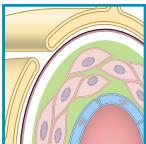


# BLOOD-BRAIN BARRIER: FROM PHYSIOLOGY TO DISEASE AND BACK

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**Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV.** Blood-Brain Barrier:

From Physiology to Disease and Back. *Physiol Rev* 99: 21–78, 2019. Published October 3, 2018; doi:10.1152/physrev.00050.2017.—The blood-brain barrier (BBB) prevents neurotoxic plasma components, blood cells, and pathogens from entering the brain. At the same time, the BBB regulates transport of molecules into and

out of the central nervous system (CNS), which maintains tightly controlled chemical composition of the neuronal milieu that is required for proper neuronal functioning. In this review, we first examine molecular and cellular mechanisms underlying the establishment of the BBB. Then, we focus on BBB transport physiology, endothelial and pericyte transporters, and perivascular and paravascular transport. Next, we discuss rare human monogenic neurological disorders with the primary genetic defect in BBB-associated cells demonstrating the link between BBB breakdown and neurodegeneration. Then, we review the effects of genes underlying inheritance and/or increased susceptibility for Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS) on BBB in relation to other pathologies and neurological deficits. We next examine how BBB dysfunction relates to neurological deficits and other pathologies in the majority of sporadic AD, PD, and ALS cases, multiple sclerosis, other neurodegenerative disorders, and acute CNS disorders such as stroke, traumatic brain injury, spinal cord injury, and epilepsy. Lastly, we discuss BBB-based therapeutic opportunities. We conclude with lessons learned and future directions, with emphasis on technological advances to investigate the BBB functions in the living human brain, and at the molecular and cellular level, and address key unanswered questions.

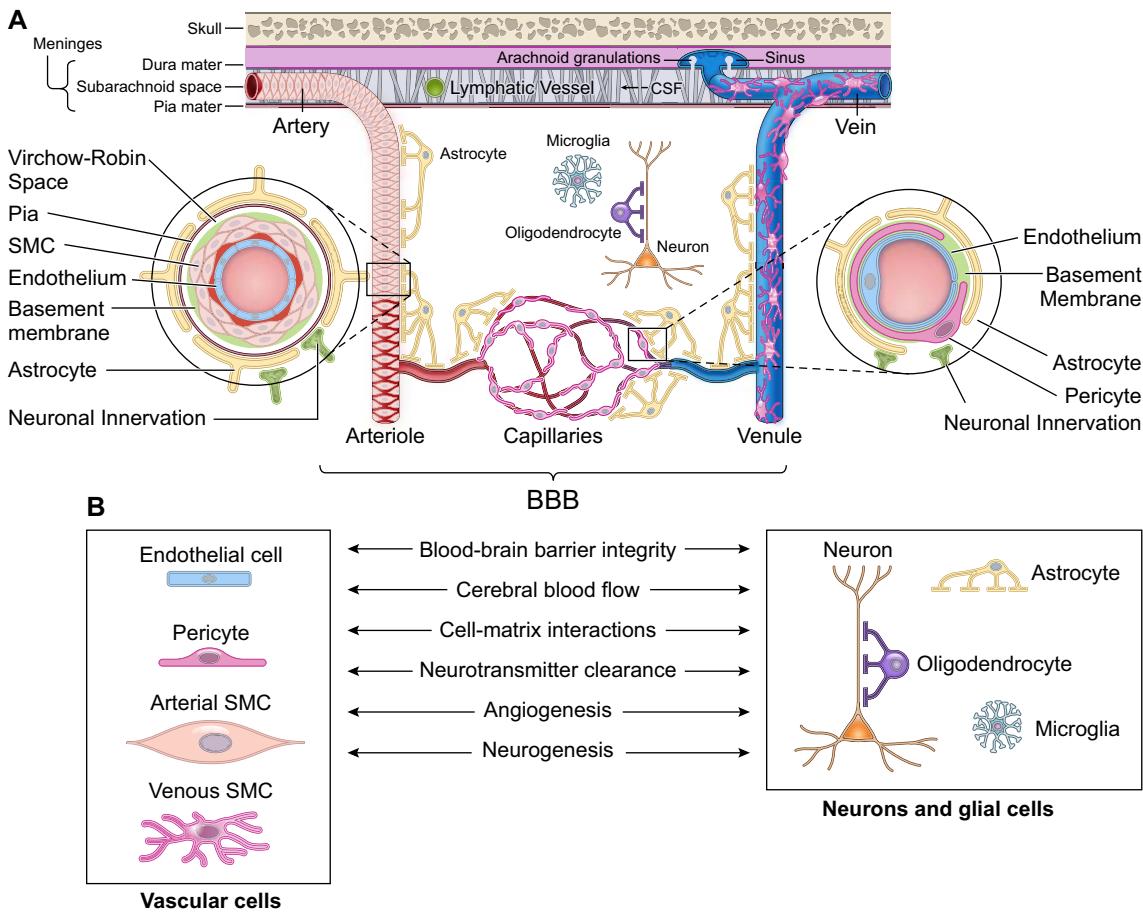
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## I. INTRODUCTION

The blood-brain barrier (BBB) prevents neurotoxic plasma components, blood cells, and pathogens from entering the brain (420). At the same time, the BBB regulates transport of molecules into and out of the central nervous system (CNS), which maintains tightly controlled chemical composition of the neuronal milieu that is required for proper neuronal functioning (682, 693). In disease states, BBB breakdown and dysfunction leads to leakages of harmful blood components into the CNS, cellular infiltration, and aberrant transport and clearance of molecules (420, 682, 693), which is associated with cerebral blood flow (CBF) reductions and dysregulation (269–271, 318), contributing to neurological deficits.

The pattern of cerebral blood vessels follows the major brain circuits tasked with sensation, memory, and motion suggesting that the cerebrovascular system plays an important role in normal CNS functioning (271, 318, 682). Under physiological conditions, the human brain receives 20% of the cardiac output and uses 20% of the body's oxygen and glucose (270). Energy substrates are consumed by the brain "on the fly" from blood via transport across the BBB, as the brain lacks a reservoir to store fuel for use when needed (271). In the mammalian brain, cerebral arteries, arterioles, and capillaries supply CNS circuits with blood in response to neuronal stimuli by increasing the rate of CBF and oxygen delivery, a mechanism known as neurovascular coupling (271, 319). Different cell types of the neurovascular unit (NVU) including vascular cells [e.g., endothelium and mural cells including pericytes and smooth muscle cells (SMCs)], glia (e.g., astrocytes, microglia), and neurons contribute to regulation of BBB permeability, neurovascular coupling, cell-matrix interactions, neurotransmitter turnover, and angiogenesis and neurogenesis (270, 271, 692, 693) (**FIGURE 1**).

The BBB is centrally positioned within the NVU and is formed by a monolayer of tightly-sealed endothelial cells



**FIGURE 1.** The neurovascular unit. *A:* the neurovascular unit comprises vascular cells including endothelial cells and mural cells such as pericytes on brain capillaries, venules, and precapillary arterioles; vascular smooth muscle cells (SMC) on arterioles, small arteries, and veins; glial cells such as astrocytes, microglia, and oligodendrocytes; and neurons. Molecular expression patterns in endothelial and mural cells vary at different levels of vascular tree creating arterio-capillary-venous heterogeneity (zonation). At the level of penetrating arteries (*left inset*), endothelial cells form the inner layer of the vessel wall. The basement membrane separates endothelium from 1 to 3 layers of SMCs that are enveloped by pia. The Virchow-Robin space is between the pia and the glia limitans formed by astrocytic endfeet. At the arteriolar level, SMCs were reduced to a single layer, whereas the endothelial layer displays a continuity with the endothelium of penetrating arteries and capillaries. At the capillary level (*right inset*), pericytes and endothelial cells share a basement membrane and exhibit different types of cellular connections. Both the arteriolar and capillary vessel wall is covered by astrocytic endfeet. SMCs, pericytes, and astrocytes all have neuronal innervation. The blood-brain barrier (BBB) is centrally positioned within the neurovascular unit and is formed by a monolayer of tightly sealed endothelial cells extending along the vascular tree and expressing low paracellular and transcellular permeability at the level of brain capillaries and along arteriovenous axis. *B:* different cells of the neurovascular unit regulate BBB integrity, cerebral blood flow, extracellular matrix interactions, and neurotransmitter clearance and participate in angiogenesis and neurogenesis.

along the vascular tree expressing low paracellular and transcellular permeability (682, 693). In the human brain, total length of cerebral blood vessels is ~400 miles with capillaries contributing to 85% of the vessel length and providing ~12 m<sup>2</sup> of the endothelial surface area available for transport exchanges (2, 460, 693). At the capillary level, BBB integrity is maintained by pericytes (28, 59, 130, 570). Pericytes, SMCs, and endothelial cells express thousands of transcripts encoding different transporters, receptors, active efflux pumps, ion channels, and regulatory molecules (28, 72, 86, 129, 242, 358, 359, 610, 675, 678), whose

expression pattern varies by zonation along the arterio-capillary-venous axis and cell type (610).

Here, we first examine molecular and cellular mechanisms underlying the establishment of the BBB. Then, we focus on BBB transport physiology including the BBB molecular junctions, endothelial and pericyte transporters, and perivascular and paravascular transport. Next, we discuss rare human monogenic neurological disorders with the primary genetic defect in vascular cells of the BBB, and the link to neurodegeneration. Then, we review the effects of genes

underlying inheritance and/or increased susceptibility for Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) on BBB in relation to other pathologies and neurological deficits. We next examine how BBB breakdown and dysfunction relates to neurological deficits and other pathologies in the majority of sporadic AD, PD, and ALS cases with no clear etiology or genetic inheritance, multiple sclerosis (MS), other neurodegenerative disorders, and acute CNS disorders such as stroke, traumatic brain injury, spinal cord injury, and epilepsy. Lastly, we discuss BBB-based therapeutic opportunities and targets. We conclude with lessons learned and future directions, with emphasis on technological advances to investigate the BBB functions in the living human brain, to provide molecular definitions of different vascular cell types, and address key unanswered questions.

## II. ESTABLISHMENT OF THE BLOOD-BRAIN BARRIER

The classic tissue transplantation chick-quail experiment (559) suggested nearly 40 yr ago that the BBB characteristics are not intrinsic to brain endothelium, but rather acquired and shaped in the neural environment during early CNS development. To date, evidence obtained from developmental studies clearly depicts an orchestrated interaction between the neural and vascular systems for proper establishment of the BBB and wiring of the brain (22, 93, 158).

### A. BBB Formation

Like any other organ, the brain is vascularized from surrounding vascular plexus during embryogenesis (138). In the developing mouse CNS, at embryonic day E10, the angioblasts of the perineural vascular plexus (PNVP; later turns into the leptomeningeal arteries and veins) sense the vascular endothelial growth factor (VEGF) signals from the neuroectoderm and invade the neural tube (480). This results in formation of nascent "leaky" blood vessels via sprouting angiogenesis (628, 682) followed by remodeling and patterning (326). The barriergenesis in mice occurs between days E10 and E15 (682), as shown by the emerging multiple features of the BBB such as 1) formation of a continuous endothelial cell membrane sealed by highly specialized intercellular junctional structures to restrict paracellular flow, including upregulation of tight junction (TJ) proteins zonula occludens-1 (ZO-1) and occludin (130); 2) elimination of endothelial fenestrae and pinocytosis to restrict transcellular flow (62); 3) establishment of highly selective transport systems eliminating toxic substances yet allowing exchanges of nutrients and metabolites between circulation and brain (62, 130); and 4) specialization of perivascular structures such as basement membrane and coverage of endothelial capillary wall by pericytes to fortify the barrier (28, 59, 130).

Both cerebral angiogenesis and BBB formation require precise cues from various growth factors, guidance molecules and other factors such as microRNA, as well as fine tuning of intracellular signaling pathways and gene expression (22, 628, 682, 689). Signaling pathways and factors that contribute to BBB formation in the developing CNS at different stages based on murine timeline (585) are illustrated in **TABLE 1**. In general, the VEGF-VEGFR2-neuropilin1 signaling drives the angiogenesis and vascular patterning (628); Wnt signaling pathway including Wnt ligands, Norgins, Frizzled receptors, Lrp5/6 coreceptors, Gpr124 and Reck cofactors, and  $\beta$ -catenin are critical for both vascular development and barriergenesis (138, 332, 558, 636, 682, 689); pericyte-derived angiopoietin acts on endothelial Tie2 receptor and maintains BBB function (26, 570, 648); and neural guidance molecules such as netrins and semaphorins also shape the growing cerebrovasculature and BBB functions (22, 475, 596, 628). Brain endothelial specific or enriched transporters are often indispensable for BBB barriergenesis, as for example, the glucose transporter-1 (GLUT1) (649), sodium-dependent lysophosphatidylcholine (LPC) symporter, the major facilitator superfamily (MFS) domain-containing protein 2a (MFSD2A) (62), and monocarboxylic acid transporter MCT8 (611). Deficiency or mutations of the genes encoding these BBB transporters often result in human genetic disorders associated with defects in the vasculature and BBB functions leading to cognitive impairment and/or neurological symptoms associated with different subtypes of microcephaly (218, 649) and Allan-Herndon-Dudley syndrome (611), respectively, as discussed below.

#### 1. VEGF

VEGF is expressed by the cells of neuroectoderm in the ventricular layer, attracting the angioblasts and tip cells of the invading capillaries to penetrate and vascularize the neural tube (480, 628). Both VEGFR2 receptor, also known as kinase insert domain receptor (KDR), and co-receptor neuropilin1 are required for the proper downstream signaling within the endothelial cells (158). Postnatally, VEGF expression persists in glial cells, further supporting vascular remodeling (387). However, aberrant activation of astrocytes and subsequent production of VEGF-A is associated with BBB breakdown in CNS inflammatory disease (24).

#### 2. Wnt

Canonical Wnt signaling governs the cerebral vascular development and BBB formation. In the developing brain, Wnt ligands activate Frizzled receptors and Lrp5/6 complexes on the endothelium; while in the retina, Norgin independently activates Frizzled and LRP5/6 receptors with the assistance of TSPAN12, a member of the phylogenetically ancient tetraspanin family, regulating

**Table I.** Establishment of the blood-brain barrier: signaling pathways and molecules

Murine Timeline	Pathway	Cell to Cell Interaction	BBB Targets	Reference Nos.
<b>Angiogenesis and vascular remodeling</b>				
E10 to postnatal	VEGF-VEGFR/neuropilin1	Neural epithelial-angioblasts, tip cells, stalk cells	Ras, PI3K, Src, p38MAPK (intracellular signaling)	243
E10 to postnatal	TGF- $\beta$ -neuropilin1	Neural epithelial-angioblasts, tip cells, stalk cells	SMAD, CDC42 (intracellular signaling)	603
E10 to postnatal	Notch-DLL4	Tip cells, stalk cells	NICD, Jagged (intracellular signaling)	65
E10 to postnatal	Wnt, Norrin, Frizzled, Grp124, Reck, LRP5/LRP6	Neural progenitors-endothelial	$\beta$ -Catenin (nuclear translocation)	609
<b>Barriergenesis and BBB maturation</b>				
E10 to E16	Wnt, Norrin, Frizzled, Grp124, Reck, $\beta$ -catenin, LRP5/LRP6	Neuron-endothelial	Claudin3 (tight junction) Plvap (transcellular flow) Laminin, collagen IV Glut1 (transporters) DR6, Troy (receptor)	350 98 542 557
E10 to postnatal	PDGF-BB-Pdgfr $\beta$	Endothelial-pericyte	PI3K, Src, p38MAPK (intracellular signaling)	553
E10 to postnatal	TGF- $\beta$ -ALK5	Endothelial-pericyte	SMAD (intracellular signaling)	621
E10 to postnatal	Angiopoietin-Tie2	Pericyte-endothelial	PI3K, Rho, NF $\kappa$ B (intracellular signaling)	26
E10 to postnatal	Semaphorin-plexin/neuropilin1	Neural progenitors-endothelial	VE-cadherin (intercellular junctions)	338
E10 to postnatal	Netrin-DCC/UNC5	Endothelial cell autonomous	JAM-A, occluding, claudin-5, ZO-1, $\alpha$ -catenin (intercellular junctions)	459, 633
E17 to postnatal	SHH, PTCH, SMO, Gli	Astrocyte-endothelial	Occludin, JAM-A, VE-cadherin, claudin-3 and claudin-5 (intercellular junctions) IL-8, ICAM-1, CCL2 (inflammatory mediator)	12
E17 to postnatal	SSeCKS	Astrocyte-endothelial	ZO-1	339
E15 to postnatal	Transporters	Endothelial cell autonomous	Glut1 (transporters) Mfsd2a (transporters)	622 61
E15 to postnatal	Junctions	Endothelial-endothelial	Claudin-5 (tight junction) Lsr (tricellular junction)	425 535
<b>BBB maintenance</b>				
Postnatal to adult	apoE- LRP1-CypA-MMP-9	Astrocyte-pericyte-endothelial	MMP-9	59
Postnatal to adult	Interferon- $\lambda$ -IFNLR1	Peripheral-BBB	ZO-1, claudin-5 (tight junction)	337
Postnatal to adult	PDGF-BB-Pdgfr $\beta$	Endothelial-pericyte	PI3K, Src, p38MAPK (intracellular signaling)	423

angiogenesis and barrier function (634). Gpr124, an orphan G protein-coupled receptor (19, 126, 332, 690), and GPI-anchored membrane protein Reck (reversion inducing cysteine rich protein with kazal motifs) act as specific co-activators of Wnt/ $\beta$ -catenin signaling contributing to CNS angiogenesis and barriergenesis (111, 479, 609). Endothelial specific knockout of Gpr124 exacerbates BBB impairment in mouse models of ischemic stroke and glioblastoma (102), indicating Gpr124 is re-

quired for the maintenance of BBB integrity under pathological conditions. Activated  $\beta$ -catenin can improve intercellular junctions by stabilizing VE-cadherin, and translocate into nucleus to induce target gene expression, including upregulation of GLUT1 (558), death receptors DR6 and TROY (576) and TJ component claudin-3, as well as downregulation of plamalemma vesicle-associated protein (PLVAP) to inhibit fenestration (361), which is all critical for the BBB formation.

### 3. Sonic hedgehog

Hedgehog signaling plays a key role in the establishment and maintenance of cell polarity, which is critical for both epithelial and endothelial barriers (13, 81). Astrocytes are the major source of sonic hedgehog (SHH) in brain, which acts on endothelial patched homolog 1 (PTC-1) receptor to release the inhibition of Smoothened on Gli transcription factors, resulting in expression of SHH-regulated genes, including occludin, junctional adhesion molecule-A (JAM-A), VE-cadherin, claudin-3, and claudin-5 (13). SHH also suppresses expression of inflammatory mediators in the brain endothelial cells, including interleukin-8 (IL-8) and chemokine ligand 2 (CCL2) and intercellular adhesion molecule-1 (ICAM-1), thereby limiting infiltration of peripheral inflammatory cells through the BBB (13).

### 4. Platelet derived growth factor-BB–platelet derived growth factor receptor $\beta$ signaling

Pericyte-endothelial interaction plays a key role in the establishment and maintenance of the BBB (27, 570, 648, 682). During angiogenesis, pericytes are recruited by platelet-derived growth factor BB (PDGF-BB) signals from the tip cells of the endothelial sprouts and PDGF-BB retained on the extracellular matrix (27), which activates multiple intracellular signaling pathways through PDGFR- $\beta$  receptor on pericytes (570, 648). Pericytes provide an important source of the basement membrane proteins at the BBB, including laminins (667) and vitronectin (242), and support endothelial tube formation and stabilization (27). Pericyte-deficient mouse models caused by aberrant PDGF-BB/PDGFR- $\beta$  signaling (365, 419, 436, 570, 575) exhibit impaired BBB formation (28, 59, 130) and maintenance (59, 436). The interaction between pericytes and endothelial cells involves other signaling pathways, including but not limited to endothelial to pericyte transforming growth factor- $\beta$  (TGF- $\beta$ )-activin receptor-like kinases signaling, pericyte to endothelial angiopoietin-Tie-2 signaling, which have been examined elsewhere (570). Future studies are still required to determine the exact contribution of each pericyte-endothelial signaling pathway to the formation and maintenance of the BBB.

### 5. Axon guidance molecules

As the nervous system and the vascular system develop closely, they not only share certain mechanisms in patterning but also common molecular pathways (22, 93, 127, 297, 349). In fact, the major axon guidance molecules have been found to be important for cerebrovascular development, which interestingly also applies to BBB formation. Sema3A, a member of semaphorin protein family, is anti-angiogenic factor acting independently of VEGF, but also increases vascular permeability by destabilizing VE-cadherin through NRP-1 and PlexinA1 receptors (349). Neu-

ropilin, a common co-receptor and regulator of many morphogens and growth factors, is required for guidance of tip cells during sprouting angiogenesis (127), by balancing the pro-angiogenic and anti-angiogenic signals between major pathways including VEGF, semaphorins and Wnt signaling; its upregulation in vessels contributes to BBB breakdown during brain injury and inflammation (564, 679). Brain endothelial cells express roundabout guidance receptor 4 (Robo4), which senses slit guidance ligand 2 (Slit2) and maintains blood-retinal barrier (BRB) integrity by inhibiting VEGF signaling and pathological angiogenesis and endothelial hyperpermeability (297). Recent studies using different ablation approaches for retinal pericytes have shown that pericytes are required for establishment of the BRB; however, whether they are required for maintenance of the BRB in adult is still inconclusive based on these reports (449, 462).

### 6. BBB specific components

The BBB characteristics include specific junctional proteins, transporters, receptors, and basement membrane components, as a consequence of neural environment-induced transcriptional changes (682). However, these components can also play a key role in the formation of the BBB. For example, mice lacking TJ protein claudin-5 have a BBB permeable to small molecules that are <800 Da (438), whereas *Lsr*<sup>-/-</sup> embryos lacking lipolysis-stimulated lipoprotein receptor (LSR), a component of tricellular junctions, exhibit a BBB open to molecules that are ~10 kDa (551). The *Slc2a1*<sup>+/-</sup> mice with haploid deficiency in glucose transporter GLUT1 in brain endothelial cells develop microvascular reductions with BBB breakdown including loss of TJ and basement membrane proteins (649), whereas knockout of murine *Mfsd2a* gene results in not only diminished brain uptake of docosahexaenoic acid (DHA) in the form of lysophosphatidylcholine, but also leads to dysregulated caveolae-mediated transcellular trafficking across the BBB causing BBB breakdown (21, 62, 684). Neurological consequences of these BBB genetic defects are discussed below.

