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Neurovascular Dysfunction and Neurodegeneration in Dementia and Alzheimer's disease

Amy R. Nelson, Melanie D. Sweeney, Abhay P. Sagare, Berislav V. Zlokovic*

Department of Physiology and Biophysics and the Zilkha Neurogenetic Institute, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90089

*Address correspondence:

Berislav V. Zlokovic, M.D., Ph.D.
Zilkha Neurogenetic Institute
1501 San Pablo Street
Los Angeles, CA 90089
Phone: 323.442.2722 / Fax: 323.666.2184
Email: zlokovic@usc.edu

Abstract

Vascular insults can initiate a cascade of molecular events leading to neurodegeneration, cognitive impairment and dementia. Here, we review the cellular and molecular mechanisms in cerebral blood vessels and the pathophysiological events leading to cerebral blood flow dysregulation and disruption of the neurovascular unit and the blood-brain barrier, which all may contribute to the onset and progression of dementia and Alzheimer's disease (AD). Particularly, we examine the link between neurovascular dysfunction and neurodegeneration including the effects of AD genetic risk factors on cerebrovascular functions and clearance of Alzheimer's amyloid-β peptide toxin, and the impact of vascular risk factors, environment and lifestyle on cerebral blood vessels, which in turn may affect synaptic, neuronal and cognitive functions. Finally, we examine potential experimental treatments for dementia and AD based on the neurovascular model, and discuss some critical questions to be addressed by future studies.

Keywords

1. Introduction

Blood vessels in the brain deliver essential nutrients to and remove metabolic waste products from the central nervous system (CNS) [1]. Although the human brain makes up only 2% of total body mass, it consumes 20% of the body's oxygen and glucose supply [2]. Proper regulation of cerebral blood flow (CBF) is critical for brain health and survival. Loss of CBF halts brain functions in seconds and causes permanent brain damage within minutes [3]. CBF is precisely regulated by the neurovascular unit (NVU) to assure that brain energy demands are met [1,4]. The NVU is comprised of several cell types including vascular cells (endothelial cells, pericytes and vascular smooth muscle cells (VSMCs)), glia (astrocytes, microglia and oligodendrocytes) and neurons [1]. A schematic representation of the NVU at the level of brain capillaries is shown in **Fig. 1**.

The blood-brain barrier (BBB) is part of the NVU that prevents uncontrolled entry of blood-derived products and pathogens into the brain, and mediates the exchange of molecules into and out of the brain parenchyma via a specialized substrate-specific transport system expressed in brain endothelium [1,5]. The BBB is quite unique when compared to the highly permeable systemic capillaries that permit the transport of larger molecules across the vessels and into peripheral tissues [6]. Brain capillary endothelial cells are connected by tight and adherens junction proteins (e.g., claudin, occludin, junction adhesion molecules, and cytoplasmic accessory proteins including zonula occludens (ZO)-1, 2, 3, cinguilin and others), forming a continuous endothelial monolayer. This anatomical barrier permits the passage of only small circulating lipid-soluble molecules (< 400 kDa) with less than nine hydrogen bonds into the brain, and allows the free exchange of oxygen and carbon dioxide [1]. The BBB isolates brain interstitial fluid (ISF) and cerebrospinal fluid (CSF) compartments from the plasma compartment, and thus prevents the entry of many blood-derived molecules into brain parenchyma [4]. The movement of large molecules across the BBB including proteins and peptides is only possible via highly specialized transport systems expressed in brain endothelium [7–9]. In the human brain there is an estimated 400 miles total length of capillaries with about 20 m^2 of microvascular surface area available for molecular transport [10]. This makes the BBB the largest exchange transport surface area in the brain and the major clearance pathway for potentially neurotoxic molecules that are produced and/or accumulate in the brain, as for example, Alzheimer's toxin amyloid-β peptide (Aβ) [11].

It is becoming increasingly apparent that cerebrovascular dysfunction contributes to dementia and AD [1,12–16], as well as other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) [17], Parkinson's disease (PD) [18] and Huntington's disease (HD) [19]. NVU disruption and BBB breakdown can

lead to entry of circulating neurotoxic molecules into the brain, faulty clearance of neurotoxic molecules from brain to blood, improper energy metabolite and nutrient delivery, and abnormal expression of growth factors, matrix molecules and vascular receptors, which all may eventually lead to synaptic and neuronal dysfunction [4]. Here, we review the cellular and molecular mechanisms in cerebral blood vessels leading to neurodegeneration including the effects of genetic risk factors for AD on cerebrovascular functions and Aβ clearance, and the impact of vascular risk factors, environment and lifestyle on cerebral blood vessels. Finally, we discuss potential experimental treatments for dementia and AD based on the neurovascular model, and review some critical questions in the field to be addressed by future studies.

2. Alzheimer's disease

AD is the most common form of dementia that currently affects 5.3 million Americans [20]. The majority of cases are sporadic late-onset, and < 5% of cases are early-onset autosomal-dominant AD (ADAD) [21]. Pathological hallmarks of AD include elevated brain parenchymal and vascular Aβ, hyperphosphorylated neurofibrillary tau tangles, gliosis and neuronal loss [1]. Mounting evidence demonstrates that vascular dysfunction contributes to dementia and AD [1,14,15]. Vascular risk factors (e.g., hypertension, diabetes) and some major genetic risk factors for AD (e.g., apolipoprotein E ε4 (*APOE4*)) lead to cerebrovascular damage [1,4,20], and cerebrovascular disorders associated with AD. Elucidating the mechanisms underlying vascular pathophysiology to aid in identifying novel therapeutic targets for AD has been declared a national research priority [14,15].

2.1. The two-hit vascular hypothesis

The two-hit vascular hypothesis of AD states that cerebrovascular damage (*hit 1*) is an initial insult that is self-sufficient to initiate neuronal injury and neurodegeneration, but can also promote accumulation of Alzheimer's Aβ toxin in the brain (*hit 2*) (**Fig. 2**) [22–25,1,16]. Cerebrovascular disruption including BBB breakdown and resting CBF reductions can lead to accumulation of neurotoxic circulating molecules (e.g., thrombin, plasminogen, fibrinogen) and hypoperfusion in the brain, respectively, that can directly initiate neuronal injury [1,23]. Vascular dysfunction can also influence the amyloidogenic pathway to diminish Aβ clearance and increase Aβ production leading to elevated Aβ levels in the brain [1,11]. Thus, the Aβ-independent and Aβ-dependent pathways interact and can independently and/or synergistically lead to the onset and progression of AD dementia. Importantly, both pathways are impacted by vascular, genetic, environment and lifestyle risk factors.

2.2. AD genetic risk factors with vascular links

Age is the number one risk factor for AD, but genetic risk factors also have a significant effect on the AD disease process. Vascular implications are now known for several of AD genetic risk factors and are emerging for additional risk genes, as discussed below.

2.2.1. APOE4

APOE is a 34 kDa glycoprotein that is primarily produced by astrocytes in the brain and by the liver in the periphery, and is important for lipid metabolism [26]. In humans, there are three alleles of *APOE*: *APOE2*, *APOE3* and *APOE4*. *APOE4* is the strongest and most highly replicated risk factor for late-onset sporadic AD [21,27]. An individual's risk of AD is increased 3.7 times in carriers of a single *APOE4* allele and 12 times in carriers of two *APOE4* alleles, compared to *APOE3* carriers [28].

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APOE4 increases BBB damage, cerebral amyloid angiopathy (CAA) and fibrinogen deposits in human brain [29–33]. Furthermore, young *APOE4* carriers with no memory impairment have reduced cerebrovascular reactivity in response to a memory task and carbon dioxide inhalation [34]. *APOE4* carriers have accelerated pericyte degeneration and BBB breakdown, compared to *APOE3* carriers, that is likely related to the activation of cyclophilin A (CypA)-matrix metalloproteinase-9 (MMP-9) pathway in blood vessels, particularly in pericytes [28,29]. In agreement with these findings, *APOE4* transgenic mice exhibit activation of the CypA-NFκB-MMP-9 pathway in pericytes that was demonstrated to result in degradation of BBB tight junction and basement membrane proteins causing BBB disruption [35]. However, *APOE2* and *APOE3* expressing transgenic mice have an intact BBB compared to *APOE4* mice [35,36], and are able to suppress the CypA-NFκB-MMP-9 BBB-degrading pathway in pericytes [35].

