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REVIEW ARTICLE

Roles of vascular risk factors in the pathogenesis of dementia

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Abstract

The number of people with dementia is rapidly growing along with the aging of society and is becoming a social issue worldwide. The results of recent clinical and basic studies have suggested that vascular risk factors, such as hypertension and diabetes mellitus, affect the pathogenesis of dementia. Cerebrovascular damage due to vascular risk factors directly triggers vascular dementia, and it is becoming more apparent that vascular risk factors also increase the risk of neurodegenerative Alzheimer's disease, which is associated with the accumulation of neurotoxic proteins in the brain. Although disease-modifying therapy for dementia has not yet been established, several studies have shown that the management of vascular risk factors could possibly contribute to reducing the risk of developing dementia, thus making them important targets for dementia prevention. In this article, we review recent findings regarding the relationship between vascular risk factors and dementia, especially focusing on Alzheimer's disease, the underlying molecular mechanisms, and the potential strategies targeting these modifiable risk factors to prevent cognitive decline.

Keywords Vascular risk factors · Hypertension · Diabetes mellitus · Dementia · Alzheimer's disease · Vascular dementia

Introduction

The number of patients with dementia has been increasing worldwide with the growing elderly population. Interestingly, more recent studies have reported unexpected results that the incidence of new-onset dementia may have actually decreased in some countries over the last decade or two [1, 2]. Although the underlying cause of this unexpected decline in age-specific dementia incidence has not yet been clarified, the improved management of vascular risk factors has been implicated [1, 3–5]. The incidence of lifestyle diseases, such as hypertension and diabetes, has increased during this period, suggesting that improved quality in the management of these vascular risk factors may consequently contribute to the prevention of dementia. Given the large number of people suffering from hypertension and diabetes worldwide, vascular risk factors can be important targets for the prevention and treatment of dementia. Here, we review recent studies regarding the relationship between vascular risk factors and dementia, especially focusing on Alzheimer's disease, and potential strategies targeting these modifiable risk factors to prevent cognitive decline.

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Hypertension, cognitive decline, and dementia

Hypertension is known to affect cognitive functions via various mechanisms. Recent studies have shown that, in addition to inducing cognitive impairment through structural and functional impairment of the cerebral blood vessels [6], hypertension also has a direct impact on the functions of the central nervous system through changes in the cerebral renin–angiotensin system (RAS) [7–9]. The central nervous system is known to have its own RAS-mediating physiological brain functions [10]. Most RAS components can be detected in the central nervous system, not only in the blood vessels but also in the neuronal and glial cells.

The correlation between hypertension morbidity and the risk of developing cognitive impairment and dementia is

greatly influenced by the patient's age and disease duration. Multiple epidemiological studies have consistently shown that hypertension in middle age significantly increases the risk of cognitive decline in older age [7, 11–15]. A long duration of hypertension in patients' 40s and 50s especially increases the risk of developing cognitive impairment 20 years later [16]. There is a strong correlation between the duration of hypertension and the onset of cognitive impairment: the presence of long-term hypertension further promotes cognitive impairment [8]. Similar correlations between hypertension and cognitive impairment have been observed in older age, up to the age range of 60–70+ years, although studies in patients of even greater age have not reached a definitive conclusion [17, 18]. It has been pointed out that not only hypertension but also hypotension may be a risk factor for developing dementia in older people [19]. The onset age and disease duration of hypertension are tightly correlated with cognitive decline in later life; thus, therapeutic intervention for hypertension during middle age is especially important from the viewpoint of dementia prevention.