## B. BBB Maturation and Maintenance

The BBB continues to mature under the influence of neural environment after day E15 in mice and over a brief period after birth (682). Astrocytes join the NVU during the maturation stage and provide additional support, including the formation of perivascular astrocytic endfeet around capillaries and the glial limitans that ensheathes the penetrating arterioles (682). Astrocytes also strengthen the basement membrane by producing laminin  $\alpha$ 1 and  $\alpha$ 2, which are important for stabilizing pericytes (667). In addition, astrocytes secrete retinoic acid and SHH, which transcriptionally regulates gene expression in endothelial cells and enhances the formation of intercellular junction functions (13). En-

endothelial-pericyte PDGF-BB-PDGFR $\beta$  signaling pathway, pericyte-endothelial TGF- $\beta$  and Ang-1-Tie-2 signaling pathways, as well as astrocyte-endothelial SHH pathway, angiotensin II-AT1 receptor and Wnt-Frizzled signaling pathways, continue to influence the BBB maturation.

The close interactions between the NVU cells are critical for the maintenance of the BBB. For example, astrocytes secrete apolipoprotein E (APOE) to signal pericytes via low-density lipoprotein receptor-related protein-1 (LRP1), which suppress the activation of cyclophilin A (CypA)-matrix metalloproteinase 9 (MMP-9) BBB-degrading pathway, while in the absence of murine APOE mouse pericytes produce active MMP-9 causing BBB breakdown (60). Additionally, in addition to regulating neuroinflammation (360), astrocytes regulate endothelial barrier function; for example, the BBB is compromised in mice lacking src-suppressed C-kinase substrate (SSeCKS), a responder of systemic inflammation in astrocytes (350). Since the BBB breakdown is associated with many CNS diseases as discussed below, future studies should focus on druggable pathways that are critical for maintaining the BBB integrity, particularly using cell-specific inducible mouse models.

### *1. Neuronal activity-induced vascular plasticity*

Neuronal activity during embryonic development and in the early days of postnatal development generates a relatively hypoxic environment that is permissive for vascular development and maturation (22). Additionally, the neural-vascular interactions and functional neurovascular coupling develop to meet the energy needs of the growing brain and support brain activities (105, 318, 319, 341, 605). Deprivation of sensory input in the mouse barrel cortex by either surgical deafferentation or genetic inhibition of neurotransmitter release results in postnatal reduction in vascular density (340), suggesting that neuronal activity remains an important regulator of vascular plasticity after birth. However, chronic stimulation by repetitive sounds, whisker deflection or motor activity, or chemically induced seizures, led to a near arrest of angiogenesis in barrel, auditory, and motor cortices in neonatal mice, which can be prevented with the nitric oxide synthase (NOS) inhibitor N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) and in mice with neuronal and inducible NOS deficiency, suggesting that excessive nitric oxide (NO) released from hyperactive interneurons and glia inhibited vessel growth (645). Abnormal neuronal activities are also detrimental to a mature BBB. For example, the widespread BBB breakdown has been well documented in a mouse model of status epilepticus (209). Additionally, BBB impairment also occurs early in the mouse model of chronic sleep deprivation (241) and the rat model of social isolation (524).

### *2. MicroRNAs and exosomal regulation*

MicroRNAs (miRNA) are small noncoding RNAs capable of silencing gene expression via the RNA-induced silencing

complex (RISC), which plays a role in regulating gene expression during CNS development, remodeling, and disease (592). miRNAs are packaged into exosomes that signal nearby cells, or over longer distances through circulating body fluids. Recent findings of a long-range crosstalk between periphery and CNS via miRNA-containing exosomes position the BBB in the center of this communication (685) under physiological (635, 660) and pathophysiological (378, 493, 498, 587) conditions. For instance, embryonic neurons in zebrafish larvae produce miR-132 in exosomes, which regulates BBB integrity by controlling expression of endothelial VE-cadherin, an adherens junction (AJ) protein at the BBB (660). Exosomes secreted by hematopoietic cells during inflammation cross the BBB and carry genetic information from periphery to Purkinje neurons in the cerebellum through miRNAs including miR-574-3p (498). miR-29b targets aquaporin-4 (AQP4) expression in the astrocytic endfeet (635), miR-125a-5p suppresses tumor necrosis factor (TNF)- $\alpha$ -induced ICAM-1 upregulation in brain endothelial cells (493), whereas miR-210 partly mediates the BBB damage in a rat model of neonatal hypoxic-ischemic brain injury through downregulation of TJ protein occludin and AJ protein  $\beta$ -catenin (378). Due to the ability of crossing BBB and regulating gene expression in the brain, the role of exosomes in controlling cerebrovascular integrity in health and disease, as well as the potential of translation into a therapeutic approach, calls for more in-depth studies (685).

### *3. Apicobasal polarity of BBB endothelium*

The apicobasal polarity of the BBB endothelium is more remarkable than those in other organs in terms of polarized distributions of lipids, glycoproteins, receptors, and transporters between apical and basal membranes (654). It is initiated during angiogenesis by the partitioning defective (PAR) protein complex, including PAR3, PAR6, and CDC42, and is tightly regulated by VEGF and Wnt signaling pathways (245, 279, 704). PAR3 interaction with VE-cadherin and JAM proteins triggers the reorganization of intercellular junction proteins including ZO1, claudin-5, and CD99, resulting in the formation of TJs on the apical side of AJs, thereby limiting paracellular flow (245, 654). On the other hand, lumen formation and expansion are achieved by redistribution of surface receptors including CD34 and glycoproteins such as podocalyxin, and reorganization of cytoskeleton networks that requires  $\beta$ 1-integrin, non-muscle myosin II, activation of RhoA pathway, and F-actin formation (245, 539). Brain endothelial cells also express the Crumbs protein complex that stabilizes the intercellular junctions (654).

### *4. Vascular cell lineages*

In vivo lineage tracing studies using mouse genetics have demonstrated the versatility of vascular cells in cell fate

during development. During embryonic heart development, pericytes can upregulate Notch3 and become coronary artery SMCs (623), while endothelial cells are capable of differentiating into cardiac pericytes and SMCs (107). This is consistent with in vitro findings based on direct differentiation of embryonic stem cells or induced pluripotent stem cells (iPSCs). For example, mesenchymal angioblasts, previously known as endothelial progenitors, can also differentiate into both pericytes with PDGF-BB and EGF2 and SMCs with TGF- $\beta$ 3 and sphingosylphosphorylcholine (333). Whether a similar vascular lineage tree exists in cerebral vasculature and BBB is still unknown and requires further characterization with markers or Cre drivers that are specific to brain endothelium and pericytes.

### 5. Immunoregulation of the BBB

The BBB is tempered by the body's immune system. This can happen as early as in embryonic development. For example, maternal gut microbiota influences the establishment of fetal BBB during gestation, by upregulating expression of TJ proteins such as claudin-5 (77). Systemic inflammation, infection, autoimmune disease, injuries, and neurodegenerative diseases often increase the BBB permeability, allowing inflammatory mediators such as cytokines and chemokines, peripheral leukocytes such as monocytes, macrophages, and CD4 $^{+}$  T cells to enter the parenchyma and accelerate disease progression (484). A handful of viruses, including poliovirus, adenovirus, Epstein-Barr virus (EBV), and West Nile virus, can directly infect human brain endothelial cells by targeting junctional proteins such as JAM-A or transporters such as GLUT1 as entry receptors to get access to the CNS (320). Viral infections in general downregulate TJ proteins and promote chemokine production and vascular cell adhesion molecule 1 (VCAM-1) expression in brain endothelial cells, thereby weakening the BBB and facilitating entry into the brain (5, 212, 399, 613). Host immune response on the other hand not only limits the spreading of the viruses, but also attenuates BBB damage (131). For example, production of interferon- $\gamma$  after West Nile infection can seal the BBB possibly by stabilizing TJs (348).

## III. BBB TRANSPORT PHYSIOLOGY

In contrast to leaky capillary endothelium in peripheral organs (391), the BBB endothelium is sealed by TJs (492, 590, 682) and has low rate of bulk-flow transcytosis (538, 682). Brain endothelial molecular junctions, transporters, receptors, and channels have been initially discovered by physiological experiments and ultrastructural studies (133, 692), which was followed by transcriptomic approaches of endothelial and vascular mural cells. These include suppressive subtractive hybridization (86, 358, 359), microarrays (28, 72, 129), and RNA-seq analysis (242, 675, 678).

Earlier studies of BBB transcriptome have been carried out on isolated rat brain capillaries containing endothelial cells and pericytes together (358, 359). More recent studies used endothelial-specific *Tie2-eGFP* (enhanced green fluorescent protein) transgenic mice to investigate transcriptomes of *eGFP*-positive brain capillary endothelial cells purified by fluorescence-activated cell sorting (FACS) (129); *GFP*-positive brain endothelial cells purified by FACS from *Tie2-GFP* and *Pdgfr\beta*-positive pericytes purified by immunopanning (678); and microvascular fragments isolated from brains of pericyte-deficient *Pdgfb*, *Pdgfr\beta*, and *Pdgfb^{ret/ret}* mice and controls (28, 72).

RNA-seq analysis of mural cell transcriptome has been recently performed in pericytes purified by FACS for two pericyte markers, PDGFR $\beta$  and NG2 (neural/glial antigen 2) that have been expressed in *Pdgfr\beta-eGFP; chondroitin sulfate proteoglycan-4 (Cspg4)-DsRed* mice (242). Single cell RNA-seq analysis of endothelial and pericyte clusters from the mouse brain has been also reported (610, 675). The recent *Nature* paper presents a landmark molecular study of cell types and zonation in the brain vasculature using a clustering approach to identify genes and protein classes that are enriched along the arterial to capillary to venous axis (610). Briefly, this study is the first to report that at the BBB endothelium transcription factors predominated at arteries and arterioles, transporters predominated capillaries and veins, and ribosomal proteins indicative of protein synthesis were spread along the arteriovenous axis (610), yielding important insights to biological functions and endothelial specialization along the brain vasculature tree. In contrast to the BBB endothelium's gradual phenotypic change along the arteriovenous axis, mural cells formed two distinct groups comprising pericyte and venous SMCs, and arterial and arteriole SMCs (610). Although this study did not examine neurons (610), an earlier single cell RNA-seq study did investigate all NVU cell types albeit with limited sequencing depth for vascular transcriptomes due to relatively low abundance of vascular clusters compared with neurons and glial cells (675). Thus a more comprehensive single cell RNA-seq study of the entire NVU is needed, in addition to regional transcriptional analysis of the NVU.

Next, we discuss BBB junctional molecules, endothelial and pericyte transport systems, and transport of molecules across brain extracellular spaces (ECS) and by perivascular and paravascular transport.

### A. BBB Junctional Molecules

#### 1. Adherens junctions

Closest to the basolateral membrane, AJ proteins, VE-cadherin, and platelet endothelial cell adhesion molecule-1 (PECAM-1) form homophilic endothelial-to-endothelial

contacts roughly 20 nm wide (139, 590, 625) (**FIGURE 2**). AJs are connected to cytoskeleton, modulate receptor signaling (203), and regulate transendothelial migration of lymphocytes (601), monocytes (12, 203), and neutrophils (642). Tyrosine phosphorylation of VE-cadherin is required for brain transendothelial infiltration of leukocytes (601, 642).

## 2. Gap junctions

Gap junctions including connexin-37 (CX37), CX40, and CX43 form hemichannels between endothelial cells (367, 427, 597), albeit with species-dependent differences in distribution, enabling endothelial intercellular communications (682). Furthermore, brain endothelial gap junctions also function to maintain tight junction integrity (427).

## 3. Other junctional molecules

These include the endothelial cell adhesion molecule (ESAM) and structurally similar JAM-A, -B, and -C that modulate junctional tightness similar as AJs, and regulate transendothelial migration of leukocytes (197, 342).

## 4. Tight junctions

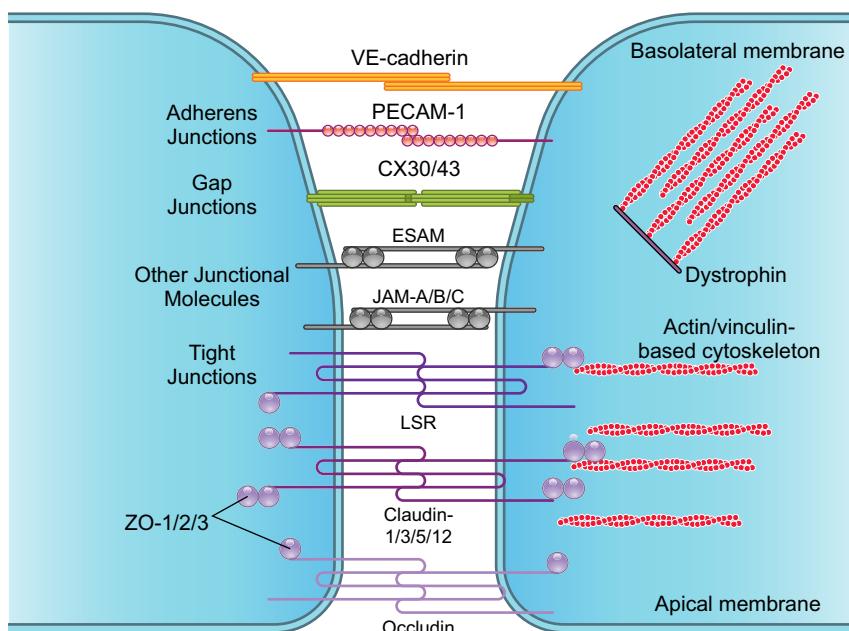
Closest to the apical membrane, TJ proteins claudin-1, -3, -5, and -12, and occludin limit paracellular diffusion of solutes and ions across the BBB (438, 590) (**FIGURE 2**). Loss of claudins is associated with BBB breakdown in human neurodegenerative disorders (155, 569) and acute CNS diseases (692), as well as in animal models of these diseases (420), as discussed below. Claudins can be therapeutically targeted to seal the BBB, as shown by increasing claudin-1

expression at the BBB in murine experimental autoimmune encephalomyelitis (EAE) model of MS (472). *Ocln* knockout mice develop male infertility, but TJs in both epithelial and CNS endothelial cells appear ultrastructurally normal and maintain normal transendothelial electrical resistance, suggesting that TJs form a functional barrier in the absence of occludin (515). Interestingly, *Ocln* knockout mice develop brain calcifications (515), similar as humans with *OCLN* mutations (448), as discussed below.

TJ proteins are connected to the actin and vinculin-based cytoskeletal filaments via scaffolding proteins of the membrane-associated guanylate kinase family ZO-1, -2, and -3 (595, 608) (**FIGURE 2**). ZO-1 deficiency leads to BBB breakdown in many neurodegenerative and acute CNS disorders (693). BBB also expresses the TJ protein LSR, also known as angulin-1, that has been previously identified at peripheral tricellular junctions (551). Additionally, dystrophin complex operates as a scaffold protein to recruit actin and vinculin filaments, which maintains the endothelial cytoskeletal network (603). Dystrophin knockout mice exhibit a notable brain microvascular phenotype with disrupted endothelial TJs, swollen perivascular glial endfeet, and degenerating microvessels (433).

## 5. Pericyte-endothelial junctions

Pericytes share a common basement membrane with brain capillary endothelial cells (570). Direct peg-and-socket contacts between pericytes and endothelial cells are formed by N-cadherin (200, 686). Gap junction CX43 hemichannels (112, 251, 347) enable intercellular communications between pericytes and endothelial cells (570, 648, 682).



**FIGURE 2.** Brain endothelial connections. Several types of junctional molecules maintain the endothelial tight structural lining. Closest to the basolateral membrane, adherens junctions consist of vascular endothelial (VE)-cadherin and platelet endothelial cell adhesion molecule-1 (PECAM-1). Gap junctions including connexin-30 (CX30) and CX43 form hemichannels between endothelial cells. Other types of junctional molecules contribute to the tight lining including the endothelial cell adhesion molecule (ESAM) and junctional adhesion molecule (JAM)-A, -B, and -C. Closest to the apical membrane, tight junctions consist of lipolysis-stimulated lipoprotein (LSR)/angulin-1; claudin-1, -3, -5, and -12; and occludin, which limits paracellular diffusion of solutes and ions across endothelial monolayer. Zonula occludens (ZO)-1, -2, and -3 attach to claudins and occludin and bind to actin and vinculin-based cytoskeletal filaments. Dystrophin functions as a scaffold to recruit actin and vinculin, which maintains the endothelial cytoskeletal network.

## 6. Astrocyte junctions

Astrocytes express gap junction proteins CX30 and CX43 (167, 377, 665). Astrocyte-specific CX43 knockout (73) and/or CX43 and CX30 double knockout (167, 377) weakens the BBB leading to astrocytic edema and loss of astrocyte endfeet perivascular polarity (167, 377), and heightened leukocyte infiltration (73).

## 7. The basement membrane

Endothelial cells interact with the extracellular matrix (ECM) proteins in the capillary basement membrane including collagen, perlecan, and laminin via  $\alpha$ - and  $\beta$ -integrin receptors, which form transmembrane heterodimers that functionally link the ECM with the cell cytoskeleton (590). Integrins mediate cell signaling by activating ECM ligands, growth factors, and growth factor receptors, which regulates multiple endothelial cell functions including survival, migration, differentiation, adhesion, and polarity (35). Integrin dysfunction leads to BBB abnormalities, as illustrated for example by  $\beta 1$ -integrin endothelial knockout mice that develop aberrant VE-cadherin signaling, loss of claudin-5, and immature BBB (663). Conditional deletion of astrocytic laminin  $\gamma 1$  and acute knockdown of laminin  $\alpha 2$  lead to breakdown of the basement membrane, loss of astrocyte endfeet polarity, reduced BBB TJs expression, and BBB disruption (667). Similarly, *Lama2* knockout mice lacking laminin  $\alpha 2$  have pronounced BBB disruption associated with reduced pericyte coverage and loss of TJ and AJ proteins (403). Thus aberrant astrocyte-capillary connections compromise BBB integrity and exacerbate microvascular dysfunction.

## B. BBB Transport Systems

The major BBB transporters, receptors, and channels in endothelial cells and pericytes have been validated by transcriptomic studies and/or protein analysis in the rodent brain (28, 72, 86, 129, 242, 358, 359, 675, 678) (**FIGURE 3**). With the exception of gases (e.g., oxygen and carbon dioxide) and small lipophilic molecules (<400 Da) that freely diffuse across the endothelium (459), brain endothelial transport systems regulate molecular exchanges between blood-and-brain and brain-and-blood (2, 128, 460, 682, 692, 693). Given the close proximity and highly interactive, cooperative signaling between brain vascular pericytes and endothelial cells, it is relevant and timely to discuss current knowledge of BBB pericyte transporters from several recent studies (242, 610). While astrocytes also influence BBB integrity and transporters at astrocytic endfeet are relevant to the BBB since astrocytic endfeet surround brain vessels (13, 667, 682), currently the transcriptome or proteome specifically enriched only in astrocytic endfeet has not been examined.

### 1. Endothelial solute carrier-mediated transport

Carrier-mediated transport (CMT) enables solutes such as carbohydrates, amino acids (AA), monocarboxylic acids, hormones, fatty acids, nucleotides, inorganic ions, amines, choline, and vitamins to cross the BBB via substrate-specific transporters (2, 128, 460, 682, 692, 693).

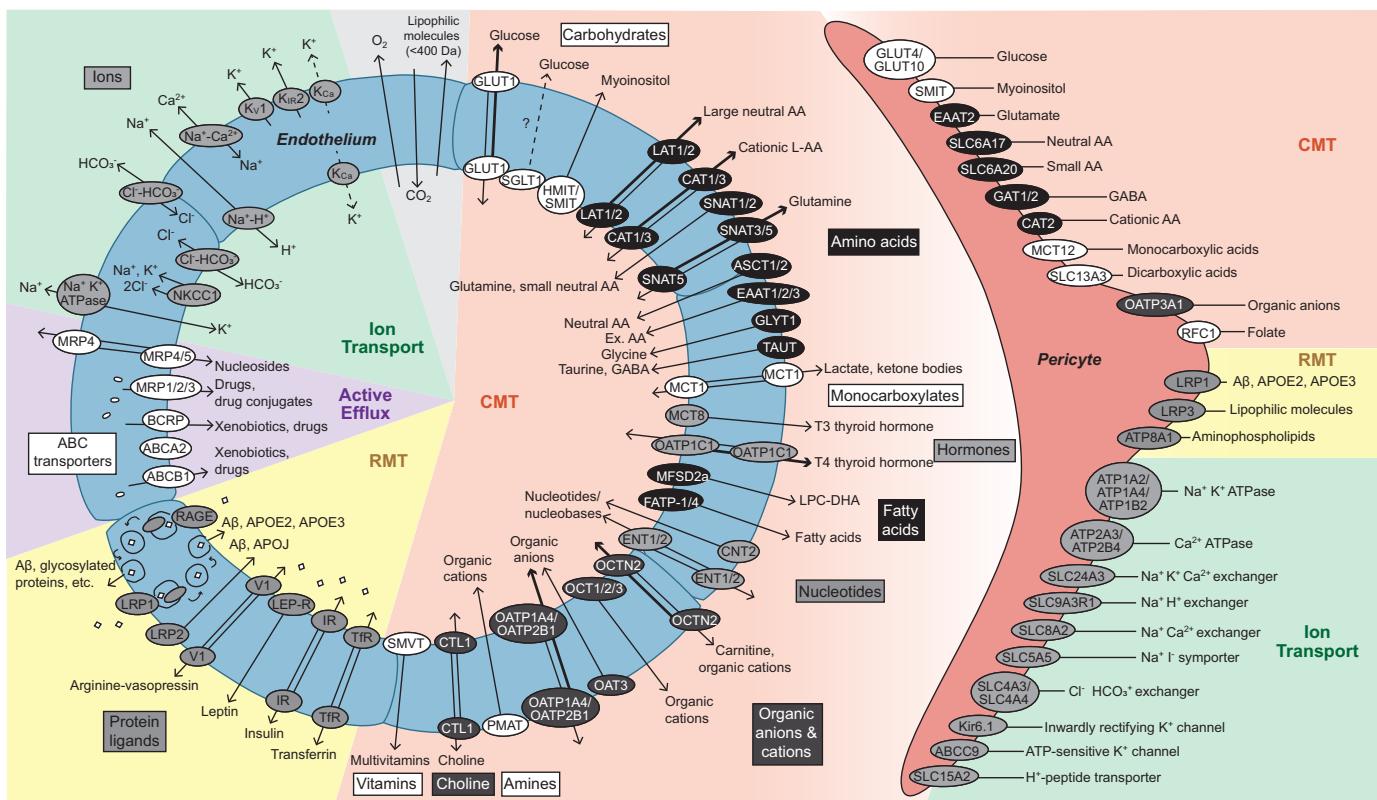
A) CARBOHYDRATE TRANSPORTERS. The GLUT1 uniporter transports glucose, the key energy metabolite for the CNS, down the concentration gradient (128, 460). GLUT1 has a single binding site that can be accessed by glucose (and other hexoses) from either side of the luminal and/or abluminal endothelial membrane extracellularly or intracellularly (141). Since glucose concentration is lower in the brain interstitial fluid (ISF) compared with plasma, GLUT1 favors blood-to-brain transport of circulating glucose (141, 390, 649).