Furthermore, APOE isoforms differentially affect binding and clearance of Aβ, where APOE2-Aβ > APOE3-Aβ complexes bind to a major Aβ clearance receptor the low-density lipoprotein receptor-related protein 1 (LRP1) at the abluminal side of the BBB and are rapidly cleared across the BBB into circulation, whereas APOE4-Aβ complexes interact poorly with LRP1 and are removed from the brain by the much slower and less efficient very low density lipoprotein receptor (VLDLR) clearance mechanism [37,38]. Thus, impaired Aβ clearance by APOE4 relative to APOE3 or APOE2 may ultimately accelerate Aβ accumulation in the brain.

2.2.2. PICALM

PICALM encodes the phosphatidylinositol-binding clathrin assembly protein that is involved in endocytosis and internalization of cell receptors and intracellular trafficking of endocytic proteins [39–41]. PICALM is highly expressed in the brain capillary endothelium lining the BBB [41]. Approximately 20 single nucleotide polymorphisms (SNPs) in the noncoding region of *PICALM* have been associated with AD in several genome wide association studies (GWAS) [21,42,43]. Recently, the molecular mechanism by which PICALM normally influences Aβ clearance across the BBB has been elucidated in an *in vitro* human model of the BBB [41]. Briefly, it has been shown that Aβ binding to LRP1 at the abluminal side of the BBB recruits PICALM and initiates rapid PICALM/clathrin-dependent endocytosis of Aβ-LRP1 complexes. PICALM then continues to guide trafficking of Aβ-containing endocytic vesicles across brain endothelium fusing sequentially with Rab5 and Rab11 and ultimately leading to intracellular transport and exocytosis of Aβ, respectively, at the luminal side of the BBB thus completing Aβ transcellular transport and clearance across the BBB [41]. Importantly, PICALM levels are reduced in AD brain endothelium, which correlates with elevated Aβ levels, Braak stage and the level of cognitive decline as shown by a recent neuropathological study [41]. Furthermore, induced pluripotent stem cell (iPSC)-derived human endothelial cells carrying the protective allele of the rs3851179 *PICALM* variant have higher *PICALM* expression and increased Aβ clearance [41]. Similarly, mice deficient in brain endothelial *Picalm* develop accelerated Aβ accumulation in the brain and behavioral deficits, which all can be reversed by endothelial-specific expression of *Picalm* [41]. Altogether, these data support the view that PICALM controls Aβ transport and clearance across the BBB and therefore could have a strong vascular link to AD.

2.2.3. CLU

Clusterin (CLU), also known as apolipoprotein J (APOJ), is a disulfide linked heterodimeric glycoprotein composed of an α- and β-subunit that aids in Aβ clearance [37]. Recent GWAS studies have identified a SNP within *CLU* on chromosome 8p21.1, rs11136000, that is significantly associated with sporadic AD [21,42,44]. The C allele is considered an AD risk factor; whereas the minor T allele has a protective effect and reduces the risk of AD by 16% [42,44]. Individuals with the *CLU* rs11136000 risk C allele exhibit reduced white matter integrity and hyperactivation of the prefrontal and limbic areas during working memory tasks, as determined

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recently via diffusion tensor imaging magnetic resonance imaging (DTI-MRI) and functional MRI, respectively [45]. CLU binds to several different proteins including Aβ, and has been shown to prevent aggregation and promote clearance of Aβ peptides across the BBB [37]. More specifically, Aβ42 bound to CLU can be cleared rapidly across the BBB via LRP2 as shown in a murine model [37,46].

2.2.4. PSEN1

Presenilin 1 (*PSEN1*) and *PSEN2* genes encode presenilins 1 and 2, respectively, that act as aspartyl proteases to facilitate γ-secretase cleavage of Aβ precursor protein (APP) to produce Aβ [21]. Many *PSEN* mutations have been identified in ADAD including 185 mutations reported in *PSEN1* and 13 mutations in *PSEN2* [21]. Most of these mutations increase the ratio of Aβ42:Aβ40 in the brain [21]. However, *PSEN1* mutations also lead to major cerebrovascular pathology in humans including disruption of small cerebral blood vessels, degeneration of pericytes and mural cells, BBB breakdown, and Aβ deposits in small cerebral arteries, arterioles and capillaries [47,48]. Similarly, prominent cerebrovascular pathology with BBB breakdown, characterized by microhemorrhages, thinned and irregular microvessels, string vessels, a thickened basement membrane and a reduction in hippocampal microvascular density, have been shown in *PSEN1* transgenic models [49,50].

2.2.5. APP

There are 24 reported mutations in *APP* in ADAD subjects and, like *PSEN* mutations, mostly result in an increased Aβ42:Aβ40 ratio in the brain [21]. Patients with hereditary CAA of the Dutch, Iowa, Arctic, Flemish, Italian or Piedmont L34V vasculotropic mutations in *APP* have degeneration of VSMCs leading to hemorrhagic strokes and dementia [1,4,16]. Furthermore, duplication of the gene encoding APP causes ADAD with CAA and intracerebral bleeding [1].

2.2.6. MEOX2

Mesenchyme homeobox gene 2 (MEOX2), a transcription factor expressed solely in the vasculature in brain, regulates vascular cell differentiation and remodeling [51]. A GWAS study using high-resolution array comparative genomic hybridization found a copy number variant in *MEOX2* in ADAD subjects [52]. Furthermore, brain endothelial cells from AD subjects express very low levels of *MEOX2* which leads to vessel regression, LRP1 proteosomal degradation and reduced Aβ clearance across the BBB, all of which were reversed by restoring *MEOX2* endothelial expression [53]. Transgenic mice with a single allele of *Meox2* develop cerebral endothelial hypoplasia with reduced brain perfusion and impaired Aβ efflux caused by reduced LRP1 expression [53].

3. Cerebrovascular dysfunction in AD

Vascular damage and dysfunction are frequently associated with neurodegeneration and contribute to AD [1,2,12,15,54,55]. Some indicators of BBB breakdown include accumulation of blood-derived proteins and cells in the brain and CSF, loss of pericytes and endothelial tight junction molecules, microbleeds, and alterations in BBB Aβ transporter expression (e.g., receptor for advanced glycation endproducts (RAGE) and LRP1). Some key pathophysiological, cellular and molecular mechanisms leading to cerebrovascular dysfunction in AD are discussed below.

3.1. Diminished CBF and neurovascular uncoupling

The brain microvasculature regulates its local capillary blood flow by maintaining a delicate balance between the anti-thrombotic and pro-thrombotic pathways within the capillary network, which normally prevents intra-vascular coagulation and allows blood to flow [56]. Regional CBF responses are normally controlled by local neuronal activity within the NVU modules, a process known as neurovascular coupling [2]. A number of studies have shown reductions in resting CBF in aged cognitively normal individuals that are at risk of developing AD [1,2,57] and in AD patients [1,2,58], as well as CBF dysregulation [2,54]. The CBF reductions may occur prior to cognitive impairment in humans [57], and were also found in *APP* transgenic models of AD [59] and pericyte deficient murine models [60].

VSMCs derived from small cerebral penetrating arteries critically regulate CBF to the brain [2]. Recent studies have shown a hypercontractile phenotype of VSMCs derived from small arteries in AD and AD models characterized with accumulation of several contractile proteins directed by elevated activity of the serum response factor (SRF)/myocardin tandem of transcription factors caused by hypoxic changes [61]. Arterial hypercontractility and impaired ability to relax can in turn diminish arterial supply of blood to the brain, which reduces CBF and creates a chronic brain hypoperfusion state that may contribute to dementia by several pathways as discussed below.

In addition to the hypercontractile phenotype, arterial VSMCs in AD also exhibit a greatly reduced ability to clear Aβ, which leads to accumulation of Aβ in the vessel wall causing CAA [62] that in turn further aggravates CBF reductions and may promote cerebral microbleeds. Recent experimental studies have suggested that in addition to a major role of VSMCs in controlling CBF [2,63], CBF can also be regulated at the capillary level by pericytes, particularly during experimental cerebral ischemia that leads to constriction of pericytes obliterating capillary blood flow during the reperfusion phase [64]. This eventually can lead to pericyte cell death and degeneration, resembling pericyte degeneration seen in AD and other neurodegenerative disorders [17–19]. However, whether pericytes play a similar role in human disease as shown in animal models remains to be addressed by future studies.

