblast growth factor (bFGF) uptake into ECs.[66] The exact role of perlecan in BBB maintenance needs further investigation.

Agrin: Agrin is a multidomain heparan sulfate proteoglycan. It exists in either a matrix-associated form found at cerebrovascular BM and neuromuscular junction, or a transmembrane form expressed mainly by neurons.[67–70] In the brain, agrin is produced by neurons, glia, and vascular cells.[67, 69, 71, 72] A recent single cell-RNAseq analysis reports that agrin is synthesized by endothelial cells, mural cells, and astrocytes at the BBB.[11]

Previous studies have demonstrated that agrin plays an important role in neuromuscular junction formation/maintenance and synaptogenesis.[72–74] Echoed with these reports, agrin-deficient mice die at birth due to neuromuscular dysfunctions.[73, 75] Recently, there is evidence suggesting that agrin contributes to BBB maintenance. For example, agrin accumulation in brain BM correlates with the development of barrier function in brain microvessels[70, 72] and agrin stabilizes adherens junctions in brain endothelial cells *in vitro*.[76]

To overcome the perinatal lethality of agrin-deficient mice and enable *in vivo* BBB permeability study, a miniaturized form of agrin was expressed in muscles of these mutant mice.[77] The resulting conditional agrin-deficient mice live to adulthood and lack agrin expression in the brain.[77] Although failed to show enhanced BBB permeability, the conditional agrin-deficient mice displayed reduced levels of adhesion junction proteins and tight junction proteins *in vitro* and *in vivo*.[76] Similarly, mice with endothelium-specific ablation of agrin fail to show BBB disruption or BM abnormalities, although AQP4 is reduced.[68] These results suggest that loss of agrin weakens the barrier function but is not sufficient to disrupt it, possibly due to compensatory mechanisms.

Ischemic stroke

Stroke is a severe medical, social, and economic burden. It is estimated that 1 in every 20 deaths in the United States is from stroke, which adds up to about 140,000 deaths each year.[78] In addition, stroke caused long-term disability costs about $34 billion every year in the United States.[79] Stroke is broadly categorized into hemorrhagic stroke, which is caused by bleeding in or around the brain, and ischemic stroke, which is caused by blockage of blood flow to the brain. Ischemic stroke, which accounts for about 87% of all strokes,[79] is the focus of this review.

Based on the cause of blood vessel blockage, ischemic stroke is often divided into three groups: atherosclerosis, cardio-embolism, and lacunar infarcts.[80] At the onset of the ischemia, a series of pathological events occur. First, cerebral blood flow (CBF) and oxygen supply are reduced and ATP quickly becomes depleted in the ischemic brain.[81] This leads to energy-dependent membrane pump failure, followed by excessive glutamate release and brain edema.[82–84] Next, reactive oxygen species (ROS) generation is enhanced[85] and BBB is disrupted,[86] resulting in inflammatory response and neuronal injury.[87]

BBB breakdown is a major pathology in ischemic stroke. Time-course studies have demonstrated a biphasic BBB disruption after ischemic stroke in the transient middle cerebral artery occlusion (tMCAO) model, which involves both ischemia and reperfusion. The first BBB opening occurs at 6–12 hours after reperfusion, while the second BBB disruption occurs at 72 hours after reperfusion[86, 88–90] (Figure 2A). Similarly, there is evidence supporting a biphasic BBB opening in the permanent middle cerebral artery occlusion (pMCAO) model, which involves ischemia without reperfusion[91] (Figure 2B). The temporal changes of BBB permeability after ischemic stroke in both tMCAO and pMCAO models are summarized in Figure 2. This biphasic BBB opening phenomenon, however, is challenged by an observation that neutrophil infiltration displays a single peak after ischemic stroke.[92] Similarly, there are many excellent reviews on how ECs, pericytes, and astrocytes alter in ischemic stroke. Thus, in this section, we mainly discuss how the BM and its individual components change in ischemic stroke. These changes are summarized in Table 1.

BM changes in ischemic stroke—Similar to the cellular components of the BBB, the BM also displays substantial changes upon the onset of ischemic stroke. Mounting studies have reported BM dissolution during ischemia. For example, loss of BM and BM degradation have been found to occur soon after ischemia.[93, 94] Echoed with this

observation, the BM becomes diffused, thickened, and electron-light after ischemia at ultrastructural levels.[95, 96] Given that the levels and activities of various proteases, including the MMPs,[97–102] are dramatically enhanced after ischemia, it is hypothesized that BM dissolution after stroke is mainly caused by increased degradation rather than reduced production. Below we discuss how each individual component of the BM changes after ischemic stroke.