GLUT1 is expressed in endothelial cells, but not in neurons (141, 649). The importance of glucose transport across the BBB is best illustrated by the fact that *Slc2a1* transcript encoding GLUT1 is one of the most abundant transcripts in brain endothelium (129). Mutations in human *SLC2A* gene have profound effects on brain function as discussed below.

Early immunogold electron microscopic studies have shown greater density of GLUT1 transporters on the abluminal endothelial membrane compared with the luminal membrane (171, 542). Crystallization of human GLUT1 in the inward open conformation (141) and crystallization of bacterial GLUT1 homologue have contributed to our understanding of how GLUT1 mediates glucose transport across the cell membrane (490, 565). Briefly, the U-shaped intracellular helical bundle of GLUT1 is formed by three helices and functions as a latch to secure GLUT1 in the outward open conformation making the sugar binding site accessible extracellularly (141). After binding to the extracellular binding site, glucose enters GLUT1, which leads to a conformational change causing extracellular transmembrane domains 1, 4, and 7 to function as a latch to secure the inward open conformation of GLUT1 enabling release of glucose intracellularly (141).

Endothelial cells also express sodium glucose cotransporter 1 (SGLT1) (159) that is found in neurons (671), but its physiological role in glucose transport across the BBB remains elusive. Myo-inositol is transported via sodium/myo-inositol transporter (SMIT) and  $H^+$ /myo-inositol symporter (HMIT) by facilitated diffusion (682).

B) AMINO ACID TRANSPORTERS. All essential AA are transported into the brain across the BBB via large neutral endothelial AA transporter 1 and 2 (LAT1/2) that transport bidirectionally large neutral AA such as tryptophan and tyrosine (450), and the cationic AA transporter 1 and 3 (CAT1/3)



**FIGURE 3.** Major blood-brain barrier transport systems. Endothelium: these include solute carrier-mediated transport (CMT), receptor-mediated transport (RMT), active efflux, and ion transport. CMT systems mediate transport of carbohydrates, amino acids, monocarboxylates, hormones, fatty acids, nucleotides, organic anions and cations, amines, choline, and vitamins with precise substrate specificity and directionality, as indicated. RMT systems transport proteins including transferrin, insulin, leptin, arginine vasopressin, amyloid- $\beta$  (A $\beta$ ), glycosylated proteins, and apolipoproteins E (APOE) and J (APOJ). Active efflux includes ATP-binding cassette (ABC) transporters which transport xenobiotics, drugs, drug conjugates, and nucleosides from endothelium to blood, as indicated. Ion transport underlies the movement of Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, H<sup>+</sup>, and Ca<sup>2+</sup> into and out of the endothelium via ATPases, uniporters, exchangers, and symporters, as indicated. Pericytes: presently, details about pericyte transporters' cellular polarity and precise direction(s) of transport remain elusive. CMT systems transport carbohydrates, amino acids, carboxylates, organic anions and cations, and folate. RMT system transports A $\beta$ , APOE, lipophilic molecules, and aminophospholipids. Ion transport of Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, H<sup>+</sup>, I<sup>-</sup>, and Ca<sup>2+</sup> occurs via ATPases, uniporters, exchangers, and symporters, as indicated. All BBB transporters indicated here are validated with RNA-sequencing and/or proteomic analysis in the rodent brain. See the main text for a more detailed discussion.

that transport cationic AA such as lysine and arginine (390, 560, 692). The concentration of essential AA is lower in brain ISF compared with plasma, which favors blood-to-brain transport (693).

Glutamine levels are higher in brain ISF (240). Glutamine is transported into endothelium via sodium-coupled neutral AA transporter 1, 2, 3, and 5 (SNAT1/2/3/5) and then hydrolyzed in endothelium to glutamate via glutaminase, and removed into circulation (351).

On the abluminal endothelial membrane, sodium-dependent transporters for excitatory AA (EAAT1/2/3) transport glutamate and aspartate out of the brain (451, 692), which limits their excitotoxic effects on neurons. Sodium-dependent AA transporters ASCT1/2 and GLYT1 at the abluminal membrane remove nonessential AA alanine,

serine and cysteine, and glycine, respectively, from brain-to-blood (240). Transporters of neutral and excitatory AA, glycine, taurine, and GABA are enriched abluminally and with high-affinity transport from brain-to-endothelium in a sodium-dependent fashion, and then, these AA are transported across the luminal membrane of the BBB into the blood via low-affinity transporters mediating AA clearance of nitrogen-rich and acidic AA into the circulation (351, 453).

C) MONOCARBOXYLATE TRANSPORTERS. Lactate released from skeletal muscles during exercise, and ketone bodies derived from liver from metabolism of fatty acids are transported from blood into the brain across the BBB by monocarboxylate transporter-1 (MCT1) (540), and then utilized as alternative energy metabolites by the brain (487).

D) HORMONE TRANSPORTERS. Hormone endothelial transporters include MCT8 transporter for T<sub>3</sub> (triiodothyronine) thyroid hormone and the organic anion transporting polypeptide 1c1 (OATP1C1) transporter for T<sub>4</sub> (thyroxine) thyroid hormone (396, 502). The effects of mutations in *SLC16A2* gene encoding MCT8 on brain function are discussed below.

E) FATTY ACID TRANSPORTERS. Essential fatty acids are important for brain development and postnatal neural functions. Brain endothelium expresses luminal transporters for fatty acids, including fatty acid transport protein 1 and 4 (FATP-1/4) (413), and the MFSD2A (430). Previously an orphan MFS transporter, MFSD2A, was identified as a BBB transporter for LPC esterified DHA supplying the brain with the essential circulating omega-3 fatty acid (430). In the brain, MFSD2a is exclusively expressed in brain endothelium and is required for proper BBB development and functional integrity (62). The effects of endothelial *MFSD2A* mutations on brain functions are discussed below.

F) NUCLEOTIDE TRANSPORTERS. Nucleotides and nucleobases, e.g., cytosine, guanine, and adenine found in RNA and DNA, thymine found in DNA, and uracil found in RNA, are all transported across the BBB via sodium-independent concentrative nucleoside transporter-2 (CNT2) and the sodium-independent equilibrative nucleoside transporter-1 and 2 (ENT1/2) (97, 460). They supply brain with key substrates for DNA and RNA synthesis.

G) ORGANIC ANION AND CATION TRANSPORTERS. Organic anions are transported via organic anion transporter-3 (OAT3) and organic anion transporting polypeptide 1a4 (OATP1A4) (588) and 2b1 (OATP2B1) (193). OATP1A4 is a known BBB transporter of statin (588). Organic cation/carnitine transporter-2 (OCTN2) transports carnitine, an essential cofactor for fatty acid oxidation in mitochondria (192). Additionally, organic cations are transported via organic cation transporters 1–3 (OCT1/2/3). OCT1/2 also transport *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin causing PD-like motor impairment (363).

H) OTHER TRANSPORTERS. Amines, choline, and vitamins are also transported across the BBB. Specifically, plasma membrane monoamine transporter (PMAT) transports organic cations from brain-to-blood, choline transporter like protein type 1 (CTL1) transports choline bidirectionally across the BBB, and sodium-dependent multivitamin transporter (SMVT) transports multivitamins from blood-to-brain (2, 128, 460, 682).

## *2. Endothelial receptor-mediated transport*

Most circulating proteins and large macromolecules (e.g., fibrinogen, immunoglobulins, albumin, thrombin, plasminogen, growth factors) are not transported across the BBB.

However, some proteins and peptides use receptor-mediated transport (RMT) to traverse the BBB and enter into the brain. In general, the transport rate of circulating peptides is slower than nutrient transport across the BBB (695).

A) TRANSFERRIN AND INSULIN RECEPTORS. Transferrin receptor (TfR) (78, 290, 461), insulin receptor (IR) (283, 458), and leptin receptor (LEP-R) (41, 206, 699) mediate blood-to-brain transport of transferrin (iron-protein carrier), insulin, and leptin across the BBB, respectively. TfR and IR have been utilized for CNS drug delivery including therapeutic antibodies and enzymes via Trojan horses' technology (459), as discussed below. Additionally, the V1 vasopressinergic receptor mediates bidirectional arginine vasopressin transport across the endothelium (698, 701).

B) LIPOPROTEIN RECEPTORS AND RAGE. LRP1 and LRP2 are expressed in brain endothelium and colocalize mainly on the abluminal side of the BBB in humans and rodents (137, 404, 535, 607, 682). LRP1 binds Alzheimer's A $\beta$  toxin and mediates its brain-to-blood clearance (58, 137, 535, 561). Specifically, LRP1 facilitates clathrin-dependent, receptor-mediated endothelial endocytosis of A $\beta$  at the abluminal membrane of the BBB, which requires phosphatidylinositol binding clathrin assembly protein (PICALM) (683). PICALM guides transendothelial trafficking of endocytotic A $\beta$ -containing vesicles to Rab5, and then to Rab11 small GTPase leading to exocytosis of A $\beta$  across the luminal membrane of the BBB into the blood (683). LRP1 also binds APOE2 and APOE3 as well as APOE2-A $\beta$  and APOE3-A $\beta$  complexes at the abluminal side of the BBB, mediating their efflux from brain-to-blood (135). LRP1 levels at the BBB are diminished in AD and AD models contributing to A $\beta$  accumulation in the brain (137, 152, 410, 535). Additionally, APOJ or clusterin (CLU) binds to LRP2 (or megalin) at the BBB, which mediates A $\beta$ 42 transport from brain to blood (58, 700). Therapeutic strategies based on LRP1-mediated A $\beta$  clearance are discussed below.

In contrast to lipoprotein receptors, the receptor for advanced glycation end products (RAGE) is expressed mainly at the luminal membrane of the BBB (134). Its expression at the BBB is increased in AD and AD models (134, 152, 410). Under pathological conditions, RAGE mediates reentry or influx of circulating A $\beta$  across the BBB into the brain, which is associated with neuroinflammatory response, CBF reductions, and BBB breakdown (134, 136). Therapeutic strategies based on pharmacological blockade of RAGE at the BBB have advanced to phase 3 clinical trial in AD patients, as discussed below.

## *3. Endothelial active efflux*

ATP-binding cassette (ABC) transporters utilize ATP as an energy source and are primarily expressed at the luminal

side of the BBB endothelium (2, 488, 682). They function to prevent brain accumulation of drugs, xenobiotics, drug conjugates, and nucleosides via active efflux from endothelium to blood. Examples include ABCB1 (also known as P-glycoprotein, P-gp), ABCA2, breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins 1–5 (MRP1/2/3/4/5). ABCB1 contributes to Alzheimer's A $\beta$  toxin clearance from brain-to-blood (115, 632). Diminished expression and/or dysfunction of ABCB1 were found in neurodegenerative disorders including AD and PD, as discussed below.

#### 4. Endothelial ion transport

The BBB has a major role in controlling concentration of ions in the CNS, which is important for proper CNS functioning (582, 692).

A) SODIUM PUMP. The abluminal sodium pump ( $\text{Na}^+ \text{-K}^+$ -ATPase) is a key regulator of sodium ( $\text{Na}^+$ ) influx into the brain and potassium ( $\text{K}^+$ ) efflux from the brain, which keeps high concentration of  $\text{Na}^+$  and low levels of  $\text{K}^+$  in brain ISF (188, 624). This, in turn, is critical for regulating electrophysiological activity of neuronal cells including the resting membrane and action potentials, and for maintaining  $\text{Na}^+$  concentration gradient at the BBB (extracellular > intracellular), which drives  $\text{Na}^+$ -dependent transport processes.

B) OTHER ION TRANSPORTERS. The luminal  $\text{Na}^+ \text{K}^+ \text{Cl}^-$  (chloride) cotransporter (NKCC1) mediates entry of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $2\text{Cl}^-$  from blood-to-endothelium (181, 447). The bicarbonate ( $\text{HCO}_3^-$ )- $\text{Cl}^-$  exchanger mediates entry of intracellular  $\text{Cl}^-$  and the extracellular release of  $\text{HCO}_3^-$  (582). The luminal  $\text{Na}^+ \text{-H}^+$  (hydrogen) exchanger transports  $\text{H}^+$  protons from the endothelium-to-blood in exchange for intracellular influx of  $\text{Na}^+$  and is a key regulator of intracellular endothelial pH (673).

C) CALCIUM TRANSPORTERS. The  $\text{Na}^+ \text{-Ca}^{2+}$  (calcium) exchanger cotransporter mediates  $\text{Ca}^{2+}$  efflux from endothelium into brain ISF, which maintains low intracellular  $\text{Ca}^{2+}$  levels in the microvascular endothelium (318). The abluminal transient receptor potential (TRP) channels, also known as non-selective  $\text{Ca}^{2+}$ -conducting cation channels, are expressed both in arterial endothelium (553) and brain microvascular endothelial cell lines (38, 249). TRP channels regulate  $\text{Ca}^{2+}$  influx into brain endothelium that releases soluble factors such as NO, prostaglandins, and endothelial-derived hyperpolarizing factor initiating endothelium-dependent vasodilation (553).

D) POTASSIUM CHANNELS. Capillary endothelial cells express voltage-gated  $\text{K}^+$  channel  $\text{K}_{\text{v}1}$  and the inward rectifier  $\text{K}^+$  channel  $\text{K}_{\text{IR}2}$  (318, 374, 408, 666). During physiological conditions, capillary endothelial  $\text{K}^+$  channels mediate outward  $\text{K}^+$  currents causing endothelial cell hyper-

polarization that propagates vasodilatory signals upstream to arterioles contributing to blood flow regulation (374, 375).

#### 5. Pericyte transporters

Recent transcriptomic studies suggest that pericytes express multiple transporters, receptors, and ion channels (28, 72, 129, 242, 675, 678). Some of these are discussed below.

A) SOLUTE CARRIER-MEDIATED TRANSPORT. Pericytes express carbohydrate transporters such as insulin-regulated glucose transporter GLUT4 (242), facilitative glucose transporter GLUT10 (242), and the sodium/myo-inositol cotransporter SMIT (28).

Several AA transporters have been recently identified in pericytes, including the high-affinity excitatory AA transporter EAAT2 (28), sodium-dependent neutral AA transporter SLC6A17 (242), sodium- and chloride-dependent transporter SLC6A20 for small AA including glycine and proline (28, 129, 242), GABA transporter-1 and 2 (GAT1; GAT2) (28), and the cationic AA transporter CAT2 (28, 242). These transporters likely contribute to the removal of excitatory and nitrogen-rich AA from the brain to prevent excitotoxicity, similar to endothelial transporters.

Pericytes also express the monocarboxylic acid transporter-12 (MCT12) that mediates creatine transport (28, 242) and sodium-dependent SLC13A3 for dicarboxylic acids (242). Organic anions are transported via the organic anion transporter OATP3A1 (28, 129, 242). Additionally, pericytes express the vitamin transporter reduced folate carrier-1 (RFC1) (28, 72, 129, 242, 675).

The precise cellular mechanisms and function of pericyte CMT systems, and whether or not some are part of serial BBB transport mechanisms supplying brain with energy metabolites and nutrients as opposed to cell-autonomous role, remain largely unexplored.

B) RECEPTOR-MEDIATED TRANSPORT. Pericytes express lipoprotein receptor LRP1 (129, 513), which mediates cellular uptake of  $\text{A}\beta$  followed by its intracellular degradation and clearance (513, 647). In the case of excessive  $\text{A}\beta$  load, accumulation of  $\text{A}\beta$  can lead to pericyte cell death (513, 647). Additionally, LRP1 on pericytes regulates cerebrovascular integrity in an APOE-dependent fashion (60). Studies in transgenic mice expressing human APOE isoforms have shown that astrocyte-secreted APOE2 and APOE3 bind to LRP1 on pericytes *in vivo*, which inhibits the proinflammatory CypA-MMP-9 pathway preventing degradation of BBB TJ and basement membrane proteins (60). On the other hand, APOE4 has a low affinity for LRP1, which activates CypA-MMP-9 pathway causing BBB breakdown (60). Activation of CypA-MMP-9 pathway associated with

BBB breakdown has been also shown in human APOE4 carriers by cerebrospinal fluid (CSF) analysis (229) and post mortem brain tissue analysis (230, 267). Additionally, pericytes express LRP-3 (242) which internalizes and transports lipophilic molecules.

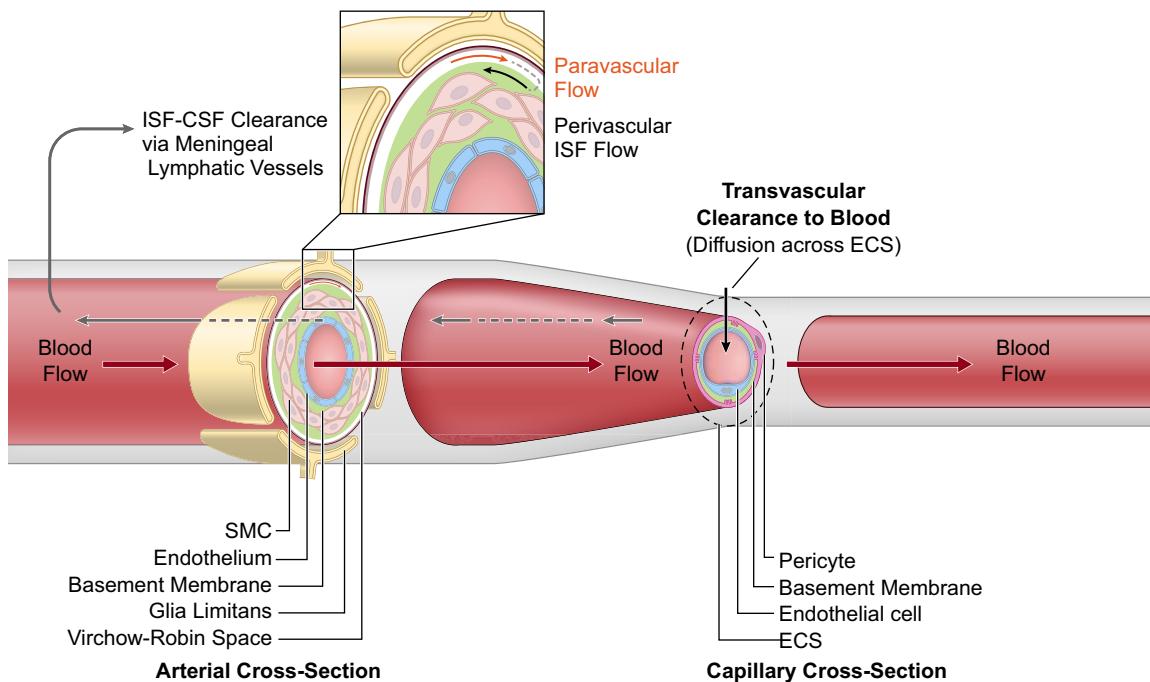
**C) ION TRANSPORT.** Transcriptomic studies suggest that pericytes express  $\text{Na}^+ \text{-K}^+$ -ATPase  $\alpha$ - and  $\beta$ -subunits (28, 129, 242), as well as  $\text{Ca}^{2+}$ -ATPases (28, 129, 242). They also express the  $\text{Na}^+ \text{-K}^+ \text{-Ca}^{2+}$  exchanger SLC24A3 (28), the  $\text{Na}^+ \text{-H}^+$  exchanger SLC9A3R1 (72, 242),  $\text{Cl}^- \text{-HCO}_3^-$  exchanger SLC4A4 (28) and SLC4A3 (242), and the  $\text{Na}^+ \text{-Ca}^{2+}$  exchanger SLC8A2 (242). Furthermore, pericytes express the ATP-sensitive  $\text{K}^+$  channel ATP-binding cassette subfamily C member 9 (ABCC9), the  $\text{H}^+$ -peptide transporter SLC15A2 (28), the  $\text{Na}^+ \text{-I}^-$  symporter SLC5A5 (242), and inwardly rectifying potassium ( $\text{K}_{\text{IR}}$ ) channel Kir6.1 (28, 72, 129, 242).

Functionally, adenosine binding to pericyte  $\alpha 1$ -adrenergic receptors activates ATP-sensitive  $\text{K}^+$  channels causing pericyte hyperpolarization and relaxation (232). Increases in intracellular  $\text{Ca}^{2+}$  in response to large increases in extracellular  $\text{K}^+$  concentrations activate voltage-gated  $\text{Ca}^{2+}$  channels in pericytes, which leads to pericyte depolarization and contraction (232). These findings coupled by recent physiological experiments on pericyte contractility support that

pericytes play an active role in regulating CBF (65, 173, 228, 318, 319, 470).

### C. Other Vascular-Mediated Transport

Besides the major role of transvascular transport in clearance of solutes across the BBB by CMT, RMT, major facilitators, and active efflux transporters (514, 682, 693), solutes diffuse across brain ECS and are cleared along the basement membranes of the arterial vessel walls by the perivascular ISF flow, which travels in the reverse direction of the blood flow (37, 514, 581) (FIGURE 4). Early studies in rabbits using radiolabeled albumin and in rats using India ink, albumin-labeled with colloidal gold, and Evans blue have suggested that perivascular ISF flow carries solutes and macromolecules to the subarachnoid space and CSF compartment for drainage into deep cervical lymph (75, 273). More recent studies in mice using fluorescent solutes have shown that brain has its own lymphatic vascular system in the dura matter, which drains ISF and macromolecules into the deep cervical lymph nodes (32, 160, 162, 376). These findings suggest that brain communicates directly with the peripheral immune system via meningeal lymphatic vessels. Recent magnetic resonance imaging (MRI) studies in the living human brain and marmosets utilized a combination of gadolinium



**FIGURE 4.** Perivascular and paravascular transport. Perivascular interstitial fluid (ISF) flows in the reverse direction of blood flow in the arterial vessel walls ultimately reaching cerebrospinal fluid (CSF)-filled subarachnoid spaces where ISF-CSF drains into the meningeal lymphatic vessels and cervical lymph nodes. Paravascular transport of solutes from subarachnoid spaces flows through Virchow-Robin spaces formed between pia membrane and glia limitans and is suggested to flow in the same direction as blood flow. At the capillary level, solutes diffuse across extracellular spaces (ECS) and undergo transvascular clearance to blood via transport systems as illustrated in FIGURE 3, and discussed in the text.

ium-based contrast agent (Gadovist) and blood-pool contrast agent (Vasovist) to demonstrate existence of the meningeal lymphatic system (4).