Mild chronic hypoperfusion, known as oligemia, can lead to a deleterious chain of events in neurons by impairing neuronal protein synthesis that is required for synaptic plasticity, a process critically involved in learning and memory [65]. Additionally, CBF reductions diminish oxygen delivery to brain that favors anaerobic brain metabolism, which in turn diminishes ATP synthesis required for the maintenance of the sodium pump or Na$^+$,K$^+$-ATPase activity that regulates ion distribution in neurons necessary for proper firing of action potentials and normal neuronal excitability [2]. Hypoperfusion also leads to imbalances in pH, electrolytes and water gradients which lead to edema, white matter lesions and ultimately neuronal death [1].

3.2. BBB breakdown

Regional BBB permeability in the living human brain during normal aging and in mild dementia patients was recently assessed quantitatively using an advanced dynamic contrast-enhanced (DCE)-MRI method [12]. This study has shown that BBB breakdown in the hippocampus increases in an age-dependent manner, worsens in individuals with mild dementia [12], and corresponds with increases in CSF levels of pericyte injury marker, soluble platelet-derived growth factor receptor-β (sPDGFRβ) [12,66]. Reflective of BBB breakdown, the CSF to plasma albumin ratio is also increased in AD patients particularly in those with vascular risk factors [67], as well as in individuals with mild dementia or mild cognitive impairment (MCI) [12] and in cognitively normal *APOE4* carriers at genetic risk for AD [29].

In post-mortem studies, an accumulation of blood-derived proteins including fibrinogen, thrombin, plasminogen, immunoglobulin G and albumin were found in the hippocampus and cortex of AD subjects [30–32,68,69], which was associated with pericyte degeneration [30,69–73]. MRI studies reveal microbleeds and

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iron accumulation in the brain of patients with preclinical AD [74] and AD [33,75,76], especially in the hippocampus [77]. In a cohort of 174 patients, lobar microbleeds were identified in 40% of AD subjects and 24.3% of MCI patients using susceptibility-weighted imaging (SWI) MRI [74]. The incidence of lobar microbleeds was positively associated with age, *APOE4* carrier status, and Aβ burden, as measured by (11)C-labeled Pittsburgh Compound-B positron emission tomography (PIB-PET) [74]. Additionally, multiple lobar microbleeds were associated with lacunar infarctions and severity of white matter hyperintensities [74]. Also, in a recent study that included 148 AD patients, 44.6% of the patients exhibited brain microbleeds [75]. Furthermore, the patients with a high number of microbleeds had several associated vascular risk factors including diabetes and hypertension [75]. Microbleeds measured by SWI-MRI and/or T2*-weighted MRI were also found in 22% of 1,504 studied dementia patients [76]. The microbleeds positively correlate with age, sex (microbleeds occur more frequently in males), and hypertension, and negatively with Mini-Mental State Examination (MMSE) cognitive score [76].

Pericyte injury and/or loss has been identified by post-mortem analysis in many neurodegenerative diseases including AD [30,69,71,72] as well as by CSF analysis of living MCI patients [12]. Degenerating pericytes accumulate intracellular inclusions, pinocytic vesicles, and large lipid granules, and show mitochondrial abnormalities [71,72]. These microstructural changes in pericytes correlate with capillary reductions, dilation of vessels and the appearance of tortuous vessels [71]. Simplified schematics of normal BBB and BBB breakdown with neurovascular pathways leading to neurodegenerative changes are illustrated in **Fig. 3**.

3.3. Reduced glucose utilization

Glucose transporter 1 (GLUT1) on cerebral microvessels is decreased in post-mortem AD brain tissue [78]. GLUT1, encoded by *SLC2A1*, is the major transporter of glucose across the BBB from the blood to the brain [1,4,79]. Cognitively normal individuals with genetic risk for AD or positive AD family history [80] and mild or no cognitive impairment that later develop AD [81] all have reduced glucose utilization in the hippocampus, parietotemporal cortex and/or posterior cingulate cortex measured by 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-PET, which occurs prior to brain atrophy and neuronal dysfunction [80]. Brain glucose uptake correlates with the level of GLUT1 on cerebral microvessels [82]. In addition to glucose transport, GLUT1 is also critical for the maintenance of proper brain capillary networks, CBF, and BBB integrity, as demonstrated in humans with *SLC2A1* mutations [83] and *Slc2a1* transgenic mice [79] which contributes to neurodegeneration and behavioral deficits in murine model of AD and GLUT1 deficiency [79]. See **Fig. 3**.

3.4. Aβ clearance

In sporadic AD, faulty Aβ clearance, rather than increased Aβ production, is thought to promote elevated brain Aβ levels [84]. Experimental studies in multiple animal models have shown that under physiological conditions, 70-85% of Aβ is cleared from the brain primarily by transvascular clearance across the BBB and a small portion is removed by ISF bulk flow [11,85,86]. The primary receptor mediating BBB transcytosis of Aβ is the LRP1, that is expressed mainly at the abluminal side of the BBB [1,4,11,41,86,87]. Aβ bound to endothelial LRP1 is rapidly internalized by PICALM at the endothelium, which mediates PICALM/clathrin-dependent endocytosis of Aβ-LRP1 complexes by endothelium and guides trafficking of Aβ-containing endocytic vesicles towards exocytosis ultimately leading to Aβ transcytosis [41], as discussed above. Additionally, a soluble form of LRP1 (sLRP1) is generated by proteolytic cleavage of LRP1 by β-secretase and circulates in the plasma binding and sequestering free Aβ40 and Aβ42 and transporting them via blood to the liver and kidney for removal from systemic circulation [11,86]. See **Fig. 3A** inset.

3.4.1. LRP1

In normal aging and AD, there is a significant reduction in LRP1 expression in brain endothelial cells [88] and VSMCs [62]. A decrease of LRP1 on microvessels negatively correlates with an increase of Aβ in brain [88]. See **Fig. 3B** inset. High levels of SRF and myocardin in VSMCs [61,62] lead to elevated expression of sterol response element binding protein 2 (SREBP2), a major LRP1 transcriptional suppressor, that leads to LRP1 depletion and thereby reduced Aβ clearance across the BBB [24]. Oxidation of surface LRP1 and sLRP1 prevents them from binding Aβ and thus limits the efficient efflux of Aβ from the brain [89,90].

3.4.2. RAGE

RAGE is the major Aβ influx receptor at the BBB that transports Aβ from the blood into the brain [4,11,91]. RAGE is normally expressed at low levels at the BBB, but its expression is increased in normal aging and in AD brain endothelium and is associated with increased cerebrovascular and brain accumulation of Aβ [91–93]. See **Fig. 3B** inset.

3.5. Concomitant vascular abnormalities

CAA, basement membrane abnormalities, string vessel formation, microinfarcts, arteriosclerosis, and/or atherosclerosis, are frequently observed in MCI and AD patients [94] and in post-mortem AD brain tissue [95]. Brain microvasculature is structurally altered in AD and other neurodegenerative diseases and some of these vascular abnormalities are discussed below.

3.5.1. Cerebral amyloid angiopathy

CAA is the deposition of amyloid along the cerebrovasculature that occurs in both familial ADAD and sporadic AD (**Fig. 3B**). Patients with hereditary Dutch, Iowa, Arctic, Flemish, Italian or Piedmont L34V vasculotropic mutations develop CAA followed by rupture of blood vessels and hemorrhagic strokes in midlife [1,4,16]. CAA is known to worsen AD pathology and occurs in 80% of AD patients [1]. CAA likely develops as a result of the ineffective transvascular and perivascular clearance of Aβ [11,96], as well as poor Aβ clearance by arterial VSMCs [62]. It was recently reported that microvascular rather than parenchymal Aβ deposits are associated with early behavioral deficits in AD transgenic mice [97]. Individuals with CAA carrying *APOE4* allele(s) have accelerated vascular pathology that can modulate Aβ accumulation [31]. Human post-mortem studies recently reported that AD patients that are *APOE4* carriers had increased fibrinogen deposits with increased CAA disease severity compared to non-carriers, and the fibrinogen deposits associated with microvascular Aβ accumulation [31].