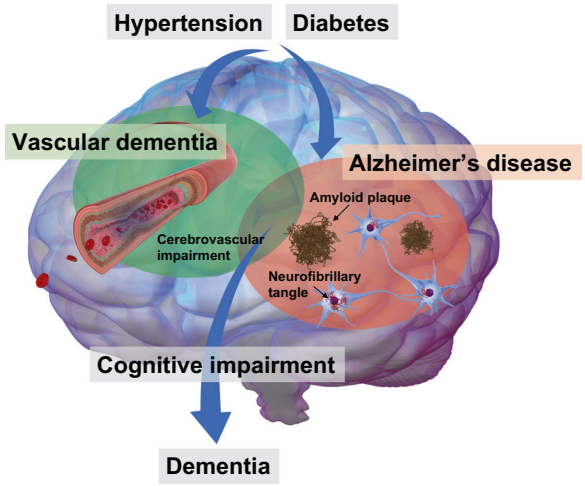

Fig. 1 Vascular risk factors, cognitive decline, and dementia. Vascular risk factors, such as hypertension and diabetes, can accelerate the progression of Alzheimer's disease and vascular dementia. Vascular risk factors damage the cerebrovascular system, leading to vascular dementia. In addition, they can affect the neuropathology of Alzheimer's disease, including amyloid plaques and neurofibrillary tangles. Overlap between the pathology of Alzheimer's disease and vascular dementia has been implicated and synergistically affects the progression rate from cognitive impairment to dementia

Hypertension and Alzheimer's disease

There are various underlying causes of dementia, with the most frequent being Alzheimer's disease and vascular dementia. These two pathologies can coexist in the brains of elderly people. Although these two types of dementia have been considered distinct diseases, recent studies have shown the possibility that they have a common pathological mechanism, as they share common risk factors, including lifestyle diseases such as hypertension and diabetes mellitus (Fig. 1).

Accumulating evidence indicates that hypertension during middle age increases the risk of developing Alzheimer's disease in later life [20]. Alzheimer's disease is characterized by two cardinal neuropathological features: senile plaques as an extracellular aggregation of β-amyloid (Aβ) and an intracellular accumulation of tau neurofibrillary tangles (NFTs) [21]. It was reported that these neuropathological features (i.e., senile plaques and NFTs) were increased in the postmortem brain tissues of hypertensive patients [22], suggesting a direct association between hypertension and the pathogenesis of Alzheimer's disease. A recent study by Zhang et al. demonstrated that hypertension-induced endothelial dysfunction is associated with cerebral Aβ deposition and cognitive impairment [23].

The results from recent studies suggest a biological link between the dysregulation of the RAS and the pathogenesis of Alzheimer's disease. Renin and angiotensin-converting enzymes (ACEs) are widely distributed throughout the brain [24]. Angiotensin II and angiotensin receptor have been identified in synaptic vesicles. Multiple studies have reported RAS activation in the brain of AD patients [25, 26]. Tian et al. and others have reported that angiotensin II could exacerbate Aβ-induced neurotoxicity using an in vitro model of Alzheimer's disease [2, 27]. ACE was reported to play a role in the degradation of Aβ in vitro and in vivo [28]. We showed that angiotensin receptor blockers prevented Aβ-induced cognitive impairment associated with the recovery of neurovascular coupling in a mouse model of Alzheimer's disease [9]. These findings support the idea that the RAS could be a potential target for cognitive dysfunction and Alzheimer's disease.

Antihypertensive treatment for the prevention of dementia

Hypertension may be involved in the development of dementia through various mechanisms. Given the mechanistic link between these diseases, is it possible to prevent dementia with antihypertensive treatment? A number of large-scale clinical trials have reported that antihypertensive drugs, such as RAS inhibitors, calcium channel blockers, and diuretics, act protectively against cognitive impairment [6, 7, 29–33]. However, other trials have reported no such preventive effect with these drugs [29]. An accumulation of further evidence will be needed before we reach a final conclusion.

It has been pointed out that inconsistent results regarding the effects of antihypertensive treatment on cognitive impairment may be due to the variety of pharmacological

mechanisms for antihypertensive drugs used in each study. A cohort study with elderly people showed that angiotensin II receptor antagonists are more effective in reducing the incidence of dementia than ACE inhibitors and other cardiovascular drugs and, notably, that they also act prophylactically against the onset of Alzheimer's disease [30]. The biological mechanisms underlying the favorable effect of angiotensin receptor blockers against dementia remain unclear. Angiotensin receptor blockers have been shown to elicit neuroprotective responses in animal [34] and cell culture models [35]. Some researchers have demonstrated that angiotensin receptor blockers ameliorated Aβ-induced vascular damage and cognitive deficits in animal models [9, 36, 37]. From the viewpoint of rescuing cerebrovascular hypoperfusion, which is a common cause of dementia, the combined use of angiotensin receptor blockers and ACE inhibitors has been suggested to provide additive benefits against cognitive impairment associated with vascular dysfunction [30]. Whether the brain-protective effects actually differ depending on the type of antihypertensive drugs has yet to be elucidated and needs further research.