In addition to potential roles in regulating brain immune responses, the lymphatic system could also play a role in removing metabolic waste products and proteinaceous toxic accumulates from brain. For example, transport studies using radiolabeled and unlabeled Alzheimer's A $\beta$  peptide have shown that under physiological conditions, the perivascular ISF flow contributes to 15–20% of A $\beta$  clearance from the mouse brain (58, 535, 659), whereas 80–85% is removed by transvascular BBB transport. Since transvascular A $\beta$  clearance fails early in AD and AD models due to diminished expression of A $\beta$  efflux transporters LRP1 (expressed at the abluminal endothelial membrane) and P-gp (expressed at the luminal endothelial membrane) at the BBB (420), the question persists whether perivascular A $\beta$  clearance system is disrupted in disease due to damaged blood vessels contributing to A $\beta$  accumulation in the arterial blood vessels and within the dura, as suggested by amyloid accumulation in the dura of Creutzfeldt-Jakob disease patients by a recent post mortem study (328). Can perivascular lymphatic system be explored therapeutically to drain A $\beta$  from brain remains an open question.

Early studies have suggested that solutes injected into the subarachnoid space can use paravascular transport from the subarachnoid space to enter the brain through Virchow-Robin spaces in the same direction to the flow of blood (496). This concept has been explored by recent studies. For example, studies using injection of fluorescent tracers into cisterna magna of mice have suggested that paravascular circulation occurs via CSF convective flow through the ECS from the para-arterial to the paravenous spaces, which is regulated by AQP4 water channels on astrocytes, and therefore the system was renamed as the “glymphatic” system (276, 293). Other recent studies (252, 255, 547, 555), however, did not support the proposed glymphatic mechanism, nor the convective, pressure-driven fluid flow of CSF from para-arterial to paravenous spaces throughout the parenchymal ECS (31, 30, 255, 296, 547, 255). A recent report in AQP4 knockout rodents has shown that loss of AQP4 does not affect transport of fluorescent solutes from subarachnoid space to brain in rats and mice, suggesting that water production by astrocyte end feet does not control transport of solutes across brain ECS (547).

Nearly half a century ago, physiologists proposed that CSF acts as a sink for brain-derived molecules (133, 253). This concept is supported by recent findings showing that under physiological conditions brain-derived molecules secreted into ISF are present at higher concentrations in the ISF than in the CSF (32, 37, 160, 162, 514, 581).

## IV. GENETIC CONTRIBUTIONS TO BBB DYSFUNCTION

### A. Human Monogenic Neurological Diseases

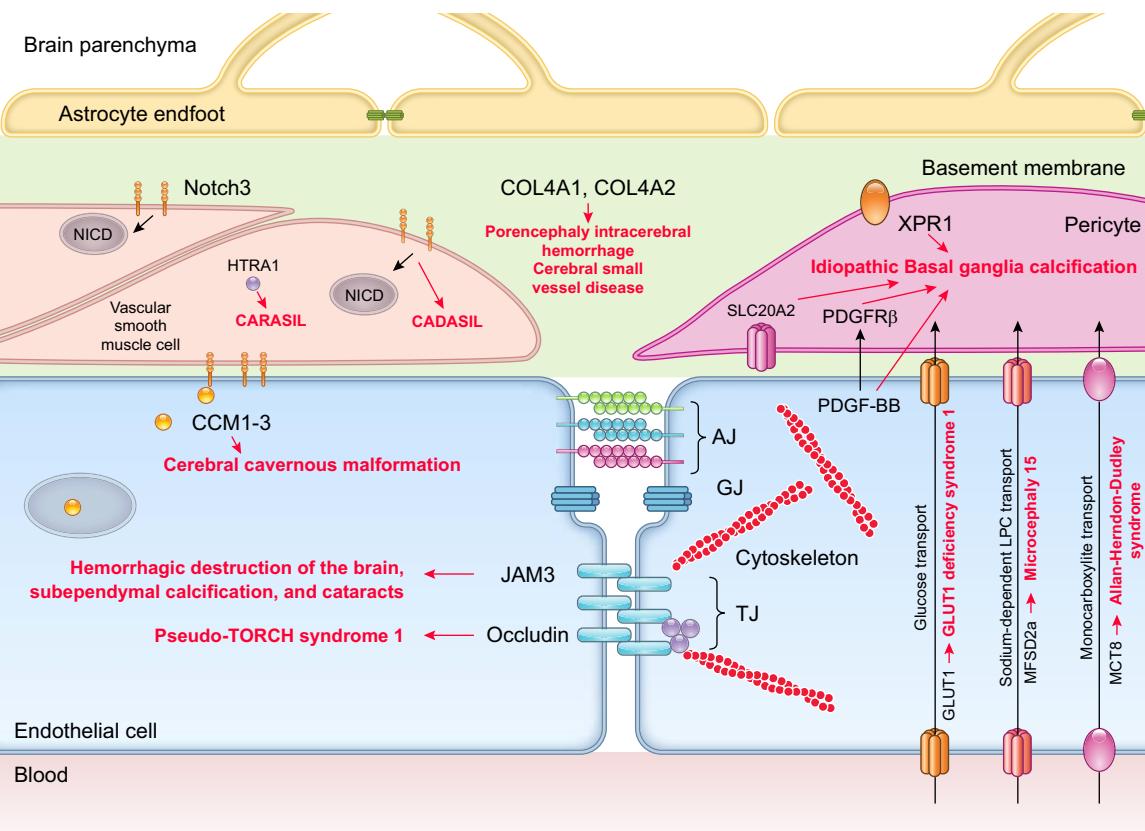
BBB disruption has been reported in several inherited human monogenic neurological diseases with genetic mutations affecting individual cell types within the BBB causing specific defects in BBB development and maintenance (682). Although rare, these neurological diseases provide direct evidence in humans for vascular and BBB contribution to neurodegeneration by demonstrating rapid disease progression from vascular defects to neurological deficits (**FIGURE 5**).

#### 1. Genetic mutations in endothelial cells

A) SLC2A1. Loss-of-function mutations in human *SLC2A1* gene, which encodes the GLUT1 glucose endothelial transporter at the BBB, result in GLUT1-deficiency syndrome in humans manifesting with early-onset seizures, microcephaly, and developmental delay (630). *Glut1*<sup>+/-</sup> mice phenocopy human pathology, and develop initially within 2–3 wk of age BBB breakdown with loss of tight junctions and diminished glucose uptake by the brain, which is followed by microvascular regression, reduced brain perfusion and development of secondary neurodegenerative changes, microcephaly, and loss of cortical and hippocampal neurons (649).

B) MFSD2A. Inactivating mutations in *MFSD2A* gene, encoding the sodium-dependent endothelial transporter that transports essential omega-3 fatty acids into the brain (430) and regulates caveolae-mediated transcellular trafficking across the BBB (21, 62, 684), lead to development of microcephaly syndrome in humans associated with loss of neurons and intellectual disability, and in case of some mutations lethal microcephaly (8, 218). As in humans, murine *Mfsd2a* is expressed in the brain exclusively in endothelium of the BBB (62, 430). *Mfsd2a*-deficient mice exhibit impaired brain uptake of lysophosphatidylcholine-long fatty acyl chains and develop BBB breakdown, which is accompanied by neuronal loss in hippocampus and cerebellum causing microcephaly and behavioral deficits (62, 63, 430, 684).

C) SLC16A2. Another disorder associated with a BBB transporter dysfunction is Allan-Herndon-Dudley syndrome caused by inactivating mutations in *SLS16A2* gene encoding MCT8 transporter for T<sub>3</sub> thyroid hormone (156, 185). These mutations lead to severe impairment in neuronal development and functional deficits causing psychomotor retardation and intellectual disability due to deficient transport of T<sub>3</sub> from blood to brain associated with altered serum thyroid parameters (92).



**FIGURE 5.** Human monogenic diseases of the blood-brain barrier. Endothelium: monogenic diseases affecting transporters include glucose transporter 1 (GLUT1) causing GLUT1 deficiency syndrome, major facilitator superfamily domain-containing protein 2a (MFSD2a) causing microcephaly 15, and monocarboxylate transporter-8 (MCT8) causing Allan-Herndon-Dudley syndrome. Cerebral cavernous malformations (CCM) are caused by mutations in endothelial proteins CCM1–3. Monogenic diseases affecting tight junctions include occludin that causes Pseudo-TORCH syndrome 1 and junctional adhesion molecule 3 (JAM3) that causes brain hemorrhagic destruction, subependymal calcification and congenital cataracts. Basement membrane: mutations affecting collagen type IV alpha 1 chain (COL4A1) and collagen type IV alpha 2 chain (COL4A2) lead to porencephaly, intracerebral hemorrhage, and cerebral small vessel disease. Pericytes: mutations in platelet-derived growth factor-BB (PDGF-BB), PDGF receptor- $\beta$  (PDGFR $\beta$ ), solute carrier family 20 member 2 (SLC20A2), and xenotropic and polytropic retrovirus receptor 1 (XPR1) lead to idiopathic basal ganglia calcification. Vascular smooth muscle cells: mutations in notch homolog protein 3 (NOTCH3) cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and mutations in HtrA serine peptidase-1 (HTRA1) protein cause cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL).

D) KRIT1, CCM2 AND PDCD10. Mutations in endothelial *KRIT1*, *CCM2*, and *PDCD10* genes encoding cerebral cavernous malformation (CCM) proteins 1, 2, and 3 lead to formation of enlarged and irregular small vessels in the brain including thin-walled capillaries and leaky vascular lesions of venous origin (178). CCMs in humans are typically located in the cortical white matter, and due to fragile vessels lead to intracerebral hemorrhages, focal neurological deficits, gait ataxia, seizures, and ischemic strokes (178). The CCM proteins form a complex that is critical for maintaining proper endothelial cell junctions as well as polarization and also inhibit endothelial-to-mesenchymal transition, which when activated contributes to the onset and progression of CCM (380). Besides familial form, the sporadic CCMs occur in people. Together, familial and sporadic CCMs are estimated to affect 1 in 200 people (179).

E) COL4A1 AND COL4A2. Mutations in *COL4A1* and *COL4A2* genes encoding the basement membrane collagen proteins *COL4A1* and *COL4A2* lead to cerebral small vessel disease in humans associated with lacunar ischemic strokes, intracerebral hemorrhages, and white matter hyperintensities (210). *COL4A1* and *COL4A2* are major proteins of the basement membranes, and their transcripts are found in vascular endothelial cells and in many other cell types (210). The exact contribution of endothelial cells versus other BBB-associated cell types to generation of mutant *COL4A1* and *COL4A2* proteins and small vessel disease is not clear at present. *Col4a1* knockout mice develop also fragile vessels that are prone to hemorrhage upon hemodynamic stress and mild trauma (337).

F) OCLN. Mutations in *OCLN* gene in humans encoding the TJ endothelial protein occludin lead to development of se-

vere neurological syndrome known as pseudo-TORCH 1 that is characterized with bands of gray matter calcification on neuroimaging, severe microcephaly with simplified gyration and polymicrogyria, early-onset seizures, and developmental delay (448).

G) **JAM3**. Homozygous mutations in *JAM-3* gene in humans encoding endothelial junctional molecule JAM-C also result in a compromised BBB, often brain hemorrhages, subependymal calcification, seizures, and congenital cataracts (7). JAM-C-deficient mice develop hemorrhages and hydrocephalus (657).

## 2. Genetic mutations in mural cells

A) ***PDGFB* OR *PDGFRB***. Loss-of-function mutations in endothelial *PDGFB* or pericyte *PDGFRB* genes can cause primary familial brain calcification also known as idiopathic basal ganglia calcification (IBGC) or Fahr's disease, which is characterized by early onset of deep brain calcification, SMCs, and pericyte loss and neurological symptoms including motor and cognitive impairments (309, 434). Mice carrying inherited deficiencies in the PDGF-B/PDGFR $\beta$  signaling pathway, e.g., *Pdgfb*<sup>ret/ret</sup> mice with deletion of the retention motif of PDGF-B causing diminished PDGF-BB bioavailability, *Pdgfb*<sup>F7/F7</sup> mice with seven mutations on the COOH terminus of PDGFR $\beta$  receptor disrupting the downstream signaling transduction, and *Pdgfr* $\beta^{+/-}$  mice with a single *Pdgfr* $\beta$  allele and reduced expression of PDGFR $\beta$  in pericytes, all develop early pericyte loss and BBB impairment (28, 59, 130). In the case of *Pdgfr* $\beta$  deficiency, BBB breakdown and vascular phenotype precede neuronal degeneration and loss (59, 319, 650), whereas pericyte-deficient *Pdgfb*<sup>ret/ret</sup> mice develop deep brain calcification at a later age resembling IBGC (309).

B) **NOTCH3**. Mutations in *NOTCH3* gene, which is specifically expressed in vascular mural cells including SMCs and pericytes, result in subcortical ischemic attacks or strokes between 35 and 55 yr of age before progressing to dementia (100). This disease named cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant stroke syndrome with a prevalence of 2–4/100,000 individuals (100). Animal models carrying *Notch3* mutations closely recapitulate human pathology and disease progression, reckoning that vascular changes or defects including BBB impairment and/or microcirculatory insufficiency can lead to secondary neuronal dysfunction and/or white matter damage. For example, mice carrying the CADASIL *Notch3*<sup>R169C</sup> mutation show accumulation of NOTCH ectodomain in pericytes, pericyte degeneration, and BBB breakdown as early as at 7 mo of age (202), while *Notch3* null mice exhibit BBB disruption shown by leakages of circulating tracers in the brain and perivascular deposits of fibrin (244), suggesting that normal NOTCH function is required for the proper maintenance of the BBB.

C) ***HTRA1***. Biallelic mutations in high-temperature requirement serine peptidase A1 (*HTRA1*) gene located on chromosome 10q25 result in subcortical lacunar infarcts and subsequent vascular dementia (591). This rare familial disease is called cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and was first described four decades ago in Japanese families with a high degree of consanguinity (381). Interestingly, *HTRA1* is highly expressed in vascular mural cells, particularly SMCs (371), and its encoded protein HTRA1 plays a key role in facilitating TGF- $\beta$  signaling through processing latent TGF- $\beta$  binding protein 1 (LTBP-1) (55). An attenuation of TGF- $\beta$  signaling caused by a lack of HTRA1-mediated LTBP-1 processing has been proposed as a mechanism underlying CARASIL pathogenesis. Dysregulation of TGF- $\beta$  activity results in microvascular dysfunction leading to white matter lesions (577). In addition, TGF- $\beta$ 1 was shown to reduce mural cell proliferation and elevate MMPs expression and proinflammatory cytokines, which may altogether disrupt BBB function (508). Experimental studies in *HTRA1*-deficient animals have recently started (55), but much more needs to be done in regards to understanding the mechanisms underlying neurovascular dysfunction and BBB breakdown.

## B. Chronic Neurodegenerative Diseases

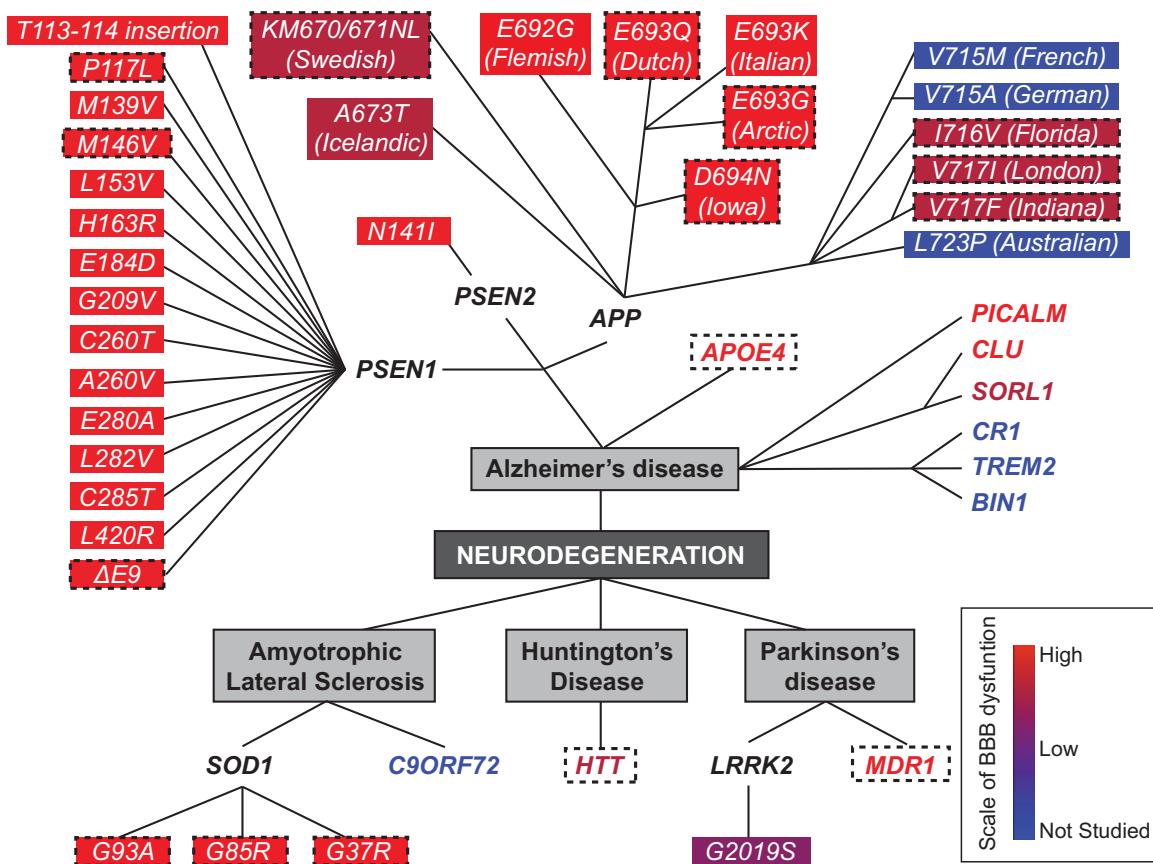
Several genetic mutations that carry inheritance or increase risk for neurodegenerative diseases such as AD, PD, HD, and ALS can lead to BBB breakdown and cerebrovascular pathology in humans and animal models (FIGURE 6).

### 1. Alzheimer's disease

Autosomal-dominant AD (ADAD) is an inherited form of AD caused by mutations in amyloid precursor protein (APP) and presenilin-1 and 2 (*PSEN1*; *PSEN2*) genes (49, 177, 303, 304, 580). ADAD accounts for ~1% of all AD cases and exhibits early age of onset (<65 yr of age) (17). Several APP and *PSEN1* mutations lead to BBB breakdown and cerebrovascular pathology, as discussed below and illustrated in FIGURE 6.

The large majority of AD cases, however, are sporadic, late-onset without clear etiology or inheritance. Nevertheless, several genes are associated with increased or lower risk for sporadic late-onset AD. Apolipoprotein E4 (APOE4) is the major genetic risk factor for sporadic AD (258, 368, 612, 681). APOE4 leads to BBB breakdown, vascular pathology, and diminished clearance of A $\beta$  across the BBB (694), as discussed below.

Genome-wide association studies (GWAS) have identified multiple loci associated with AD including to name a few, variants in *PICALM*, *CLU*, ATP-binding cassette transporter A7 (*ABCA7*), sortilin related receptor-1 (*SORL1*),



**FIGURE 6.** Effects of genetic mutations carrying inheritance or increasing risk for neurodegenerative disorders on blood-brain barrier. *Alzheimer's disease* (AD): APP: amyloid precursor protein (APP) vasculotrophic mutations E692G (Flemish), E693Q (Dutch), E693K (Italian), E693G (Arctic), and D694N (Iowa) lead to prominent cerebral amyloid angiopathy (CAA) causing extensive cerebrovascular pathology and blood-brain barrier (BBB) breakdown in humans (orange red). Dotted boxes denote validation of BBB breakdown in transgenic rodents carrying the respective human vasculotrophic mutations. APP NH<sub>2</sub>-terminal KM670/671NL (Swedish) mutations and A673 (Icelandic) mutations lead to a moderate CAA and BBB breakdown in humans (berry red). Dotted box denotes validation of BBB breakdown in transgenic animals expressing Swedish mutation. Cerebrovascular function in human carriers of APP COOH-terminal V715M (French), V715A (German), I716V (Florida), V717I (London), V717F (Indiana), and L723P (Australian) mutations has not been examined (blue; not studied). However, the BBB breakdown has been shown in transgenic models carrying Florida, London, and Indiana mutations (berry red). *PSEN1*: BBB breakdown and cerebrovascular dysfunction have been reported in humans carrying different PSEN1 mutations including T113–114 insertion, P117L, M139V, M146V, L153V, H163R, E184D, G209V, C260V, E280A, L282V, C285T, L420R, and ΔE9 deletion (orange red). Dotted boxes denote validation of BBB breakdown in transgenic animal models carrying the respective human PSEN1 mutations. *PSEN2*: the most common PSEN2 mutation N141I in humans is associated with BBB breakdown (orange red). *APOE4*: apolipoprotein E (APOE4), the major genetic risk factor for sporadic AD, leads to BBB breakdown in humans and transgenic models expressing human APOE4 gene (orange red, dotted box). *Others*: phosphatidylinositol binding clathrin assembly protein (PICALM) and clusterin (CLU) regulates clearance of amyloid-β peptide across the BBB (orange red), while sortilin-related receptor-1 (SORL1) expressed in brain endothelial cells regulates PDGF-BB and LRP1 signaling at the BBB (berry red), as shown in animal studies. Complement receptor 1 (CR1), triggering receptor expressed on myeloid cells-2 (TREM2), and bridging integrator 1 (BIN1) have not been studied for their cerebrovascular effects. *Amyotrophic lateral sclerosis* (ALS): transgenic rodents expressing human superoxide dismutase-1 (SOD1) G93A, G85R, and G37R mutations develop an early and pronounced BBB and blood-spinal cord barrier (BSCB) breakdown (dotted box), also confirmed in humans with familial ALS (orange red). Vascular pathology has not been studied in C9ORF72 mutation carriers (blue; not studied). *Huntington's disease*: mutation in huntingtin protein causing the disease (i.e., HTT CAG repeat expansions) leads to BBB pathology in humans and animal models (orange red + dotted box). *Parkinson's disease* (PD): leucine-rich repeat kinase-2 (LRRK2) mutation leads to familial PD and LRRK2 G2019S leads to a moderate BBB breakdown in humans (purple). Mutations in multi-drug resistance gene (MDR1) lead to BBB dysfunction in humans and animal models (orange red). The color scale: BBB breakdown is pronounced (orange red), moderate (berry red), modest (purple), or not studied (blue). See the main text for more detailed discussion.

complement receptor 1 (*CR1*), triggering receptor expressed on myeloid cells 2 (*TREM2*), and bridging integrator 1 (*BIN1*) genes (219, 236, 254, 300, 343, 344, 528, 543). Below, we examine variants that affect BBB transport and clearance functions associated with *PICALM*, *CLU*, and *SORL1* genes (FIGURE 6).

