Blood-brain barrier pathology in cerebral small vessel disease

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From the Contents

Abstract

Cerebral small vessel disease is a neurological disease that affects the brain microvasculature and which is commonly observed among the elderly. Although at first it was considered innocuous, small vessel disease is nowadays regarded as one of the major vascular causes of dementia. Radiological signs of small vessel disease include small subcortical infarcts, white matter magnetic resonance imaging hyperintensities, lacunes, enlarged perivascular spaces, cerebral microbleeds, and brain atrophy; however, great heterogeneity in clinical symptoms is observed in small vessel disease patients. The pathophysiology of these lesions has been linked to multiple processes, such as hypoperfusion, defective cerebrovascular reactivity, and blood-brain barrier dysfunction. Notably, studies on small vessel disease suggest that blood-brain barrier dysfunction is among the earliest mechanisms in small vessel disease and might contribute to the development of the hallmarks of small vessel disease. Therefore, the purpose of this review is to provide a new foundation in the study of small vessel disease pathology. First, we discuss the main structural domains and functions of the blood-brain barrier. Secondly, we review the most recent evidence on blood-brain barrier dysfunction linked to small vessel disease. Finally, we conclude with a discussion on future perspectives and propose potential treatment targets and interventions.

Key Words: blood-brain barrier dysfunction; cerebral blood flow; cerebral hypoperfusion; endothelial dysfunction; hypertension; inflammation; magnetic resonance imaging; neurovascular unit; oxidative stress; small vessel disease; tight junctions; transcytosis

Introduction

Cerebral small vessel disease (SVD) is a neurological disorder that consists of pathological processes affecting cerebral arterioles, capillaries, and venules, leading to white and gray matter lesions including white matter hyperintensities (WMH), lacunes, enlarged perivascular space, among other radiological hallmarks (Moretti and Caruso, 2022). With the aging population, the incidence of SVD continues to rise, and to some extent, it is present in virtually every individual ≥ 60 years of age (Nichols et al., 2019; Moretti and Caruso, 2022). Although SVD was initially regarded as innocuous, it has been linked to 25% of all strokes and is considered to be the most important vascular cause of dementia, exacerbating the social and economic impact of global cerebrovascular diseases (Evans et al., 2021; Moretti and Caruso, 2022). There are six etiological categories of SVD, with atherosclerosis-associated SVD being the most common (Litak et al., 2020). It is not exactly known which pathological changes lead to SVD, however, the involvement of brain-blood barrier (BBB) impairment is obvious. The blood vessels of the central nervous system (CNS) have unique barrier properties via the so-called BBB, which tightly regulates brain homeostasis by protecting the CNS from pathogens in the blood and selectively exchanging substances between circulation and brain parenchyma (Huang et al., 2020). BBB dysfunction appears to be common in the elderly population (Kurz et al., 2022; Ng et al., 2022). Moreover, BBB dysfunction seems to precede the structural damage visible on magnetic resonance imaging (MRI) and is thought to be one of the earliest manifestations of SVD (Kurz et al., 2022). BBB dysfunction disrupts the delicate balance of the brain's microenvironment, affecting cerebral blood flow (CBF) regulation, and metabolic processes (Yu et al., 2020). The compromised BBB also hinders the removal of toxic metabolic byproducts, which can detrimentally compromise neurons, and is therewith associated with neurodegenerative processes (Sweeney et al., 2019).

In this review, we will provide information on BBB structure and function and the neurovascular unit (NVU). We will thereafter focus on BBB dysregulation in atherosclerosis-related SVD and possible mechanisms that contribute to BBB dysfunction and the impact of SVD risk factors hereon. Finally, we will discuss potential treatment targets and interventions, and future perspectives.

Search Strategy

We searched the PubMed database, using the following keywords and their combinations to select articles: "blood-brain barrier"; "cerebral small vessel diseases"; "stroke"; "dementia"; "endothelial cells"; "blood-brain barrier dysfunction"; "astrocytes"; "pericytes"; "hypertension"; "hyperglycemia"; "aging"; "hyperlipidemia"; "neuroimaging"; "MRI". Selected literature was restricted to human and rodent studies published in English from 2013 to 2023.

Neurovascular Unit

The BBB is a neurovascular structure that regulates transport to and from the CNS (Keaney and Campbell, 2015). Cerebral microvascular endothelial cells (ECs) and their tight junctions (TJs) are surrounded by pericytes and covered by astrocyte terminals, which together with the extracellular matrix constitute the BBB (Liebner et al., 2018). With advanced research, it has become evident that the structure and integrity of the BBB require more than just the involvement of ECs, and the concept of NVU was coined (Iadecola, 2017). As shown in **Figure 1**, in addition to the abovementioned components, also neurons, perivascular microglia, and smooth muscle cells (SMCs) are involved in the NVU (Liu et al., 2020; Kugler et al., 2021). The emergence of the NVU concept not only demonstrates the sub-molecular connections between various cells but also emphasizes the critical interdependence that exists between brain cells and the vascular system.

ECs are a major component of the BBB. In particular, the establishment of the BBB during embryonic development is closely associated with ECs since vascular endothelial growth factor secreted by nerve cells guides angioblasts to form new blood vessels and initiates BBB formation (Zhao et al., 2015). The Frizzled receptor and LRP5/6 complex on ECs are activated by the Wnt signal, contributing to the formation of BBB (Sweeney et al., 2019). Moreover, the canonical Wnt signaling pathway controls TJs, brain angiogenesis, and other BBB-related receptors like Glucose transporters (Glut). Glut are important proteins that facilitate the transport of glucose across the BBB to meet the energy demands of the brain (Sweeney et al., 2019). The platelet-derived growth factor and vascular endothelial growth factor secreted by ECs can

