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REVIEW ARTICLE

The interaction between dysfunction of vasculature and tauopathy in Alzheimer's disease and related dementias

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Abstract

Tauopathy is one of the pathological features of Alzheimer's disease and related dementias (ADRD). At present, there have been many studies on the formation, deposition, and intercellular transmission of tau in neurons and immune cells. The vasculature is an important component of the central nervous system. This review discusses the interaction between vasculature and tau in detail from three aspects. (1) The vascular risk factors (VRFs) discussed in this review include diabetes mellitus (DM), abnormal blood pressure (BP), and hypercholesterolemia. (2) In ADRD pathology, the hyperphosphorylation and deposition of tau interact with disrupted vasculature, such as different cells (endothelial cells, smooth muscular cells, and pericytes), the blood–brain barrier (BBB), and the cerebral lymphatic system. (3) The functions of vasculature are regulated by various signaling transductions. Endothelial nitric oxide synthase/nitric oxide, calcium signaling, Rho/Rho-associated coiled-coil containing Kinase, and receptors for advanced glycation end products are discussed in this review. Our findings indicate that the prevention and treatment of vascular health may be a potential target for ADRD combination therapy.

KEYWORDS
Alzheimer's disease and related dementias, tauopathy, vasculature

Highlights

- Persistent VRFs increase early disruption of vascular mechanisms and are strongly associated with tau pathology in ADRD.
- Cell dysfunction in the vasculature causes BBB leakage and drainage incapacity of the cerebral lymphatic system, which interacts with tau pathology.
- Signaling molecules in the vasculature regulate vasodilation and contraction, angiogenesis, and CBF. Abnormal signaling transduction is related to tau hyperphosphorylation and deposition.

1 | INTRODUCTION AND BACKGROUND

Dementia is a generic term used to describe chronic or progressive cognitive decline, which is found to have the same pathological changes in some senile people and, consequently, has been reclassified as neurodegenerative disease.[1] Over 50 million people live with dementia globally, and this number is projected to triple by 2050.[2] The causes of age-associated cognitive decline involve prodromal Alzheimer's disease (AD), Lewy body disease, age-related vessel diseases, and cerebral hypoperfusion, resulting in the progress of AD and related dementias (ADRD).[3] AD is the major form of dementia, which accounts for about 60% or more of all cases.[4] It is estimated that global costs related to dementia will exceed US$1 trillion, or 1% of global gross domestic product annually.[5] Without any proven disease-modifying therapies for neurodegenerative diseases, symptomatic medications are foundational to dementia treatment.[6] There are currently three cholinesterase inhibitors broadly available, as well as one N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine was the last medication approved for the treatment of dementia by the US Food and Drug Administration (FDA) in 2003, and there have been no new medications approved in nearly two decades.[7] A breakthrough in medication was on July 2, 2024 – donanemab (donanemab-azbt; Kisunla), an amyloid beta (Aβ)-directed antibody, had received the FDA's approval.[8] Donanemab is recommended for a confirmed presence of Aβ in patients with mild cognitive impairment (MCI) or mild dementia of diseases.[9] In a randomized controlled trial (RCT) of early symptomatic AD, it slowed tau accumulation in addition to clearing Aβ plaques.[10] Tau is a protein mainly expressed in the brain that has six isoforms produced by alternative mRNA splicing of the microtubule-associated protein tau (MAPT) gene, which comprises 16 exons on chromosome 17q21.[11] The primary physiological function of tau protein is to stabilize microtubule (MT) networks within neurons, whereas the hyperphosphorylated condition will significantly reduce its biological activity.[12] The distribution of tau pathology tends to correlate with cognitive decline, and tau misfolding and aggregation are considered to be a link to common downstream mechanisms of neurodegeneration.[13–18] Tau functions are regulated by a complex array of posttranslational modifications, such as phosphorylation, glycation, acetylation, isomerization, nitration, sumoylation, O-GlcNAcylation, and truncation,[19,20] suggesting that tau plays diverse roles in physiology and pathology. Dysfunctional tau is one of the neurotoxic proteins, accumulated in neurons, gliocytes, vascular endothelial cells (ECs), and others. Tau conformers have a prion-like transmission among neurons, reactive astrocytes, and microglia, which can internalize and secrete tau from the extracellular space. Tau accumulation accelerates the senescence of vascular ECs and the dysfunction of vascular smooth muscle cells (VSMCs), which is associated with decreased cerebral blood flow (CBF) and cortical atrophy in cognitive impairment.[21–24] Recent research showed tau aggregates drove the senescence of vascular ECs and its hyperphosphorylation mediated the switching of proinflammatory phenotypes in VSMCs.[21,22] In patients with cognitive impairment, soluble platelet-derived growth factor β(sPDGFRβ), a landmark of vascular dysfunction, has a significant positive correlation with tau, while CBF has a significantly negative association with tau.[23] Furthermore, tau significantly mediates the relationships between CBF/sPDGFRβ and the different levels of cognition performance.[23] In aging mice with tau overexpression, changes in the number and structure of vessels in the brain were observed, including abnormal spiral, reduced diameter, and increased density in the brain cortex. Blood flow was changed as a result of cortical atrophy and increased genes related to angiogenesis (Vegfa, Serpine1, and Plau) in vascular ECs with CD31-positive expression.[24] It is indicated that tau affects the biology of ECs and leads to the resulting disruption of vessels. Conversely, annexin A1 can restore vascular architecture integrity and reduce tau phosphorylation.[25] The association between tau protein and vascular pathology in ADRD has not been well discussed. In this review, we aim to update the knowledge about the interaction between tau and vascular structure and function.

RESEARCH IN CONTEXT

1. **Systematic review**: Vascular function is strongly related to ADRD, and tau pathology is an important pathological feature of ADRD. The interaction between vascular dysfunction and tau pathology is worthy of discussion.
2. **Interpretation**: The cerebrovascular system is an important part of the central nervous system. Clinical VRFs continue to disrupt vascular structure and function, which is related to tau pathology. Tau pathology interacts with the dysfunction of vascular cells, mitochondria, and barrier structures, involving abnormal signaling transduction mechanisms.
3. **Future directions**: Vascular mechanisms are a valuable target for the prevention and treatment of ADRD. Further studies on the relationship between vascular mechanisms and tau are still needed to investigate (1) the causal relationship between the medication regimen of VRFs and tau pathology; (2) the relationship between different vascular cells/structures and tau pathology.

2 | RELATIONSHIP BETWEEN TAU AND VASCULAR RISK FACTORS IN ADRD

Investigations of gender and racial differences in the distribution of ADRD in the United States have found that women and African Americans have a higher prevalence of ADRD.[26] Women were found to have more apolipoprotein E epsilon 4 (*APOEε4*) carriers and higher levels of Aβ in CSF.[27] *APOEε4* is known as a risk factor for hyperlipidemia. A cohort study found *APOEε4* carriers accelerated Aβ-related tau accumulation, regardless of the level of Aβ.[28] In contrast to the prevalence, levels of total t-tau, and t-tau/Aβ_{42} in patients with cognitive impairment were higher in Caucasians than in African Americans, and the

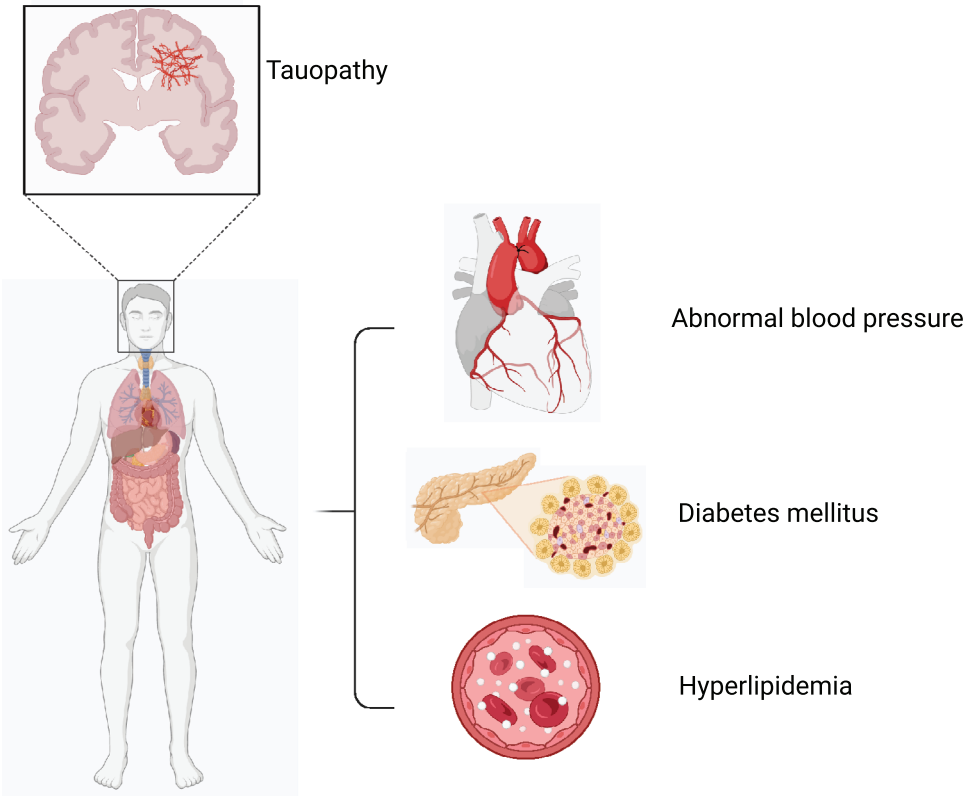

FIGURE 1 Tau and vascular risk factors. Created from https://app.biorender.com (accessed on 12 February 2025).