A) APP. Approximately 40 *APP* mutations have been identified causing ADAD (52). *APP* mutations can lead to cerebrovascular pathology including BBB breakdown and cerebral amyloid angiopathy (CAA), as shown in humans (49, 211, 356, 674) and transgenic animal models expressing human *APP* mutations (56, 57, 137, 321, 322, 331, 336, 405, 420, 464, 467, 512, 513, 579, 606). CAA is caused by A $\beta$  deposition in the vascular wall of small brain arteries and capillaries and develops as a result of an imbalance between A $\beta$  production and clearance, particularly faulty transvascular and perivascular clearance of A $\beta$  from the brain (318, 420, 581, 640). CAA is a major cause of SMC vascular degeneration that is associated with BBB breakdown at the arterial and/or arteriolar level, lobar microbleeds, infarcts, white matter changes, and cognitive impairment worsening AD pathology (514, 640).

Individuals with “vasculotropic” *APP* mutations within A $\beta$ 21–23 residues including Dutch (E693Q), Arctic (E693G), Flemish (A692G), Iowa (D694N), and Italian (E693K) mutation (49, 211, 335, 356, 526, 674) develop prominent CAA (238, 640) causing extensive cerebrovascular pathology. For example, the Dutch mutation leads to recurrent hemorrhages due to damage of the arterial vessel wall by the CAA, known as hereditary cerebral hemorrhage with amyloidosis (HCHWA-D), which is often fatal by mid-life (302, 356). Patients with HCHWA-D rarely develop parenchymal amyloid plaques and neurofibrillary tangles (428). CBF reductions have also been reported in humans carrying vasculotropic *APP* mutations (49). Experimental studies have shown that the vasculotropic A $\beta$  mutant peptides are poorly cleared from brain across the BBB into circulation due to their low affinity for the BBB clearance receptors including LRP1 compared with wild-type A $\beta$  peptides (137, 416); therefore, A $\beta$  mutant peptides accumulate rapidly along the vessel walls.

In contrast to vasculotropic mutations, *APP* NH<sub>2</sub>-terminal mutations such as Swedish (KM670/671NL) mutation and *APP* COOH-terminal mutations including A713T, A714I, A714A, V715M (French), V715A (German), I716V (Florida), I716T, V717I (London), V717F (Indiana), V717G, V717L, and L723P (Australian) mutations lead aberrant and increased A $\beta$  production by affecting  $\beta$ -secretase and  $\gamma$ -secretase processing activities of *APP*, respectively (303, 304, 356, 580). Compared with vasculotropic mutations, *APP* NH<sub>2</sub>- and COOH-terminal mutations are associated with less pronounced CAA and cerebrovascular pathology (356). The NH<sub>2</sub>-terminal *APP* A673T (Icelandic) mutation,

however, makes *APP* a less favorable substrate for  $\beta$ -secretase, resulting in decreased A $\beta$  production (299). Interestingly, despite sparse parenchymal amyloid deposition, the Icelandic mutation leads to mild CAA and vascular pathology including microinfarcts (311) and ischemic stroke (468), suggesting vascular vulnerability.

Similar to humans, transgenic mice expressing different human *APP* mutations exhibit pronounced vascular pathology including severe BBB permeability changes (322, 467, 579, 606), microbleeds (56, 321, 322, 336, 579), BBB leakages of blood-derived molecules (109, 331, 336, 467, 513), impaired A $\beta$  clearance at the BBB (57, 137, 464, 512), endothelial cell degeneration (336, 513), loss of VSMCs (336, 464) and pericytes (336, 464, 513), and CAA (57, 151, 186, 257, 405, 583).

Some studies in transgenic murine models have examined the temporal sequence of appearance of different pathologies, revealing that progressive BBB breakdown develops early in *APP*<sup>Sw/0</sup> mice beginning at 1–3 mo of age (467, 513, 606) before A $\beta$  deposition, CAA, and behavioral memory recognition deficits that are observed beginning at 10–12 mo of age (151, 336, 606, 638). These studies suggest that CAA is not the only cause of BBB breakdown in *APP* transgenic models. Although the precise mechanism of early BBB breakdown in *APP* mice is currently unclear, oligomeric A $\beta$  toxic species and/or direct *APP*-mediated vasculotoxicity could play a role in CAA-independent early BBB breakdown and vascular pathology.

B) *PSEN1*. To date, 228 *PSEN1* mutations have been identified causing ADAD (49, 303, 304, 440, 566, 580). *PSEN1* is the catalytical component of  $\gamma$ -secretase (304). *PSEN1* mutations increase the faster release of long A $\beta$  peptide species due to altered carboxypeptidase-like  $\gamma$ -secretase activity that increases the proportion of A $\beta$ 42, A $\beta$ 43, and even longer A $\beta$  peptide species (A $\beta$ 45, A $\beta$ 46) (104, 172, 489, 572). Moreover, the ratio of A $\beta$ 42:A $\beta$ 40 is altered in most, but not all, *PSEN1* mutations carriers (572), and the significance of the altered ratio is not well understood. *PSEN1* mutations lead to faster soluble-to-fibrillar conversion of A $\beta$ 42 promoting amyloid deposition in the brain (303, 566, 580). Some *PSEN1* mutations lead to very early onset ADAD (<35 yr of age) (177, 304).

Human *PSEN1* mutation carriers have notable BBB breakdown and cerebrovascular dysfunction including cerebellar amyloid angiopathy and CAA (143, 183, 274, 280, 354, 389, 440, 500, 544, 573, 639, 668); disrupted meningeal, subpial, and cortical arterioles (274, 389, 440); degeneration of pericytes and SMCs (573); cerebral perivascular amyloid deposits (25, 274, 289, 354, 573, 668); and diminished FDG transport across the BBB in an early asymptomatic stage (53, 61). Particularly, cerebrovascular pathology with BBB breakdown was shown by neuropathological

studies in patients with *PSEN1* T113–114 insertion (544), P117L (573, 639), M139V (183, 389), M146V (389), L153V (289), H163R (280), E184D (668), G209V (389), A260V (389), C260T (274), E280A (354), L282V (143), C285T (274), and L420R (440) missense mutations, and Δe9 deletion (280).

Similar to humans, mice expressing human *PSEN1*<sup>M146V</sup> mutations driven by the neuronal Thy1 promoter develop BBB breakdown with microhemorrhages and basement membrane degeneration in the absence of A $\beta$  pathology or CAA (191). Additionally, *PSEN1*<sup>-/-</sup> mice exhibit severe microbleeds and endothelial degeneration in the neocortex at embryonic day 18.5 (641), indicating that *PSEN1* loss of function induces BBB damage. Interestingly, hemorrhages and vascular abnormalities in *PSEN1*<sup>-/-</sup> mice can be corrected by neuron-specific *PSEN1* expression (641), suggesting that impaired vascular-neuronal cross-talk contributes to vascular pathophysiology (191, 641).

C) *PSEN2*. *PSEN2* mutations account for only ~5% of all ADAD cases (394). The mutations N141I (Volga German pedigree) and M239V represent ~75% of all *PSEN2* mutations (91). Similar to *PSEN1*, *PSEN2* mutations may also cause increased production of long A $\beta$  peptide species (481, 523), although this needs more investigation. *PSEN2* N141I mutation carriers have severe CAA and hemorrhagic strokes, but sparse parenchymal amyloid and neurofibrillary tangles (442). Thus far, few studies have investigated cerebrovascular dysfunction in individuals with other *PSEN2* mutations.

D) *APOE4*. *APOE4* is the major genetic risk factor for sporadic, late-onset AD (199, 368, 580, 612). One and two *APOE4* alleles increase risk for AD by ~3.8- and ~12-fold, respectively, compared with *APOE3/APOE3* genotype. The effect of one *APOE4* allele on AD risk is stronger in females than in males. One copy of *APOE2* allele decreases risk by ~0.6-fold relative to *APOE3/APOE3* genotype. Additionally, *APOE4* increases risk for CAA.

*APOE* exerts toxic effects on the cerebrovascular system (694) and neurons (383, 384) and influences A $\beta$  clearance (60, 64, 98, 135, 256, 266, 278, 294, 315, 693), amyloid deposition (39, 256, 258, 266, 278, 314, 518, 612), and tau-related neurodegeneration (533) in an allele-dependent manner *APOE4* > *APOE3* > *APOE2*. Human *APOE4* carriers compared with non-carriers develop accelerated BBB breakdown and pericyte degeneration (229, 230, 267, 516, 691, 702), early neurovascular dysfunction (494, 531, 584), impaired cerebrovascular reactivity (227, 568), and diminished regional BBB uptake of glucose (457, 486). Cerebrovascular effects of *APOE4* are associated with AD, stroke, and brain hemorrhage (314, 506, 549, 614, 693).

Studies in animal models support that *APOE4* compared with *APOE3* and *APOE2* diminishes A $\beta$  clearance across the BBB (58, 135), which has been confirmed in transgenic *APOE4* mice (98). Transgenic mice expressing human *APOE4* gene, but not *APOE3* and *APOE2*, develop an early BBB breakdown (60, 437), cerebral microhemorrhages (85), and loss of endothelial GLUT1 expression (9) that is followed by secondary neurodegenerative changes (60). Transgenic mice lacking *Apoe* also develop an early BBB breakdown (60, 99, 147, 187, 226, 233, 406, 426, 437, 554), indicating that *APOE* is essential for maintaining BBB integrity. *Apoe*<sup>-/-</sup> mice also develop secondary neurodegenerative changes after BBB breakdown in the absence of A $\beta$  pathology (60).

*APOE* in the brain is primarily synthesized by astrocytes and microglia, as indicated by a recent single cell RNA-seq study in the mouse (610). *APOE3* promotes enzyme-mediated degradation of A $\beta$  in microglia more efficiently than *APOE4* (295), suggesting the *APOE* and microglia play a role in the innate immune response in AD (368). Nevertheless, the role of *APOE* secreted by other cell types such as pericytes (82, 96, 646) and SMCs (661) should be further explored.

E) *PICALM*. The association of *PICALM* polymorphisms with late-onset AD has been reported by the majority of GWAS studies (94, 119, 236, 265, 298, 344, 528). Although most of the *PICALM* single nucleotide variants (SNPs) associated with late-onset AD are located outside of the coding regions (683), the risk alleles of rs3851179 (236) and rs10792832 (344) lead to lower expression of *PICALM* isoform 2 in the frontal and temporal cortex in the human brain on the expression quantitative trait loci (eQTLs) (586), indicating that lower *PICALM* levels may increase the risk for AD.

The NH<sub>2</sub> terminus of *PICALM* contains an epsin NH<sub>2</sub>-terminal homology domain for phosphatidylinositol-4,5-bisphosphate binding, which allows *PICALM* to sense membrane curvature (284) and regulate the size of clathrin-coated vesicles (409). *PICALM* controls receptor internalization and subsequent intracellular trafficking (683), via R-SNARE-mediated fusion of clathrin-coated vesicles with endosomes (411). These functions are central to its role in the clearance of both tau through autophagy (423) and A $\beta$  via transvascular transport across the BBB (683).

*PICALM* is enriched in the endothelium of human cerebral vessels including capillaries, but is downregulated in AD patients (683). As shown in the *Picalm*<sup>+/−</sup>; *APP<sup>Sw</sup>* mice, diminished *PICALM* levels at the BBB accelerate amyloid pathology and behavioral deficits, which can be ameliorated by endothelial re-expression of *Picalm* using an adeno-associated virus (AAV) (683). Endothelial cells derived from human iPSCs carrying homozygous protective rs3851179<sup>A</sup> alleles exhibited increased *PICALM* expres-

sion and improved transvascular clearance of A $\beta$  across human BBB in vitro, when compared with isogenic cells from iPSCs carrying homozygous risk rs3851179 $G$  alleles (683). Overexpression of PICALM in the primary rat cortical neurons attenuated the toxicity of soluble A $\beta$  oligomers (598). However, reducing or overexpressing PICALM levels in hippocampal neurons of *APP<sup>Swe</sup>*; *PSEN1<sup>L166P</sup>* mice with AAV8-mediated delivery of *PICALM* shRNA or cDNA, respectively, indicated that PICALM might regulate A $\beta$  production (658). Moreover, PICALM-guided APP intracellular trafficking to autophagosome for degradation (589) limits A $\beta$  production working in harmony with A $\beta$  transvascular BBB clearance to keep low levels of A $\beta$  in the brain.

F) CLU. Several GWAS studies have identified *CLU* as a significant genetic risk factor for sporadic AD (94, 119, 236, 343). The functional impact of *CLU* polymorphisms is currently elusive (304). *CLU* gene encodes clusterin or APOJ that besides its functions in lipid transport, membrane recycling, cell adhesion, and apoptosis (90, 444, 600, 677) affects transvascular A $\beta$  clearance by promoting A $\beta$ 42 efflux across the BBB (580). In the brain, astrocytes primarily secrete clusterin which acts as a chaperone molecule that binds soluble A $\beta$  (444). LRP2 also known as glycoprotein 330 (gp330) or megalin mediates transport of A $\beta$ -clusterin complexes across the BBB (58, 700).

G) SORL1. *SORL1* was identified through GWAS as a risk factor for sporadic AD (495, 503). *SORL1*, a vacuolar protein sorting-10 (Vps10) domain-containing protein, binds PDGF-BB (205, 247) and LRP1 ligands (205). Proper interactions with PDGF-BB and LRP1 ligands are necessary for functional downstream signaling of PDGFR $\beta$  and LRP1, respectively. *SORL1* mutations may impact PDGFR $\beta$  signaling in mural cells causing pericyte dysfunction and/or degeneration that is reported in AD, and may also impair LRP1-mediated transvascular clearance, a key mechanism by which A $\beta$ 40 and 42 peptides are cleared from brain-to-blood (696).

H) OTHER GENES. AD risk genes affect various biological functions, including vascular, immune, metabolic, trafficking, transcription and adhesion, or a combination. Some additional highly replicated risk genes include *CR1*, *BIN1*, and *TREM2* (94, 119, 219, 300, 344, 543). *CR1* is predominantly expressed by erythrocytes (343, 344) and A $\beta$ -C3b-CR1-mediated interactions sequester A $\beta$ 42 to promote clearance to periphery (180, 338), suggesting that *CR1* variants can increase free blood A $\beta$  levels (343), which in turn can promote RAGE-mediated A $\beta$  re-entry across the BBB into the brain. *BIN1* is broadly expressed in brain cell types (344), but the effect of *BIN1* variants on cerebrovascular function has not been explored. Microglial *TREM2* variants (300, 344) are partial loss of function with impaired transport of APOE-containing lipo-

proteins (633). *TREM2* (219, 300, 543) and two novel rare coding variants, *PLCG2* and *ABI3*, implicate innate immunity in AD pathophysiology (543), but whether these variants can influence vascular-inflammatory cross-talk contributing to AD pathophysiology remains unclear.

## 2. Parkinson's disease

PD is the second most common neurodegenerative disease after AD. It is characterized by filamentous and oligomeric  $\alpha$ -synuclein ( $\alpha$ -syn) accumulation, and degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) leading to motor impairments (357, 616). About 10–15% of PD cases have familial genetic etiology (616).

A) LRRK2. Leucine-rich repeat kinase 2 (*LRRK2*) missense mutations cause late-onset PD (>50 yr) (259). The most common *LRRK2* mutation, G2019S (gain of function), is associated with 2% of sporadic cases and 6% of familial cases (357). Recently, increased monocyte attachment was observed in the presence of endothelial cells expressing *LRRK2* G2019S (259), suggesting endothelial dysfunction. Beyond this study, additional measures of vascular integrity and function have not been explored in *LRRK2* mutation carriers.

B) MDR1. *MDR1* mutations are associated with familial and sporadic PD (6, 189). Highly expressed at the BBB endothelium, *MDR1* encodes for ABCB1 (P-gp) that has reduced expression in vivo in PD patients, and is proposed to contribute to PD progression (327).

## 3. Huntington's disease

A) HTT. HD etiology is entirely due to autosomal-dominant *HTT* mutations with abnormal CAG repeat expansion in exon 1, producing mutant huntingtin protein that aggregates and leads to neurodegeneration (379). HD manifests with motor, cognitive, psychiatric, and metabolic abnormalities. Although not often associated with HD pathophysiology, BBB dysfunction is evident in HD (155, 263, 364). Specifically, HD patients exhibit increased BBB permeability in the caudate nucleus as shown by dynamic contrast-enhanced (DCE)-MRI analysis that associates with disease burden, and increased gray matter cerebral blood volume (155). Histological analysis of BBB breakdown shows perivascular capillary fibrin(ogen) deposition, diminished endothelial tight junction proteins claudin-5 and occludin (155), and reduced pericyte coverage (263) in HD brains. The ratio of capillaries to arterioles is increased in the HD putamen (155), cortex, and substantia nigra (155, 364), suggestive of microvascular angiogenesis. Furthermore, mutant huntingtin aggregates accumulate in brain endothelial cells, perivascular macrophages, SMCs, and vascular basal lamina in HD (155), and in genetically unrelated neural allografts within the brains of patients with advanced HD (114), suggesting that cerebral vasculature

may contribute spreading of mutant huntingtin. Similarly, HD R6/2 transgenic mice with 160 CAG repeats exhibit increased BBB permeability (155), increased microvascular density (263), and loss of TJs that precedes disease onset (148).

#### 4. Amyotrophic lateral sclerosis

ALS is characterized by excessive motor neuron loss in the spinal cord, motor cortex, and brain stem that causes progressive paralysis, muscle atrophy, and death ~3–5 yr following symptomatic onset (157, 313). Approximately 10% of ALS cases are familial with autosomal dominant inheritance of mutations reported in at least 15 genes, including to name a few *SOD1*, *TARDBP*, *FUS*, *ANG*, and *OPTN* (11, 18, 174, 465), and an expanded hexanucleotide repeat of GGGGCC in a noncoding region of the *C9ORF72* gene (140, 497).

A few post mortem studies revealed BBB disruption with red blood cells (RBCs) extravasation, pericyte reductions, and reduced levels of TJ proteins in the spinal cord of ALS patients with both familial and sporadic form of disease (243, 652). Next, we discuss experimental studies showing BBB breakdown in transgenic rodents carrying human *SOD1* mutations.

**A) *SOD1*.** Mutations in *SOD1*, which encodes the antioxidant enzyme superoxide dismutase 1, account for 2% of all ALS cases (11). Mutated *SOD1* can form intracellular aggregates in a trimeric form that interfere with motor neuron survival (485). Motor neuron injury in *SOD1* mutations results from toxic gain-of-function rather than loss of dismutase activity (275).

Studies in *SOD1* transgenic mice expressing dismutase-active (G93A and G37R) and dismutase-inactive (G85R) mutations have suggested that BSCB breakdown occurs before motor neuron injury (194, 415, 651, 687, 688). For instance, *SOD1*<sup>G93A</sup> mice develop ultrastructural capillary alterations, extravasation of RBCs, and deposition of fibrin(ogen) and hemosiderin deposits in the brain stem and spinal cord early in the disease (194, 651, 687). BBB disruption including diminished levels of TJ proteins, immunoglobulin G (IgG) and hemosiderin perivascular deposits, and GLUT1 reduction has been shown to precede neuroinflammation, motor neuron loss, and motor impairment in different types of *SOD1* mutants (415, 687, 688). Early BBB breakdown was also shown in *SOD1*<sup>G93A</sup> rats at a presymptomatic stage (431) and has been confirmed using different contrast-enhanced MRI techniques (20, 51). One study, however, failed to detect any T1-enhancement after gadolinium injection in *SOD1*<sup>G93A</sup> mice, suggesting no change in BBB and BSCB integrity (166), in contrast to several independent previous studies discussed above showing disrupted BSCB and BBB in *SOD1*<sup>G93A</sup> mice (20, 50, 51, 194, 196, 415, 431, 432, 687, 688). Whether or not

BBB breakdown is detectable in ALS patients carrying familial *SOD1* mutations, as shown in *SOD1* mutant models, has not been explored.

**B) *C9ORF72*.** The GGGGCC repeat expansion suppresses the production of *C9ORF72* protein by inhibiting transcription (140, 153, 225, 369, 497, 520). The role of the *C9ORF72* protein in *C9ORF72* ALS disease remains, however, unclear, as is whether or not GGGGCC repeat plays any role in vascular integrity.

## V. BBB BREAKDOWN AND DYSFUNCTION IN NEUROLOGICAL DISORDERS

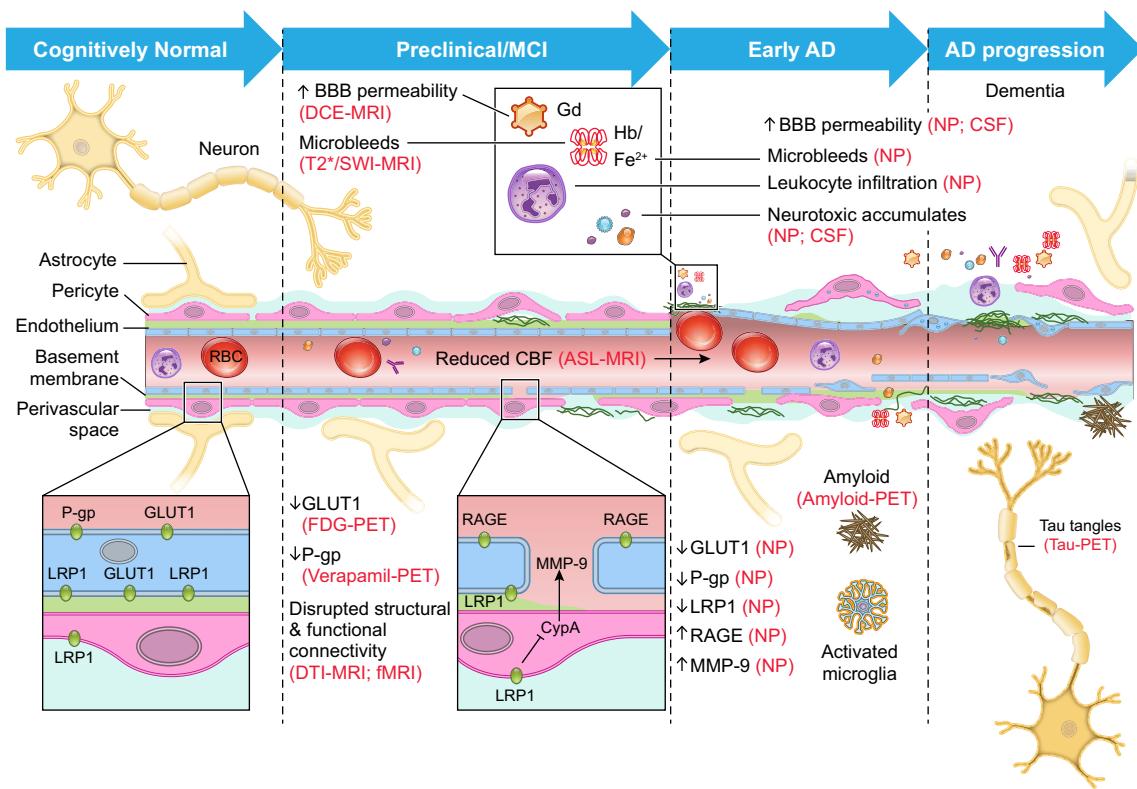
Next, we examine sporadic forms of common neurodegenerative disorders that are not clearly linked to genetic mutations but are associated with BBB breakdown, dysfunction, and vascular pathology. We also discuss briefly BBB damage in acute neurological disorders.