3.5.2. Basement membrane abnormalities

The basement membrane of the vessel wall has been shown to thicken, split, and develop abnormal inclusions (e.g., accumulation of collagen and perlecans) in the aging brain that is increased in AD as shown by post-mortem human brain tissue studies [1,98].

3.5.3. String vessels

String vessels are thin connective tissue strands composed of basement membrane that are remnants of capillaries without endothelial cells or blood flow [99]. The number of string vessels is significantly increased in AD post-mortem brain tissue [99,100] and in *APOE4* carriers compared to non-carriers [100]. Preliminary studies found that Aβ accumulates substantially along string vessels [101].

4. Vascular risk factors, lifestyle and environment

In addition to genetic risk factors discussed above that can trigger neurovascular damage and cognitive decline, vascular conditions such as hypertension, diabetes, atherosclerosis, and hyperhomocysteinemia can also contribute to dementia and influence one's risk for AD. Additionally, every person is differentially affected by lifestyle (e.g., education, sleep, diet and exercise) and environment (e.g., pollution/nanoparticles and environmental enrichment) that can further modify one's risk for dementia. It is estimated that nearly half of AD cases might be attributed to modifiable risk factors and that effective control of vascular factors, pre-existing disease(s) and psychological condition(s), as well as lifestyle-based interventions may offer promising preventative strategies to delay disease onset and/or progression [102]. Below, we detail some of these factors related to AD.

4.1. Hypertension

Hypertension is one of the vascular risk factors for dementia. Several epidemiological studies indicate association of midlife hypertension with late-life dementia [103,104]. A meta-analysis of six longitudinal studies showed significant association of hypertension with increased risk and incidence of vascular dementia [105]. Hypertension causes regional CBF reduction and impairs cerebrovascular reactivity [54]. Compelling evidence suggests that chronic hypertension fuels atherosclerosis in cerebral arteries, and also increases the risk of microvascular damage, white matter lesions, ischemic stroke and intracranial hemorrhage in the presence of CAA [106–108]. In animal models, hypertension caused BBB impairment, induced brain Aβ accumulation, enhanced Aβ-induced neurovascular dysfunction and neurodegeneration [109–112]. Circulating plasma levels of markers of endothelial activation including soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and endothelin-1 (ET-1), an endothelial cell-derived potent vasoconstrictor, are increased in hypertensive subjects suggesting vascular injury [107,113,114]. Anti-hypertensive agents have been shown to reduce the risk of dementia and cognitive decline [115,116], thus proper management of hypertension is an important protective strategy against cognitive impairment.

4.2. Diabetes

Increasing evidence suggests that type 2 diabetes mellitus (T2DM) is a major vascular risk factor contributing to the development of AD [117–119]. Evidence of vascular alterations and increased BBB permeability have been reported in T2DM patients [120,121] and in several experimental models of diabetes [122–125]. Multiple mechanisms may explain the link between T2DM and pathological changes in brain microvasculature, neurons and glial cells including increased levels of advanced glycation end-products (AGEs) and RAGE, vascular inflammation, oxidative stress, reduced insulin transport across the BBB, impaired insulin signaling, insulin resistance and endoplasmic reticulum stress [126,127].

4.3. Atherosclerosis

Atherosclerosis is hardening and narrowing of the inner wall of arteries due to the buildup of plaques composed of fatty deposits, cholesterol and other blood derived substances. Atherosclerosis has been implicated in the pathogenesis of dementia and AD, and it has several overlapping risk factors including diabetes, hypercholesterolemia and aging [128]. Recently, a large cohort autopsy found that 77% of 410 AD subjects had grossly apparent circle of Willis atherosclerosis, which occurred more often than in non-AD subjects [129]. In non-demented patients, the carotid intima-media thickness, a marker of atherosclerosis, was found to be inversely related to annual cognitive measures of executive function [130]. A large population-based study of 4,371 stoke-free middle-aged patients found that atherosclerosis could predict future lower cognitive scores after 7 years [131]. Furthermore, a longitudinal study of 1,651 participants found that intima-

media thickness was associated with a higher risk of developing cognitive impairment in a 10 year follow up study [132].

4.4. Hyperhomocysteinemia

Elevated plasma homocysteine, known as hyperhomocysteinemia, has been reported in subjects with atherosclerosis [133], stroke [134], cerebral small vessel disease [135,136], and AD [134,136]. Cerebrovascular damage, endothelial dysfunction, oxidative stress, demethylation, and thrombosis have been proposed to elucidate the link between hyperhomocysteinemia and AD [135,137,138]. Diet induced hyperhomocysteinemia in wild-type [139] and *APP/PS1* AD [140] mice leads to spatial memory deficits, microhemorrhages, neuroinflammation and increased activity of MMP-2 and MMP-9.

4.5. Traumatic brain injury

Traumatic brain injury (TBI) increases the production of Aβ and also heightens the risk of developing AD [141]. Like AD, TBI leads to BBB leakage and vascular breakdown involving NVU impairment [141]. Experimental studies in rats have demonstrated that TBI leads to focal microbleeds, BBB and endothelial damage, gliosis, macrophage-mediated inflammation and myelin loss [142].

4.6. Sleep

Sleep inadequacy and daytime sleepiness increase the risk of AD and development of Aβ pathology [143]. Sleep-wake cycle alterations in AD subjects contribute to "sundowning syndrome," when AD patients become agitated, confused, anxious and aggressive in the late afternoon and evening. Patterns of sleep are also affected, for instance rapid eye movement sleep duration is reduced in AD, but not in normal aging, and has been proposed to be a biomarker for AD [144]. Recent studies found an increased clearance rate of Aβ in sleeping mice compared to awake mice following intracerebral injection of ^{125}I-Aβ40 into the frontal cortex [145]. This increased Aβ clearance was mediated 40% by perivascular ISF-to-CSF bulk flow and the remaining 60% was likely due to increased transvascular transport across the BBB [86,145].

Not only is sleep impaired in AD, but it has also been proposed that disturbances in sleep can lead to AD. There is mounting evidence that obstructive sleep apnea (OSA) could contribute to AD [146]. Severe OSA leads to sleep fragmentation, intermittent hypoxia, oxidative stress and increased production of Aβ via hypoxia-inducible factor-1α and β-secretase 1 [146]. Following intermittent hypoxia, reoxygenation results in damage to blood vessels and endothelial cells, and oxidative stress [146]. Furthermore, mice undergoing chronic sleep restriction have decreased expression and function of GLUT1, impaired tight junction expression and BBB transport, and suppressed vascular reactivity with reduced inducible nitric oxide synthase (iNOS), endothelial NOS (eNOS) and ET-1 [147]. Also, rats subjected to sleep deprivation exhibited BBB breakdown and leakage [148].

4.7. Pollution/nanoparticles

Air pollution has been shown to increase the risk of AD and AD-like brain pathologies [149,150]. Young residents of the Mexico City Metropolitan Area (MCMA) exposed to air pollution display cognitive impairment, BBB disruption, Aβ42 plaques and hyperphosphorylated tau accumulation [151], which are exacerbated in *APOE4* carriers [152]. Furthermore, children from the MCMA have increased serum autoantibodies against neuronal proteins, likely due to compromised brain immunity and BBB breakdown [153]. In mouse experimental studies, aerosolized nickel nanoparticles caused a rapid and drastic increase in Aβ40 and Aβ42 [154]. Also, *APOE* null mice exposed to mixed vehicle exhaust have accelerated BBB breakdown, decreased

expression of tight junction proteins (e.g., occludin, claudin-5) and increased generation of reactive oxygen species activity [155].

Many types of nanomaterials are emerging in medical science and research for their potential as biosensors, biomaterials, tissue engineering, DNA modification or drug delivery [156]. The sources of nanoparticles that humans are exposed to are numerous and include nanoscaled debris from hip replacements, prostheses, cosmetics, sunscreen, and many others. Unfortunately, nanoparticles have proven to be toxic in a number of host systems [156]. Highly active nanoparticles (e.g., silica coated to be hydrophilic, hydrophobic or amphiphilic) can be taken up by cellular membranes, including the BBB, and cross the membrane passively or by carrier-mediated endocytosis [156]. Experimental studies in rodents have shown that silver, copper or aluminum/aluminum oxide nanoparticles disrupt the BBB, reduce the expression of endothelial tight junctions, decrease CBF, and induce edema, synaptic dysfunction and neurodegeneration [157–160]. Interestingly, silver and copper nanoparticle exposure exacerbated BBB dysfunction when accompanying sleep deprivation [148] or diabetes [158].