high expression level of the endothelial marker (soluble vascular cell adhesion molecule 1) in Caucasians was significantly associated with vascular risk factors (VRFs).[29] Although African Americans had a lower level of t-tau and t-tau/Aβ_{42}, their low degree of cognitive impairment was associated with white matter hyperintensities (WMHs).[29] The aggravation of WMHs is a strong risk factor for cognitive decline[30] and dementia.[31] It is suggested that the interacting differences between VRFs and tau exist in races.

For vascular biology in dementia, sustained VRFs and poor lifestyle habits lead to early disruption of vascular mechanisms, neuroinflammation, and hypoperfusion.[32] Modifiable VRFs have been reported, including hypertension, hypercholesterolemia, obesity, type 2 diabetes mellitus (T2DM), and smoking, and are associated with an increased risk of AD.[33,34] Vascular dementia (VD) is a series of cognitive disorders with a vascular etiology characterized by a heterogeneous group of disorders.[35] VD can occur alone or in combination with AD, the most common form of mixed dementia. In mixed dementia, vascular lesions modulate AD progression, and AD-related lesions enhance vascular damage.[36] Vascular pathology underlying VD affects both large- and small-caliber vessels and results from a wide array of vascular diseases ranging from cerebral small vessel disease (CSVD), ischemic or hemorrhagic stroke, asymptomatic carotid stenosis, and heart disease.[37] In CSVD-related dementia, brain arterioles and capillaries are predominantly impacted, causing reduced brain perfusion, blood–brain barrier (BBB) damage, lacunar infarcts, and microhemorrhages, which ultimately lead to cognitive impairment.[38] Note that CSVD does not necessarily lead to VD, although CSVD increases the risk for VD.[39] In this section, we will review the impacts of VRFs and the pathology of the cerebrovasculature on ADRD and related tauopathy (Figure 1).

2.1 | Diabetes mellitus

Long-term complications induced by DM depend on the extent of vasculopathy. Diabetic macroangiopathies can lead to atherosclerosis and cardiovascular diseases, while diabetic microangiopathies will damage kidneys, nerves, and eyesight, among others. DM includes type 1 (T1DM) and type 2 (T2DM). The onset of T1DM is due to hypoinsulinemia because of the autoimmune destruction of beta cells of pancreatic islets, while T2DM is a chronic multisystem disease based on insulin resistance and a subsequent deficiency of insulin actions. T2DM is associated with a 70% increased risk of dementia.[40] A recent large longitudinal cohort study with a median follow-up of 32 years showed that younger age at the onset of diabetes was significantly associated with a higher risk of subsequent dementia.[41] Mendelian randomizations (MRs) can overcome some of the limitations of observational studies, including confounding and reverse causation. Using the inverse-variance weighted method, Xue et al.[42] found that T2DM was causally linked to the risk of AD.

The cognitive impairment in patients with T2DM may correlate with increased amounts of cytokines and cortisol, which is linked to vascular pathology.[43,44] The BBB is formed by cerebral ECs and the closely

apposed astrocyte and is responsible for various substances transport, including glucose, amino acids, and others.[45] Because of insulin resistance, hypo/hyperglycemia, and the release of excess free fatty acids, along with other metabolic abnormalities,[46,47] BBB integrity and permeability are affected by a series of events, including endothelial dysfunction, platelet hyperreactivity, oxidative stress (OS), and inflammation. The resulting BBB dysregulation exacerbates vascular dysfunction and further promotes ADRD. T2DM regulates tau hyperphosphorylation by insulin signaling. The impairment of insulin signaling leads to the halted PI3k/Akt pathway, and subsequently no hyperphosphorylation of downstream GSK-3β kinase can cause increased tau hyperphosphorylation.[48] In an observational study, cognitively normal participants with untreated DM presented greater tau pathology than normoglycemic participants with DM, and they progressed to dementia at significantly higher rates than controls.[49] Moreover, in *APOEε4* postivecarriers of patients with mild cognitive impairment or early dementia, the t-tau CSF level also has a significant association with DM.[50] The insulin treatment can improve cognitive function and memory and decrease tau-P181/Aβ42 ratio.[51,52] T2DM promotes cerebrovascular damage and tau pathology, both of which are associated with cognitive impairment. The region of tau deposition can observe the disruption of BBB, suggesting tau pathology involvement in BBB dysfunction.[53] Because the progression of AD is related to the impairment of the insulin signaling pathway, which includes tau hyperphosphorylation, Aβ plaque deposition, and energy metabolism disorders in the end stage, and this shares a common pathophysiology with DM, AD could be referred to as type 3 diabetes.[54,55]

2.2 | Abnormal blood pressure

In the form of either hypertension or hypotension, abnormal blood pressure (BP) affects the progression of dementia. Hypertension has been associated with an increased risk of dementia and is listed by the Lancet Commission report on dementia prevention, intervention, and care as one of 12 modifiable risk factors that could delay or prevent 40% of cases of dementia.[56]The contribution of hypertension to dementia varies by age. Hypertension in midlife has been associated with greater cognitive decline and elevated dementia risk in observational studies for decades.[57] The population attributable fraction (PAF) was quantified and stratified by age to assess the proportion of dementia risk attributable to hypertension, over a follow-up time spanning 32 years, the PAFs of dementia cases with non-normal BP by age 80 was approximately 15% to 20%, with the strongest estimates for stage 2 hypertension.[58] The indicators of BP were various, including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), and BP variability (BPV). The relationship between BP and tau pathology was age-related. A study from the Chinese Alzheimer's Biomarker and Lifestyle database showed cognitive impairment and tau pathologies were associated with midlife (< 65 years) hypertension, late-life (≥65 years) lower DBP, and total higher PP, BPV only had a strong correlation with cognition, but not with tau and Aβ in cerebrospinal fluid (CSF).[59] In contrast, Sible et al.[60] found that increased BPV in adults (age 55 to 91) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) was related to tau accumulation (underwent ≥1 tau-PET), especially in the entorhinal cortex. Another study from the ADNI database revealed that AD participants who were p-tau positive had elevated PP, as well as higher SBP in very old participants (≥80 years) and reduced DBP in younger participants (55 to 79 years).[61] In MCI patients (age 74.75 ± 7.24) with high PP, the levels of inflammatory markers in CSF were positively correlated with t-tau and p-tau.[62] Given that a profound increase in aortic stiffness is a major alteration in aging and hypertension,[63] the specific mechanisms by which BP affects tau pathologies and cognition may be revealed by an analysis of their correlation. Carotid-femoral pulse wave velocity (cfPWV) and central PP are common outcomes reflecting arterial stiffness, while forward wave amplitude (FWA) is used to measure pressure pulsatility. cfPWV was found to mediate the association between age and cognitive ability after microvascular oxygen deficiency due to ischemia.[64] In addition, a cross-sectional study found that higher central PP and FWA were associated with greater tau deposition in the entorhinal and rhinal cortex, but not with the global Aβ plaques or tau accumulation in the other cortex.[65] The findings indicate the peripheral microvascular system is a possible target to prevent tauopathy in ADRD.