Collagen IV: How collagen IV changes after ischemic stroke is controversial. On one hand, there is evidence suggesting that collagen IV is degraded. For example, collagen IV level has been found to decrease in rat brains after ischemic stroke in a variety of ischemic stroke models.[103–105] Another study on the non-human primates has also shown that the ratio of collagen IV-containing vessels decreases from 1.02±0.03 to 0.57±0.10 in basal ganglia after 3 hours of ischemia followed by 24 hours of reperfusion.[106] On the other hand, there is also evidence showing increased or unaltered collagen IV after ischemic stroke. One study reported increased collagen IV level in the spinal cord after ischemic stroke.[107] In addition, it has been shown that reduction of collagen IV is not detected after ischemic stroke in a tMCAO model, although it is observed when these mice are further challenged with systemic inflammation.[108] Similar to this finding, in a human case study of ischemic stroke with hemorrhagic complications, collagen IV degradation is found in brain regions with neutrophil infiltration but not those without neutrophil infiltration.[109] These different findings may be due to distinct animals, ischemic models, and/or time points. Future research should address this discrepancy by utilizing both rodents and human samples, performing multiple ischemic models, and analyzing at a variety of time points after stroke.

Laminin: Like collagen IV, controversial findings exist on how laminin changes after ischemic stroke. On the one hand, there is evidence supporting a reduction of laminin after ischemic stroke. It has been shown that laminin expression is significantly reduced in tMCAO model at 24 hours after reperfusion in mice.[110] A similar result is found in Mongolian gerbils after ischemia-reperfusion injury.[111] In addition, laminin expression is also significantly decreased after tMCAO and reperfusion in non-human primates (baboons).[106] Consistent with these reports, laminin level has been found to decrease after ischemic stroke in a clinical study involving 50 patients, although it is gradually recovered to control level by day 12 after stroke.[112] On the other hand, there are also reports showing unaltered or up-regulated laminin level after ischemic stroke. For instance, laminin expression has been found unchanged in ischemic brains with or without systemic inflammation.[108] Additionally, significantly elevated laminin level is observed in reactive astrocytes in the brain 32 days after ischemia.[113] Furthermore, a transient up-regulation of laminin has been reported in both ischemic brain and in ECs after OGD.[114] Again, these controversial results may be due to different animal models and distinct time points. In addition, laminin antibodies used in these studies may also contribute to this discrepancy. A pan-laminin antibody rather than subunit-specific laminin antibody was used in most previous studies. Thus, the changes of specific laminin isoforms after ischemic stroke remain elusive. Given that distinct cells express distinct laminin isoforms with possibly different functions,[115, 116] it is important to understand how each laminin isoform changes after ischemic stroke. Future studies should answer this important question.

Nidogen: How nidogen changes after ischemic stroke remain unknown. One study reported that stroke patients had increased plasma nidogen levels, although the increase was not statistically significant.[117] Additionally, an *in vitro* study showed that oxidative stress, a critical pathology of ischemic stroke, up-regulated nidogen level in human brain ECs.[117] These findings suggest that nidogen expression may be increased after ischemic stroke. The underlying molecular mechanisms, however, need further investigation.

Perlecan: Perlecan is one of the most sensitive ECM proteins in ischemic brain. It has been demonstrated that there is a 37–61% reduction of perlecan within 2 hours after tMCAO in baboons.[118] Similarly, using two different perlecan monoclonal antibodies, it has been shown that perlecan signal is significantly decreased in the striatum after tMCAO.[118] Interestingly, unlike other ECM proteins, perlecan is not degraded by proteolysis. Instead, it is cleaved into small fragments. Perlecan domain V, one proteolytic fragment of perlecan, is significantly increased after ischemic stroke in both rodents and humans.[119, 120] Functional studies support a beneficial role of perlecan, especially its domain V, in ischemic stroke. For example, larger infarct volume and exacerbated BBB damage were found in conditional perlecan-deficient mice.[62] Subsequent studies demonstrated that perlecan exerts a beneficial role in ischemic brain by enhancing pericyte recruitment through cooperative action of PDGFRβ and integrin-α5β1.[62] Additionally, recombinant perlecan domain V has been shown to reduce infarct volume, attenuate neuronal death, promote angiogenesis, and improve neurological function in ischemic stroke.[62, 119, 121, 122] The therapeutic potential of perlecan domain V is currently under investigation.