4.8. Peripheral inflammation

Peripheral inflammation is being considered a possible risk factor for AD [161] and dementia [162]. Infectious agents including pneumonia, *B. burgdorferi, Helicobacter pylori* and herpes simplex virus 1 (HSV-1) have been identified in AD post-mortem brain tissue [163]. Interestingly, HSV-1 infections are found more often in *APOE4* carriers [164], which have increased BBB permeability [30]. Additionally, dementia patients have a two-fold increased mortality rate from pneumonia [165], and pneumonia patients have elevated MMP-9 levels in their serum [166], which is known to be linked to BBB breakdown [29]. Furthermore, poor oral hygiene, oral inflammation and tooth loss worsen with age and are risk factors for AD [167]. Recently, fungus was identified in post-mortem brain tissue from AD subjects [168], and was found to localize around blood vessels in AD brain tissue [169]. In AD, infectious agents likely enter the brain through a leaky, disrupted BBB and cause more detrimental effects than they would normally if the BBB were intact.

4.9. Alcohol and substance abuse

Alcohol abuse increases CBF and blood pressure and disrupts the BBB causing vascular remodeling by oxidative stress, endothelial tight junction phosphorylation and changes in expression of BBB-degrading gelatinases MMP-2 and MMP-9 [170,171]. Likewise, drug abuse has been shown to have detrimental effects on the BBB. Psychostimulant drugs of abuse including methamphetamine, ecstasy/MDMA (3,4-methylenedioxymethamphetamine), cocaine and nicotine cause increased BBB permeability through alterations in tight junction protein expression and conformation, glial activation, enzyme activation related to BBB cytoskeletal remodeling, and induction of neuroinflammation [172–174]. In addition to increased BBB permeability, experimental studies have found that even a single acute exposure to methamphetamine causes profound CBF reductions [175]. Also, recent preliminary studies have found that heroin use leads to microvascular damage and microcirculation dysfunction, collapse and fracture of the myelin sheath and vacuole formation in white matter regions around microvessels, as identified in post-mortem human brain tissue [176,177].

5. Vasculoprotective approaches

With the substantial amount of evidence supporting the vascular link to AD and related dementias, using approaches to repair neurovascular damage is intuitive and may hold promise to delay and/or slow down cognitive decline. Likely, the best approach for treatment will be multi-targeted and potentially individualized, patient-specific, since AD, CAA and vascular dementia present complex and heterogeneous etiologies. Below,

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we focus on some approaches that could potentially restore neurovascular functions and/or protect the neurovascular system from pathophysiological changes seen in dementia and AD.

5.1. Restoring BBB Aβ transport machinery

5.1.1. LRP1 upregulation

LRP1 expression in cerebral vessels is reduced in AD [11,84], and therefore increasing microvascular LRP1 expression levels may increase Aβ clearance to thereby prevent development of Aβ-dependent pathologies. Future studies should investigate novel therapeutic drugs and/or gene therapy vectors to restore LRP1 levels in endothelial cells and pericytes at the BBB. In addition to increasing LRP1 on cerebral microvessels, restoration or selective enhancement of LRP1 by gene therapy in the liver could function as a systemic "vacuum" to increase the concentration gradient driving Aβ out of the brain by creating a peripheral "sink" [87]. In general, gene therapy targeting neurological disorders remains challenging due to the restricted entry of vectors across the BBB into the brain. However, targeting cell surface (e.g., GLUT1, LRP1) or cytoplasmic (e.g., PICALM) proteins whose expression is reduced in AD brain endothelium (**Fig. 3B**) would likely be more achievable due to the favorable anatomical position, as endothelial cells are directly accessible to therapeutic interventions by intravenous administration. Importantly, studies have used *in vivo* phage panning to identify modifiable epitopes on adeno-associated virus type 2 (AAV2) vectors to enable endothelial-specific gene therapy delivery [178,179].

Soluble LRP1 and/or its wild-type recombinant cluster IV, WT-LRPIV, bind to free Aβ aiding in its peripheral clearance and preventing it from reentering the brain via the RAGE receptor [180]. Recently, a mutant of LRPIV (LRPIV-D3674) was developed to preferentially and selectively bind neurotoxic Aβ compared to other LRP1 ligands [181]. LRPIV-D3674 is ~25% more effective at replacing oxidized sLRP1 and clearing endogenous Aβ in hippocampus and cortex in AD transgenic mice [181]. Therefore, LRPIV-D3674 has a therapeutic potential in AD to restore reduced or oxidized sLRP1, regulate peripheral Aβ levels and reestablish the Aβ homeostatic peripheral "sink" [180].

5.1.2. PICALM upregulation

As described above, PICALM critically regulates transcytosis and clearance of Aβ across the BBB and its levels are reduced in AD brain endothelium, as well as in individuals carrying non-protective PICALM alleles [41]. To date, there are no known drugs or gene therapy vectors that can increase PICALM expression levels. Future studies are needed to determine the benefit of increasing PICALM levels in AD models and AD.

5.1.3. GLUT1 upregulation

GLUT1 levels at the BBB correlate with brain glucose uptake [82,182] and also are critical for maintaining BBB integrity [79]. Importantly, the levels of GLUT1 in cerebral microvessels are reduced in AD [78,183]. Only a few studies have investigated drugs to upregulate GLUT1 expression. For example, one study found that ginsenoside Rb1, an active component of ginseng, can activate the insulin signaling and AKT pathways to increase expression of GLUT1 and GLUT4 in adipocytes of diabetic (db/db) mice [184]. Studies in rats found that cerebrolysin, an approved neurotrophic peptide for vascular dementia treatment in humans, increased GLUT1 expression and improved hippocampal learning and memory [185]. Although these few studies demonstrate increased GLUT1 expression, the molecular mechanisms underlying GLUT1 reductions in AD remain unknown. Furthermore, it is not known whether manipulating GLUT1 expression at the BBB in dementia and in AD patients will have an effect on BBB permeability, cognitive performance and Aβ pathology as shown in an animal model of AD and GLUT1 deficiency [79].

5.1.4. Blocking RAGE

Two highly specific, low molecular weight, high affinity RAGE inhibitors, FPS2 and FPS-ZM1, have been recently reported [91]. FPS-ZM1, a novel multimodal RAGE blocker that crosses the BBB, reduced influx of Aβ into the brain, improved CBF responses, downregulated β-secretase activity, decreased amyloid load, suppressed neuroinflammatory responses, and reduced behavioral deficits in a mouse model of AD [91]. Similarly, in a rodent model of hypertension, RAGE inhibition by FPS-ZM1 significantly reduced hypertension-induced AD pathology as shown by improved cognitive performance and reduced parenchymal Aβ deposition [110]. RAGE inhibitors are currently being examined in Phase 3 clinical trials for efficacy in mild to moderate AD (NCT02080364) [186,187]. See **Fig. 3B**.

5.2. Microvascular stabilization

5.2.1. Activated protein C (APC)

APC is a vasculoprotective protease that promotes cytoprotective signaling in injured and ischemic brain endothelium at the BBB [188,189]. APC also stimulates post-ischemic brain angiogenesis, vascular repair and neurogenesis [188–191]. In the CNS endothelium, APC activates protease activated receptor-1 (PAR-1), which elicits protective signaling by enhancing the BBB integrity via Rac1-dependent cytoskeletal stabilization, suppression of cerebrovascular MMP-9 activity, and inhibition of proinflammatory cytokines expression and apoptosis [188,189,192–194]. A genetically engineered variant of APC, 3K3A-APC, with normal cell signaling and greatly reduced anticoagulant activity has an excellent safety profile in primates and humans [195,196] and is currently being studied as a neuroprotective agent in a Phase 2a clinical trial for ischemic stroke (NCT02222714). APC therapy holds potential to protect and restore cerebrovascular function and BBB breakdown in various other neurological disorders, as shown in different experimental models, and might have also applications in dementia and AD.