### A. Alzheimer's Disease

In addition to the classic hallmark pathology, A $\beta$  plaques, hyperphosphorylated tau neurofibrillary tangles, and neuron loss, increasing evidence supports that early cerebrovascular dysfunction contributes to AD pathophysiology and cognitive impairment (29, 285, 418, 421, 429, 569, 571, 593, 682, 693). Some studies have suggested that during preclinical stages, vascular dysfunction is among the first detectable biomarker changes reported before symptomatic onset and before changes in other standard AD biomarkers, including amyloid deposition and CSF A $\beta$ 42, phosphorylated tau (pTau), and total tau (285, 421). Moreover, neuropathological studies indicate that early cerebrovascular disorder increases risk for dementia including AD (29) and is associated with AD and other neurodegenerative disorders independently of mixed dementias including vascular dementia (593). Vascular risk factors including hypertension (169, 272), diabetes (43, 110), hyperlipidemia (74), and cardiovascular disease (594), as well as environment (e.g., pollution) (87–89, 207) and lifestyle (e.g., obesity, sedentary lifestyle) (281, 643) all affect cerebrovascular and BBB dysfunction (429, 571), and may influence onset and progression of AD.

Several AD animal models derived from ADAD human mutations including *APP* and *PSEN1*, and *APOE4* transgenic mice develop an early BBB breakdown before AD pathology, as discussed above and recently reviewed (420). Additionally, tau transgenic models (*TetO-Tau*<sup>P301L</sup>) also exhibit BBB leakage, microbleeds, IgG deposits, and leukocyte infiltration detected before tau pathology and with no evidence of A $\beta$  pathology (66), supporting that cerebrovascular dysfunction contributes to AD progression.

**FIGURE 7** illustrates BBB breakdown and dysfunction during different stages of AD progression based on clinical



**FIGURE 7.** Blood-brain barrier breakdown and dysfunction in sporadic Alzheimer's disease. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has shown blood-brain barrier (BBB) breakdown in the hippocampus in individuals with mild cognitive impairment (MCI) and in different gray and white matter regions in early Alzheimer's disease (AD), before brain atrophy and dementia occur. Microbleeds reflecting loss of cerebrovascular integrity and BBB breakdown have been shown by T2\*-MRI and susceptibility-weighted imaging (SWI)-MRI during MCI stage, which progresses and augments through early stages of AD. Fluorodeoxyglucose positron emission tomography (FDG-PET) has indicated diminished BBB GLUT1 transporter activity mediating glucose uptake by the brain before brain atrophy, dementia, or amyloid- $\beta$  ( $A\beta$ ) pathology. Similarly, diminished active efflux ABCB1 (P-gp) BBB transporter activity was shown by verapamil-PET in early AD. Early BBB breakdown and vascular dysfunction in MCI and AD has been confirmed by some studies by elevated levels of vascular biomarkers in cerebrospinal fluid (CSF) and blood before  $A\beta$  and tau pathology, and dementia. Neuropathological (NP) analysis of mild and advanced AD cases confirmed accumulation of perivascular blood-derived deposits including, to name a few, fibrinogen, thrombin, red blood cells (RBC)-derived iron-containing products that all are potentially toxic for the neural tissue. In addition, pericyte degeneration, endothelial degeneration, and brain infiltration with circulating macrophages and neutrophils were associated with BBB breakdown of AD cases on NP analysis. Diminished expression levels of BBB GLUT1 and ABCB1 (P-gp) transporters have been shown by post mortem NP analysis of AD cases, as well as downregulation of  $A\beta$  BBB clearance receptors LRP1 and ABCB1, suggesting impaired  $A\beta$  clearance. Furthermore, *APOE4* carriers develop accelerated BBB breakdown associated with activation of proinflammatory cyclophilin A (CypA)-matrix metalloproteinase-9 (MMP-9) pathway at the BBB, which degrades endothelial tight junction and basement membrane proteins enhancing BBB damage. How changes in BBB permeability as measured by advanced neuroimaging techniques in the living human brain relate to disrupted structural and functional connectivity as measured by diffusion-tensor imaging (DTI)-MRI and functional MRI (fMRI), and amyloid-PET and tau-PET findings remains unclear at present.

findings, neuroimaging, and neuropathological and biomarker biofluid studies, as discussed next.

### 1. Neuroimaging findings

A) DCE-MRI. Recent neuroimaging studies in individuals with mild cognitive impairment (MCI) and early AD reveal BBB breakdown in the hippocampus, including its CA1 and dentate gyrus subfields (421), and several gray and white matter

regions (220–222), respectively, before brain atrophy and dementia. These studies used advanced DCE-MRI to quantify the regional BBB permeability constant,  $K_{trans}$ , to the contrast tracer gadolinium relative to each individual's arterial input tracer function (421). These studies used Patlak analysis (46, 47, 466), which allows detection of subtle changes in BBB permeability (46, 248, 418, 421). Earlier studies using longer resolution time and semiquantitative analysis indicated a possible trend of increased BBB perme-

ability in the hippocampus in MCI compared with controls (631), and suggested that accumulation of contrast agent in brains of individuals with probable AD likely occurs via blood-to-brain-to-CSF pathway (556), consistent with increased blood vessel permeability.

B) T2\* AND SWI MRI. Microbleeds are RBC-derived iron-containing perivascular hemosiderin deposits that can be visualized as small hypointense regions on T2\*- and/or susceptibility-weighted imaging (SWI) MRI sequences (620). CNS microbleeds reflect loss of cerebrovascular integrity and are found in 25% of individuals with MCI (669) and 45–78% of individuals with early AD without dementia (83, 208, 246, 452, 476, 529, 604, 702). This broad range of detection could likely be attributed to the magnet field strength, with clinical strength 1.5 and 3T magnets likely underestimating the incidence of microbleeds compared with the research-grade 7T magnet (83, 246, 452, 530, 604, 669). Although microbleeds are believed to result from CAA (514), many studies investigating microbleeds in AD did not simultaneously conduct amyloid PET imaging making it difficult to directly compare the degree of CAA to the incidence of microbleeds (83, 208, 246, 452, 476, 529, 604, 702). Importantly, microbleeds develop in the absence of A $\beta$  pathology and are associated with cognitive impairment and dementia, as shown in patients with small vessel disease of the brain that is estimated to contribute to 50% of all dementias worldwide including AD (224, 550, 637).

C) FDG-PET AND VERAPAMIL-PET.  $^{18}\text{F}$ -fluoro-2-deoxyglucose (2-DG) (also known as FDG) is a radioactive glucose 2-DG analog that does not enter the glycolytic or Krebs cycle metabolic pathways in the brain (124, 397, 504, 552). FDG-positron emission topography (PET) is clinically used as a surrogate for glucose uptake by the brain. As previously reviewed, FDG-PET reflects mainly the transport activity of GLUT1 BBB transporter (420, 569). Individuals with MCI and early AD have diminished regional brain uptake of 2-DG, as measured by FDG-PET, before MCI-AD conversion, brain atrophy, or neurodegenerative changes (268, 345, 424, 425, 517). This is consistent with AD post mortem studies showing diminished expression of GLUT1 in brain capillaries (261, 301, 422, 541). Experimental studies also support diminished transport of  $^{14}\text{C}$ -labeled glucose across the BBB in haploinsufficient *Slc2a1*<sup>+/−</sup> mice lacking ~50% copies of the GLUT1 BBB transporter (649).

Studies using [ $^{11}\text{C}$ ]verapamil, an ABCB1 (P-gp) ligand and PET, have shown increased uptake of verapamil in certain brain regions in individuals with early AD, suggesting diminished ABCB1-mediated active efflux of xenobiotics and drugs at the BBB (33, 142), and possibly faulty A $\beta$  BBB clearance based on experimental studies (115, 400, 632).

## 2. Neuropathological studies

A) BBB BREAKDOWN. Post mortem studies show vascular capillary leakages of blood-derived proteins in the prefrontal and entorhinal cortex and hippocampus of AD patients including perivascular accumulation of fibrin(ogen), thrombin, albumin, immunoglobulin G (IgG), and iron-containing proteins such as hemosiderin (120, 125, 230, 267, 412, 509, 527, 691). These blood-derived proteins are often found colocalized with A $\beta$  (267, 509, 527) and are more pronounced in *APOE4* carriers compared with noncarriers (230, 267, 516, 691).

B) PERICYTE DEGENERATION. Ultrastructural studies using electron microscopy reveal accumulations of osmiophilic materials in the capillary mural cells in AD cortex suggestive of pericyte loss (40, 170). Pericyte loss has been confirmed by decreased levels of pericyte marker PDGFR $\beta$  in the precuneus (412) and loss of pericytes in the subcortical white matter (419). Similarly, PDGFR $\beta$  immunostaining revealed significantly reduced pericyte coverage of brain capillaries as well as reduced pericyte numbers in AD cortex and hippocampus compared with control brains (527), which is accelerated by *APOE4* gene (230).

C) ENDOTHELIAL DEGENERATION. Further evidence of BBB breakdown in AD is repeatedly observed in numerous post mortem human studies showing reduced capillary length and microvascular degeneration with diminished TJ protein expression, capillary basement membrane alterations, and brain endothelial degeneration (36, 40, 230, 516, 527, 656).

D) CELL EXTRAVASATION. RBC extravasation (125) and brain infiltration by peripheral macrophages (175, 267) and neutrophils (676) are reported in AD post mortem studies, suggesting that the brain's innate immune system is activated, which can contribute to pathophysiological changes.

E) DYSREGULATED MOLECULAR TRANSPORT. The levels of endothelial-specific GLUT1 transporter at the BBB are greatly reduced in AD (261, 301, 422, 541). AD brain microvessels also exhibit reduced levels of LRP1, a major A $\beta$  clearance receptor at the BBB (137, 152, 230, 410, 535). Besides oxidative stress and A $\beta$  causing faulty LRP1 folding leading to its proteosomal degradation (137), reduced GLUT1 levels may also inhibit LRP1 transcriptionally via sterol regulatory element binding protein 2 (SREBP2) (649). In contrast to LRP1, expression of RAGE, a major A $\beta$  influx receptor, is increased in AD brain endothelium and mural cells (134, 152, 410), likely contributing to circulating A $\beta$  influx, neuroinflammation, and reduced CBF (134, 136).

Brain pericytes and endothelial cells in AD *APOE4* carriers exhibit increased activity of BBB-degrading CypA-MMP-9

pathway compared with noncarriers (230). CypA mRNA is also increased in AD brains (118).

F) ANGIOGENESIS. Increased levels of several angiogenic factors in response to reduced CBF and regional hypoxic changes have been reported in AD brains (213). Despite a pronounced pro-angiogenic response, AD brains fail to mount an adequate angiogenic response to renew lost capillary networks likely due to the loss of the homeobox gene MEOX2 from endothelium (656), and ongoing pericyte degeneration (570).

### 3. Biomarkers biofluid studies

The most common biofluid marker of BBB breakdown is the albumin quotient (Qalb), which is the ratio of CSF albumin levels to serum albumin levels. Qalb is elevated in individuals with preclinical AD (229), MCI (421), AD without vascular risk factors (287, 545, 546), and AD with vascular risk factors (67, 68, 74, 629). Given that brain macrophages, microglia, astrocytes, neurons, and neuroglial antigen 2-positive cells can take up albumin (76, 286, 355), additional measures of BBB permeability such as MRI

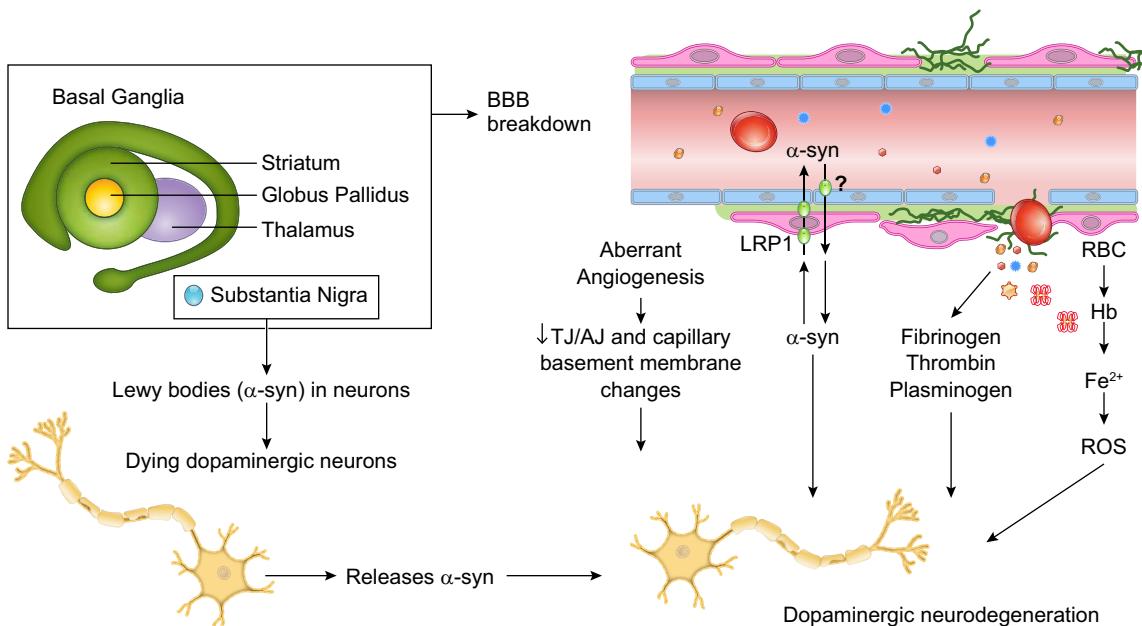
(e.g., DCE, T2\*, SWI) should be used alongside Qalb to accurately assess the degree of BBB breakdown.

## B. Parkinson's Disease

Idiopathic PD has unknown etiology. It has been suggested that vascular risk factors accelerate the onset and severity of motor and cognitive impairments during early stages of PD (386), and that cerebrovascular dysfunction can influence development and progression of PD, as discussed next. FIGURE 8 illustrates BBB disruption in PD based on neuroimaging as well as neuropathological and biomarkers biofluid studies.

### 1. Neuroimaging findings

A) DCE-MRI. Using gadolinium contrast agent, DCE-MRI, and Patlak quantification analysis of BBB permeability (46, 47, 421), recent studies have demonstrated BBB breakdown in the basal ganglia in PD patients compared with controls (10).



**FIGURE 8.** Blood-brain barrier breakdown and dysfunction in sporadic Parkinson's disease. Vascular dysfunction occurs throughout the basal ganglia of Parkinson's disease (PD) patients, consisting of blood-brain barrier (BBB) breakdown and dysfunction, as shown by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), T2\*-MRI and susceptibility-weighted imaging (SWI)-MRI demonstrating microbleeds, and diminished active efflux of xenobiotics and other potential toxins, as indicated by verapamil-PET. Aberrant angiogenesis with increased number of endothelial cells, decreased tight junction (TJ) and adherens junction (AJ) proteins, and capillary basement membrane changes have been shown both in humans with PD and animal models. BBB breakdown can lead to neurotoxic accumulates of fibrinogen, thrombin, and plasminogen, and red blood cell (RBC) extravasation, release of hemoglobin (Hb) and iron ( $Fe^{2+}$ ) causing reactive oxygen species (ROS), which all can injure dopaminergic neurons. Concurrently, localized to the substantia nigra pars compacta, Lewy bodies form from filamentous and oligomeric  $\alpha$ -synuclein ( $\alpha$ -syn) that accumulate within dopaminergic neurons. Recent studies suggested that  $\alpha$ -syn can cross the BBB and contribute to  $\alpha$ -syn pool in the brain, and is also cleared from brain across the BBB via LRP1-mediated transcytosis.

B) T2\* AND SWI MRI. Cerebral microbleeds reflecting BBB breakdown and deposition of RBC-derived hemosiderin deposits have been detected throughout deep gray matter, cortical, and white matter regions in PD patients using T2\*- and SWI-MRI (231, 288). Interestingly, they are more prevalent in PD patients with dementia compared with those without dementia and controls, and positively correlate with white matter lesions (231, 288).

C) VERAPAMIL-PET. Diminished activity of a major BBB active efflux transporter ABCB1 (P-gp) has been shown in the mid-brain regains of PD patients by accumulation of [<sup>11</sup>C]verapamil using PET technique (327).

## 2. Neuropathological studies

A) BBB BREAKDOWN. Throughout the basal ganglia, histological analysis of PD patients reveals BBB breakdown in the striatum as shown by capillary leakages and accumulation of perivascular fibrin(ogen) (214) and IgG (473) deposits, hemosiderin (214, 373), and RBCs extravasation (214). In accordance with human studies, compromised BBB integrity is also observed in rodent models of PD induced by systemic administration of MPTP (108, 680) or intrastriatal administration of 6-hydroxydopamine (6-OHDA) (95), including leakage of fluorescein isothiocyanate (FITC)-labeled albumin (95, 108, 680), horseradish peroxidase (95), and Evan's blue (108) in the substantia nigra and striatum. MPTP models also show leukocyte infiltration (113).

B) ENDOTHELIAL DEGENERATION. In the PD, there is a substantial loss of endothelial cells in the basal ganglia, reduced levels of TJ proteins, and alteration of capillary basement membrane (473). Reduced expression of TJ proteins has also been shown in MPTP PD models (108).

C) BBB MOLECULAR TRANSPORT. Recent studies reveal that  $\alpha$ -syn crosses the BBB bidirectionally, which could signify an important contributory event in PD pathogenesis (469, 563). Specifically,  $\alpha$ -syn injected intraventricularly and intravenously in rodents undergoes brain-to-blood efflux and blood-to-brain influx, respectively (469, 563). Administered systemically,  $\alpha$ -syn oligomers, ribbons, and fibrils crossed the BBB into the brain, where  $\alpha$ -syn amplification and strain-specific pathology and neurotoxic phenotypes are observed (469). P-gp did not affect  $\alpha$ -syn efflux; however,  $\alpha$ -syn inhibited A $\beta$  efflux suggesting that endothelial LRP1 is a potential efflux transporter for  $\alpha$ -syn (563). If LRP1 is similarly downregulated in PD as in AD (137, 561), this could result in impaired  $\alpha$ -syn BBB clearance and accumulation of  $\alpha$ -syn in brain. Furthermore,  $\alpha$ -syn influx is increased following lipopolysaccharide (LPS)-induced BBB breakdown (563), suggesting that the high levels of  $\alpha$ -syn produced peripherally can enter the brain in the presence of BBB breakdown, which may also contribute to development of PD pathology.

D) ANGIOGENESIS. Aberrant angiogenesis is frequently observed in PD patients, as shown in the substantia nigra pars compacta, locus caeruleus, and putamen (144, 627). Similarly, increased angiogenesis is observed throughout the basal ganglia of 6-OHDA-treated rats (44, 501). Of note, BBB disruption caused by a single intra-nigral injection of VEGF in rats induces dopaminergic neuron loss in the substantia nigra (501), suggesting that BBB disruption is capable of causing neurodegeneration. Aberrant angiogenesis occurs early in PD raising the question: is it driven by local tissue hypoxia, diminished local CBF, and/or increased metabolic demand?

## 3. Biomarkers biofluid studies

Increased Qalb (287, 288, 362, 474) and CSF-to-serum IgG ratio (474) are observed early in PD patients before dementia.

Additionally, plasma exosomal  $\alpha$ -syn levels are markedly higher in PD patients and correlate with disease severity (532). However, the functional role of the exosome-mediated  $\alpha$ -syn clearance and whether it reflects increased CNS  $\alpha$ -syn production in PD patients is presently unclear.

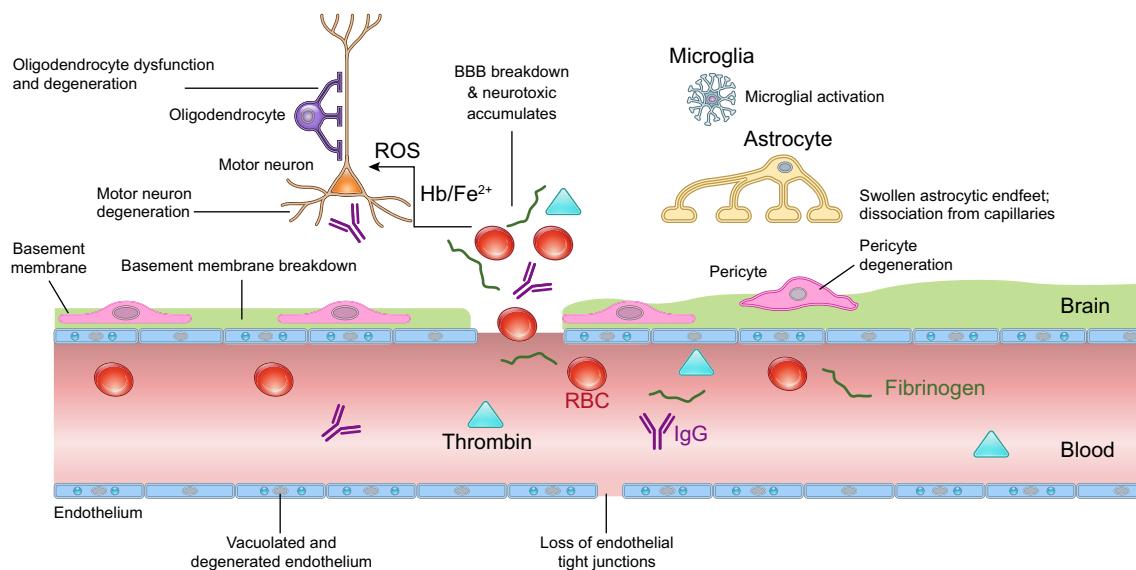
CSF angiogenesis biomarkers are altered in PD compared with controls including increased levels of VEGF, placental growth factor (PIGF), and soluble VEGF receptor-2 (sVEGFR-2) and decreased angiopoietin-2 (Ang2) (288). These biomarkers are further altered as patients progress into more advanced PD stages with dementia (288, 474).