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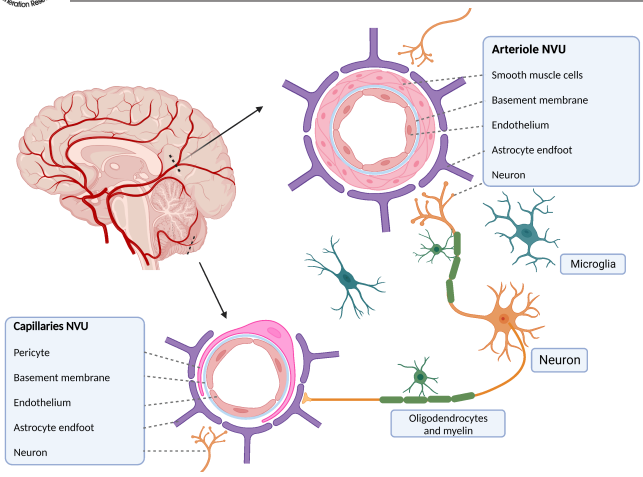

Figure 1 | **Structure of neurovascular unit (NVU).**
Vascular endothelial cells and brain cells interact and function as a unit. At the arteriolar level, endothelial cells (ECs) form the inner layer of the vessel wall, and a basement membrane separates the endothelium from the wrapping smooth muscle cells (SMCs). At the capillary level, pericytes replace SMCs and share the basement membrane with ECs. Arteriole and capillary walls are covered by the terminal end feet of astrocytes. SMCs, pericytes, and astrocytes are all in close contact with neurons. Created with BioRender.com.

promote the formation of neurovascular patterns. Additionally, vasoactive substances produced by ECs, such as nitric oxide (NO), prostacyclin, and endothelin, can also control the contraction and relaxation of vessel SMCs, which directly affects CBF (Kisler et al., 2017).

In the BBB, pericytes anchor to capillary ECs through nail-like structures formed by cadherins and connexins, therewith interacting with ECs (Iadecola, 2017; Perrot et al., 2020). This interaction is important for the formation and maintenance of the BBB. At the early embryo stages, pericytes participate in the formation of the BBB prior to astrocytes (Daneman et al., 2010). Moreover, evidence from mice studies showed that pericytes' deficiency is linked to BBB disruption and reduced amount of microvessels (Zhao et al., 2015). Several signaling pathways associated with pericyte-endothelial cells, such as angiopoietin/Tie-2 and transforming growth factor-β-mediated pathways, have a continued impact on the BBB by influencing vascular maturation and angiogenesis (Gürler et al., 2022). Pericytes wrapped around capillaries ensure close paracrine contacts between these two cell types, contributing to the maintenance of the BBB (Sun et al., 2020, 2021; Elabi et al., 2023). Pericytes might also have a regulatory effect on the CBF, which may depend on the ability of pericytes to actively relax or contract (Brown et al., 2019). Whereas, due to the difficulty in delineating the specific boundaries of capillary pericytes and capillary sphincters, there is some controversy as to whether pericytes can regulate CBF. Some have suggested that constriction of the anterior capillary sphincter that perforates the arterioles may be responsible for changes in capillary CBF (Uemura et al., 2020). However, accumulating evidence supports the role of pericytes in the regulation of CBF, but at the same time, there is a growing need to better define pericytes (Hall et al., 2014; Nortley et al., 2019; Grubb et al., 2020).

Astrocytes, the most abundant glial cell type in the CNS, are located between neurons and ECs in the context of NVU (Liu et al., 2020). Their primary role involves regulating BBB function, neurotransmitter release, neuronal excitability, and synaptic plasticity (Nagai et al., 2019). Cerebral vessels are almost completely covered and surrounded by extended terminal endfeet of astrocytes, thereby interacting with the ECs (Michinaga and Koyama, 2019; Liu et al., 2020). Astrocyte terminal endfeet express aquaporin 4 (AQP4), which is important in regulating water homeostasis in all brain cells and tissues, helping to maintain optimal neuronal activity (Salman et al., 2022). This may be achieved through changes in the subcellular localization of AQP4 (Salman et al., 2022). Astrocytes preserve the optimal composition of extracellular fluid by utilizing specialized ion transporters, including potassium channels (Kir4.1), and excitatory amino acid transporters (Sweeney et al., 2019). Astrocytes respond to adrenergic neurons, by increasing intracellular calcium ions and participating in the regulation of CBF through vasoconstriction (Iadecola, 2017; Takahashi, 2022). Furthermore, astrocytes-transduced sonic hedgehog signaling can also strengthen the BBB by stimulating the expression of TJ components such as claudin-5 and occludin (Langen et al., 2019; Xing et al., 2020).

Tight junctions and transcellular pathways

ECs in cerebral blood vessels are connected by TJs and adherens junctions (AJs), resulting in high transmembrane resistance of the BBB therewith drastically reducing paracellular transport.

As shown in **Figure 2A**, TJs in the cerebrovasculature contain occludin, claudins (notably claudin-5), and junctional adhesion molecules (JAMs), which are crucial for regulating the paracellular permeability of the BBB (Langen et al., 2019). Occludin, the first TJ protein identified, is associated with high levels of transmembrane resistance and is important in the regulation and maintenance of BBB function, but it is not essential for TJ formation (Pandit et al., 2020). Claudin-5 is a tetraspanin expressed on ECs and has been shown to have a strong interaction capacity with other members of the claudin family, which constitute the backbone of TJ (Tachibana et al., 2020). Junctional adhesion molecules are type I transmembrane proteins of the immunoglobulin superfamily, mainly related to leukocyte adhesion and migration (Tachibana et al., 2020). Moreover, TJ connects to the actin cytoskeleton by forming complexes with scaffold proteins from the membrane-associated guanylate kinase family, such as zona occludens 1 (ZO-1) (Zhao et al., 2022b).

AJs between ECs are critical in the formation of TJ and adhesion between ECs. Cadherins in AJs are calcium-dependent transmembrane proteins that can upregulate the expression of claudin-5 and play important roles in vessel assembly and stability and cell-to-cell adhesion (Pandit et al., 2020). β-catenin, p120, and plakoglobin are examples of cytoplasmic plaque proteins, another type of AJs that build connections between ZO-1 and the actin cytoskeleton (Pandit et al., 2020).