Agrin: There is evidence showing that agrin is degraded after ischemic stroke. One study showed a gradual decline of agrin at both mRNA and protein levels at 1–24 hours after reperfusion in a transient global cerebral ischemia model.[123] Another study reported that agrin was cleaved by matrix metalloproteinase-3 at 1–7 days after injury in a transient focal cerebral ischemia model.[71] These findings suggest a negative correlation between agrin and ischemic stroke. The functional significance of agrin in ischemic stroke, however, remains unknown. Future studies should address this important question.

Targeting BBB in the therapies of ischemic stroke

So far, the only FDA-approved drug for ischemic stroke is tissue plasminogen activator (tPA). Although tPA can efficiently restore blood supply to the ischemic area by breaking down blood clots, its narrow therapeutic window greatly limits its clinical use.[124–126] It is estimated that tPA helps less than 10% of stroke patients.[127] Therefore, finding novel and effective treatments for ischemic stroke is urgent.

The BBB, a dynamic structure that actively regulates stroke pathogenesis and progression, may be targeted to treat ischemic stroke. First, preventing degradation of the BM is one strategy.[128] Mounting evidence suggests that inhibiting MMP activity is able to improve stroke outcome. For example, it has been shown that both MMP-9-neutralizing antibody[100] and MMP-9 knockdown[129] reduce infarct volume after ischemic stroke. More importantly, MMP inhibitors display promising therapeutic effects in ischemic stroke in several clinical trials.[130–133] Next, certain BM components may have a therapeutic effect in ischemic stroke.

It has been shown that perlecan domain V plays a neuroprotective role in ischemic stroke and is able to improve stroke outcome.[134] Thus, perlecan domain V may be used to treat ischemic stroke. Like perlecan, laminin also contributes to the pathogenesis of ischemic stroke. For instance, we recently reported that mice lacking mural cell-derived laminin-α5 demonstrated decreased infarct volume, less severe BBB disruption, and better neurological function after tMCAO.[135] Similarly, mice deficient in integrin-α5, a receptor for laminin and other ECM proteins on ECs at the BBB,[116] showed significantly smaller infarct volume and attenuated BBB damage following transient tandem ipsilateral common carotid artery/MCA occlusion.[136] These findings suggest that laminin-α5 and integrin-α5 play a detrimental role in ischemic stroke, and that blocking this signaling pathway may have a therapeutic effect in ischemic stroke. Future studies should address: (1) what are the specific laminin (-α5β?γ?) and integrin (α5β?) isoforms involved in this process? and (2) how to target these laminin/integrin isoforms specifically without affecting other isoforms? Answering these important questions will enable us to develop innovative BM-based therapies for ischemic stroke.

Conclusions

BBB breakdown is not only a consequence, it also actively regulates the progression of ischemic stroke. Understanding how exactly the BM and its individual components change in ischemic stroke will enrich our knowledge in stroke pathogenesis, identify novel targets with therapeutic potential, and promote the development of innovative therapies for this devastating disorder. Compared to the cellular constituents of the BBB, its non-cellular component, the BM, is understudied. In this review, we introduce the structure & function of the BM and summarize the alteration of each individual BM component in ischemic stroke. Furthermore, we also discuss novel molecular targets with therapeutic potential and key questions in the field.

Acknowledgments

MK searched the literature and drafted the article. YY gave suggestions and edited the article. All authors read and approved the final article.

Sources of Funding

This work was partially supported by the NIH/NHLBI R01 HL146574 to YY and American Heart Association Scientist Development Grant 16SDG29320001 to YY.