For antihypertensive treatment, it had inconclusive results in reducing the risk of dementia. In a meta-analysis of RCTs and prospective studies published through 2018, antihypertensive treatment was associated with a non-significant reduced risk of dementia in RCTs and prospective studies and with reduced AD risk in prospective studies.[66] Another RCT treating patients with visible white matter lesions found that intensive antihypertensive treatment (24-h mean SBP: ≤130 mm Hg) did not significantly differ from standard antihypertensive treatment (24-h mean SBP: ≤145 mm Hg) with respect to cognitive function, but WMHs volume increases were smaller in the intensive treatment.[67] However, in cognitively normal adults (55 to 90 years), Kim et al.[68] found that WMH volume with global Aβ deposition had no synergistic interaction effects on tau accumulation, suggesting that cerebrovascular injury measured by WMHs did not mediate the synergistic effect of high BP on tau pathology. Any intervention that targets a VRF bases on a causal link between the risk factor and the disease could help in obtaining more encouraging outcomes. However, MRs were reported and showed contradictory results.[69–72] Although DBP and PP were causally linked with an increased risk of vascular brain injury,[70] the incidence of AD had no causal association with BP indexes, including DBP, SBP, and PP.[70,71] Surprisingly, higher SBP had a causal effect on the lower risk of AD.[69,72] It possibly associated with treatment with antihypertensive drugs.[72]

Hypotension also causes cardiovascular damage due to chronic hypoperfusion. Under the premise of cardiovascular and cerebrovascular diseases, orthostatic hypotension increases the risks of dementia.[73] The causal link may be that orthostatic hypotension increases the risk of heart disease and leads to cognitive deficits after the accumulation of its effects such as inflammation, OS, and vascular damage.[74,75] Mice with cognitive impairment induced by persistent orthostatic hypotension can observe tau hyperphosphorylation and loss of dendritic spines,

increasing the risk of AD-like pathological alterations and behavioral impairment.[76]

2.3 | Hypercholesterolemia

Hypercholesterolemia is defined as high plasma cholesterol levels with normal plasma triglycerideses.[77] Cholesterol exists widely in the body, with about a fourth of it distributed in the brain. Brain cholesterol is mostly in unesterified form, with a third of it present in cellular membranes and mostly in myelin sheaths.[78] Hypercholesterolemia is a major risk factor for atherosclerosis, which is associated with AD.[79] *APOE* participates in lipid metabolism, and its polymorphism affects the lipid phenotypes in familial combined hyperlipidemia (FCHL).[80,81] In relatives of Chinese families with FCHL, the levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) within the *APOEε4* subset were significantly higher than those within the APOE3 subset.[80] The functional domains of APOE influence binding capability to heparan sulfate proteoglycans (HSPGs), which paly a bidirectional regulatory role in the pathogenesis of AD.[82] *APOEε4* is the strongest genetic factor associated with AD, while *APOEε2* has a protective effect against AD.[83] Thus, the effects of *APOE* variants on AD pathology have been investigated. For instance, the homozygous *APOE*-R136S mice was found to rescue the *APOEε4*-driven tauopathy and neuroinflammation in tau-P301S and *APOE* cross-bred mouse.[82] Furthermore, chronic hypoperfusion and thrombosis are key events in VD.[84] 85% of 12-month-old $LDLR^{-/-}$ mice fed a high-fat diet developed thrombotic occlusion, while almost none of the 12-month-old wild-type mice did, suggesting that hyperlipidemia promotes CSVD. [85] The correlation between tau protein and cholesterol metabolism has been reported. On the one hand, the regulation of cholesterol affects tau binding and aggregation. In general, kinesin transports cargo by attaching its lipid membrane,[86–88] and MAPT blocks kinesin-binding sites on the MT.[89–91] Cargo membrane with added cholesterol amplifies the inhibitory effect of tau on kinesin binding by reducing the kinesin diffusion in the cargo membrane, suggesting that cholesterol has an interaction with tau and may associate with aging and neurological diseases. In addition, tau entry into neurons is independent of clathrin and dynamin but dependent on lipoprotein receptor LRP1 and HSPGs.[92] Low cholesterol potentiates seeded aggregation of tau at a low concentration, and the addition of cholesterol to cholesterol-depleted neurons can result in the reduction of tau entry.[92] On the other hand, tau disrupts cholesterol metabolism. In human cerebral organoids carrying the V337M and R406W tau mutations, the cholesterol biosynthesis pathway in astrocytes was upregulated significantly.[93] Pregnenolone is well known as the precursor of all neurosteroids.[94] Pregnenolone and downstream neuroactive steroids serve important functions in the nervous system, including in neuroprotection, neuroplasticity, and memory processes.[95] As the major site of cholesterol metabolism, mitochondria associated membranes (MAMs) is impaired by P301L-tau mutation, resulting in a decreased pregnenolone level converted from cholesterol.[96] Meanwhile, increased hippocampal hyperphosphorylated tau was observed in C57BL/6 mice fed a fat/cholesterol diet, which altered insulin/IGF signaling levels.[97] GSK3β, downstream insulin signaling, can inhibit excessive tau hyperphosphorylation and recover the conversion between cholesterol and pregnenolone in MAMs.[96] It is indicated that hypercholesterolemia may have a complex link with tau. Hypercholesterolemia also leads to the disruption of the BBB. In rabbits fed a fat cholesterol diet, BBB disruption was reflected in attenuated expression of tight junction proteins and increased IgG.[98] $LDLR^{-/-}$ mice can show increased permeability to sodium fluorescein and downregulated claudin-5 and occludin mRNA, indicating damaged BBB function.[99] As mentioned previously, BBB disruption has a link to tau. Moon et al. reported BBB permeability had a positive correlation with the level of total tau (t-tau) proteins in patients with amyloid-negative AD.[100]

3 | CORRELATION BETWEEN CEREBROVASCULAR MECHANISM AND TAU

VRFs are related to tau abnormalities. Current evidence shows that the tau accumulation area caused by VRFs is distributed in different brain regions, but the influence of tau on the vascular system has not been elucidated. Braak tau stages I to VI present the progression of neurofibrillary tangle (NFT) pathology in AD.[101] Cerebral artery wall remodeling based on the Braak tau pathology-dependent process precedes cerebral amyloid angiopathy (CAA) in AD, arterial elastin degrades significantly at Braak stage III and is associated with tau pathology and significant CAA-independent alpha-smooth muscle actin (α-SMA) loss in arteries from Braak stage I to III, accompanied by the deposition of phosphorylated paired helical filament (PHF) tau in the perivascular space of intraparenchymal vessels.[102] The vascular system mainly includes ECs, pericytes, SMCs, and platelets. Different cells of the vascular system form the BBB, lymphatic system, and other barrier structures, which are related to the pathogenesis of ADRD (Figure 2). Therefore, it is necessary to further elucidate the interaction between tau and the vascular system from the perspective of cerebrovascular mechanisms.

3.1 | Endothelial cell

Like neurons, ECs also express tau.[103,104] The accumulation of tau oligomers have been found in the brain microvasculature in ADRD, including AD, progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), and Tg2576 mouse model.[105] Furthermore, soluble tau aggregates colocalize with markers of cerebrovascular ECs,[105] indicating that tau may diffuse from neurons to ECs.[105,106] Next, internalized soluble tau of ECs causes MT destabilization, endothelial nitric oxide synthase (eNOS) inactivation, and reduced nitric oxide (NO) production. The dysfunction of eNOS/NO signaling is important for memory and learning. In ECs, eNOS/NO signaling is fundamental to the production of brain-derived neurotrophic factor (BDNF). Impaired eNOS/NO can hinder the synthesis of BDNF, thereby inhibiting synaptic plasticity and nerve regeneration.[107] Furthermore, NO reduction weakens the inhibition of platelet aggregation and leuko-