Figure 2B shows how substances are transported across the BBB. Small fat-soluble molecules (< 400 Da) and gases such as oxygen can pass through the BBB in a passive diffusion manner along the concentration gradient (Zhao et al., 2022b). In addition to passive diffusion, receptor-mediated and adsorption-mediated transcytosis, mainly caveoli, can move macromolecules bidirectionally, participating in transport across the BBB (Zhao et al., 2022b). Under physiological conditions, hypotranscytosis of the BBB into the brain is maintained by the docosahexaenoic acid transmembrane protein on ECs, a major facilitator of superfamily structure and protein 2a, which can inhibit the formation of caveolae vesicles (Peng et al., 2021). Other modes of transport across the BBB are carrier-mediated transport and active efflux. Carrier-mediated transport mainly depends on the transport proteins of the solute carrier superfamily, such as glucose transporters, sodium pumps, and potassium channels. These can facilitate the passage of various molecules including carbohydrates, amino acids, monocarboxylic acids, hormones, and fatty acids across the BBB and maintain the physiological functions of nerve cells (Knox et al., 2022). Active efflux transport largely involves adenosine triphosphate-binding cassette transporters such as P-glycoprotein. They use adenosine triphosphate to excrete drugs and harmful metabolites into the blood, and are essential to prevent the accumulation of toxic metabolites (Knox et al., 2022). Once the abovementioned transcellular pathways are damaged, the normal physiological functions of the brain will be impaired and the risk of brain diseases will be increased.

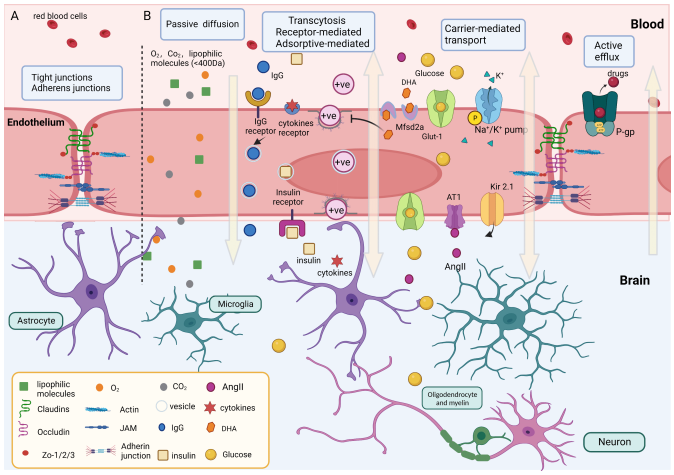

Figure 2 | **Endothelial intercellular junctions and transport pathways across the BBB.**
(A) Under physiological conditions, brain endothelial cells form tight junctions that seal paracellular diffusion pathways. Tight junction complex includes occludin, claudins (especially claudin-5). The tight junction complex is linked to the direct proteins ZO-1, ZO-2, and ZO-3 and is anchored to the cytoskeleton. Adherens junctions and junctional adhesion molecules contribute to the formation of tight junction complexes. (B) There are four main ways for molecules to cross the BBB under physiological conditions. Passive diffusion: fat-soluble molecules, gases, and substances with a molecular weight of less than 400 Da can enter the brain through this method; endothelial transcytosis: mainly includes receptor-mediated and caveolae-mediated. They are vesicle-based transport systems that can carry macromolecules in both directions. Carrier-mediated transport: Many necessary polar molecules such as glucose, amino acids, and ions are transported by this method, and this transport can also be bidirectional. Active excretion: Drugs, drug conjugates, and nucleosides are transported to the blood mainly through the ATP-binding cassette transporter. Created with BioRender.com. Ang II: Angiotensin II; AT-1: angiotensin II type 1 receptor; BBB: blood-brain barrier; CO2: carbon dioxide; DHA: docosahexaenoic acid; Glut-1: glucose transport protein 1; IgG: immunoglobulin G; JAM: junctional adhesion molecules; Kir: inwardly rectifying potassium channel; Mfsd2a: major facilitator of superfamily structure and protein 2a; O2: oxygen; P-gp: P-glycoprotein; ve: electronic; ZO-1/2/3: Zona occludens 1/2/3.

Blood-Brain Barrier Dysfunction in Small Vessel Disease

Cognitive decline in SVD patients has been recently associated with the degree of BBB leakage, and therefore BBB impairment may be an early indicator of cognitive impairment (Nation et al., 2019; Kerkhofs et al., 2021b). BBB damage in SVD can lead to leakage of plasma or cellular components from blood vessels, causing cerebral microvascular damage, brain tissue edema, and neuroinflammation (Blevins et al., 2021; Kurz et al., 2022). Notably, Wong et al. (2019) also found increased BBB permeability in normal-appearing white matter near the WMH, implying that damage to the BBB could be involved in the etiopathogenesis of WMH. BBB degradation preceding WMH has been confirmed as having a critical role in the pathology of SVD through longitudinal studies (Kerkhofs et al., 2021a). Primary risk factors currently associated with SVD comprise aging, hypertension, hyperlipidemia, and hyperglycemia (**Figure 3**; Wang et al., 2021). Nonetheless, it is important to note that the aforementioned risk factors frequently interplay with one another, potentially causing, or worsening BBB dysfunction. Therefore, studying the mechanism of SVD risk factors underlying BBB dysfunction will help to understand the pathogenesis of SVD and the prevention and treatment of future diseases.

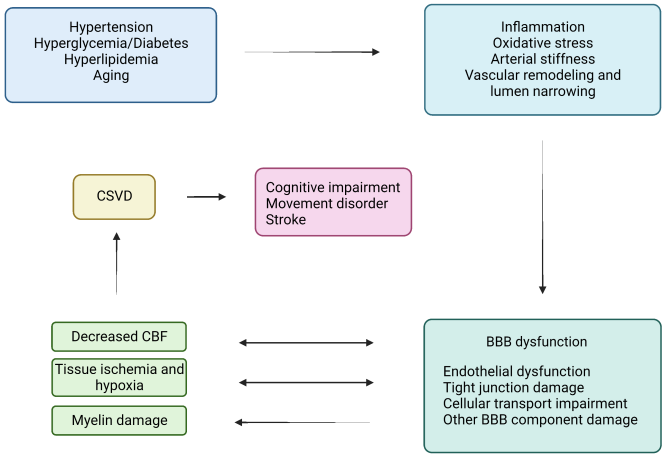

Figure 3 | **Influence of risk factors on BBB.**
Created with BioRender.com. BBB: Blood-brain barrier; CBF: cerebral blood flow; SVD: small vessel disease.

