

Contribution of cerebral microvascular mechanisms to age-related cognitive impairment and dementia

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ABSTRACT

Cognitive impairment and dementia are significant health burdens worldwide. Aging, hypertension, and diabetes are the primary risk factors for Alzheimer's disease and Alzheimer's disease and related dementias (AD/ADRD). There are no effective treatments for AD/ADRD to date. An emerging body of evidence indicates that cerebral vascular dysfunction and hypoperfusion precedes the development of other AD pathological phenotypes and cognitive impairment. However, vascular contribution to dementia is not currently well understood. This commentary highlights the emerging concepts and mechanisms underlying the microvascular contribution to AD/ADRD, including hypotheses targeting the anterograde and retrograde cerebral vascular pathways, as well as the cerebral capillaries and the venous system. We also briefly discuss vascular endothelial dysfunction, oxidative stress, inflammation, and cellular senescence that may contribute to impaired cerebral blood flow autoregulation, neurovascular uncoupling, and dysfunction of cerebral capillaries and the venous system.

KEYWORDS

aging, dementia, cerebral blood flow, neurovascular coupling, capillary, cerebral venous system

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INTRODUCTION

Cognitive impairment and dementia are global healthcare crises. Alzheimer's disease (AD) and vascular dementia are the most common forms of dementia, accounting for 50–75% and 20% of all cases, respectively. There are no cures for AD and AD-related dementias (AD/ADRD). Among six drugs (rivastigmine, galantamine, memantine, donepezil, memantine combined with donepezil, and aducanumab) approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD to date, only aducanumab potentially slows the progression of AD [1]. Many risk factors have been identified contributing to the onset and development of cognitive impairment and dementia, including age, genetics, cardiovascular and cerebral vascular diseases, traumatic brain injury, spinal cord injury, inadequate physical activity or sleep, excessive alcohol use, smoking, depression, and many more [2, 3]. In the United States, eleven percent of people age 65 and older have dementia, and an estimated 6.2 million have AD as of 2021. The costs of treating and caring for dementia in 2021 were \$355 billion. Moreover, AD is the fifth leading cause of death in people age 65 and older. In patients age 85 and older who died of COVID-19, eight and twenty percent had AD and vascular dementia, respectively [1].

AD/ADRD are progressive neurodegenerative disorders associated with memory deficits. Age is the greatest risk factor for AD/ADRD, especially in the late-onset cases correlated with genetic mutations in the apolipoprotein e4 gene (*APOE-e4*), the genes for amyloid precursor protein (APP) and the presenilin 1 and 2 (PS1 and PS2) proteins. However, these genetic mutations account for only a small percentage of AD cases, and cognitive impairment appears many years after pathological changes are detected in the brains of AD/ADRD patients and animals [4]. Beta-amyloid ($A\beta$) plaques and intraneuronal tau-containing neurofibrillary tangles (NFTs) were thought to initiate the neurodegeneration and cognitive impairment seen in AD, but the failure of clinical trials targeting these pathways has led the community to reconsider other treatment options [5]. Emerging studies have demonstrated that brain hypoperfusion is one of the causal factors of neurodegeneration that induces dementia in AD/ADRD [6]. Cerebral microvascular mechanisms are now considered to be one of the major players in age-related cognitive impairment and dementia, similar to the original thoughts from Alois Alzheimer's time (1900s) to the 20th century [7]. Although underlying mechanisms remain elusive, the vascular hypothesis has been repeatedly validated in many community-based clinical-pathological studies and a recent human brain vascular atlas study demonstrating that 30 of the top 45 AD genome-wide association study (GWAS) genes are expressed in the cerebral vasculature [8]. This editorial seeks to discuss the current understanding of the contribution of cerebral microvascular mechanisms to age-related cognitive impairment and dementia.