## 4. Deep brain stimulation

Deep brain stimulation (DBS) is commonly used to improve PD-related motor symptoms, and its effectiveness is credited to microvascular improvements (250, 473). PD patients that underwent DBS exhibit increased capillary length and density, increased TJ and AJ protein expression, and reduced perivascular IgG leakage at post mortem tissue analysis (473). Additionally, resting CBF increases in the premotor cortex following DBS treatment, which correlated with improved gait velocity and cadence (250). Altogether, these data suggest that DBS may restore disrupted BBB integrity in PD, which in turn could be critical for control of motor symptoms.

## C. Amyotrophic Lateral Sclerosis

Ninety percent of ALS cases are sporadic with no clear genetic linkage (11, 313). Below, we discuss studies showing BBB breakdown in ALS patients. Based on these studies, and experimental studies in transgenic rodents carrying different *SOD1* mutations, as discussed above, we propose a model how BBB and BSCB disruption can contribute to development of ALS pathology (**FIGURE 9**).



**FIGURE 9.** Blood-brain barrier breakdown and dysfunction in amyotrophic lateral sclerosis. Blood-brain barrier (BBB) breakdown with loss of tight junction proteins and pericyte and endothelial cell degeneration leads to red blood cells (RBCs) extravasation and perivascular accumulation of plasma-derived proteins such as fibrinogen, thrombin, and IgG that is found in the spinal cord and motor cortex both in humans with sporadic and familial forms of ALS, as well as in rodents expressing different human *SOD1* mutations. The RBC extravasation leads to the release of neurotoxic hemoglobin (Hb), and free iron ( $\text{Fe}^{2+}$ ) causing generation of reactive oxygen species (ROS), which is toxic to motor neurons. Serum proteins such as fibrinogen can activate microglia enhancing non-autonomous motor neuron cell death. Astrocytic endfeet become swollen and dissociate from capillaries, and the perivascular space becomes enlarged and basement membrane breaks down. The effects of BBB breakdown on oligodendrocyte precursor cells that proliferate and mature oligodendrocytes that degenerate remain elusive at this time.

### 1. Neuroimaging studies

A) T2\* MRI. A few MRI studies showed hypointensities indicative of microbleeds in the brains of ALS patients (277, 339, 445), whereas another study failed to detect microhemorrhages in sporadic ALS (615).

### 2. Neuropathological studies

A) BBB BREAKDOWN. Several independent post mortem studies of brain stem and spinal cord tissue from patients with sporadic and familial ALS found that there is a significant reduction in tight junction proteins, accumulation of blood-derived proteins (e.g., thrombin, IgG, hemoglobin, hemosiderin), capillary basement membrane changes, astrocytic end-feet detachment from endothelium, reduced microvascular density, and enlarged perivascular spaces suggestive of BBB and BSCB breakdown (195, 243, 339, 415, 652, 662). These findings support earlier observations showing that the BBB and BSCB are damaged in a subset of ALS patients as demonstrated by accumulation of plasma-derived IgG in the spinal cord and motor cortex in 40% (154) to 90% (163) of studied cases, and accumulation of peripheral blood cells in 70% (164) to 100% (599) of studied cases.

B) PERICYTE DEGENERATION. Immunohistochemical analysis for pericyte biomarkers on the spinal cord capillaries from patients with sporadic and familial ALS found pericyte degeneration and loss that is associated with BSCB breakdown and fibrinogen and IgG perivascular deposits (652). This was confirmed recently in 25 sporadic ALS patients having a prominent reduction in pericyte coverage in the ventral horn (662).

### 3. Biofluid studies

A subset of ALS patients shows increased Qalb ratio and elevated CSF levels of several blood-derived proteins (79, 652). For example, increased Qalb values were found in 40% of all studied ALS cases (i.e., 55/138 from 4 independent studies) (23, 79, 407, 525), suggesting that at least a subset of ALS develop vascular pathology.

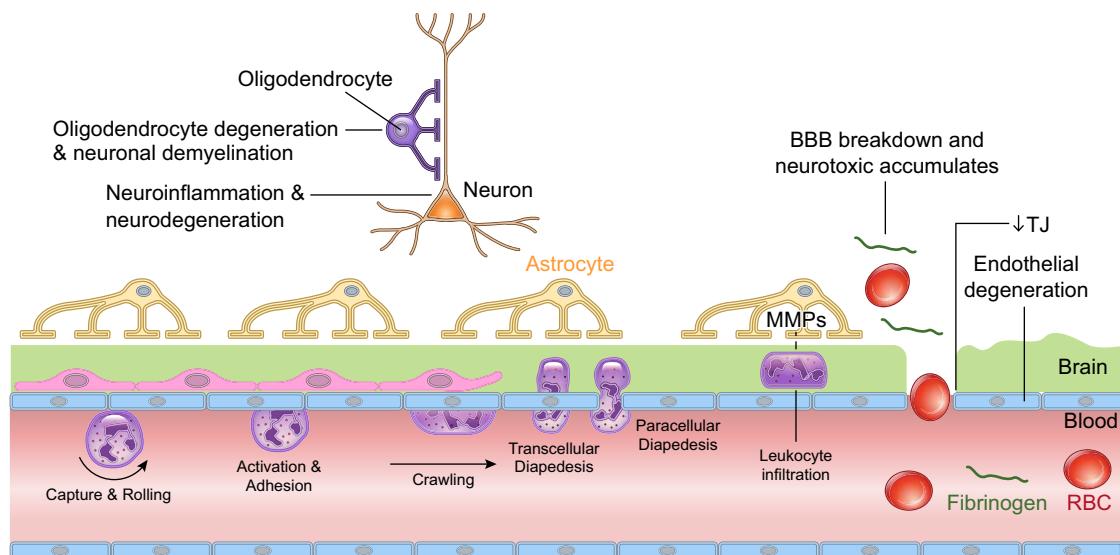
### D. Multiple Sclerosis

MS is an autoimmune and neurodegenerative disease (184) in which the myelin sheath surrounding axons is attacked by immune cells, including leukocytes, T cells, B cells, and peripheral macrophages that enter the brain through a disrupted BBB (456). Experimental findings in MS mod-

els of chronic and relapsing EAE have shown that a key pathophysiological event is encephalitogenic leukocyte CNS infiltration across the BBB that occurs via sequential steps of capture, rolling, activation, adhesion, crawling, and diapedesis in postcapillary venules, capillaries, and mid-capillaries (161, 182, 215, 216, 456, 617), as illustrated in **FIGURE 10**.

Mechanistically, leukocyte capture and rolling are mediated by interactions between leukocyte P-selectin glycoprotein ligand 1 (PSGL1) and endothelial E- and P-selectin (521). Both leukocytes and the endothelium become activated, causing upregulation of cell surface receptors mediating leukocyte-endothelial adhesion (215, 216, 537). Ad-

hesion occurs via interactions between leukocyte integrins lymphocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) with endothelial ICAM-1 and VCAM-1, respectively (215, 216). Crawling is predominantly mediated by upregulated endothelial ICAM-1 and ICAM-2 (557). Endothelial ICAM-1 expression is essential for transcellular diapedesis, for example, ICAM-1- and ICAM-2-deficient endothelial cells prevent CD4+ T cell crawling and diapedesis (1). Additional essential protein interactions for transendothelial diapedesis include endothelial JAM-A, caveolin-1, PECAM1, and CD99 and leukocyte LFA-1, proteins  $\alpha$ 4-integrin (CD49), PECAM1, and CD99 (165, 215, 655). Paracellular diapedesis is regulated by endothelial VE-cadherin, JAM-A, ESAM, PECAM1,



Leukocyte Infiltration Step	Capture & Rolling	Activation & Adhesion	Crawling	Transcellular Diapedesis	Paracellular Diapedesis
Endothelial cell adhesion molecules	E-selectin P-selectin	ICAM-1 VCAM-1	ICAM-1 ICAM-2	ICAM-1 JAM-A Caveolin-1 PECAM CD99	VE-cadherin JAM-A ESAM PECAM1 CD99
Leukocyte adhesion molecules	PSGL1 L-selectin	LFA-1 VLA-4	LFA-1 VLA-4 Mac-1	LFA-1 CD49 PECAM CD99	LFA-1 PECAM1 CD99

**FIGURE 10.** Blood-brain barrier breakdown and dysfunction in multiple sclerosis. Hallmark features of multiple sclerosis (MS) include vascular dysfunction, neuroinflammation, and oligodendrocyte degeneration causing neuronal demyelination and loss. An early blood-brain barrier (BBB) breakdown, neurotoxic fibrin(ogen) accumulation, reduced tight junction (TJ) protein expression, and endothelial degeneration are features of both human MS and animal MS models. Leukocytes infiltrate across the BBB in a multistep sequential process involving capture, rolling, activation, adhesion, crawling, and trans- or paracellular diapedesis. This process requires crosstalk between leukocytes and endothelial cells via precise molecular interactions, as illustrated in the diagram. See the main text for details. MMPs, matrix metalloproteinases; RBC, red blood cell.

and CD99 and leukocyte LFA-1, PECAM1, and CD99 (161, 215, 617) (**FIGURE 10**). Comprehensive mechanistic details and discussion of leukocyte infiltration have been reviewed extensively elsewhere (161, 215, 456, 617).

A substantial body of evidence is increasingly showing BBB disruption as an early feature of MS in both human patients as well as animal models, as discussed next.

### *1. Neuroimaging studies*

Neuroimaging studies using gadolinium enhancement have established that BBB disruption is an early feature of MS pathogenesis (14). Gadolinium enhancement is associated with active MS lesions and is considered as one of the key diagnostic criteria for an acute MS lesion. Furthermore, MRI changes suggestive of BBB disruption were also found in normally appearing white matter before enhancing lesions (176), and in nonenhancing areas (626), suggesting BBB dysfunction likely precedes the onset of symptoms and other MRI disease-related changes. The BBB changes appear to extend to the initial stages of disease, as suggested by findings of global BBB disruption at the onset of optic neuritis in patients who go on to develop MS (122).

More recently, an increase in BBB permeability has been shown in MS patients by DCE-MRI in the cortex and adjacent white matter (392), corpus callosum and internal capsule (121–123, 421, 574), as well as thalamic gray matter (123). Interestingly, increased BBB leakage is prominent around new developing MS lesions centralized around small, inflamed veins (190). Recent studies using radioactive MMP PET found that increased MMP activity localizes around active lesions that associate with leukocyte infiltration (201).

Increased BBB permeability has been also detected early in the EAE model in marmosets using high-field MRI indicating a 3.5-fold increase in BBB permeability 4 wk before the onset of MS lesions (382).

### *2. Neuropathological studies*

A) **BBB BREAKDOWN.** Seminal characterization of the MS lesion by Dawson in 1916 recognized that myelin breakdown invariably originated around parenchymal blood vessels (483). This is supported by evidence of fibrinogen perivascular deposition in the developing lesions (317, 626). Post mortem findings of perivascular immune infiltrates have established that BBB disruption is an early feature of MS pathogenesis (14). BBB dysfunction has also been confirmed by decreased levels of TJ proteins (i.e., occludin, ZO-1, and claudin-5) and basement membrane abnormalities (317). These abnormalities are seen across the brain in both relapsing-remitting and progressive stages of MS (352) being most common in active lesions. Reduced levels of TJ

proteins were associated with fibrinogen leak and perivascular astrogliosis (14).

Longitudinal studies in spontaneous relapsing-remitting-EAE mice have shown that BBB disruption occurs before immune cell infiltration in focal lesions (15). A recent study also confirmed that BSCB disruption occurs following a caudo-rostral progression over time using both Evans blue dye injection and fibrin(ogen) immunostaining in EAE mice (182).

### *3. Biofluid studies*

Elevated Qalb values (355), increased MMP-9 activity in CSF and serum (122, 168), and increased CSF leukocyte count (122), all indicative of BBB breakdown, have been shown in MS patients at different stages of the disease.

## **E. Other Chronic Neurodegenerative Disorders**

### *1. HIV-1-associated dementia*

Human immunodeficiency virus (HIV)-1 prognosis greatly improved with the era of anti-retroviral therapy; however, many HIV-1-positive individuals today still develop HIV-1-associated dementia (HAD) (292, 511). BBB disruption plays a major role in HAD development by allowing HIV-1-infected monocyte-macrophages to traverse the BBB and enter the brain (562). Post mortem brain tissue studies in HAD or HIV encephalitis report microvascular degeneration and BBB breakdown including reduced pericyte coverage (439), reduced and disrupted TJs (471, 664), capillary basement membrane changes (471), perivascular macrophage infiltration (471), and reduced brain endothelial ABCB1 (P-gp) expression (346). MRI studies reveal that small-vessel cerebral ischemic disease is also prominent in HAD (401). Whether treatments directed at the BBB can delay or prevent HAD development to improve the lives of individuals with HIV-1 is currently not known.

### *2. Chronic traumatic encephalopathy*

Chronic traumatic encephalopathy (CTE) is characterized by accumulation of TAR DNA-binding protein-43 (TDP-43) and neurofibrillary tangles of hyperphosphorylated tau beginning perivascularly (54), and is reported in football (454, 455), wrestling (455), boxing (325), and soccer (366) players, as well as in veterans (237). Post mortem CTE studies reveal cerebral edema, perivascular hemosiderin-burdened macrophages, mural cell mineralization, enlarged perivascular spaces, and leukocyte infiltration (149, 325, 454, 455), supporting that repeated microvascular injury, ischemia, and axonal injury triggers a neurodegenerative cascade. To date, the majority of CTE studies have analyzed post mortem brain tissue. Future MRI studies would help to

determine how the degree of regional BBB breakdown relates to structural and functional changes in brain connectivity and onset of CTE symptoms.

## F. Acute Neurological Disorders

### 1. Stroke

BBB dysfunction is a prominent pathological feature of both ischemic and hemorrhagic stroke and is typically associated with poor outcome (307, 312, 482). Comprising 85% of all strokes, ischemic stroke exhibits extravasation of blood-borne cells, chemicals, and fluid into brain parenchyma across the impaired BBB as a result of increased paracellular and transcellular permeability and endothelial degeneration (305). Water and ion homeostasis of the brain is also disrupted, leading to cerebral edema (505). Leukocyte infiltration further exacerbates inflammatory responses and worsens brain injury (264). During and after ischemic stroke, BBB disruption facilitates injury progression and increases the risk of hemorrhage, predicting poor patient outcome and limiting the use of thrombolytic treatment with recombinant tissue-type plasminogen activator (tPA) (308, 370).

In preclinical models of ischemic stroke, opening of BBB has been shown to be a biphasic phenomenon (482). The first phase is controlled by subtle endothelial cytoskeleton alterations 30–60 min after ischemia/reperfusion injury, followed later by enzymatic cleavage of TJ proteins after inflammatory cell recruitment (324, 534, 703). Hemorrhagic stroke transformation is sometimes a consequence of thrombolytic tPA therapy for ischemia, and dysfunctional BBB is the primary initiator of the pathology (306, 312).

The existence of stroke comorbid conditions, such as hypertension and hyperglycemia, induces anatomical and functional changes to the brain microvasculature and often exacerbates BBB breakdown after stroke. Below we discuss clinical trials that are using DCE-MRI to visualize BBB permeability changes following acute ischemic stroke (619). Having received much less attention than warranted, BBB research should be better prioritized, with an emphasis on BBB-related mechanisms of neurovascular injury and developing therapeutic strategies to improve BBB integrity after ischemic stroke, as for instance with 3K3A-activated protein C (3K3A-APC) (217).

### 2. Traumatic brain injury

Loss of vascular integrity has a key role in mediating tissue damage after traumatic brain injury (TBI) (48, 223, 402, 536). Disruption of the walls of microvessels in the BBB activates the coagulation cascade. Intravascular coagulation leads to ischemia in the areas surrounding the impact site resulting in severely decreased blood flow; this is known

as the “no-reflow” phenomenon. Since the integrity of the BBB is compromised after injury, blood-borne factors such as fibrin(ogen), thrombin, and albumin, among others, can now enter the brain.

Similar to the pathophysiology of stroke, BBB alterations after TBI occur in two phases based on preclinical models, first occurring within hours of tissue damage and the second 3 days after injury (48, 223). Early opening of BBB is caused by the shear injury of cerebral blood vessels causing physical damage to BBB integrity, and is later followed by the activation of inflammatory cells (48). However, there is still controversy especially about the cascades leading to secondary BBB breakdown in TBI due to scattered methodology as extensively discussed elsewhere (548).

### 3. Spinal cord injury

BSCB disruption following spinal cord injury (SCI) allows white blood cells to infiltrate the injured parenchyma and contribute to secondary injury (3, 239, 334, 692). On the basis of experimental rodent studies, BSCB disruption occurs within 5 min after spinal cord trauma (385), lasts for up to 28 days after the initial injury, and spreads along the entire length of the cord (441, 478, 644). The BSCB can remain compromised even at 56 days after SCI as assessed using DCE-MRI (117). The extended time course of barrier breakdown has been confirmed by MRI analyses (117, 507), but the time course for reestablishment of BSCB function is less clear, with results varying widely among studies (385, 441, 478). Some reports suggest that SCI generates a biphasic opening of the barrier. The first peak of abnormal leakage occurs within several hours after injury, whereas the second peak is evident between 3 and 7 days post-injury (644).

### 4. Epilepsy

Epilepsy is a family of neurological disorders with recurrent seizures that affects more than 50 million individuals worldwide (653). Increased microvascular density, loss of tight junctions, and IgG leakage are observed in hippocampal resections from humans with temporal lobe epilepsy (499), and are also observed in rodent epileptic models (145, 499). BBB dysfunction positively correlates with seizure frequency and is independent of neuronal loss (234, 499). BBB dysfunction is localized to epileptic regions, suggesting that the BBB plays a contributory role to epileptic disorders. The connection between epilepsy and BBB breakdown is known to be bidirectional (316). BBB breakdown caused by TBI and underlying inflammatory reactions can trigger epilepsy (204, 618). On the other hand, changes in BBB permeability may lead to progression of epilepsy making it more difficult to treat (621, 622). Multiple anti-inflammatory treatment strategies have demonstrated the beneficial effect of maintaining BBB integrity in this condi-

tion (393). Several past and current clinical trials are related to BBB function in epilepsy, as discussed below.

## VI. BBB-BASED THERAPEUTIC OPPORTUNITIES

The BBB poses two major challenges for the development of therapeutics for CNS disorders. First, with its barrier function and highly effective active efflux systems, the BBB rejects most of the small molecule drugs and large therapeutic molecules including growth factors and antibodies (42, 567, 682). Second, focal BBB breakdown in the disease leads to perivascular accumulation of blood-derived toxic products and macromolecules, immune and/or inflammatory responses, vascular regression, and local CBF reductions (318, 693). These focal vascular changes limit CNS distribution of neurotherapeutics in disease-affected regions by disrupting diffusional transport across brain ECS and/or by blocking normal ISF flow dynamics (519, 569).

Selecting drug analogs with better permeability may traverse the BBB. A successful example is L-3,4-dihydroxyphenylalanine (L-DOPA) for PD over dopamine, as it crosses the BBB via LAT1 neutral amino acid transporter (459). On the other hand, approaches to circumvent the BBB have been utilized clinically for treatment of some CNS disorders. These include intracerebroventricular administration of Cerliponase for Batten's disease (395), intrathecal administration of antisense oligo Spinraza targeting the survival motor neuron 1 gene (SMN1) for infantile spinal muscular atrophy (150), intrathecal Ziconited peptide for chronic pain (398), and intranasal administration of insulin, leptin, and oxytocin (103).

Here, we discuss recent approaches developed to protect the BBB and eliminate secondary vascular-mediated CNS changes, and/or to effectively traverse the BBB to improve CNS drug delivery (**TABLE 2**).

### A. Protecting Damaged BBB

#### 1. Sealing broken BBB

A few pharmacological agents have been reported to restore BBB function in animal models of acute neurological disorders (217, 697) and neurodegeneration (420). APC, for example, exerts pleotropic beneficial activities including protection of the BBB integrity, anti-inflammatory effects, direct neuroprotection, and pro-neurogenic and pro-angiogenic effects, as shown in rodent models of stroke, TBI, and ALS (217). APC cleaves protease-activated receptor 1 (PAR1) in brain endothelium and subsequently activates  $\beta$ -arrestin-2-dependent biased signaling pathway, which targets phosphatidylinositol 3-kinase (PI3K) for cytoprotection and Rac1 GTPase for sealing the BBB (217). 3K3A-

APC, a recombinant variant of APC with reduced anticoagulant activity, has advanced from bench to bedside and has completed phase 2 clinical trial for stroke (NCT02222714). 3K3A-APC also holds promise for TBI, ALS, and possibly other neurodegenerative disorders (217).

Treatment with glucocorticoids also offers BBB protection (446). Progesterone and allopregnanolone can reduce neuroinflammation and improve barrier function by down-regulating expression of metalloproteinases as shown in a mouse model of ischemic stroke (282). Allopregnanolone is beneficial for type C Niemann-Pick disease, AD, and MS based on preclinical studies in animal models (443). Interferons produced during viral infections, e.g., West Nile virus, protect the BBB integrity to virions by restricting their entry into brain parenchyma (131, 348).

Inhibition of CypA-MMP-9 BBB degrading pathway by cyclosporine, a CypA inhibitor, restored BBB integrity and reversed secondary neurodegenerative changes in transgenic humanized *APOE4* mice (60). Activation of CypA-MMP-9 pathway associated with BBB breakdown has also been shown in human *APOE4* carriers compared with non-carriers, as indicated by CSF (229) and post mortem BBB tissue (230) analyses. Whether a nonimmunosuppressive cyclosporine analog Debio 025, which is used in humans in phase III trial for hepatitis C (NCT01318694), can also protect cerebrovascular integrity and improve cognitive impairment in human *APOE4* carriers at risk for AD remains worth exploring.