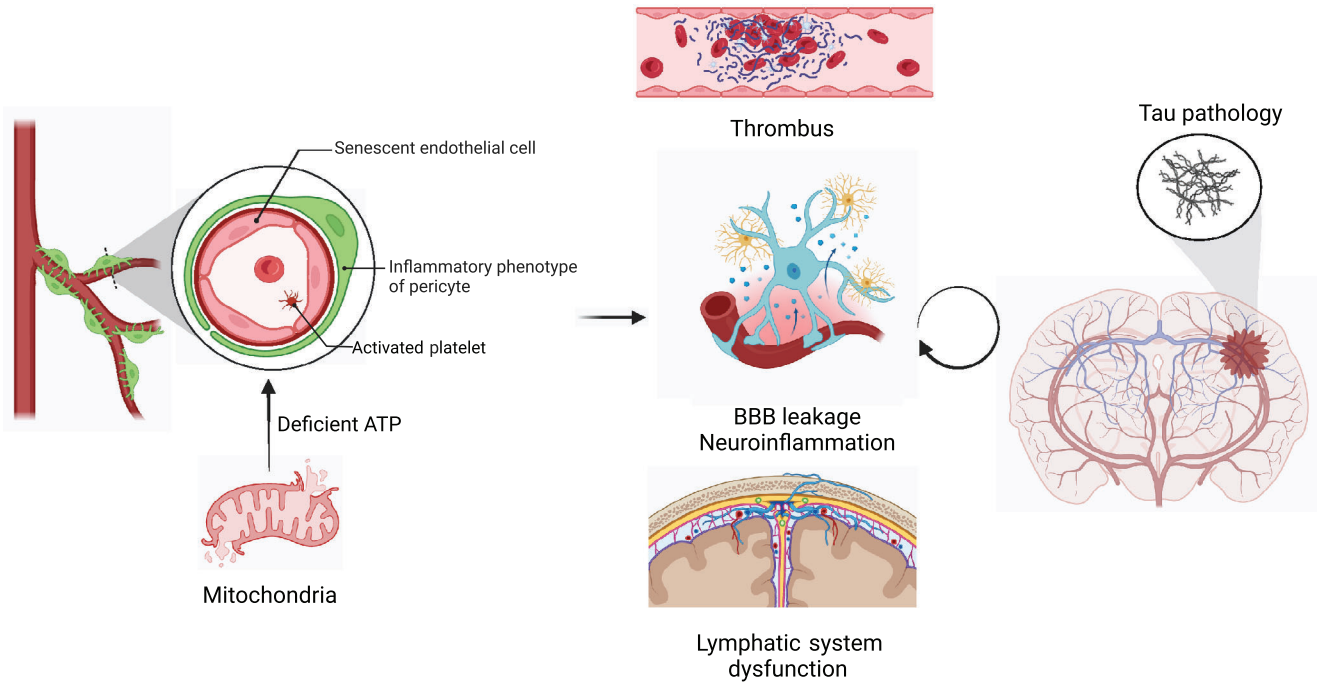

FIGURE 2 Tau and vasculature. Created from https://app.biorender.com (accessed on 12 February 2025).

cyte adhesion,[108] and inflammatory cells and toxic proteins infiltrate into the brain, which may cause neurotoxic effects. Troy Stevens's team performed RT-PCR in rat lung tissue and primary pulmonary microvascular ECs and identified a large tau isoform and three additional tau isoforms (0N4R, 1N4R, and 2N4R) that are similar to neuronal tau.[109] Infection and critical disease are important causes of cognitive impairment.[110,111] During infection, the monomer tau in lung ECs is modified and separated from MTs. The resulting instability of MTs leads to increased cell permeability and the release of cytotoxic tau into interstitial fluid (ISF).[112] For example, exposed by *Pseudomonas aeruginosa* exotoxin Y, the cAMP/cGMP-generating cyclase was stimulated, which led to tau serine 214 phosphorylation, pulmonary interendothelial gap formation, and macromolecular permeability.[104,113] Under the premise of effective antibiotic treatment, tau was detected in the CSF within 48 h of infection, which was associated with the impairment of long-term potentiation in the hippocampus.[112,114] In vivo and in vitro studies confirmed *pseudomonas aeruginosa* induced the generation of cytotoxic tau variants in pulmonary ECs, consequently causing neuronal tau aggregation.[109] It is suggested that cytotoxic tau in the pulmonary ECs can cause the propagation of neuronal tau via cerebral circulation or within the brain; BBB destruction induced by systemic inflammation after infection may be an important pathway.[114] Notably, abnormal EC function also leads to abnormal phosphorylation of tau. Vacuolar protein sorting-associated proteins (VPSs) make up the retromer complex system of brain ECs, and VPS26-VPS29-VPS35 is important for the transcytosis process of cargo across the endothelium of the BBB.[115] The neuronal dysregulation of VPS35 causes trafficking and degradation of altered proteins and consequently leads to neurodegeneration. The genetic silencing of VPS35 in ECs showed attenuated proteasome activity, increased LC3B2/1 expression, the markers of ubiquitination and autophagy, and significant deposition of tau and its phosphorylated isoforms.[115]

3.2 | Mural cell

Brain vascular mural cells include pericytes and SMCs. SMCs are a critical component of brain artery and arteriole walls, which participate in the regulation of blood flow.[116] In patients with AD, accumulation of tau oligomer is observed in SMCs, reflecting an associated immunoreactivity between oligomeric tau-specific antibody (T22) and SMA.[105] Rho-associated kinase (Rho-kinase/Rho-associated coiled-coil kinases [ROCK]/ROK) and myosin binding subunit (MBS) of myosin phosphatase are effectors of Rho small GTPase and have been shown to be implicated in inducing smooth muscle contraction.[117,118] Rho–kinase–MBS–myosin phosphatase cooperatively regulate tau phosphorylation, suggesting that the contracting function of SMC links to tau phosphorylation.[119] Of note, mural cell dysfunction also causes altered tau uptake or tau hyperphosphorylation in brain vessels. Under AD-like conditions, VSMCs turn into pro-inflammatory phenotype in both in vivo and in vitro experiments, whose changes are in accordance with tau hyperphosphorylation at residues Y18, T205, and S262.[22] Moreover, an in vitro experiment showed that the rank order for the uptake of tau was microglia > SMCs > pericytes ≫ brain endothelia = astrocytes, indicating that vascular mural cells contribute to the elimination of extracellular tau.[120] Pericytes in the central nervous system (CNS) are responsible for maintaining BBB stability regulating capillary density and diameter, participating in angiogenesis and ISF macromolecular waste clearance.[121] Pericytes are mainly located in capillaries and constitute most of the resistance to the vascular bed

of the CNS.[122] The SMCs of arterioles and the pericytes of capillaries regulate CBF together.[123] Clinical and animal studies on AD have found that decreased CBF is associated with pericellular contraction, which in turn leads to cognitive decline.[124,125] At the same time, pericellular loss and degeneration are also vascular pathological changes in AD. PDGF is a ligand that promotes pericellular proliferation and migration by activating PDGFRβ on the plasma membrane. None of the APPs$^{w/0}$ or PDGFR$\beta^{+/-}$ mice showed tau aggregates in the early stages of the disease until 9 months of age, suggesting that pericellular-driven vascular injury and elevated Aβ predated tau pathology and induced tau aggregates.[126] In addition, the deposition of hyperphosphorylated and aggregated tau in the brain is observed in traumatic brain injury (TBI).[127] Nevertheless, there was no difference in the mural cell population between r-mTBI and r-sham animals, which reflected mural cell degeneration but not cellular loss. Thus, the decreased tau uptake and caveolin-1 levels in r-mTBI animals indicated that repeated injuries to the brain may alter the tau uptake ability of vascular mural cells and result in tau accumulation and aggregation in the brain.[120]

3.3 | Blood-brain barrier

BBB, known as a boundary of peripheral circulation and the CNS, is structurally formed by capillary brain endothelial cells (BECs), pericytes, astrocyte end feet, and the basement membrane,[128] maintaining the permeability of plasma protein and inorganic solute, as well as exchanging brain water. BBB disruption has been regarded as a hallmark of aging and neurodegenerative diseases.[129–133] BBB imaging plays an essential role in elucidating BBB dysfunction. Using endogenous water as a tracer, a diffusion-prepared pseudo-continuous arterial spin labeling (DP-pCASL) technique was developed and applied to assess the rate of water exchange across the BBB.[134–136] The calculation of BBB water exchange rates (K_w) is based on the water extraction ratio between the capillary and brain tissue compartments, CBF, and the volume of water tracer in the capillary space.[137] BBB permeability has been widely measured by dynamic contrast-enhanced MRI (DCE-MRI) through injecting gadolinium-based contrast agents into veins.[138] The rate at which a contrast agent penetrates into the extravascular space per volume of plasma and tissue is the BBB permeability index (K_{trans}).[137] Iron is an essential mineral for brain development and function, and deficiency or excess can lead to neurobehavioral dysfunction and neurodegenerative diseases.[139,140] Quantitative susceptibility mapping (QSM) is a unique non-invasive test for quantifying iron deposits in the brain.[141,142] Rapid iron accumulation in the globus pallidum, thalamus, and substantia nigra was observed during the first 2 years of children's development, and the relationship with K_w/CBF showed an S-shaped curve.[143] Excessive iron deposition is associated with decreased K_w. Reduced K_w indicates a decreased waste clearance capacity in the BBB. Yuto Uchida's team[144] found decreased K_w in APOE4-positive carriers, which correlated with high QSM values and amyloid deposition in the frontal and medial temporal lobes, as well as cognitive decline. In addition, several studies based on DCE-MRI found BBB permeability increased in early AD, VD, and MCI.[145–147]