CEREBROVASCULAR MECHANISMS IN AGE-RELATED COGNITIVE IMPAIRMENT AND DEMENTIA

The brain is perfused by the internal carotid artery and the vertebral artery systems. These two arteries rejoin at the Willis circle, which acts as a base for the main cerebral arteries and provides blood flow to different brain regions. Pial large arterioles in the pia mater become smaller penetrating arterioles and parenchymal arterioles (PAs) that dive into the cortex to irrigate the gray and white matter. Vascular smooth muscle cells (VSMCs) or pericytes, endothelial cells



(ECs), and extracellular matrix are major components of arteries and both large and small arterioles. The neurovascular unit (NVU) is located at the cerebral capillaries downstream of the PAs, which is composed of the ECs, pericytes, astrocyte end-feet, dendrites of neurons, and extracellular matrix [9]. Several mechanisms have been suggested to contribute to cerebrovascular dysfunction, brain hypoperfusion and dementia. Here, we summarize as mechanisms targeting the anterograde and retrograde cerebral vascular pathways, as well as the cerebral capillaries and the venous system (Fig. 1).

Mechanisms targeting the anterograde cerebral vascular pathway

One of the most commonly affected vessels within the cerebral vasculature is the middle cerebral artery (MCA), which is the largest branch of the internal carotid artery [10]. The PAs are high resistance vessels and key regulators of cerebral blood flow (CBF) that fine-tune capillary pressure and flow [11]. Damage to the VSMCs and alpha-smooth muscle actin (α -SMA) positive pericytes have been reported to impair the myogenic response (MR) of cerebral arteries and arterioles, such as the MCAs and PAs, which diminishes CBF autoregulation in AD/ADRD [12–14]. Impaired CBF autoregulation fails to prevent elevated pressure transmission to downstream capillaries resulting in blood-brain barrier (BBB) leakage, neurodegeneration, and cognitive impairment [15, 16]. Diminished CBF autoregulation has been implicated in cerebral vascular disease, stroke, AD, hypertension-, and diabetes (DM)-related ADRD animal models [17–21]. Thus, the MR and CBF autoregulation are mechanisms targeting the anterograde (artery-

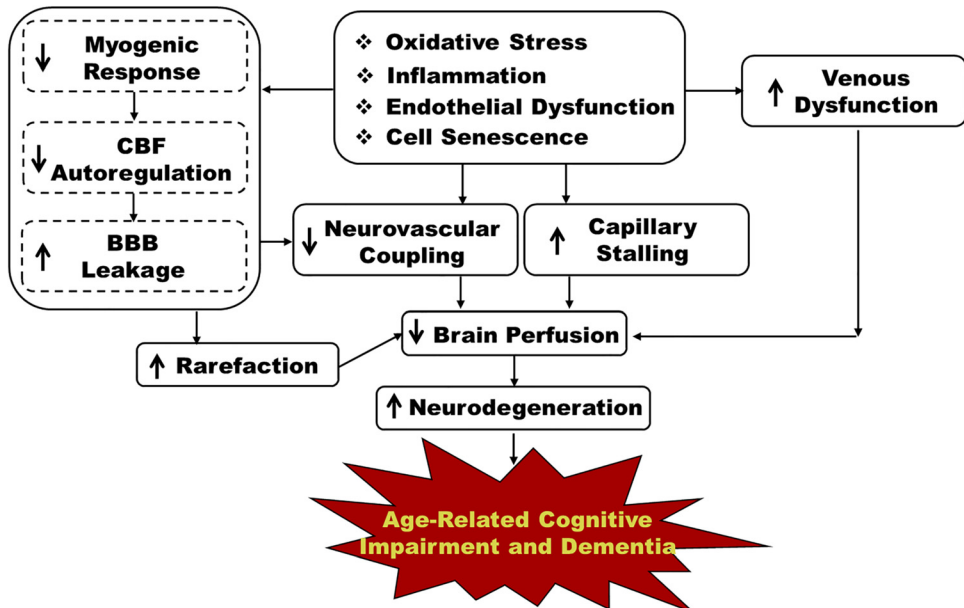


Fig. 1. Mechanisms that target the anterograde and retrograde cerebral vascular pathways, as well as the cerebral capillaries and the venous system for age-related cognitive impairment and dementia.

CBF: cerebral blood flow; BBB: blood-brain barrier



arteriole-capillary) cerebral vascular pathway to regulate brain perfusion and contribute to the development of age-related cognitive impairment and dementia.