Aging, as a physiological process, leads to a certain degree of decline in the functionality of all organs and tissues in the body. Research has indicated that a small percentage (3%) of individuals over the age of 40 years exhibited noticeable arteriolosclerosis-related SVD (Blevins et al., 2021). However, this percentage dramatically increases to 19% of people over the age of 70, and the proportion was even more pronounced among those over the age of 80 (Blevins et al., 2021). In addition, age-related WMH accumulation correlates with increased BBB leakage (Zhang et al., 2019). While the exact mechanisms by which aging leads to an increased risk of SVD have not been elucidated yet, RNA sequencing analyses revealed a correlation between aging and damage to the BBB, attributed to several pathways such as cell adhesion, oxidative stress, and vascular remodeling (Yousef et al., 2019). Most of these pathways are related to brain ECs. Studies have found that aging can reduce CBF and increase BBB permeability by affecting the secretion of endothelial vasoactive substances and BBB transcellular transport (De Silva and Faraci, 2020). Moreover, aging often interacts with other risk factors to jointly worsen the pathological changes of the disease.

Hypertension is the foremost risk factor linked with WMH burden and microbleeds. Research has indicated that long-term hypertension can lead to a high prevalence of SVD and a greater SVD burden (Petrea et al., 2020; Solé-Guardia et al., 2023). A four-year cohort study of older adults revealed a significant correlation between hypertension and the severity of the white matter disease (Abraham et al., 2016). Another study on SVD patients demonstrated increased brain tissue water content and greater BBB leakage in patients with hypertension and elevated pulse pressure (Wardlaw et al., 2017). During hypertension, changes in blood pressure stimulate the release of vasoactive mediators from ECs, causing vascular constriction or dilation to maintain normal CBF (Ashby and Mack, 2021). However, prolonged exposure to hypertension can induce vascular remodeling and arteriosclerosis, resulting in brain tissue ischemia, oxidative stress, and neuroinflammation (Evans et al., 2021). Consequently, these processes lead to endothelial dysfunction, causing heightened arterial fragility and stiffness. Subsequently, these yield a decrease in CBF, reduced integrity of the BBB, and diminished brain activity, ultimately resulting in cognitive decline (Meissner, 2016; Robert et al., 2022). And because endothelial dysfunction and BBB damage can also cause oxidative stress and neuroinflammation, antihypertensive drug intervention can slow the progression of SVD to some extent, but is not always effective (Rajani et al., 2018).

Hyperglycemia, particularly its prolonged exposure, has the potential to negatively impact the microvasculature, likely resulting in retinopathy and neurological issues that can significantly impact both quality of life and life expectancy (Faselis et al., 2020). The presence of a genetic predisposition to type 2 diabetes and hyperglycemia has been linked to an increased risk of ischemic stroke as well as white matter loss (Georgakis et al., 2021). However, the pathogenesis and causation are still unclear. It has been reported that people who suffered from diabetes for over ten years have a threefold increased risk of ischemic stroke compared to people without diabetes (Mosenzon et al., 2023). BBB damage is considered to be one of the factors responsible for cerebrovascular complications caused by hyperglycemia (Rom et al., 2020). Numerous studies have demonstrated that hyperglycemia contributes to arteriosclerosis, disrupts normal CBF, and may result in vascular endothelial damage, therewith facilitating the onset and progression of SVD (van Sloten et al., 2020; Evans et al., 2021).

Hyperlipidemia generally refers to abnormally elevated blood lipids or lipoproteins, mainly caused by eating disorders and obesity. Hyperlipidemia may lead to cerebral hypoperfusion and cognitive impairment in addition to its well-known proatherogenic effects (Appleton et al., 2017). Studies have established a link between particularly abdominal obesity, and an increased risk of cerebrovascular disease (Marini et al., 2020). In fact, the risk of ischemic stroke was found to have increased by 30% per each standard deviation increase in abdominal obesity (Dale et al., 2017). Furthermore, there is evidence suggesting that hypercholesterolemia is positively associated with perivascular space enlargement (Wang et al., 2019). However, the extent to which hypercholesterolemia is linked to WMH and lacunar infarction has not yet been definitively proven. The disruption of BBB appears to be a crucial factor in the onset of hypercholesterolemia-induced brain alterations. Lipoprotein metabolites can affect BBB permeability by regulating TJ protein post-translational modification and disrupting cell-cell junctions (Tóth et al., 2020). Hyperlipidemia-induced inflammation and oxidative stress can also participate in the development of cognitive dysfunction by damaging ECs and regulating BBB transporters (Tóth et al., 2020).

Changes in Different Cellular Components of the Blood-Brain Barrier

Endothelial dysfunction

Preclinical evidence from SVD rat models showed a significant increase in brain edema and cerebrospinal fluid protein concentration when compared to control rats (González-Marrero et al., 2022). These findings suggest damage to the integrity of the BBB and a possible correlation with impaired endothelial homeostasis. Endothelial dysfunction is the most important pathological change to appear in SVD and precedes BBB breakdown (Rajani et al., 2018). Stable CBF ensures adequate nutrient supply and waste removal for optimal neuronal function. ECs can integrate signals of neuronal activity and metabolic state to precisely control CBF to meet the dynamic demands of the brain by releasing vasoactive substances and regulating blood vessel diameter (Ashby and Mack, 2021). Individuals with SVD show decreased CBF levels, closely related to SVD severity (Wong et al., 2019; Neumann et al., 2022). In the case of aging and hyperlipidemia, low CBF can also result in oscillatory shear stress in arterial bifurcations. Existing research reveals that increased WMH volume could be associated with elevated endothelial oxidative stress and further endothelial damage induced by oscillatory shear stress (Chen et al., 2019). Additionally, low shear stress has been linked to early imaging and cognitive changes in SVD (Kamimura et al., 2022).