For the BBB water exchange rate detected by DP-pCASL, the findings varied. The BBB water exchange rate decreased both in older adults with MCI and AD subjects with low Aβ_{42} concentration in CBF.[148,149] But in Shao's study, the BBB water exchange rate was higher in aged patients with VRFs, such as T2DM and hyperlipidemia.[134] Different pathological states may affect the water exchange rate of BBB. Compared with peripheral ECs, BECs have an abundant mitochondrial content and low expressions of leukocyte adhesion factors, as well as a lack of perforated fenestrations. Consequently, BECs can generate ATP for substance transportation and restrict inflammatory infiltration and vesicle-mediated endocytosis. Tight junctions (TJs) at the apical end of BECs in a healthy state can build a continuous intercellular barrier between BECs.[128] In addition, the BBB is surrounded by microglia, oligodendrocytes, and neurons, which is linked to the regulation of the integrity and permeability of the BBB.[147,150,151] The BBB is disrupted in pathological conditions, like proinflammatory cytokine stimulation, decreased expression of TJ proteins, and dysfunction of transport proteins.[152] The hippocampus is known as the central brain region of learning, memory, and cognitive function, and it is featured with sparse capillary density and relatively long distance between microvessels.[153,154] When hypoxia/ischemia occurs, it is difficult for the hippocampus to maintain the necessary perfusion, thus affecting neuronal function. Importantly, the BBB in the hippocampus is more fragile than other brain regions.[130,147,155,156] A study in rodents showed that not exceeding 48-h increased BBB permeability in the hippocampus caused 7-day impaired spatial memory, suggesting transient disruption of hippocampal BBB led to prolonged memory impairment.[157] Tau proteins can cross the BBB bidirectionally, including tau-441 (2N4R), tau-410 (2N3R), truncated tau 151-391 (0N4R), and truncated tau 121-227. In the tetracycline-regulatable rTg4510 tau transgenic mouse model, the deterioration of BBB function was observed at a similar time point as the emergence of perivascular tau along hippocampal vessels, later than the appearance of alterations, such as tau accumulation, neuroinflammation, and neurodegeneration. While doxycycline suppressed tau, BBB integrity could be restored, reflecting the reduced extravasation of IgG and the Evans blue dye.[106] Furthermore, brain tau activates microglia and triggers EC damage.[19] Interestingly, when microglia activation was blocked, LPS-induced inflammation still caused BBB disruption and promoted P301L-hTau transmission from medial entorhinal cortex to hippocampal subsets.[158] It is suggested that tau triggers BBB damage and promotes its own transmission through microglia activation and a microglia-independent mechanism. Considered as one of the key therapeutic targets, it has been found that the integrity of the BBB was repaired after anti-inflammatory treatments, as well as the reduction of tau phosphorylation and the inhibition of tau transregional transmission in the brain.[25,158]

3.4 | Glymphatic system and meningeal lymphatics

Before the discovery of lymphatic vessels (LVs), glial cells were considered to be the immune cell population of the CNS. Composed

of blind-ended vessels, LVs are distributed throughout most of the body,[159] responsible for collecting ISF and entering into blood circulation via the thoracic duct.[160] Immunosurveillance is a process in which potential peptides containing antigen recognition are transported by lymph fluid to lymph nodes, where antigens are presented to lymphocytes by dendritic cells. However, the immunosurveillance contribution of the lymphatic system in the brain is always neglected, because LVs are considered to be absent in the brain. Since the brain's high metabolism and rich blood vessels inevitably lead to the leakage of its substances into ISF, the ability of the brain to remove waste has become the focus of research.[161] The discovery of the glymphatic system and meningeal lymphatics has overturned our understanding of brain immunity.

3.4.1 | Glymphatic system

The glymphatic system is a paravascular pathway composed of vessels that are regulated by the water channel aquaporin 4 (AQP4) in the astroglial end feet of the glia limitans.[162] Tracers injected into CSF cross the glial limitans along paravascular spaces and mix with ISF, and ultimately the tracers may drain back into the CSF of the subarachnoid space or drain along the walls of veins.[163] The exchange of CSF-ISF mixture facilitates the efficient clearance of interstitial proteins and peptides, including Aβ.[163–166] Aggregation of tau is one of the pathological features in TBI, which is known as a risk factor for ADRD.[167] Of note, the function of the glymphatic system in patients with TBI is reduced by ~60%. In AQP4$^{-/-}$ mice with TBI, impairment of the glymphatic pathway deteriorated and promoted the aberrant accumulation of p-tau in the ISF of brain parenchyma.[168]

3.4.2 | Meningeal lymphatics

Meningeal lymphatics is located in the dura mater and near the meningeal blood vasculature.[169,170] Tracer injected into ISF can be absorbed into brain parenchyma through meningeal lymphatics.[169,170] In the zebrafish brain, brain lymphatic endothelial cells (BLECs) were discovered and hallmarked with lymphatic marker genes, such as the transcription factor prosperohomeobox 1a (PROX1A), the LV endothelial hyaluronan receptor 1 (LYVE-1), and the vascular endothelial growth factor receptor 3 (VEGFR3).[159,171,172] BLECs and microglia have a division of labor in waste removal and immune function. BLECs more effectively uptake proteins, polysaccharides, and virus particles, while microglia is exclusively responsible for larger particles like bacteria.[161] In this case, meningeal lymphatics is considered a possible drainage path for macromolecules in CSF directly into the cervical lymph nodes (CLNs), such as Aβ and tau protein in ADRD.

Aging, as the most substantial risk factor for ADRD development, was found to impair meningeal lymphatic function associated with decreased VEGFC expression in aged mice.[173] Although Da Mesquita did not find a significant alteration of VEGFR3 in lymphatic ECs in aging mice (20 to 24 months), the differential expression of lymphangiogenic growth factors indicated impaired meningeal lymphatics.[174] As a result of AAV1-CMV-mVEGF-C treatment, meningeal lymphatic function was enhanced, which was reflected in increased CSF tracer drainage into deep CLNs and the higher rate of tracer influx into the brain parenchyma; however, LV coverage in the nodes was not increased.[174] On the one hand, 5xFAD mice generally have a marked deposition of Aβ in the brain at 3 months of age,[175] but their morphology and coverage of meningeal LVs had no difference with WT mice; on the other hand, in the 5xFAD mice of a control group, no significant Aβ deposition could be detected in the meninges, while obvious deposition of Aβ was found in 5xFAD mice with ablated meningeal LVs.[174] This finding supports the idea that the meningeal lymphatics is a drainage path involved in the removal of Aβ. Moreover, K14-VEGFR3-Ig mice with a complete lack of LVs had a significantly higher amount of tau in the brain than WT mice,[176] indicating the loss of meningeal lymphatics impairs the function of tau clearance.

A model hypothesis of tau clearance between the glymphatic and meningeal lymphatic systems was proposed, that is, tau is cleared by the glymphatic lymphatic system to the CSF after ISF release, subsequently drained by the meningeal lymphatic system to CLNs, and finally to the periphery.[176]

3.5 | Tau and platelet

Platelets are responsible for hemostasis and thrombosis, so its activation plays a pivotal role in the progression of atherosclerosis and vascular events. Human platelets generate more than 90% of the circulating amyloid precursor protein (APP).[177,178] As a proteolytic fragment of APP, Aβ peptide is released after platelet activation.[179,180] Notably, Aβ in plasma can come from platelets or the brain through the BBB, because Aβ is able to cross the BBB in pathological conditions.[181,182] Subsequently, Aβ in plasma motivates platelet activation,[183–185] platelet adhesion, and thrombus formation. But it was found that platelet aggregation in brain vessels preceded the appearance of amyloid deposition in APP-Swedish Dutch Iowa mice.[186] In addition, platelet activation in AD patients with rapid cognitive decline is possibly caused by the stimulation of platelets via damaged cerebral ECs[187] or membrane abnormalities in platelets.[188] In aged 3xTg-AD mice, platelets have a more avid adhesion on matrices compared to age-matching WT mice, including fibrillar collagen, von Willebrand factor, fibrinogen, and amyloid peptides, though the number and glycoprotein expression of platelets are normal.[189] Binding GPIIb-IIIa and P-selectin, activated platelets adhere on ECs at the sites of vascular lesions and recruit leukocytes on vascular wall, cotriggering vascular inflammation and contributing to dementia progression.[190,191] Platelet activation increased the risk of vasoconstriction and prothrombotic atheroemboli to the brain, which is linked to cognitive impairment.[192,193] In this context, it is observed that CBF is reduced in early AD patients.[194] Maccioni et al. first found tau present in platelets.[195] Characterized by a highly fragmented form, the expression of platelet tau in AD patients decreased.[196] Interestingly, high molecular weight (HMW) tau (80 to 240 kDa) increased in AD