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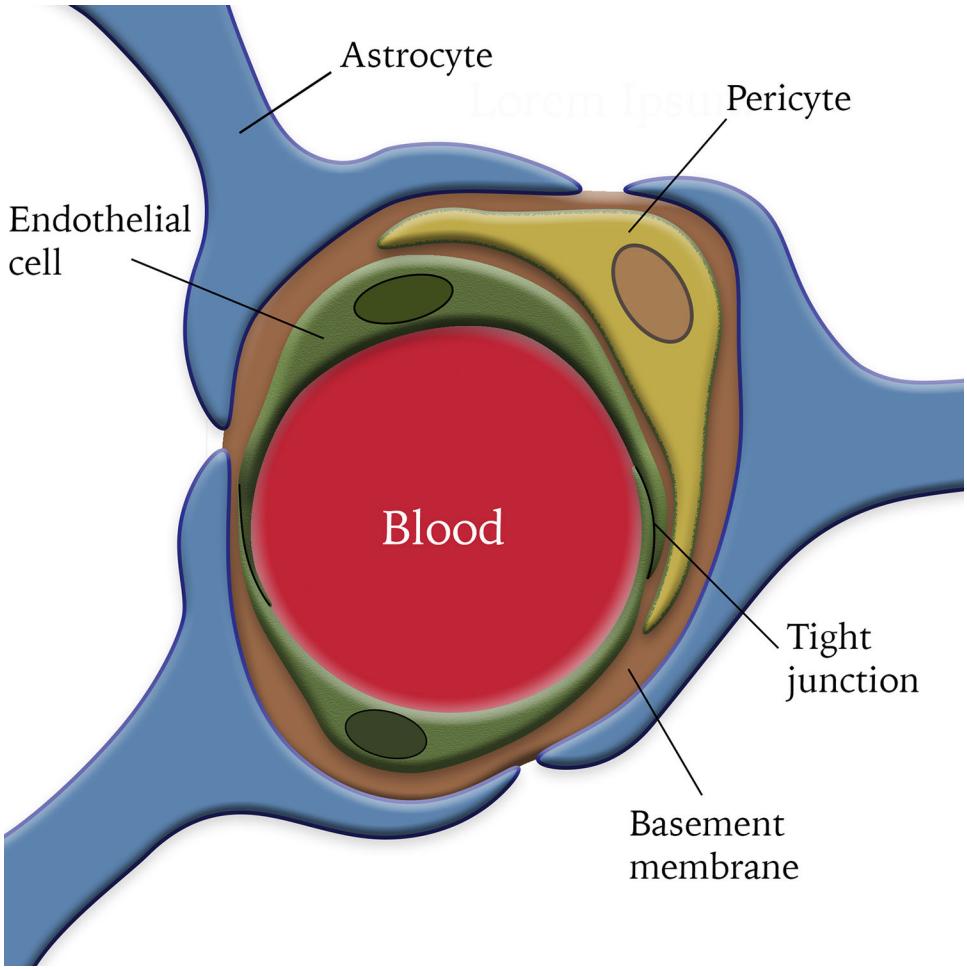

Figure 1.
Diagram illustration of the blood-brain barrier. Endothelial cells connect with each other via tight junctions. Pericytes are embedded in the basement membrane and cover endothelial cells. Astrocytes wrap endothelial cells and pericytes with their endfeet.