Mechanisms targeting the retrograde cerebral vascular pathway

During intense local neuronal activation, independent of changes in blood pressure, healthy individuals display enhanced brain perfusion, which is achieved by functional hyperemia. This is due to the activation of an inward-rectifier K^+ (Kir2.1) channel that hyperpolarizes capillary ECs at the NVU. The hyperpolarization signaling rapidly propagates, in a retrograde manner, along capillaries to upstream PAs via gap junctions, resulting in robust vasodilation and increased local CBF in the neuronal activated area. Neurovascular uncoupling has been found in AD/ADRD patients and animals associated with reduced cerebral capillary EC Kir2.1 activity [22–25].

Mechanisms targeting the cerebral capillaries

Another mechanism contributing to age-related cerebral microvascular dysfunction is capillary stalling and cessation of capillary blood flow. Many of the mechanisms underlying capillary stalling can be traced back to increased inflammation and reactive oxygen species (ROS) production, EC dysfunction, glial activation, capillary pericyte constriction, and altered leukocyte rolling and adhesion to the vascular wall [26, 27]. The phenomenon of capillary stalling has been observed in older individuals and in AD/ADRD [27], therefore we depict it as a cerebral vascular mechanism targeting the capillaries to regulate brain perfusion.

Mechanisms targeting the cerebral venous system

There have been fewer studies focusing on understanding potential mechanisms targeting the cerebral venous system in age-related cognitive impairment and dementia. The blood pressure and flow velocity are low in the venous circulation, although it contains a large volume of fluid. In the elderly with AD/ADRD, cerebral venous system-related dysfunction potentially contributes to venous distension, BBB leakage, neuroinflammation, thrombosis and micro-hemorrhages, and neurodegeneration, which results in brain hypoperfusion and ischemic neuronal damage [28, 29].

Cerebral microvascular alteration in aging, DM and hypertension

Notably, despite the high prevalence, mortalities, and morbidities of AD/ADRD most commonly found in the elderly, aging alone is insufficient to cause AD/ADRD [1]. Aging and associated pathophysiological processes alter the structural and functional integrity of cerebral vasculature that can significantly reduce brain perfusion [30, 31]. Underlying mechanisms that contribute to these alterations include inflammation, oxidative stress, mitochondrial dysfunction, cellular senescence and apoptosis in all types of vascular cells concurrent with the activation of matrix metalloproteinases (MMPs) and enhanced vascular fibrosis that affect all cerebral vascular segments along the vascular beds [24, 32–38].

DM and hypertension are the most common diseases in the aging population that are associated with a higher risk of AD/ADRD. Recent studies suggest that aging, hypertension or DM-related ADRD and AD all exhibit cerebral microvascular dysfunction via various



mechanisms that eventually lead to a final common outcome of localized cerebral hypoperfusion, neurodegeneration, brain atrophy, and cognitive impairment [6, 22, 39, 40]. Our recent studies demonstrated that BBB leakage and the neurocognitive deficit in an old non-obese type 2 DM rat were reversed by a sodium-glucose co-transporter 2 inhibitor (SGLT2i) without altering blood pressure. These effects were possibly due to the reversal of hyperglycemia-induced mitochondrial dysfunction in cerebral VSMCs and pericytes, the restoration of impaired MR of cerebral arteries and arterioles, the reversal of neurovascular uncoupling, and enhanced reduced pericyte and tight junction coverage in the cortex and hippocampus [13, 14, 18, 23, 41]. In young spontaneously hypertensive rats (SHRs) and angiotensin II (Ang II) rodent models of hypertension and young patients with essential hypertension, elevations in blood pressure promote inward remodeling of cerebral arteries and arterioles, resulting in an increase in the wall-to-lumen ratio and elevated cerebral vascular resistance which enhances the MR [34, 42, 43], similar to what is observed in young hypertensive individuals. Gradual loss of this crucial vascular protective mechanism in normal aging, especially when combined with other risk factors (such as DM and hypertension), shifts CBF autoregulation to lower pressures that fail to protect the cerebral microcirculation and the brain from damage [15, 33, 34]. In addition, continued hypertrophy of vessels and endothelial damage in the elderly promotes arteriosclerosis which can further exacerbate cerebral hypoperfusion, neurodegeneration, and loss of cognitive function. Moreover, the elevated vascular resistance may have direct effects on the cerebral capillaries to reduce capillary perfusion. In contrast, Dahl salt-sensitive (Dahl SS) and Fawn-hooded hypertensive (FHH) rat models of hypertension display impaired MR of the MCAs and PAs and CBF autoregulation [44, 45]. The Dahl SS and FHH rats contain genetic variants in the *Cyp4a* and *Add3* vasoconstrictor genes, respectively, which are homologous mutations in *CYP4A* and *ADD3*, found in participants in the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study) that have AD-like symptoms and pathological and cognitive features [46, 47]. Therefore, these hypertension models with genetic defects in genes involved in CBF autoregulation seem to directly enter the pathological status of essential hypertension in aging that is associated with brain hypoperfusion due to BBB leakage-related ischemic damage (Fig. 2). Additionally, loss of membrane expression of the ADD3 protein in the FHH rats dysregulates the actin cytoskeleton in VSMCs and podocytes, which also results in impaired renal hemodynamics and glomerular injury [48, 49].