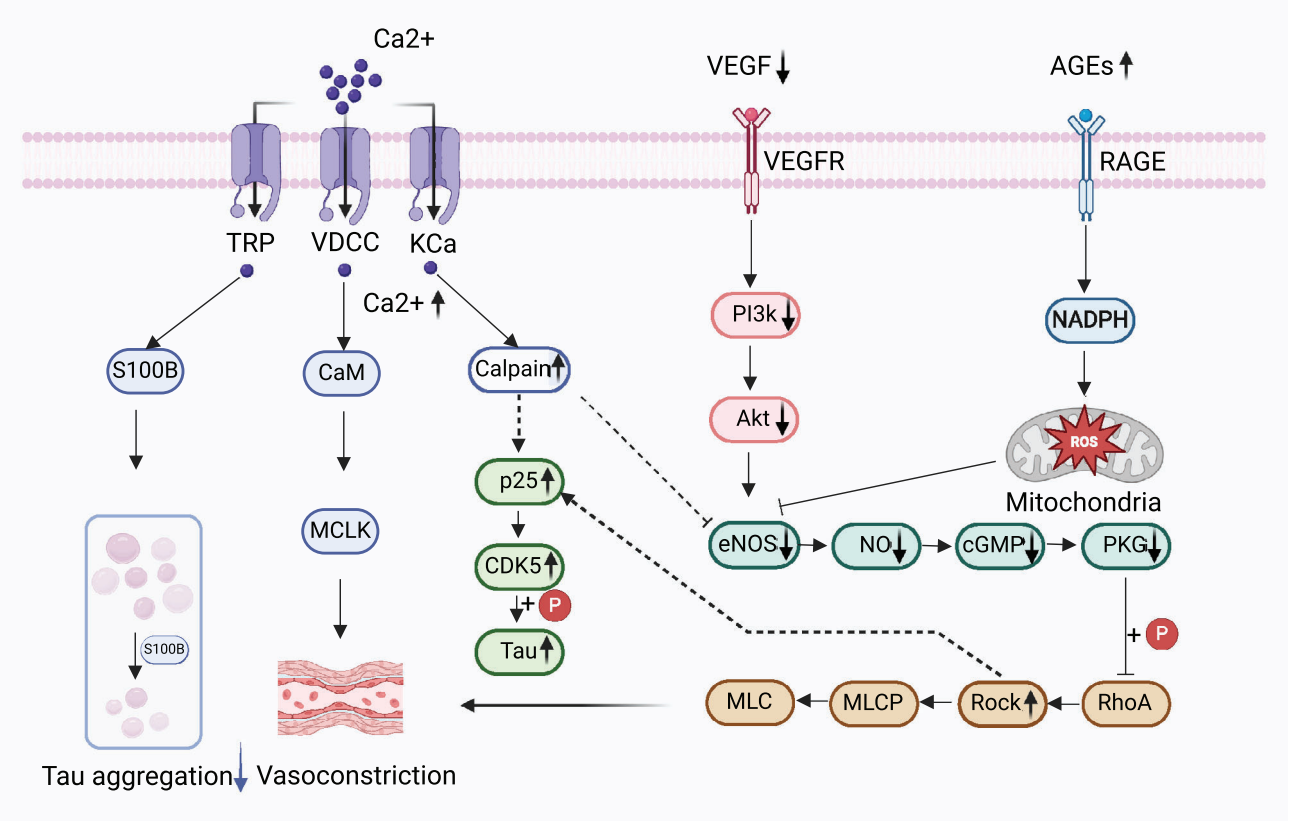

FIGURE 3 Tau and potential molecular mechanism in vasculature. Created from https://app.biorender.com (accessed on 12 February 2025).

patients.[195] However, the mechanism between platelets and tau is not clear.

3.6 | Tau and mitochondria

Mitochondria play a central role not only in neuronal energy metabolism and cognitive function but also in maintaining the normal physiological state of blood vessels. Meanwhile, mitochondrial dysfunction is a key factor in neurodegenerative diseases, including AD.[197,198] The mitochondria-derived peptide SHLP2 regulates energy homeostasis by activating hypothalamic neurons.[198] Mitochondrial dysfunction can lead to ATP depletion, which impairs neurotransmitter release and disrupts cellular energy supply, contributing to neuronal damage, especially in conditions such as cerebral ischemia.[199] In the context of TBI, mitochondrial dysfunction triggered by cortical spreading depolarization alters vascular cell function, disrupting neurovascular coupling and CBF.[200] OS exacerbates mitochondrial dysfunction, affecting mitochondrial morphology and energy metabolism. Under OS, mitochondria undergo adaptive responses such as increased mitochondrial biogenesis and fission to cope with damage. However, if this adaptive response persists, it can compromise long-term cellular function and health.[201] In glial cells, tau proteins help alleviate OS by clearing reactive oxygen species (ROS), but imbalances in tau levels – either deficiency or excess – can disrupt these protective functions and contribute to neurodegeneration.[202] Under stress conditions, such as cellular damage or disease, mitochondria accumulate unfolded proteins and activate the mitochondrial unfolded protein response, which helps restore cellular homeostasis and protects vulnerable cells.[203] Impaired mitochondrial calcium signaling has been shown to enhance the inflammatory response in macrophages, which links mitochondrial dysfunction to age-related inflammation.[204] Mitochondrial dysfunction directly affects energy metabolism and survival of neurons, and is closely tied to both Aβ deposition and tau pathology, which highlights its potential as a therapeutic target for intervention.[205]

4 | MOLECULAR MECHANISM BETWEEN CEREBRAL VASCULATURE AND TAU

Vascular dysfunction is closely associated with neurodegenerative diseases, especially those characterized by tau pathology. Risk factors like hypertension, diabetes, and atherosclerosis contribute to BBB disruption, ischemia, and OS, which promote tau aggregation and abnormal phosphorylation. These tau-induced changes, including endothelial dysfunction, BBB breakdown, and impaired CBF, exacerbate neuronal damage and accelerate disease progression. Understanding the molecular mechanisms behind these vascular–neuronal interactions is critical for revealing how tau pathology affects the vasculature and for identifying potential therapeutic targets (Figure 3). The different molecular mechanisms discussed are summarized in Table 1.

TABLE 1 Interactions between tauopathy and molecular mechanisms.

Targets	Vasculature	Tauopathy	Main findings
eNOS/NO	(1) Vasorelaxation (2) Cerebral vascular growth (3) Angiogenesis	NFTs	VEGF and eNOS-positive microvessels inversely correlated with the presence of NFTs in AD.
		Insoluble tau	8-nitro-cGMP modified by NO decreased insoluble tau.
		Hyperphosphorylated tau	Decreased eNOS associated with the elevated expression of CDK5 and p25, as well as 25/p35 ratio.
Ca^{2+} related channel	(1) Vasorelaxation (2) Vascular contraction	Aβ and/or NFT	Enhanced SKCa/IKCa channels function and hyperpolarization-induced $[Ca^{2+}]_i$ increase was observed only in males.
		Hyperphosphorylated tau	VDCCs activated PKCα/Akt, which enhanced the Ser9-phosphorylation of GSK3β and inhibited tau Ser396-phosphorylation.
		Hyperphosphorylated tau	The activated TRPV4 upregulated the cholesterol levels in primary neurons and aggravated the tau hyperphosphorylation.
		Hyperphosphorylated tau	The activated TRPV1 facilitated the degradation of tau and inhibited the hyperphosphorylation of tau.
Ca^{2+}-related regulators	(1) Neuroinflammation (2) BBB integrity	NA	Tauopathy disrupting BBB integrity is involved in C3a/C3aR signaling, resulting in Ca^{2+} release and VE-cadherin junctions.
		Hyperphosphorylated tau	Disrupting the activation of Ca^{2+}/CaMKIV reversed tau phosphorylation.
		Tau aggregation	S100B released from astrocytes binds several sites of tau sequence in a strict Ca^{2+}-dependent manner, and that inhibits tau aggregation and seeding.
		Tau droplet	Ca^{2+} binding activates the incorporated S100B chaperone of tau droplets, prompting the shift of tau droplets from miscible liquid phase.
		Hyperphosphorylated tau	Ca^{2+} regulates the action of calpain to cleave p35 to form p25, activates p25/CDK5, and causes the hyperphosphorylation of tau.
Rho/Rock	(1) EC permeability (2) VSMC contractility (3) Inflammation	Hyperphosphorylated tau	Activated GEF-H1/Rho pathway, resulting in the increased EC permeability and inflammation, which may be associated with the hyperphosphorylation of tau.
		Hyperphosphorylated tau and oligomeric tau	Rho-kinase inhibitors reduced the levels of phosphorylated tau and oligomeric tau.
		Hyperphosphorylated tau	ROCK inhibition reduced the p25 protein level in hippocampus of cerebral ischemia rats, which is associated with the reduction of tau phosphorylation.
RAGE	(1) Endothelium dilation (2) BBB integrity (3) Mitochondrial disruption	Uptake of tau	In SH-SY5Y cells, RAGE promoted the uptake and internalization of tau, but the uptake and transneuronal propagation of tau reduced in rTg4510 mouse with RAGE knockout.
		Hyperphosphorylated tau	The activation of RAGE in VSMCs inhibited endothelium-dependent dilation, which may be associated with tau phosphorylation.