On the other hand, oxidative stress and inflammation are two potential mechanisms of endothelial dysfunction triggered by primary risk factors such as hypertension. Studies demonstrated that vascular oxidative stress can be triggered by angiotensin II and endothelin-1, a production that is promoted by angiotensin II, eventually causing neurovascular dysfunction (Iadecola and Gottesman, 2019). In addition, increased levels of ROS in the brain can lead to decreased endothelial nitric oxide synthase expression and NO bioavailability, inducing endothelial dysfunction and BBB dysfunction (De Silva and Miller, 2016; De Silva and Faraci, 2020; Hannawi et al., 2022). Mitochondrial oxidative stress is another form of intracellular oxidative stress. It is known that excessive superoxide production in EC mitochondria can cause extreme oxidative stress and endothelial dysfunction, resulting in impaired endothelium-dependent vasodilation (Clyne, 2021). NADPH oxidase, the sole known enzyme responsible for generating ROS, may play a role in vascular remodeling and exacerbate BBB destruction under hypertension (De Silva and Miller, 2016). Research shows that reducing the expression of mitochondrial sirtuin 3 can affect NADPH activation and the mitochondrial oxidative process (Dikalova et al., 2020; Griendling et al., 2021). Oxidative stress comprises not only an increase in oxidative substances but also damage to the antioxidant process. The enzyme superoxide dismutase plays a crucial role in antioxidant activities related to redox reactions. Studies have suggested that decreased superoxide dismutase levels are linked to a higher likelihood of cognitive impairment in patients with SVD (Mu et al., 2021). Therefore, further exploration is needed to identify the targets of redox reactions within the brain and decipher the specific downstream mechanism by which oxidative stress induces SVD.

Additionally, the abovementioned risk factors can cause low systemic and vascular inflammation that promotes SVD progression (Gao et al., 2022; Mosenzon et al., 2023). For example, activating immune cells such as neutrophils, macrophages, and T cells, and aggravating white matter damage

(Cai et al., 2021; Huang et al., 2021; Del Cuore et al., 2022). Activated immune cells promote the release of proinflammatory mediators such as interleukin-1β, interleukin-17, and tumor necrosis factor-α, and stimulate ECs to produce ROS, leading to EC dysfunction (Norlander et al., 2018; Evans et al., 2021). Damaged ECs can further release vascular inflammation-related factors, such as cell adhesion molecules and von Willebrand factor, which promote SVD progression and cognitive impairment through endothelial activation and immune cells adhesion and aggregation (Denorme et al., 2019; Yousef et al., 2019; Kadry et al., 2020). Moreover, immune cell migration to the brain parenchyma, and microglia activation, which generally initiate neuroinflammation, can be facilitated by cell adhesion molecules (Yousef et al., 2019; Evans et al., 2021; Youwakim and Girouard, 2021). Under chronic hypertension, activation of Toll-like receptor 4, has been observed as a key signal transduction receptor in inflammatory responses, which may represent one of the key mechanisms of SVD vascular cognitive impairment (Gao et al., 2019). Microglial activation and senescence with age also cause impaired immune cell phagocytosis and migration (Del Cuore et al., 2022). The activated microglia will further secrete ROS, cytokines, and chemokines, resulting in an intensified inflammatory response of astrocytes and ECs that would ultimately damage neurons and the BBB (Liu et al., 2020; Youwakim and Girouard, 2021). However, the underlying inflammatory response and its initiation remain elusive in the context of SVD. Further research is required to determine its exact causal relationship with BBB damage, and thereafter optimal treatment strategies to ameliorate the progression of SVD.

Tight junction proteins alteration: deterioration, translocation, and modifications

As shown in **Figure 4**, the reliability of the BBB is predicated upon the establishment and preservation of TJs among ECs. Changes in the TJs between endothelium and trans-BBB transporters can lead to increased BBB permeability, in turn allowing harmful substances such as cytokines to enter the brain, causing inflammation and oxidative stress, damaging neurons (Han and Jiang, 2021). The deterioration of these TJs may cause BBB permeability, resulting in inflammation and tissue swelling. During hypertension, angiotensin II and angiotensin 1 receptor activation can damage TJs and increase BBB paracellular permeability (Katsi et al., 2020). Cerebral hypoperfusion can also downregulate TJ protein expression, leading to increased BBB paracellular permeability, causing white matter damage and neuronal loss (Ashby and Mack, 2021; Rajeev et al., 2022). This damage may be attributed to the increased expression of matrix metalloproteinases (MMP) resulting from hypoperfusion (Che et al., 2023). MMPs are a family of calcium-dependent zinc-containing endopeptidases that can damage the endothelium and BBB by degrading the extracellular matrix and TJ proteins (Rempe et al., 2016). Its upregulation is associated with hypoxia-induced angiogenic signaling, and aberrant angiogenesis is increasingly an important factor in BBB breakdown. Studies showed that SVD patients exhibit elevated serum MMP-9, with a discernible gender-based variation (Tsiknia et al., 2022; Zhao et al., 2022a).

Notably, some BBB leakage models did not exhibit alterations in claudin-5 and occludin mRNA levels (Situ et al., 2022), suggesting that the functionality of TJ may not solely rely on the expression of TJ genes and proteins, but also on the position of TJ proteins. In addition to decreasing TJ protein expression, excessive oxidative stress within the brain can trigger the redistribution of TJ proteins, leading to a decrease in endothelial transepithelial resistance and an increase in BBB paracellular permeability (Situ et al., 2022). In circumstances involving ischemia and hypoxia, this redistribution may potentially be associated with adsorption-mediated transcytosis. Moreover, the cAMP/protein kinase A signaling pathway can contribute to BBB paracellular leakage by instigating modifications in the cellular actin cytoskeleton arrangement (Cong and Kong, 2020).

Furthermore, post-translational modifications of TJ proteins, specifically phosphorylation, and dephosphorylation, can impact the permeability of the BBB (Kim et al., 2022). Post-translational modifications of TJ proteins such as phosphorylation and dephosphorylation can also affect BBB permeability. In the case of ischemic stroke, the increased secretion of inflammatory mediators in the brain will elicit a rise in the phosphorylation of occludin and ZO-1, ultimately resulting in BBB paracellular leakage (Abdullahi et al., 2018). Protein kinase C, protein kinase A and RhoA/ROCK signaling pathway may be involved in the post-translational modification of TJ protein (Cong and Kong, 2020; Zhao et al., 2021).