Molecular and cellular mechanisms associated with cerebral vascular dysfunction in age-related cognitive impairment and dementia

Many potential molecular and cellular mechanisms have been proposed to contribute to cerebral vascular dysfunction in age-related cognitive impairment and dementia. Here, we briefly discuss several aspects that have been actively studied.

Oxidative stress

A large number of studies have implicated that increased oxidative stress contributes to cerebral microvascular dysfunction in aging. Excessive oxidative stress has been associated with aging, age-related cardiovascular, cerebral vascular, and neurodegenerative diseases in humans and animal models [30, 50–52]. Elevated ROS may attribute to the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, dysfunction of mitochondria in the vascular



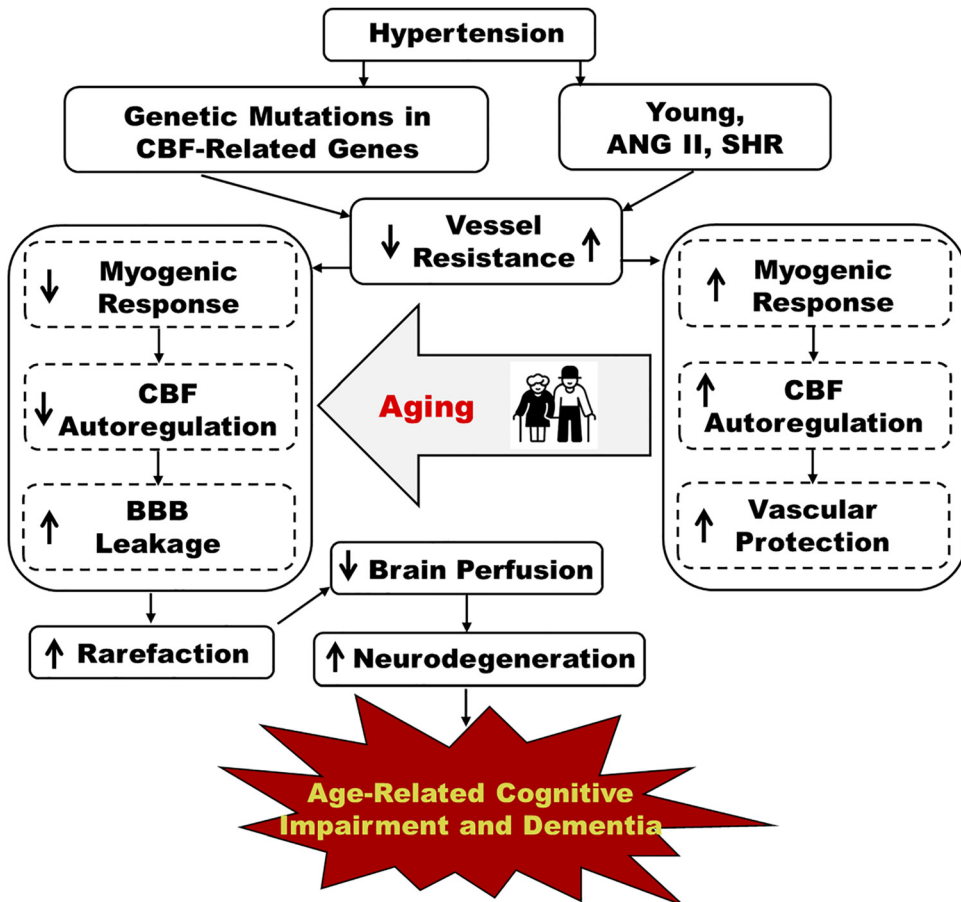


Fig. 2. Effects of Hypertension on age-related cognitive impairment and dementia.