Abbreviations: BBB, blood—brain barrier; CaMKIV, calmodulin-dependent protein kinase IV; CDK5, cyclin-dependent kinase 5; eNOS, endothelial nitric oxide synthase; GEF-H1, guanine nucleotide exchange factor-H1; MT, microtubule; RAGE, receptor for advanced glycation end products; TRPV1, transient receptor potential vanilloid 1; VDCCs, voltage-dependent calcium channels; 8-nitro-cGMP, 8-Nitroguanosine 3,5 -cyclic monophosphate; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

4.1 | eNOS/NO

As a potent vasodilator in regulating blood flow, eNOS has been reported to be involved with abnormalities associated with AD.[206] Generated by eNOS in the vascular endothelial layer, NO plays an important role in the regulation of vasorelaxation.[207] The production of cyclic 3′-5′ guanosine monophosphate (cGMP) is stimulated by NO through the activation of soluble guanylate cyclase (sGC), ultimately producing vasodilatory effects of smooth muscle via actin-myosin light chain (MLC).[208] Thus, the eNOS/NO/cGMP pathway is

one of the approaches that affect vasorelaxation. In addition, eNOS is involved in the mechanism of alterations in BBB permeability and inhibition of cerebral vascular growth and influences angiogenesis, neurogenesis, and axonal transmission.[209] Located on ECs, vascular endothelial growth factor (VEGF) binds its receptor and triggers several downstream signaling pathways, such as phosphoinositide 3-kinase (PI3K)/protein kinase (PKG) B (Akt) and eNOS, which has a regulatory effect on angiogenesis.[210,211] In addition to regulating blood vessels, eNOS/NO has been found to affect the modification of tau and may be a target for the treatment of ADRD. Controlled with non-demented individuals, significant inverse correlations exist between both VEGF and eNOS-positive microvessels and the presence of NFTs in AD cortices, and VEGF density significantly positively correlates with eNOS density. In view of eNOS being a downstream target of Akt, VEGF may regulate eNOS through the PI3K/Akt signaling pathway.[212] Moreover, intermolecular cysteine disulfide bonds among tau accelerate their aggregation.[213] NO also modified 8-Nitroguanosine 3,5-cyclic monophosphate (8-nitro-cGMP) and contributes to the binding between cysteine residues of tau and cGMP, a process termed protein S-guanylation.[214] In HEK293T cells, the aggregation and fibrils of tau are inhibited by S-guanylated tau, and in P301L tau-expressing Neuro2A cells, sarcosyl-insoluble tau was reduced after 8-nitro-cGMP intervention.[215] It is indicated that 8-nitro-cGMP may be a regulator between NO and tau pathology. Austin et al. provided another mechanism by which eNOS protected neurons from tau phosphorylation.[216] The hyperphosphorylation of tau is partly caused by abnormal cyclin-dependent kinase 5 (CDK5). The expressions and activity of regulatory targets of APP/PS1/eNOS$^{-/-}$ mice were significantly higher than WT mice and APP/PS1 mice, including the higher level p25 and 25/p35 ratio and higher activity of CDK5.[216] Notably, the entry of tau oligomers into ECs leads to the blocking of eNOS activation, resulting in a vicious circle of tau pathology secondary to the inhibition of NO production and EC senescence.[21]

4.2 | Calcium

The calcium hypothesis of AD and brain aging was first proposed by Khachaturian,[217] but it only focused on neurons. The breakdown of calcium homeostasis, especially in intracellular compartments, disrupts the equilibrium governing the regeneration and degeneration of neurons through various regulators.[217] In addition, Ca^{2+} concentration ($[Ca^{2+}]_i$) affects the vasculature function.

4.2.1 | Ca^{2+}-related channel

Voltage-dependent calcium channels (VDCCs), also referred to as Ca^{2+}-Na^{+} channels, which permeate both calcium ions and sodium ions and widely exist at the cell membrane. With membrane depolarization, activated VDCCs lead to Ca^{2+} influx and resulting cellular contraction.[218] In ischemic stroke (IS), underperfused capillaries are mainly due to pericyte constriction.[219,220] Either cytoplasmic $[Ca^{2+}]_i$ accumulation or rising vasoconstrictors aggravate pericyte constriction in IS.[221] Deteriorative ischemic damage causes pericellular death and loss over time.[219,220] Subsequently, the decrease of CBF and BBB damage also becomes the crucial pathological mechanism in IS.[222] Korte et al.[221] found Cl^- efflux was triggered, which was attributed to a small increase in cytoplasmic $[Ca^{2+}]_i$ in pericytes, further led to cell depolarization and voltage-gated calcium channels opening. The transmembrane protein 16A (TMEM16A), as the Ca^{2+}-activated channel of Cl^- efflux, is a crucial regulator of cerebral capillaries.[223] In a rodent stroke model, blocking TMEM16A improved cerebrovascular reperfusion via various effects, including slowing an ischemia-evoked $[Ca^{2+}]_i$ rise in pericytes, delaying capillary constriction, and reducing pericyte death.[221]

On the other hand, as a result of the increase in intracellular $[Ca^{2+}]_i$ that produces vasodilator autacoids (such as NO, PGI_2, and epoxides of arachidonic acid), the activation of endothelium-derived "hyperpolarization" (EDH) contributes to vascular relaxation via transmission through myoendothelial gap junctions to SMCs, ultimately ensuring sufficient blood supply to organs or tissues.[224] Stimulation of G_q-protein-coupled receptors (GPCRs) and/or Ca^{2+} influx facilitates the rise of intracellular $[Ca^{2+}]_i$, subsequently activating small and intermediate Ca^{2+}-activated K^+ (SK_{Ca}/IK_{Ca}) channels to increase the membrane potential (V_m).[225,226] SK_{Ca}/IK_{Ca} channel function in cerebrovascular ECs was reduced in old female C57BL/6N mice (vs young female and old male). In 3×Tg-AD mice, compared to the phase without Aβ and NFT, their presence lowered the coupling of ΔV_m-to-$\Delta[Ca^{2+}]_i$ of cerebrovascular ECs in both sexes, in the pathology of Aβ and/or NFT, enhanced SK_{Ca}/IK_{Ca} channel function, and a resulting hyperpolarization-induced $[Ca^{2+}]_i$ increase was observed only in males.[227] The results are consistent with a higher incidence of AD in females in the clinic,[228,229] but the mechanism between sex difference and the SK_{Ca}/IK_{Ca} channel function impacts CBF still needs further study. Moreover, in bovine adrenal chromaffin cells with Nav1.7 isoform, veratridine-induced Na^+ influx via Nav1.7, and successively Ca^{2+} influx via VDCCs activated downstream PKCα and Akt, which enhanced the Ser^9-phosphorylation of GSK3β and consequently, inhibited tau Ser^{396}-phosphorylation.[230] VDCCs also are activated by transient receptor potential channels (TRPCs), which are Ca^{2+}-permeable non-selective cation channels. Membrane depolarization is triggered by cation influx via TRPCs, leading to Ca^{2+} influx via VDCCs. Increased $[Ca^{2+}]_i$ concentration enhances the binding of calmodulin-Ca^{2+} complexes to MLCK, which is directly involved in vascular contraction.[231,232] However, different TRPCs have opposite effects on tau. Although the activated TRPV4 promoted NO release, contributing to vasodilation, it upregulated cholesterol levels in primary neurons and aggravated tau hyperphosphorylation in the cortex and hippocampus of the P301S tauopathy mouse model.[233,234] Conversely, the activation of TRPV1 had a neuroprotective effect on facilitating the degradation of tau and inhibiting the hyperphosphorylation of tau, possibly by initiating autophagy and a decrease in phosphorylated GSK3β(ser9) levels in neurons.[235,236] Thus, the disruption of calcium homeostasis is an effector of AD.