Alteration of BBB transcellular pathways

Apart from changes in cellular and TJ proteins, the role of transcytosis in the impairment of BBB function in SVD is also significant. Upregulated transcytosis is currently suggested to be an early sign of BBB dysfunction in disease conditions (Langen et al., 2019; Kadry et al., 2020). Reduced expression of Mfsd2a in ischemia rats increases adsorption-mediated transcytosis that in turn increases BBB permeability (Zhou et al., 2022). A study found that rats overexpressing Mfsd2a can protect the BBB by reducing vesicle transport in the BBB, thereby improving cognitive impairment caused by cerebral hypoperfusion (Qu et al., 2020). A recent cohort study revealed a significant association between the development of dementia and genetic variation in genes responsible for BBB transcytosis, such as phosphatidylinositol-binding clathrin assembly protein, which gets worse with age (Juul Rasmussen et al., 2019; Yang et al., 2020; Knox et al., 2022). Other transcellular transport pathways are also altered in pathological conditions. Elevated Glut-1 was found in plasma exosomes of both cognitively normal and cognitively impaired patients with SVD, indirectly reflecting elevated levels of trans-BBB transport in SVD (Abner et al., 2020). In addition, studies also found that the increase of Glut and P-glycoprotein expression can be observed in the early stage of ischemia, and returned to the baseline level after reperfusion (Huang et al., 2022; Sharma et al., 2022). Additionally, *in vitro* experiments found that acute hypoxia can increase the level of Glut-1 (Ozgür et al., 2022). However, in the case of continuous ischemia and hypoxia, Glut and P-glycoprotein will eventually decrease, resulting in insufficient glucose supply in the brain and obstacles to the elimination of harmful products (Han and Jiang, 2021).

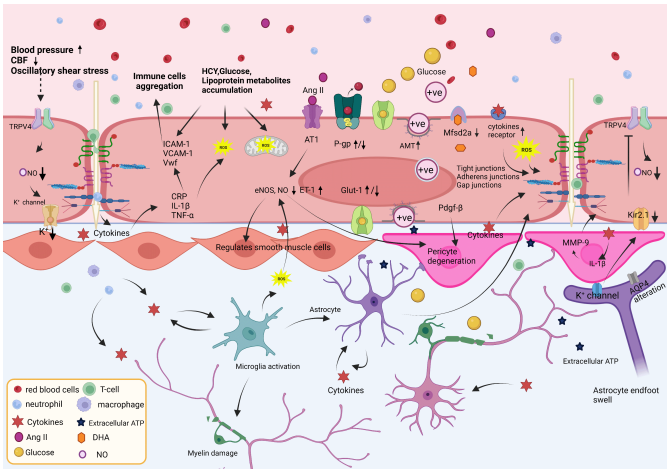

Figure 4 | **BBB dysfunction in cerebral small vessel disease.**
Risk factors such as hypertension and hyperglycemia can cause immune cell infiltration and activation of microglial cells, release cytokines, chemokines, and reactive oxygen species, damage endothelial cells and tight junctions, and eventually lead to BBB dysfunction. Released cytokines also damage pericytes, astrocytes, and neurons, further enhancing neuroinflammation and BBB damage. On one hand, the damaged endothelial cells will further express adhesion factors and reactive oxygen species, strengthening the adhesion and infiltration of immune cells, thereby starting the inflammatory cascade reaction. On the other hand, endothelial cells will produce vasoactive factors, reduce the utilization of NO, regulate the contraction and relaxation of peripheral vascular smooth muscle, and affect cerebral blood flow. In hypoxic-ischemic conditions, transcytosis is increased. While Glut- and P-gp-related transport increases early in ischemia, persistent ischemia eventually leads to decreased transport. Created with BioRender.com. AMT: Absorption-mediated transport; Ang II: angiotensin II; AT-1: angiotensin II type 1 receptor; ATP: adenosine triphosphate; BBB: blood-brain barrier; CRP: C-reactive protein; eNOS: endothelial nitric oxide synthase; ET-1: endothelin-1; Glut-1: glucose transport protein 1; ICAM-1: intercellular adhesion molecule-1; IL-1β: interleukin-1 beta; Kir: inwardly rectifying potassium channel; Mfsd2a: major facilitator of superfamily structure and protein 2a; MMP-9: matrix metalloproteinase-9; NO: nitric oxide; Pdgfβ: platelet-derived growth factor beta; P-gp: P-glycoprotein; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-alpha; TRPV4: transient potential channel subfamily V member 4; VCAM-1: vascular cell adhesion molecule-1; Vwf: von Willebrand factor.

Other cell dysfunction

Other components of the BBB such as pericytes, astrocytes, and oligodendrocytes are also considered as potential factors causing vascular injury and endothelial dysfunction in SVD. Recent studies have shown that the expression of soluble platelet-derived growth factor receptor β, a marker of pericyte damage, is increased in the cerebrospinal fluid of cognitively impaired patients and is associated with increased BBB permeability (Montagne et al., 2015; Miners et al., 2019; Nation et al., 2019; Lv et al., 2023). Chronic cerebral hypoperfusion in SVD mice leads to decreased pericyte coverage, increased BBB permeability, and subsequent neuronal damage (Liu et al., 2019). In addition, hyperglycemia and its glycation end products also reduce endothelial cell TJ protein and pericyte coverage by inducing inflammation and oxidative stress, enhancing BBB permeability and subsequent cognitive impairment (Rom et al., 2020). Moreover, pericytes can promote the expression of TJs in ECs and change the arrangement of TJs, thereby affecting the BBB. *In vitro* experiments showed that interleukin-1β can induce pericytes to secrete MMP-9, destroy AJs and TJs, and increase BBB permeability (Qin et al., 2019). Genetically associated SVD is caused by mutations in NOTCH3, which is mainly expressed in pericytes and vascular SMCs (Manini and Pantoni, 2021). Extensive research has indicated that inhibitors targeting NOTCH3 can effectively disrupt the nuclear factor-kappa B pathway, thereby minimizing the secretion of MMP-9 in pericytes and protecting the integrity of BBB (Qin et al., 2019). Pericytes can also cause astrocytes to exacerbate white matter injury in the state of arteriolar sclerosis by producing bone morphogenetic protein 4 (Uemura et al., 2018).