Vascular remodeling and elevated myogenic tone protect the cerebral microcirculation from damage in young patients and Ang II and SHR animal models of hypertension. This vascular protection is lost with aging, and genetic hypertension models with mutations in CBF-related genes, leading to impaired autoregulation, BBB leakage, capillary damage, and decreased CBF that contribute to age-related cognitive impairments and dementia. ANG II: angiotensin II; SHR: spontaneously hypertensive rat; CBF: cerebral blood flow; BBB cognitive dysfunction

cells, and increased numbers of perivascular macrophages. Increases in ROS influence many facets of vascular function, including reduced production or inactivation of endothelium-derived NO, induction of redox-sensitive transcription factors, and oxidation of critical proteins involved in vascular contractile mechanisms. Reduced NO diminishes vascular protective effects, inhibits platelet aggregation and endothelial apoptosis, and reduces anti-inflammatory properties. Additionally, increased ROS promotes cerebral microhemorrhages by activating ROS-MMP axis in old hypertensive mice [53]. Mitochondria-derived H_2O_2 induces inflammation in

the ECs by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), resulting in overexpression of cytokines in aged rats [30, 50]. Loss of VSMC and pericyte contractile capabilities that contribute to the impaired MR and CBF autoregulation have been found in old DM rats with cognitive deficits, which was thought to be due to increased mitochondrial fission protein expression associated with reduced adenosine triphosphate (ATP) production [13, 14].

Inflammation

Continuous low-grade inflammation has been reported in laboratory animals and humans with age-related cognitive impairment and dementia, which is closely linked to increased activity of NADPH oxidases and ROS production in the cerebral vasculature. On the other hand, inflammatory mediators are potent inducers of cellular oxidative stress. Moreover, growing evidence also suggests a significant interaction between vascular inflammation and endothelial cell senescence [30]. Potential mechanisms of cerebral vascular inflammation in aging individuals with dementia may be attributed to BBB leakage due to impaired CBF autoregulation, EC dysfunction, and capillary stalling, which leads to infiltrate circulated inflammatory factors, such as tumor necrosis factor (TNF)- α , interleukin 6 (IL-6), IL-1 β to the microenvironment in the brain. The activation of perivascular macrophages and gut microbiome also contribute to neurovascular and cognitive deficits [54].

Endothelial dysfunction

Age-dependent endothelial dysfunction is a multifactorial process associated with the deterioration of cerebral vascular ECs. It is closely associated with increased production of ROS, inflammation, cellular senescence, altered leukocyte rolling and adhesion to the vascular wall [26, 27, 30]. The common end-points of EC dysfunction are the reduction and release of vasodilatory endothelial factors, such as nitric oxide (NO), prostacyclin, and the other endothelium-derived hyperpolarizing factors. Loss of critical roles of ECs in cardiovascular homeostasis also results in dysregulation of blood fluidity and fibrinolysis, angiogenesis, and platelet aggregation [30].

Cell senescence

Cell replicative senescence is a fundamental biological process in aging that can be evoked by age-associated pathophysiological or environmental stress events [55–57]. It is a phenomenon of the cessation of cell proliferation, leading to cell cycle arrest due to the shortening of telomeres-induced DNA damage, oxidative stress, inflammation, mitochondrial dysfunction, autophagy, and many other stressors. Accelerated cell senescence has been found in cerebral VSMCs, ECs, and other vascular cells in age-related cognitive impairment and dementia, which may play a role in the development of vascular dysfunction and brain hypoperfusion in these individuals [30, 50].

CONCLUSION

In summary, age-related cognitive impairment and dementia are often seen in DM and hypertension, which are all associated with cerebral vascular dysfunction that leads to cerebral



hypoperfusion. Potential underlying mechanisms include EC dysfunction, oxidative stress, inflammation, and cellular senescence, resulting in impaired CBF autoregulation, neurovascular uncoupling, and dysfunction of cerebral capillaries and the venous system. Reversing cerebral vascular dysfunction to enhance brain perfusion could be a potential treatment for AD/ADRD.

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DISCLOSURES

None.

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