4.2.2 | Ca^{2+} related regulators

As an immune signal in neuroinflammation, C3 is secreted by astrocytes and in favor of aggravating neurodegenerative pathology.[237,238] C3a, the active peptide of the complement component C3, is released and binds on its cognate receptor C3aR. Aged brain of WT mice (20 months) showed positive C3aR staining in VE-cadherin^{+} cerebrovascular ECs, $CD8^{+}$ T-cell infiltration, decreased average cross-sectional area of blood vessels, more tortuose vessels, and increased BBB permeability.[239] As the secondary messenger of C3a, Ca^{2+} release was triggered, which further activated the calcium-dependent kinase calmodulin. Ultimately, this pathway formed actin stress fibers and initiated tensile stress at the cell membrane, leading to the disruption of VE−cadherin^{+} junctions and BBB integrity.[239–241] Of note, comparison of gene expression between PS19 and PS19 C3ar1$^{-/-}$ transgenic mice showed consistent results with endothelial responses to C3a, including inflammatory infiltration, regulation of cell adhesion molecules, and cytoskeleton.[239] Thus, the mechanism of tauopathy disrupting BBB integrity is involved in C3a/C3aR signaling, resulting in Ca^{2+} release and VE−cadherin junctions. The progression of tauopathy may be involved in immune signaling dysfunction, which leads to calcium dyshomeostasis. In addition, in HEK293 cells, tau phosphorylated at Thr205 in the nuclear fraction was found and caused increased nuclear Ca^{2+} concentrations and levels of phosphorylated Ca^{2+}/calmodulin-dependent PKG IV (CaMKIV).[242] Meanwhile, disrupting the activation of Ca^{2+}/CaMKIV reversed tau phosphorylation.[242] The link of increased Ca^{2+} concentration and tau hyperphosphorylation is mutual and forms a harmful loop. Ca^{2+} also modulates the activity of inflammatory alarmins, such as S100B. Released from astrocytes, S100B binds several sites of tau sequence in a strict Ca^{2+}-dependent manner, and that inhibits tau aggregation and seeding.[243] The droplets formed by tau liquid–liquid phase separation (LLPS) enhances the formation of toxic conformers and oligomerization of tau. Ca^{2+} binding activates the incorporated S100B chaperone of tau droplets, prompting a shift of tau droplets fromto the miscible liquid phase.[244] Ca^{2+} also regulates the action of calpain to cleave p35 to form p25, ultimately activating p25/CDK5 and causing the hyperphosphorylation of tau.[245] Acivated eNOS/NO signaling attenuates the increased activity of Ca^{2+}/calpain/p25 in vasculature[246–248] and neurons, which inhibits tau hyperphosphorylation.

4.3 | Rho/Rock

Small GTPases of the Rho family are essential for the regulation of physiological functions, including RhoA, Rac1, and cdc42.[249] Both Rho-associated kinases and Rho-associated coiled-coil forming PKGs (ROCKs) are the downstream effectors of RhoA, playing an important role in regulating VSMC contractility, EC permeability, neuronal plasticity, and so forth.[249] ROCKs promote VSMC contraction via three pathways: activated myosin light chain kinase (MLCK), increased MLC and protein phosphatase 1 regulatory subunit 14A (CPI 17) phosphorylation, a resulting increased phosphorylated MLC after phosphorylating and inactivating MLC phosphatase (MLCP).[249] Furthermore, ROCKs and endothelial function have mutual crosstalk. Vasoactive factors released by ECs can regulate RhoA activity and modulate the contractile state of VSMCs.[250] NO increases intracellular cGMP levels and the subsequent activation of cGMP-dependent PKG by entering freely into VSMCs, ultimately leading to the inactivation of RhoA.[251] Meanwhile, the RhoA/ROCK pathway effects eNOS activity and eNOS mRNA stability.[252,253] MT is an important component of the cytoskeleton. Belonging to the family of MT-associated proteins, tau stabilizes and promotes MT assembly.[254] It has been reported that *Staphylococcus aureus* destabilized MT and subsequently activated the MT-bound Rho-specific guanine nucleotide exchange factor-H1(GEF-H1)/Rho pathway, resulting in increasing EC permeability and inflammation.[255] Notably, tau at Ser262 has been verified as the phosphorylation site of Rho-kinase or ROCKs.[119] There may be an interaction between tauopathy and ROCK activity. Once tau is abnormally phosphorylated, its affinity for MTs is weakened, resulting in the formation of tau oligomers and ultimate NFTs. In a tauopathy model of nerve cells and animal models, Rho-kinase inhibitors reduced the levels of phosphorylated tau and oligomeric tau.[256] In addition, ROCK inhibition reduced the p25 protein level in the hippocampus of cerebral ischemia rats, which is associated with a reduction of tau phosphorylation.[257] It is known that soluble tau oligomers damage the functions of ECs, which leads to a deterioration of tauopathy.[21] However, the regulation of tau by Rho/ROCK is confined to neurons, and its effect on tau in the vasculature remains unclear and warrants further study.

4.4 | RAGE

Advanced glycation end products (AGEs) are mainly produced by glycoxidation and accumulate along the lifespan.[258] In addition to AGEs, the receptor for AGEs (RAGE) binds a number of distinct ligands, such as S100/calgranulins and high mobility group box 1 (HMGB1), and oligomeric forms of Aβ peptide.[259,260] Thus, RAGE is integral to oxidative and inflammatory stress. Pathological conditions, like diabetes, aging, ischemia, inflammation, and cancer, enhance the production of ligands, leading to a higher expression of RAGE.[261] Most of them are also known as risk factors for ADRD. In the CNS, RAGE is expressed in a wide variety of cells, such as neurons, microglia, and brain vascular cells.[262] Endothelial cell dysfunction precedes and promotes the deterioration of vascular function in diabetes.[263] OS induced by methylglyoxal produced from diabetes metabolism causes EC dysfunction in an AGE-RAGE regulatory manner, while anti-OS treatment can reverse damage.[263,264] The accumulation of AGEs disrupts mitochondrial energy metabolism and exacerbates OS and inflammation, thereby undermining the integrity of the BBB.[265,266] In SH-SY5Y cells, RAGE promoted the uptake and internalization of tau; however, when RAGE was knocked out in rTg4510 mouse, the uptake and transneuronal propagation of tau diminished.[267] In addition, AGE combined with RAGE activates NADPH oxidase (NOX) to produce ROS, and this has been investigated in the CNS, such as neurons,

astrocytes, and endothelium.[268,269] In rat vascular smooth muscle, the activation of RAGE by AGEs enhances the formation of NOX subtype 1/4 and ROS, which inhibits the production of NO and the activity of the voltage-sensitive K^+ channels and large-conductance K_{Ca}, consequently causing the inhibition of endothelium-dependent dilation.[269] In ECs, eNOS is known as an upstream factor that produces NO and regulates vasodilation, and the knockout of eNOS of APP/PS1 mice had a higher activity of CDK5/p25, which was linked to the hyperphosphorylation of tau.[216] T2DM is one of the crucial vascular clinical risk factors in ADRD, and vascular endothelial dysfunction becomes the early driving pathogenesis. Since AGEs are produced by T2DM, the possibly resulting pathway of tau hyperphosphorylation in ECs may be involved in the activation of ROS and the inhibition of NO.

5 | CONCLUSION

Vasculature is an important part of the CNS, which affects CBF, central immune and metabolic functions. Clinical VRFs such as abnormal BP, diabetes, and hyperlipidemia affect the normal structure and function of the vasculature, leading to the disruption of the BBB and vasoconstriction and dilation dysfunction, which are involved in the accumulation of AGEs, the disruption of calcium homeostasis, the reduction of vasodilator factors, and the activation of vasoconstriction modulators. Tauopathy is one of the pathological features of ADRD. Preventing the abnormal formation, deposition, and spread of tau in ADRD has become an essential goal. This review found that the interaction of abnormal vasculature and tau pathology has formed a harmful loop, which may become a therapeutic target in addition to neurons and immune cells.

AUTHOR CONTRIBUTIONS

Chuyao Huang and Wei Zhao selected the topic and conceived the study. Zhenwen Wei, Ningxiang Zheng, and Jingsi Yan screened the eligible studies and collated the manuscript. Jiayu Zhang and Xinyi Ye were responsible for proofreading and drawing the figures. Chuyao Huang drafted the manuscript of the current review. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

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