5.2.2. CypA and MMP-9 inhibitors

The detrimental effects of APOE4 on BBB and NVU function are mechanistically linked to the CypA-NFκB-MMP-9 proinflammatory pathway [29,35]. There are several new CypA inhibitors recently developed and investigated for use against hepatitis-C and HIV infections including CPI-431-32 [197], compound 25 [198], SCY-635 [199] and MM284 [200], which all may have a potential to stabilize the BBB in *APOE4* carriers. In addition to CypA inhibitors, there are a number of identified MMP-9 inhibitors including minocycline [201], curcumin [202], SB-3CT(2) [203] and compound 18 [204]. For example, minocycline has been demonstrated to reduce hemorrhage frequency and increase endothelial tight junction and basement membrane proteins in aged 5xFAD/*APOE4* transgenic mice [201]. Furthermore, recent studies showed that minocycline significantly reduced the infarct size, prevented tissue loss, improved perfusion, reduced BBB permeability, and increased tight junction protein levels in spontaneously hypertensive stroke-prone rats [205,206]. Future studies should determine the benefit of CypA and MMP-9 inhibitors on vascular dysfunction in AD and *APOE* transgenic mouse models.

5.2.3. Anti-hypertensive drugs

Many studies in experimental animal models and clinical studies show that pharmacological intervention by angiotensin receptor blocker, angiotensin converting enzyme inhibitor, or RAGE inhibitor is effective in treating hypertension related vascular injury [207–209], reducing AD related pathological changes in brain [209,210], and slowing cognitive decline [209,211]. Furthermore, developing future therapies capable of lowering expression of VCAM-1, ICAM-1 and/or blocking ET-1 receptor hold promise to further reduce hypertension-induced cerebrovascular dysfunction.

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5.2.4. Fibrinogen depletion

Ancrod is a drug derived from the Malayan pit viper that contains a serine protease that cleaves fibrinopeptide A (FPA), essentially preventing conversion of fibrinogen to fibrin that results in fibrinogen depletion [212]. The potentially beneficial mechanism of Ancrod is its ability to lessen fibrinogen clot propagation and improve CBF via activation of endogenous fibrinolysis [212]. Studies in *TgK21p55*^{+/-} mice, a MS model that exhibits clinical symptoms of paralysis and BBB breakdown, found that Ancrod treatment delayed the onset of inflammatory demyelination by diminishing fibrinogen deposition [213]. Additionally, clinical trials of Ancrod in ischemic stroke have yielded different results depending on time of treatment; for instance, Ancrod was clinically beneficial when administered within 3 hours post-stroke [214] but exhibited no benefit when administered within 6 hours post-stroke [215]. Ancrod's mechanism was recently studied *in vitro* in cultured human endothelial cells grown in ischemic conditions and in stroke subjects. In both cases Ancrod decreased fibrinogen levels and increased FPA levels and reduced clot formation [212].

5.3. Lifestyle improvements for vascular health

5.3.1. Diet

Recent studies report that diet can mediate the vasculoplastic reserve of the hippocampus. For example, consuming high levels of cocoa flavanols increased capillary density and enhanced dentate gyrus-associated cognitive function in cognitively normal healthy subjects [216]. This suggests an interaction between vasculoplasticity and neuronal plasticity during normal aging and dementia, but how this relationship is affected by lifestyle and vascular risk factors is currently unclear and should be investigated in future studies [13].

Growing evidence supports the benefits of a Mediterranean diet in protecting against dementia and prolonging one's cognitive reserve during aging. Age-related cognitive decline was attenuated in individuals consuming a Mediterranean diet, as found in a recent study of the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) diet intervention for neurodegenerative delay (MIND) [217]. In comparing Mediterranean and Western diets, the primary difference is the source and proportion of dietary fats, with olive oil specifically being the main fat consumed in the Mediterranean diet and high levels of saturated fatty acids and simple carbohydrates being consumed in Western diets [218]. Microvascular dysfunction is evident in rodent models fed unhealthy diets, namely those fed diets of Western culture [219], high fat [220], and high cholesterol [221]. An intact BBB is needed for proper cholesterol metabolism [222]. In CSF, decreased cholesterol levels correlate with decreased Aβ42 and increased CSF APPα and APPβ (products of APP processing) levels, supporting an association between disrupted cholesterol metabolism and increased amyloidogenesis [223].

Resveratrol is a biologically active plant-derived phytoalexin. Resveratrol has been shown to cross BBB, and regulate expression of MMPs, reduce pericyte loss, maintain integrity of BBB, and promote Aβ clearance [224–226]. Treatment with resveratrol completely reversed diabetes-induced vascular dysfunction by reducing capillary leakage, pericyte degeneration, and VEGF protein expression in the murine retina [227]. An earlier study has shown that resveratrol inhibits RAGE expression in vascular cells [228], which is implicated in Aβ transport into the brain and accelerated Aβ pathology in a mouse model [91]. Furthermore, long-term consumption of resveratrol reduced oxidative stress and prevented behavioral deficits in a rat model with disrupted NVU [229].

Olive oil is high in essential omega-3 fatty acids, the major component of which is docosahexaenoic acid (DHA), and has long been reported to benefit cognition and overall brain health [230]. DHA cannot be synthesized by the body and thus must be consumed, and the primary transporter of DHA from blood-to-brain is the major facilitator superfamily domain containing 2A (MFSD2A) at the BBB [231]. Individuals with AD have

lower CSF DHA lipid levels, and those with mild dementia have lower CSF α-liolenic acid levels [232]. Interestingly, reduced MFSD2A expression at the BBB can lead to a loss of its important functions, including maintenance of BBB integrity and omega-3 fatty acid transport into the brain [231,233,234]. Of note, transgenic *APOE4* mice also exhibit reduced uptake of DHA into the brain compared with transgenic *APOE2* mice [235], but whether this is related to reduced *Mfsd2a* expression is currently unknown. Additional studies are needed elucidate the underlying mechanisms of MFSD2A and fatty acids in relation to dementia and AD.

5.3.2. Exercise and environmental enrichment

Regular exercise and physical activity, particularly during midlife, are associated with improved cerebrovascular function and reduced rates of dementia and AD [236]. Individuals that exercised regularly for 28 days exhibited reduced plasma homocysteine levels and increased endothelial progenitor cells in peripheral blood, factors that protect against vascular damage and cognitive impairment [237]. Experimental studies in diabetic rats have shown that treadmill exercise maintains claudin-5 expression at the BBB compared to rats not receiving exercise [238]. Mechanistically, physical activity and cognitive stimulation in the form of enriched environment (e.g., tunnels, balls, ladders, and running wheel) accelerated Aβ enzymatic degradation and enhanced transvascular Aβ clearance, reducing Aβ accumulation in brains of AD transgenic mouse models [239,240]. Additionally, physical activity promoted Aβ clearance from brain to blood via upregulation of LRP1 [241,242] and downregulation of RAGE [91] at the BBB. Mice without access to a running wheel had decreased occludin tight junction levels and disrupted BBB integrity [243]. Although recent attention has been given to exercise, additional studies are needed to more completely understand the mechanism underlying its beneficial effects.

6. Conclusions and critical questions

Here, we have described the compelling evidence supporting the neurovascular link to cognitive impairment, dementia and AD. Specifically, how cerebrovascular functions in humans and animal models are affected and/or altered by genetic risk factors for AD and modifiable vascular risk factors, lifestyle and environment, which in turn can all influence development of dementia and AD.

The exact role of the vascular system in the pathophysiogenesis of dementia and AD and whether the vascular system is a viable therapeutic target for dementia and AD still remains, however, to be better understood and/or defined by future studies. Some critical questions that perhaps need to be addressed by studies in humans are, for example: i) Do cerebrovascular changes drive the initial pathogenic events in the living human brain leading to neuronal injury, disrupted structural and functional brain connectivity and early cognitive decline in sporadic AD and/or individuals with genetic risk for AD (i.e., *APOE4*) or ADAD (i.e., *PSEN1*) compared to those at a lower risk? ii) Do cerebrovascular changes lead to cognitive decline in individuals with vascular risk factors such as diabetes or hypertension? iii) Do reductions in the resting CBF and/or CBF dysregulation and BBB breakdown precede changes in structural and functional brain connectivity in the living human brain, and can these cerebrovascular abnormalities be detected early in the disease process in AD and ADAD patients and/or in individuals with vascular risk factors?