#### 2. Eliminating consequences of BBB breakdown

When the BBB is open, plasma proteins enter the neuroglial space and often exert toxic effects on various cell types in the CNS (682, 693). Therefore, neutralizing toxic accumulates represents another valuable therapeutic approach for neurodegenerative diseases associated with neurovascular dysfunction and BBB pathology. For example, fibrinogen and its polymeric form fibrin can activate integrin receptors on glial cells and neurons to inhibit regeneration (45, 522), or receptors on microglia and bone-derived macrophages to exacerbate neuroinflammation and induce antigen-presenting genes (45, 132, 510). Depleting fibrinogen and/or preventing its accumulation in the brain, as for example with ancrod, a defibrinogenating agent, attenuated both neuroinflammation and vascular pathology in AD mice (467) and in an MS model (132). On the other hand, BBB damage causing extravasation of RBCs that leads to iron accumulation and oxidant stress can be successfully controlled by the iron chelation therapy and/or antioxidant treatment, as shown in *SOD1*<sup>G93A</sup> mutant mice with ALS-like disease (651).

#### 3. Enhancing clearance function

The BBB is a major clearance site for many brain-produced potentially toxic substances, which is particularly impor-

**Table 2.** Circumventing, protecting, and traversing the blood-brain barrier

Approach	Therapeutics	Mechanism	Disease	Animal Model	Clinical Trials	Reference Nos.
<b>Circumventing BBB for CNS drug delivery</b>						
Alternative routes of administration	Cerliponase	Intracerebroventricular	Batten's disease	Multiple species and models	FDA approved	382
	Spinraza	Intrathecal	Infantile SMA		FDA approved	144
	Ziconited peptide		Chronic pain		FDA approved	385
	Insulin	Intranasal	Cognitive impairment		Phase II/III	99
	Leptin		Obesity		Phase I	99
	Oxytocin		Autism		Phase II	99
<b>Protecting damaged BBB</b>						
BBB sealing	APC and its analogs	$\beta$ -Arrestin-mediated PAR1-biased signaling	Stroke	Rodent stroke models [arterial occlusion, embolic stroke]	Phase II	208
			ALS	SOD1 mutant models	NA	208
	Glucocorticoids	Upregulation of intercellular junctional proteins, suppression of MMPs and inflammation	Niemann-Pick disease, type C	NPC1	NA	500
Eliminating consequences of BBB breakdown	Ancrod	Depleting fibrin(ogen)	AD	TgCRND8	NA	452
			MS	EAE		126
	Deferoxamine	Iron chelation	ALS	SOD1 (G93A)	NA	624
	Glutathione monoethyl ester	Antioxidant				
Enhancing clearance function	APC and its analogs	PI3K/Akt-mediated neuroprotection, endothelial protection	Stroke	MCAO, dMCAO, embolic stroke	Phase II	208
			ALS	SOD1 mutants	NA	208
	LRP1 minigene	Improve efflux	AD	Tg2576	NA	624
	RAGE inhibitor (Azeliragon)	Reduce influx			Phase III	128
	Allopregnanolone	Promoting A $\beta$ and cholesterol clearance		3xTgAD	Phase I	79
Cell therapy	Mesenchymal stem cells transplantation	Improve BBB functions	CNS injuries	Rodent experimental models	NA	250, 448, 559
	Pericytes transplantation		ALS	SOD1		110
Other BBB-targeted clinical trials	DCE-MRI	Identifying and tracking sites of BBB permeability	Ischemic stroke	Rodent experimental models	Observational trials	300
			MS		Phase I	13
			Epilepsy			139, 482
	P-gp inhibitor	Prevent anti-epileptic drug resistance	Epilepsy		Phase II	649
	Anti-VLA-4 humanized monoclonal antibody (Natalizumab)	Block CNS leukocyte infiltration	Relapsing remitting MS		Phase IV	510
	Anti-CD52 humanized monoclonal antibody (Alemtuzumab)				FDA approved	662

*Continued*

**Table 2.—Continued**

Approach	Therapeutics	Mechanism	Disease	Animal Model	Clinical Trials	Reference Nos.
<b>Traversing BBB for CNS drug delivery</b>						
Direct opening of the BBB	Focused ultrasound	Doxorubicin delivery	Brain tumor	Multiple species and models	Phase I	82
		To promote therapeutic delivery	AD PD		Phase I Phase I	461 461
Colloidal carriers	Nanoparticles Exosome	Entrap within or covalently bind to drugs	A broad spectrum of CNS diseases	Multiple species and models	Phase 1 NA	503
CMT	L-DOPA	LAT-1 large amino acid transporter	PD	MPTP	FDA approved	654
RMT	Bispecific antibodies	Anti-TfR-BACE1 Anti-TfR-A $\beta$	AD	Tg2576 PS2APP	33 422	
	Molecular Trojan horses	L-Iduronidase fused with anti-TfR Iduronate 2 sulfatase fused with anti-ID	Mycopolysaccharidosis I Mycopolysaccharidosis II	Rhesus monkey	Phase II	68
Viral vectors and variants	Gene delivery	Brain tropic AAV9 variants	PD	TgSNCA-A53T mouse	NA	140

AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; FDA, United States Food and Drug Administration; NA, not applicable.

tant in maintaining brain A $\beta$  homeostasis (682, 693). Targeting the BBB clearance machinery in AD is an emerging therapeutic approach to shift the balance between A $\beta$  production and clearance. For example, LRP1 minigene delivery to the BBB by viral vectors facilitates A $\beta$  clearance and attenuates A $\beta$  pathology (649). On the other hand, blocking RAGE at the BBB (134) effectively reduces A $\beta$  reentry into the brain, inhibits neuroinflammation, and improves CBF in a mouse model of AD (134, 136). On the basis of a better understanding of RAGE biology, a small molecule RAGE inhibitor has advanced to phase 3 clinical trial in AD patients (NCT02080364). The PICALM-dependent transcytotic machinery at the BBB can also be targeted therapeutically by gene therapy to enhance A $\beta$  clearance across the BBB (682). Additionally, allopregnanolone promotes A $\beta$  and cholesterol clearance in preclinical studies in animal models (80) and is currently in phase 1 clinical trials for MCI and early AD (NCT02221622).

$\alpha$ -Syn, a key protein found in Lewy bodies of both Lewy body dementia and PD, is also transported in and out of the brain and is cleared across the BBB (682) by LRP1-mediated transcytosis (563); thus enhancing its clearance through the BBB could be beneficial for these neurological conditions.

#### 4. Cell therapy

Preclinical transplantation studies in animal models have demonstrated the potential of cell therapy for treating neurodegenerative diseases and acute CNS injuries, with some showing benefits for cerebral vasculature and BBB. For ex-

ample, transplantation of allogeneic mesenchymal stem cells and neural stem cells, in addition to offering neuroprotection, can stabilize BBB and promote BBB integrity as shown in stroke models (260, 463, 578). Pericytes derived from adipose tissues extended the survival of ALS mice carrying *SOD1*<sup>G93A</sup> mutation after transplantation in the spinal cord, and protected iPSC-derived motor neurons from an ALS patient (116). Whether treatments with iPSC-derived pericytes can be beneficial to other neurological or neurodegenerative diseases associated with pericyte dysfunction and/or degeneration and BBB breakdown, such as AD, HIV-1 infection, and others (570), remains to be explored. In addition, transplantation of mesenchymal cells or endothelial progenitors that are capable of differentiating *in vivo* into vascular cells such as pericytes has shown promising results as vascular regeneration therapy (353) and repair BBB damage treatment after stroke (198). Genetic engineering and editing offers great opportunities to improve the safety of cell therapy, as shown by removing the immune barrier by reprogramming the polymorphic MHC locus to increase the transplant acceptance (310), which should also be considered for BBB cell therapy with endothelial cells and pericytes.

#### 5. Other BBB-targeted clinical trials

Numerous clinical trials for BBB protection have been used in various acute and chronic neurological conditions, as discussed above. Briefly, relating to BBB integrity, trials aim to visualize BBB permeability using DCE-MRI in ischemic stroke (NCT00715533; NCT02077582), MS (NCT0-

1836055), and epileptic regions (NCT02531880; NCT0-0419874). Additional trials relating to BBB function aim to prevent anti-epileptic drug resistance with ABCB1 (P-gp) inhibitors in epilepsy (NCT02144792; NCT01126307; NCT01663545; NCT00605254), and block leukocyte infiltration across the BBB with anti-VLA-4 antibodies (NCT00859482) or anti-CD52 antibodies (NCT03193086) in relapsing remitting MS.

## B. Traversing BBB for CNS Drug Delivery

Traversing BBB remains a major challenge for neurotherapeutics. Strategies have been developed to breach the barrier, including 1) direct opening of the BBB with intravenous bolus injection of hypertonic sugar solution (491) or focused ultrasound (FUS) scanning with microbubbles (84, 106); 2) encapsulation in nanoparticles made from biocompatible and/or biodegradable polymers and liposomes that can penetrate the BBB (414, 670); 3) utilizing CMT systems for better penetrability of drug analogs (459); 4) engineering therapeutic peptides, oligonucleotides (e.g., antisense oligos and antagomir), and monoclonal antibodies that target RMT systems at the BBB (78, 459, 460), or specific transport system such as system L amino acid transporter in case of anti-CD98hc/BACE1 antibodies (705); and 5) viral vector-mediated gene delivery to CNS (101, 146).

### 1. Opening the BBB

Temporal opening of the BBB can be achieved with transient uprise of osmotic pressure (491) or physically with FUS (84), which is supposed to grant a short therapeutic window for CNS drug delivery. However, the impact of BBB opening on the diseased brain has yet to be carefully examined, especially the long-term effects. Particularly, clinical safety issues associated with osmotic challenge limit its current use to rare and specific situations such as certain brain tumors. In addition, due to the preclinical success of FUS with microbubble for noninvasive, transient, and targeted delivery of therapeutics through the BBB (84) and use in brain tumors (NCT02343991; NCT01473485), this technology is rapidly moving towards clinical testing for early AD (NCT02986932) and PD (NCT02347254; NCT02252380) (477). It is noteworthy, however, that FUS with microbubble may induce brain inflammatory responses that are comparable with ischemic injury or mild TBI (329). The exact mechanism of action in neurodegenerative disorders and long-term side effects remain unclear at present.

### 2. Colloidal carrier-based drug delivery systems

Colloidal carriers such as nanoparticles, polymers, liposomes, and micelles have become perhaps the most versatile approach for delivering compounds and macromolecules into inaccessible regions behind tissue barriers, particularly

the brain (372, 519). Nanoparticles can derive from synthetic polymers or natural biomaterials such as albumin and polysaccharides, with targeted drug entrapped within or covalently attached. To cross the tissue barriers, nanoparticles are either negatively charged on the surface (519), or capable of binding to receptors on the cell surface (670), or densely packed around a metal core (291). Polybutyl cyanoacrylate-, polylactide-co-glycolide-, or chitosan-based nanoparticles have been tested for delivery in mouse models of AD. In addition, exosomes have also been tested in pre-clinical models for delivering proteins and small RNA across the BBB (16, 235, 323). Due to promising outcomes from animal studies, colloidal carriers are now moving into clinical trials in humans (71, 330), e.g., spherical nanoparticle conjugated RNAi (NU-0129) for glioblastoma (NCT03020017), and polymeric nanoparticle (BIND-014) for brain metastasis (NCT01792479).

### 3. Utilizing CMT systems

L-DOPA is an example of structural drug analogs that cross the BBB utilizing the large LAT1 neutral amino-acid transporter in contrast to dopamine that does not cross the BBB (459). L-DOPA is used to increase dopamine concentrations in the brain in PD and dopamine-responsive dystonia patients, and after crossing the BBB is converted in the brain into dopamine by aromatic L-amino acid decarboxylase.

### 4. Engineering therapeutics for RMT systems

RMT is part of the highly specialized transport system at the BBB, allowing the exchange of certain macromolecules between circulating blood and brain ISF (682). A properly functioning RMT is highly selective due to specific interaction between ligands and their preferred receptors, as well as the spatial distribution of the receptors (luminal vs. abluminal), which ensures exclusive entry of essential peptides and proteins into the brain and effective clearance of toxic waste products from brain to blood. Targeting the RMT systems offers a tremendous opportunity for CNS drug delivery, especially at the receptor level by selecting or even engineering therapeutic ligands. In fact, approaches such as molecular Trojan horses and bispecific or brain shuttle monoclonal antibodies targeting the BBB RMT systems have shown great promises for BBB penetrance in preclinical animal models (459), including anti-TfR-BACE1 antibody in Alzheimer's Tg2576 mice (34) and nonhuman primates (672) or anti-TfR-A $\beta$  antibody in PS2APP mouse model (435).

Molecular Trojan horses are therapeutic peptides or proteins fused to antibodies that target BBB RMT receptors for delivery across the BBB (459). Currently, molecular Trojan horse-based drugs are advancing in clinical trials for Hunter syndrome, L-iduronidase fused with monoclonal antibody against transferrin receptor (AGT-181), which is in phase 2

trial for mycopolysaccharidosis I disease (70), and iduro-nate 2 sulfatase fused with monoclonal antibody against insulin receptor (AGT-182) that is in phase 1 trial for mycopolysaccharidosis II disease (69).

### 5. Viral vector-mediated gene delivery to CNS

Adeno-associated virus serotype 9 (AAV9) is perhaps the best known vector for gene therapy that potentially passes the BBB and infects brain cells, based on studies in neonatal and adult mice (388). However, the tropism repertoire of wild-type AAV9 is limited and favors peripheral organs rather than CNS. A few recent studies have attempted to engineer viral capsid proteins to achieve brain enrichment, resulting in novel variants that can deliver genes to different cell types in the brain and spinal cord. For example, AAV-PHP.B (146) and AAV-PHP.eB (101) offer a more than 40-fold increase in delivery efficiency to the whole CNS. AAV-PHP.A exhibits selective astrocyte tropism (146), while AV-PHP.S is more specific for dorsal root ganglion neurons as well as and cardiac and enteric neurons (101). These tools offer great opportunities for application in neurodegenerative diseases.

## VII. LESSONS LEARNED AND FUTURE DIRECTIONS

Recent research has greatly advanced our understanding of BBB functions at the molecular and cellular level and has raised awareness about the role of BBB dysfunction in the pathogenesis of different CNS diseases. At the same time, these advances have uncovered gaps in our knowledge of vascular health and have provided us with the roadmap to ask new questions that should be addressed by the future studies.

The most critical evidence for the importance of vascular health for brain functions comes from human genetic studies and the corresponding studies in transgenic animal models showing that several genes mutated in monogenic neurological diseases have their principal site of expression in vascular cells (682). The many examples discussed in this review provide a direct link between BBB dysfunction and neurodegeneration. But, more than that, these genetic examples raise a question: What is the role of altered expression of BBB transporters, receptors, tight junction proteins, active efflux systems, and ion channels in common, sporadic neurodegenerative diseases such as AD and others? To name one of the many examples discussed in this review, late-onset, sporadic AD is characterized with an early loss of BBB transporters including GLUT1 transporter for glucose (268, 424, 425, 345, 517), which we know leads to severe neurological phenotype in the GLUT1-deficiency syndrome (630, 649). This begs a question whether changes in the BBB molecular makeup like one we see with the GLUT1 transporter in AD are innocent bystanders in the

disease process or may have a major influence on the course of the disease, as in monogenic disorders, by synergistically promoting AD pathophysiology?

We also learned that several genetic mutations underlying inheritance or increasing risk for chronic neurodegenerative diseases are associated with BBB breakdown and cerebro-vascular pathology in humans and animal models. However, the exact role of BBB dysfunction in the disease process in humans with genetic risk for neurodegenerative disorders remains still elusive. For example, *APOE4* carriers at risk for sporadic AD compared with non-carriers develop BBB breakdown (229, 230, 267, 516, 691, 702) and early cerebrovascular dysfunction (227, 457, 486, 494, 531, 568, 584), and in animal models, *APOE4* compared with *APOE3* and *APOE2* leads to impaired clearance of  $\text{A}\beta$  across the BBB (58, 98, 135) and an early BBB breakdown and transporters' dysregulation (9, 60, 85, 437). These vascular changes precede neuronal dysfunction and neurodegeneration, but can be reversed by sealing the BBB (60). Similarly, sealing BBB reversed the course of motor neuron disorder in *SOD1*<sup>G93A</sup> mutant ALS mice (651). Would similar BBB-directed therapeutic approaches work in humans?

Additionally, laboratory studies tell us that BBB disruption develops early in *APP* transgenic models carrying human ADAD mutations (467, 513, 606) before  $\text{A}\beta$  accumulation, CAA, and behavioral deficits (151, 336, 606, 638), introducing a question: What are the molecular and cellular changes in BBB endothelial and mural cells that lead to such dysfunction? Are these changes caused by oligomeric  $\text{A}\beta$  species before amyloid deposition or direct APP vasculotoxicity, and/or could these changes be due to associated pathophysiology leading to early brain hypoperfusion and hypoxic changes (271)? Furthermore, *PSEN1* mutant and knockout transgenic models that are not crossed with *APP* models exhibit significant vascular pathology such as BBB breakdown, hemorrhages, and loss of pericytes (191, 641), suggesting that vascular dysfunction caused by *PSEN1* mutations can develop independent of amyloid pathology. Although, impact of vascular pathology to overall CNS pathology in human *PSEN1* ADAD mutation carriers is not clear at present, the time courses and the exact contributions to cognitive impairment of BBB and cerebrovascular pathology (25, 53, 61, 143, 183, 274, 280, 289, 354, 389, 440, 544, 573, 639, 668) versus accelerated  $\text{A}\beta$  production remains to be determined by future studies.

Findings like these examined in this review pose a set of new questions and tasks, which require accurate and in-depth understanding of molecular definitions of the principal blood vascular and vessel-associated cell types, and the differences between endothelial and mural cells at the level of brain capillaries and along the arteriovenous axis. While we learned about organotypic differences between brain endothelial cells and peripheral endothelial cells, several ques-

tions persist about vascular mural cells, such as 1) Are pericytes heterogeneous or homogeneous cell group? 2) Does organotypicity extend to pericytes? 3) How different at the molecular level are pericytes from SMCs? 4) Does abundance and variety of molecular transporters in pericytes, as shown in rodents, imply that pericytes contribute to BBB transport functions? Some of the answers can be obtained by using large-scale analysis of vascular single cell transcriptomes and proteomes in BBB cell-specific transgenic models, and by performing cryo-EM structural analysis of the BBB. We can also learn about the role of BBB transporters, receptors, active efflux mechanisms, and ion channels by selectively knocking down these molecules from endothelial cells and pericytes, which for the majority of key BBB molecules has yet to be done.

While our understanding of the BBB at the molecular and cellular level will continue to grow based on findings in rodent models, the question remains to what extent these findings are translatable to human BBB. To address this issue, perhaps we should attempt to develop molecular and cellular atlas for human BBB, and molecularly define vascular cell types in cerebral vasculature in humans using comparable single cell RNA-seq and proteomic analysis, as in animal models. Interestingly, comparison of 114 endothelial proteins between mice and humans revealed some striking differences in expression; for example, the active efflux ABCG2 transporter exhibited greater expression in humans, whereas LAT1 and MCT1 CMTs, TfR RMT, and ABCB1 and MRP4 active efflux transporters exhibited greater expression in mice (602). Another study compared protein expression between species (i.e., mice, rats, marmosets, cynomolgus monkeys, and humans) reporting that humans are most similar to marmosets with less than twofold differences in all measured proteins, whereas rats and humans exhibited the most differences (262). Elucidating species-specific similarities and differences in endothelial and pericyte expression profiles remains to be fully determined at the transcriptome and proteome levels.

In terms of studying BBB function in humans, recent neuroimaging studies made important advances to allow us to measure regional BBB integrity and quantify subtle changes in BBB permeability in CNS regions as small as hippocampal CA1, CA3, and dentate gyrus subfields, which has not been possible before (421). We expect that imaging methods will continue to improve our ability to detect BBB changes in humans, particularly with the use 7T human research magnet, and determine how they relate to blood flow changes, changes in structural and functional brain connectivity, and cognitive and motor deficits in different neurodegenerative disorders, as well as cell-specific biomarkers of the vascular injury and NVU in biofluids. This should remain an exciting area for future research, particularly in asymptomatic individuals at genetic risk for the disease such as, to name a few, *APOE4* carriers for AD,

*PSEN1* mutation carriers for ADAD, and *HTT* mutation carriers for HD or CADASIL patients.

In general, at present we have limited imaging probes to study function of brain endothelial transporters in the living human brain, and no probes at all for pericyte transporters. Besides FDG-PET and verapamil-PET that have been used to test functions of BBB GLUT1 transporter and activity of ABCB1 (P-gp) efflux transporter in AD and PD (420, 569), respectively, we should also develop new probes such as those that have been used in animal models, like anti-VCAM-1 iron oxide microparticles to detect endothelial activation and/or inflammation by MRI (417), and probes to image health and function of mural vascular cells that are often affected early in the disease process.

The systems biology approach used to study establishment of the BBB in the developing CNS has provided invaluable insights into key molecular and cellular events governing BBB formation, maturation, and maintenance. These studies not only revealed key molecular mechanisms establishing the BBB, but also tell us how deficiency in certain pathways can lead to BBB disruption and secondary CNS injury and neurodegeneration, teaching us about potential BBB-directed therapeutic approaches in the adult and aging brain affected by disease. Although it remains challenging to understand how the systems biology work will translate to human brain and formation of the BBB in humans, use of stem cell technology, particularly iPSC-derived models of the BBB carrying disease associated risk genes (683), and combined three-dimensional models of the BBB and iPSC-derived neurons, will help us to overcome this hurdle.

Last but not the least, although nearly all of the neurodegenerative diseases are still incurable, technological advances have brought new hopes by facilitating the development of therapeutics that are more likely to circumvent, protect, and traverse the BBB. These include the colloidal carrier-based drug delivery systems, engineering new therapeutics for RMTs, and/or viral vector-mediated gene delivery to CNS, that hold promise for CNS delivery of neuropharmaceuticals currently blocked by the BBB.

Finally, based on the current state of our knowledge, it is probably time to think about BBB not only as an impermeable cellular membrane which protects brain from peripheral influences and should be breached for therapeutic CNS drug delivery, but also as an enormous source of understudied molecular and cellular targets in the disease state, which if explored could change the way we think about brain diseases and could lead to development of important new BBB-based approaches to treat them.

## ACKNOWLEDGMENTS

M. D. Sweeney and Z. Zhao contributed equally to this work and are co-first authors.

We apologize to those authors whose original work we were not able to cite.

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## GRANTS

The work of B. V. Zlokovic is supported by the National Institutes of Health Grants R01AG023084, R01NS-090904, R01NS034467, R01AG039452, 1R01NS100459, 5P50AG005142, and 5P01AG052350, in addition to the Cure Alzheimer's Fund, Alzheimer's Association, and the Foundation Leducq Transatlantic Network of Excellence for the Study of Perivascular Spaces in Small Vessel Disease reference no. 16 CVD 05.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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