The insufficient follow-up period in clinical trials on antihypertensive treatments has been a major bottleneck in demonstrating the prophylactic effect of antihypertensive treatment on dementia, despite the growing body of evidence showing the mechanistic relationship between hypertension and dementia [38, 39]. Due to the relatively low incidence of dementia, study sample sizes need to be large, and the length of study must be long enough to demonstrate a statistically significant reduction in dementia cases. Along the same line, the quantitativity and the sensitivity of the traditional neuropsychological tests for the assessment of cognitive function are likely to be inadequate for detecting subtle changes in cognitive function. Recent advances in biomarker development, including cerebrospinal fluid biomarkers and brain positron emission tomography imaging for detecting neurodegeneration and disease-specific pathological proteins, have allowed us to quantitatively and objectively evaluate the pathology of dementia [40–43]. The use of quantitative biomarkers for dementia may allow us to detect the prophylactic effects of antihypertensive treatments on dementia more precisely and efficiently.

How should we think about the indication of hypertension treatment for patients who have already developed dementia? Sufficient evidence regarding this issue has yet to be accumulated. Observational studies have been reported indicating that patients taking antihypertensive drugs have significantly lower rates of progressing from mild cognitive impairment (MCI) to dementia than those not taking antihypertensive drugs [30, 44, 45]. Given the high risk of progression to dementia in patients with MCI, active intervention in hypertension, as well as in other cardiovascular risks, may be encouraged in patients with MCI.

A recent clinical trial on hypertension management has shown promise in preventing cognitive decline in older people [46]. A substudy of the Systolic Blood Pressure Intervention Trial (SPRINT), SPRINT Memory and Cognition in Decreased Hypertension (MIND), compared two strategies for controlling hypertension in cognitively healthy older adults: the intensive strategy targeting a blood pressure of less than 120 mmHg vs. the standard care targeting a blood pressure less than 140 mmHg. The SPRINT MIND study examined whether intensive management had any favorable effect on the incidence of dementia or MCI. The intensive management of hypertension successfully reduced the incidence of MCI by 19% with statistical significance, implying that the intensive management of hypertension may be considered a disease-modifying therapy against cognitive decline. In addition, researchers found that the intensive management of blood pressure had a favorable effect on preventing white matter lesions on brain MRI [47], which are known to be associated with hypertension and a higher risk of developing stroke and cognitive decline [48].

Link between diabetes mellitus and Alzheimer's disease

Findings from clinical studies have raised the possibility that diabetes mellitus may have a direct impact on the pathogenesis of Alzheimer's disease [49–51]. Insulin can be involved in neuronal functions via multiple mechanisms that are potentially independent of glucoregulatory function. Insulin receptors can be detected in neurons in the central nervous system, and a downregulation of insulin-signaling-related molecules has been reported in the Alzheimer's disease brain [52, 53].

Insulin can regulate levels of Aβ in the brain by modulating the enzyme involved in the generation and degradation of Aβ [54, 55]. Insulin is also known to affect tau pathology via the activation of protein kinases involved in tau phosphorylation, which leads to the hyperphosphorylation and aggregation of tau [56]. A mouse model of Alzheimer's disease with diabetic conditions showed an early-onset cognitive deficit associated with a dysregulation of brain insulin signaling [50]. Interestingly, diabetic Alzheimer's disease mice showed an accelerated diabetic phenotype, implying reciprocal interactions between diabetes mellitus and Alzheimer's disease.