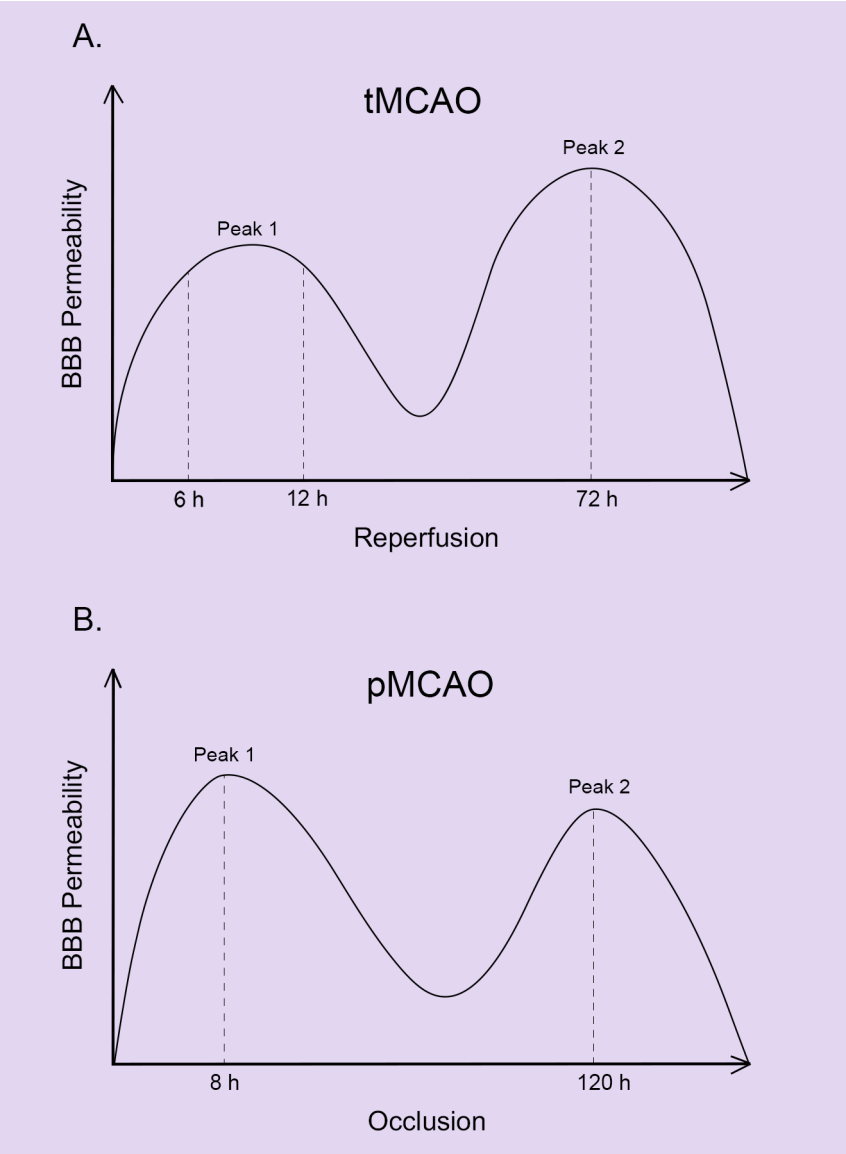

Figure 2.

Temporal changes of BBB permeability after ischemic stroke. **A**. BBB permeability follows a biphasic pattern in the tMCAO model with the first peak at 6–12 hours after reperfusion and the second peak at 72 hours after reperfusion. **B**. BBB permeability follows a biphasic pattern in the pMCAO model with the first peak at 8 hours after occlusion and the second peak at 120 hours after occlusion.

Table 1.

Changes of BM components after ischemic stroke

BM/BM Component	Changes after ischemic stroke	Time Course (post injury)	Model	Species	References
Basement Membrane	Dissolution	24 hours	tMCAO	Rat	93
		As early as 10 minutes	Focal cerebral ischemia/ reperfusion	Rat	94
		12–48 hours	pMCAO	Rat	96
	Thickening	3–72 hours	Photothrombotic stroke	Mouse	95
Collagen IV	Decrease	24 hours	tMCAO	Rat	104, 137
		24 hours	tMCAO	Baboon	106
		1–6 hours	Thromboembolic model of MCAO	Rat	105
		4–24 hours	tMCAO with systemic inflammation	Mouse	108
		6 hours after death	Ischemic stroke: in regions with neutrophil infiltration	Human	109
	Unaltered	4–24 hours	tMCAO without systemic inflammation	Mouse	108
		6 hours after death	Ischemic stroke: in regions without neutrophil infiltration	Human	109
	Increase	24 hours	Infrarenal aorta clamping/ removal (spinal cord)	Rat	107
Laminin	Decrease	3 hours	tMCAO	Mouse	110
		24–72 hours	Transient forebrain ischemia	Mongolian gerbil	111
		1–24 hours	tMCAO	Baboon	106
		1–12 hours after death	-	Human	112
	Unaltered	4–24 hours	tMCAO	Mouse	108
	Increase	32 days	Transient ischemia	Rat	113
		6–24 hours	pMCAO	Mouse	114
Nidogen	Unknown	-	-	-	-
Perlecan	Decrease	1 hour-7 days	tMCAO	Baboon	118
	Fragmentation	1–7 days	Focal cerebral ischemia	Rat	119
		1–7 days	Transient tandem ipsilateral CCA and distal MCA occlusion	Mouse	119
Agrin	Decrease	1–24 hours	Transient global cerebral ischemia	Rat	123
		1–7 days	tMCAO	Rat	71