In parallel to addressing these translational questions, there is an emerging need for novel molecular and imaging biomarkers to predict cognitive decline, dementia and AD, including development of biomarkers for neurovascular dysfunction, and to determine whether these biomarkers can serve as reliable new diagnostic and/or prognostic tools for predicting cognitive impairment and the decline to dementia. From the experimental preclinical laboratory side, it would be extremely interesting to evaluate whether genetic, vascular and/or mechanical manipulation of the cerebrovascular system to advance vascular/BBB injury functions

influence the course of neurological disorders and AD-like pathology in animal models of dementia and AD, as it does in some models of human rare monogenic diseases [83,244–246].

Finally, new experimental studies should reveal whether therapeutic targeting of cerebrovascular dysfunction, including BBB breakdown and dysregulated CBF, could influence the course of disease in experimental models of AD, and importantly, could these findings then be translated to humans affected by dementia and AD.

Acknowledgments

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Figure Legends

Figure 1. The neurovascular unit (NVU) at the level of brain capillary is comprised of vascular cells (pericytes and endothelial cells), glia (astrocytes, oligodendrocytes, and microglia) and neurons.

Figure 2. The two-hit vascular model of Alzheimer's disease (AD) dementia. Vascular factors, such as hypertension and diabetes, and/or genetic risk factors for AD, such as apolipoprotein E ε4 (*APOE4*), can all lead to cerebrovascular damage (hit 1; green boxes). Within the amyloid-β peptide (Aβ)-independent pathway, cerebrovascular damage leads to blood-brain barrier (BBB) dysfunction and accumulation of blood-derived neurotoxic molecules in the brain, from one hand, and oligemia or reduced cerebral blood volume, from the other. Additionally, within the amyloidogenic Aβ pathway, BBB dysfunction can disrupt Aβ clearance across the BBB and oligemia leads to overexpression and enhanced processing of Aβ precursor protein (APP), which both can promote Aβ accumulation in the brain (hit 2; black boxes). The converging Aβ-independent and Aβ-dependent pathways can each independently and/or synergistically lead to synaptic and neuronal dysfunction, neurodegeneration, and disruption of brain structural and functional connectivity that ultimately leads to dementia.

Figure 3. Blood-brain barrier (BBB) pathways to neurodegeneration in dementia and Alzheimer's disease (AD).

A. In the normal capillary, there is an intact BBB composed of tightly joined endothelial cells and supported by mural pericytes, as shown in this simplified schematic. The BBB normally selectively regulates the passage of molecules from blood to brain and vice versa, and restricts entry of blood-derived products and toxins into the brain. There are many transporters and receptors along the BBB that permit molecules to cross the BBB via substrate-specific transport systems, some of which are particularly relevant to AD pathophysiogenesis, as illustrated in the inset. For example, the normal BBB has high expression of the glucose transporter (GLUT1), moderate expression of low density lipoprotein receptor related protein-1 (LRP1) and minimal expression of receptor for advanced glycation end-products (RAGE).

B. In the AD capillary, there is a vicious cascade of events that can lead to neurodegeneration, as shown in this schematic and described as follows. 1. Pericytes degenerate and detach. 2. The BBB becomes leaky. 3. Blood-derived molecules like fibrinogen, thrombin and plasminogen leak from vessels and are directly toxic to neurons and can further induce BBB damage. Erythrocyte extravasation induces accumulation of hemoglobin derived-iron which causes generation of reactive oxygen species (ROS) and oxidative stress to neurons, and albumin promotes local tissue edema. 4. BBB transporter expression is altered, e.g., LRP1 and GLUT1 expression are significantly reduced, whereas RAGE expression is increased. The alterations in LRP1 and RAGE reduce the clearance and increase the uptake of Aβ into the brain, respectively, leading to Aβ accumulation in the brain. Also, normal cerebrovascular functions are disrupted by vascular pathologies including 5. Cerebral amyloid angiopathy, 6. Damaged and thickening of the basement membrane, and 7. String vessels.
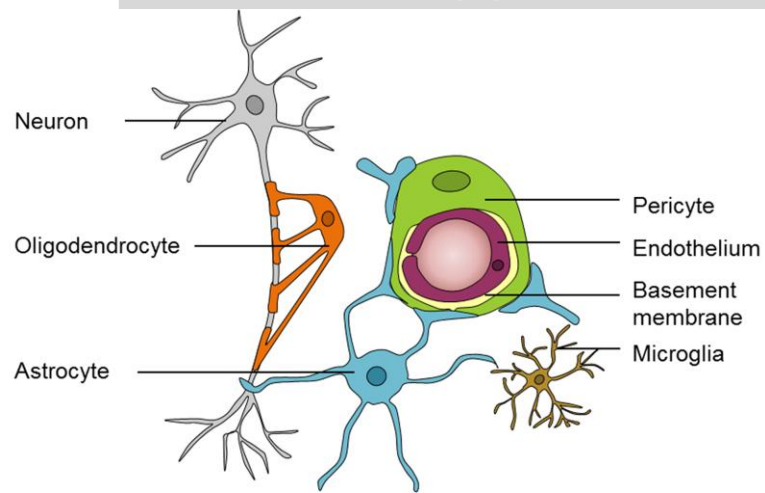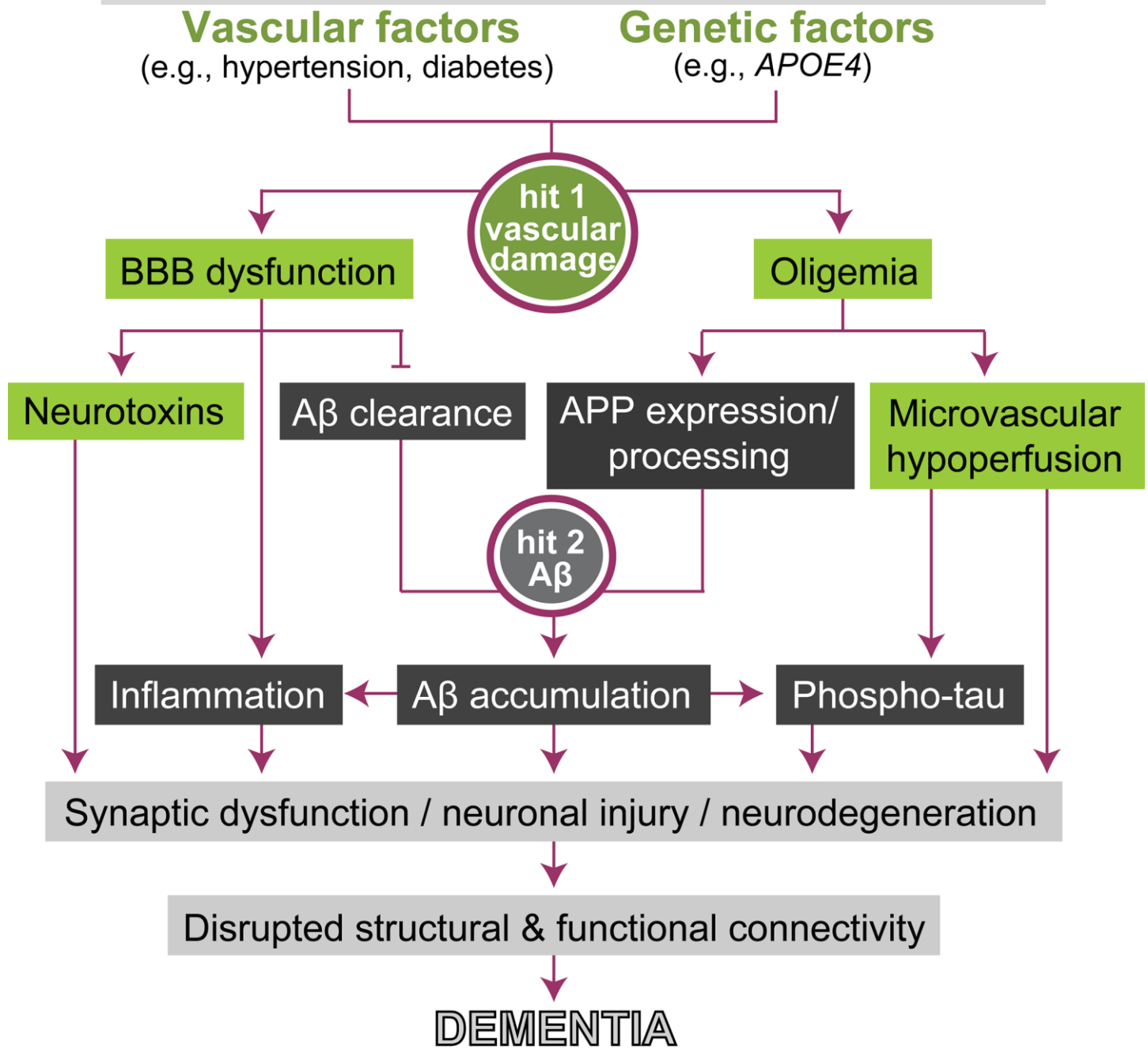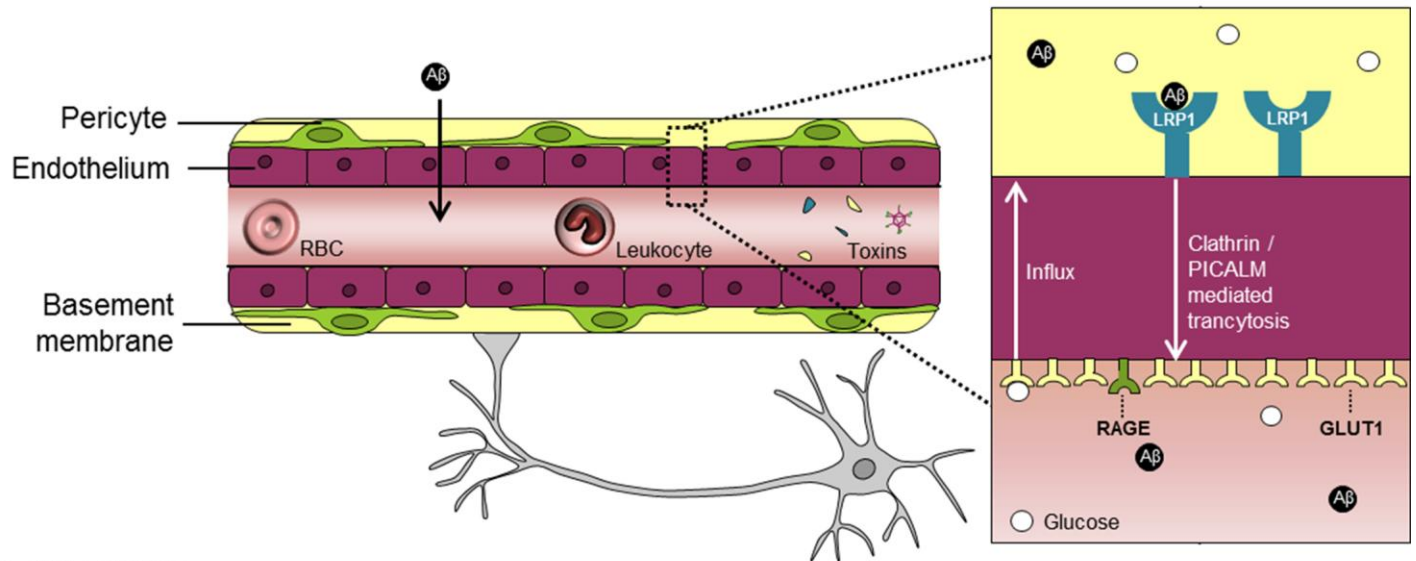
Figure 1