More recent clinical studies have reported favorable effects of antidiabetic medication against dementia and Alzheimer's disease [57, 58]. Wium-Andersen et al. reported in a case-control study with a large cohort of individuals with type 2 diabetes that the use of diabetic medications, including metformin, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 (GLP-1) analogs, and

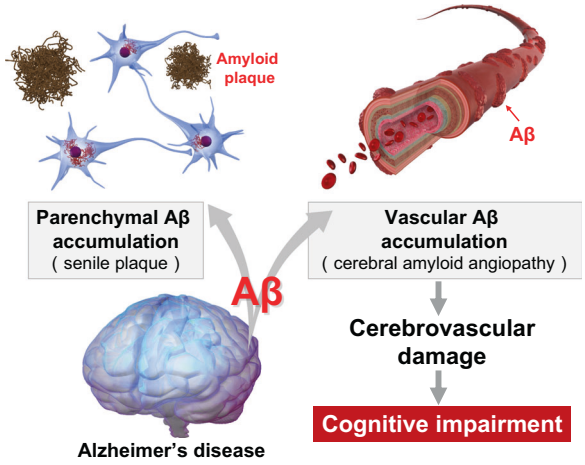

Fig. 2 Alzheimer's disease-related β-amyloid (Aβ) affects both neuronal and cerebrovascular functions. In Alzheimer's disease brain, Aβ is known to accumulate not only in the brain parenchyma as amyloid plaque but also in the brain blood vessels (cerebral amyloid angiopathy [CAA]). CAA induces the dysfunction and degeneration of the cerebrovascular system, leading to cognitive impairment. CAA may be a key player linking vascular dementia and Alzheimer's disease

sodium-glucose transport protein 2 inhibitors, was associated with a lower risk of developing dementia in patients with diabetes [57]. Gejl et al. demonstrated in a randomized, placebo-controlled, double-blind clinical trial that the treatment of diabetes with GLP-1 analogs prevented the alteration of cerebral glucose metabolism in patients with Alzheimer's disease [58], implying the direct impact of diabetic medication on synaptic function. As in the management of hypertension, treatment with antidiabetic medications may be considered a disease-modifying therapy against Alzheimer's-related cognitive decline.

Cerebral amyloid angiopathy (CAA), vascular risk factors, and the pathogenesis of dementia

Alzheimer's-related Aβ is known to accumulate not only in the brain parenchyma but also in the cerebral blood vessels (CAA) [59]. CAA can be observed in the brains of healthy elderly people, while it occurs more frequently and severely in those of individuals with Alzheimer's disease [60]. CAA is also known to contribute to the pathogenesis of vascular dementia [61]. Aβ potentially has vasoconstrictor activity, and Aβ accumulation causes direct cerebrovascular damage [9]. A recent study also reported that hypertension exacerbates the vascular-damaging activity of Aβ [62], suggesting that Aβ plays a role in the development of hypertension-induced cerebrovascular disease and cognitive impairment (Fig. 2).

CAA may be a key player linking vascular risk factors, vascular dementia, and Alzheimer's disease [63]. Evidence from recent research suggests that cardiovascular risks may exacerbate CAA [61]. Ellis et al. reported a correlation between the severity of CAA and cerebrovascular atherosclerosis in autopsy-confirmed Alzheimer's disease cases [64]. This finding suggests an interplay between Alzheimer's disease and atherosclerosis, both of which can be influenced by vascular risk factors. Using a diabetic Alzheimer's animal model, we reported an increase in the deposition of Aβ in the cerebrovascular system, which was associated with an exacerbation of the cognitive deficit of the mice [50, 65].

CAA induces the degeneration of the cerebrovascular walls, leading to cerebrovascular breakdown, hemorrhagic or ischemic stroke, and eventually cognitive dysfunction [66]. The intensive management of vascular risk factors can be important in a patient with CAA in terms of dementia prevention.

Summary

Here, we reviewed recent findings regarding the relationship between vascular risk factors and the pathophysiology of dementia. Dementia will continue to be a large worldwide public health issue with the aging of society. There is a compelling need to find an intervention strategy to reduce the risk of dementia. A better understanding of the risk factors for dementia and the molecular mechanisms linking them will give us additional avenues to explore for the strategies of dementia prevention. Given the multiple risk factors for and the heterogenicity of the pathogenesis of dementia, the development of multimodal preventive strategies will be needed to tackle dementia. Interventions against modifiable risk factors for dementia, including hypertension and diabetes mellitus, could have large implications for social and healthcare costs worldwide.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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