A study revealed a reduction in the rate of water exchange across the BBB in the brains of patients with genetically linked SVD (Li et al., 2023). This phenomenon may be linked to dysfunctional AQP4 in astrocytes. AQP4 aquaporin, expressed by astrocytes, serves to regulate water transport within astrocytes, maintain water homeostasis in the brain, and is crucial for the clearance of amyloid beta protein from the brain. Studies demonstrated that AQP4 expression increased significantly around blood vessels in the brains of SVD patients (Hoshi et al., 2012). These findings were corroborated by the proteomic results of SVD rats wherein AQP4 expression increased

drastically (Schrader et al., 2022). The expression of AQP4 was also observed to increase with the occurrence of hypertension (Ishida et al., 2006). This variance may be attributed to changes in the function or phenotype of astrocytes (Owasil et al., 2020). Additionally, during ischemic conditions, the number of activated astrocytes increases, leading to the opening of gap junctions and the breakdown of TJ proteins (Haley and Lawrence, 2017; Hannawi et al., 2022). Activated astrocytes can also damage the BBB by triggering neuroinflammation (Yuan et al., 2022). Furthermore, cerebral hypoperfusion and intracerebral inflammation also stimulate astrocytes and neurons to release extracellular adenosine triphosphate, which exacerbates endothelial dysfunction (Lee et al., 2021). Interestingly, downregulation of the endothelial potassium channel Kir2.1 was found in both hypertensive mice and genetically related SVD mice, impacting local blood flow regulation and causing functional congestion (Dabertrand et al., 2021; Koide et al., 2021). This may be related to K^+ channels in astrocytes during neuronal activity. Moreover, inhibition of the Kir2.1 channel can inhibit the TRPV4 channel and reduce NO production, providing evidence for crosstalk between endothelial-astrocytes (Moccia et al., 2022).

Ischemia and hypoxia can also affect oligodendrocytes (OLs), which play a crucial role in producing myelin sheaths, which protect neurons and facilitate the efficient transmission of action potentials along axons. Research on animal models and SVD patients has revealed myelin damage and loss, as reflected in white matter impairment and mobility issues (Rajani and Williams, 2017; Hase et al., 2018; Boa Sorte Silva et al., 2022). OL dysfunction might be secondary to endothelial dysfunction, with WNT signaling being a vital component (Manukjan et al., 2020). The activation of microglia and the infiltration of immune cells in the brain after ischemia and hypoxia can also damage oligodendrocytes and regulate remyelination (Xu et al., 2020). However, considering the insufficient attention OLs have received, further investigation is imperative to comprehensively ascertain the role and the underlying mechanism of OLs in SVD.

Summarizing

Based on the above evidence, endothelial dysfunction not only affects the function of the BBB, but also plays an important role in the maintenance of brain homeostasis. Therefore, the development of novel therapeutic interventions that target ECs should be central to the aim of preventing or reversing cerebrovascular disease.

Novel Tools for Blood-Brain Barrier Research

A growing interests in the role of the BBB and its effects on various neurodegenerative diseases has become increasingly prevalent. BBB integrity protects the brain from external harm. However, it also presents a potential barrier to therapeutic drug efficacy. The implementation of innovative research methodologies will aid in deepening our understanding of the mechanisms involved in brain EC and NVU interactions in SVD and may also ultimately aid in the development of future drug screening processes.

***In vitro* model**

Conventional BBB studies *in vitro* models predominantly use Transwell co-culture systems alongside monolayer cell culture. However, this model is relatively simplistic and static compared to BBB's complex physiology. Additionally, the Transwell model is unable to analyze the impact of the blood and brain microenvironment on the BBB, which emphasizes exploring new *in vitro* research methods. Microfluidic BBB chips replicate the physiological environment of the BBB *in vivo* and examine its transport mechanism and cellular interactions (Cai et al., 2022). The BBB chip not only retains the advantageous properties of the Transwell model but also explores both the comprehensive physiological functions of the BBB and the cellular behavior of individual BBB constituents simultaneously (Chen et al., 2021). BBB chips are currently being used in researching numerous ailments, including brain tumors, AD, and SVD (Wevers et al., 2021; Yoon et al., 2021). Additionally, research indicates that ultrasound can open the BBB on a chip-like BBB *in vivo* (Cai et al., 2022). Investigating the underlying mechanics of this process will facilitate comprehension and enable the development of innovative drug-delivery strategies for the brain. Furthermore, BBB chips have significant practicality in screening therapeutic drugs due to their superior throughput and automation compatibility (Wevers et al., 2021).

***In vivo* model**

Although numerous *in vitro* research models exist, *in vivo* research remains irreplaceable. An optimal animal model should possess pathological characteristics comparable to those observed with SVD in human brain tissue. Various methods and animal models have been created thus far to tackle distinct facets of SVD.

Various types of animal models have been developed to evaluate SVD in rodents (Mustapha et al., 2019). One of the most commonly used and the most promising is the BACS mouse model, which reflects ischemic injury (Bink et al., 2013). Additionally, the NOTCH3 transgenic mouse model has been utilized for studying SVD resulting from genetic mutations. However, the spontaneously hypertensive stroke-prone rat is the most commonly utilized animal model, owing to its demonstration of significant characteristics associated with SVD disease (Hainsworth and Markus, 2008). Based on the exploration of the abovementioned classic animal models, some new translational rodent models have also been developed for the exploration of the specific mechanisms of SVD. These models include, but are not limited to, endothelial nitric oxide synthase-deficient mice, Ang II-induced hypertensive mice, vascular smooth muscle cell-specific myosin phosphatase target subunit 1 (MYPT1) knockout ($MYPT1^{SMKO}$) mice, and salt-sensitive "Sabra" hypertensive-prone rats (SBH/y) (Meissner et al., 2017; Liao et al., 2021; Guy et al., 2022a; Chen et al., 2023). To explore the specific mechanism of SVD caused by risk factors, some animal models previously used to explore hyperlipidemia, diabetes, obesity, and other metabolic diseases are now also used to explore SVD. For example, the low-density lipoprotein receptor knockout ($LDL^{-/-}$) mouse model can be used to explore the relationship between hypercholesterolemia, hypertension, and SVD (Arnoldussen et al., 2017).