Figure 2

A. Normal capillary

Pericyte

Endothelium

RBC

Leukocyte

Toxins

Basement
membrane

Aβ

LRP1

LRP1

Influx

Clathrin /
PICALM
mediated
trancytosis

RAGE

GLUT1

Aβ

Aβ

Glucose

B. AD capillary

Aβ Aβ Aβ Aβ

Aβ

1

6 Aβ Aβ Aβ

Aβ

5

Aβ

7 Aβ Aβ

Aβ Aβ

2

2

2

Aβ

Hemoglobin

3 Albumin, Plasmin, Thrombin, Fibrin

ROS
Iron

4

Aβ Aβ

Aβ

Aβ

Aβ Aβ

LRP1

Influx

Clathrin /
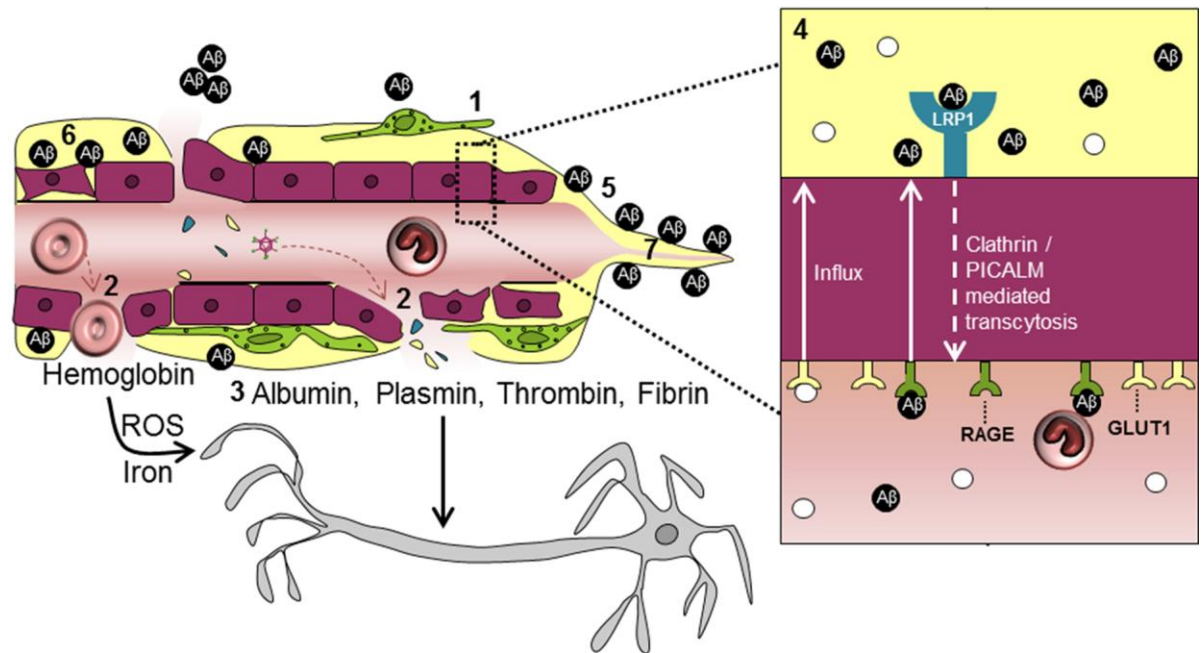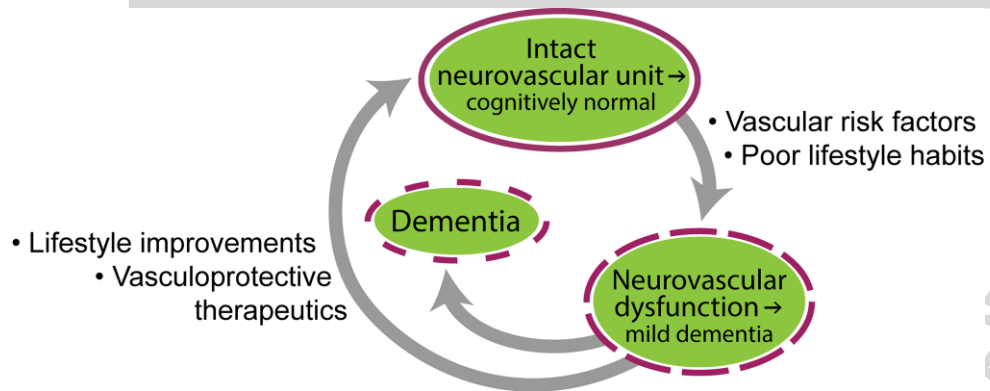PICALM
mediated
transcytosis

Aβ

RAGE

GLUT1

Aβ

Aβ

Figure 3

Graphical abstract

Highlights

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- Cerebrovascular damage may initiate molecular events leading to neurodegeneration
- Major genetic risk factors for AD are linked to brain vascular dysfunction
- Vascular risk factors increase incidence of sporadic AD
- Mid-life lifestyle changes may protect the neurovasculature and prevent AD
- Vasculoprotective therapies may delay the onset and progression of AD