As SVD is frequently an initial stage of a number of conditions, including stroke and dementia, selecting the appropriate translational animal model can enhance our comprehension of SVD development and assess its pathological progression. Advanced animal experiments are also critical in facilitating improved treatment and preventative measures to mitigate the impact of future disorders associated with SVD.

Imaging

BBB leakage is a subtle, dynamic process that cannot be detected with conventional MRI. However, great advances have been made in perfusion MRI, allowing the visualization of the brain microvasculature at a remarkably high spatial resolution (Rosen et al., 1990; Catana et al., 2013). DCE-MRI is a magnetic resonance imaging modality utilized to analyze angiogenesis and vascular permeability and has emerged as the preferred imaging technique for evaluating BBB disruption in SVD (Thrippleton et al., 2019). Briefly, the underlying principle of DCE-MRI involves the assessment of BBB permeability by measuring the uptake of contrast agents, most typically Gadolinium-based compounds (Raja et al., 2018), or tracers that typically do not penetrate the BBB under normal physiological conditions. Unfortunately, this method is an invasive technique that relies on the injection of a contrast agent. Consequently, there is a need for non-invasive methods to examine BBB integrity.

Positron-emission tomography offers molecular quantitative non-invasive approaches to study BBB permeability (Okada et al., 2015). However, the application of positron-emission tomography imaging *in vivo* is hindered by different limitations, such as costly performance, and poor tissue penetration, leading to low resolution. Moreover, positron-emission tomography scans depend on a cyclotron as well as expertise for their application, and thereby these are not universally available.

Arterial spin labeling is a non-invasive technique that employs intravascular water molecules as endogenous dynamic tracers to detect changes in BBB permeability. This method relies on the distinctive (pseudo) diffusion coefficient in capillaries and brain tissue to differentiate the proportion of labeled water in capillaries and brain tissue. As previously noted, trans-capillary water exchange is governed by AQP4, which is situated at the terminus of astrocyte endfeet processes. ECs constitute the primary constituents of capillaries, and their paracellular diffusion and regulation of CBF through endothelial vasoactive substances also exert a certain impact on trans-BBB water exchange. Therefore, arterial spin labeling holds immense potential in sensitively tracking alterations in the BBB vascular component and might aid in dynamically evaluating BBB integrity.

Future Treatment

SVD is currently recognized as the primary cause of dementia and has been linked with other neurodegenerative conditions. BBB damage is thought to play a central role in the pathology of SVD. EC dysfunction is a critical contributor to BBB injury, with research in SVD focusing heavily on EC-related inflammation, oxidative stress, and changes in TJ protein expression. Changes in biomarkers of circulating and cerebrospinal fluid samples can facilitate early detection of patients with SVD and early treatment to reduce the burden and progression of brain diseases. Given the important role of ECs in BBB and SVD, some drugs that can stabilize ECs, such as anti-inflammatory drugs and antioxidant stress agents, have been found to delay the progression of SVD (Li et al., 2021; Guy et al., 2022b). However, due to the complex etiology and pathogenesis of SVD, further development of therapies targeting endothelial injury seems to be a feasible direction.

There are still many unknown aspects of endothelial biology, including the post-translational modifications of TJ proteins and their dynamic behavior. The role of transcytosis in promoting nutrient absorption and metabolic waste removal cannot be ignored in BBB function (Ayloo and Gu, 2019). Although some regulatory mechanisms of BBB transcytosis have been explored, the molecular pathways involved, especially in the real-time dynamics of transcytosis in the brain, are still poorly understood. Understanding the aforementioned changes in the BBB endothelium, the proteins, and signaling pathways involved, and how they affect EC and BBB responses may provide new insights and evidence for future research on regulating BBB permeability and promoting drug delivery to the brain.

Potential future preclinical studies should also consider cellular interactions within NVU. While the interplay between endothelial-pericyte and endothelial-astrocyte has been found to significantly impact metabolite clearance, TJ protein damage, and inflammation, a more comprehensive understanding of these mechanisms is still required. Notably, research is lacking on the interactions between nerve cells, microglia, and oligodendrocytes and the three aforementioned cell types. Furthermore, increased attention is being given to the interplay between NVU and

systemic processes. Gut dysbiosis has been found to be associated with neuroinflammation and cognitive impairment (Mou et al., 2022). Moreover, regulatory effects of the BBB by the gut microbiota can begin early on in fetal development and continue throughout life, damaging endothelial TJ proteins (Liu et al., 2021). Studies exploring gut-brain communication can yield approaches to developing novel methods for treating BBB damage and SVD.

Various risk factors associated with SVD such as hypertension, and hyperglycemia, among others, have also been identified as risk factors for BBB damage. Maintaining strict control over blood pressure levels can potentially provide clinical benefits in preventing and postponing the onset of SVD (Rajani et al., 2018). According to a recent study, the use of statins for diabetes has been shown to reduce BBB breakdown and improve nerve damage in ischemic stroke patients (Christophe et al., 2020). In addition to the use of conventional therapeutic drugs, a healthy lifestyle is the most important preventive measure. Its interventions focus on avoiding the development of the aforementioned SVD risk factors, of which hypertension and atherosclerosis are the most important. Exercise training was shown to reduce BBB permeability in rats with SVD (Candido et al., 2023). Although data on this topic are limited, interventions on SVD risk factors can serve as an effective strategy to safeguard the BBB and reduce the SVD burden. With further investigation into the mechanisms underlying SVD and the development of drugs targeting its associated risk factors, an opportunity arises for providing optimized, personalized treatment for SVD patients.

Conclusion

To summarize, endothelial dysfunction and subsequent BBB leakage are important pathophysiological mechanisms of SVD. Of note is the observation that BBB leakage often occurs prior to the presentation of MRI-detected lesions in patients with SVD. This highlights the potential of BBB detection as an important diagnostic tool in the early identification and targeting of SVD. Furthermore, imaging means can dynamically monitor the changes of SVD, which plays an important role in clinical diagnosis, evaluation of treatment effects, and formulation of prevention strategies. Therefore, modern imaging techniques are vital to further developing our understanding of the underlying mechanisms related to BBB changes observed in SVD.

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