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REVIEW

High blood pressure, Alzheimer disease and antihypertensive treatment

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ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is a complex disease, the mechanisms of which are poorly understood. AD represents 70% of all dementia cases, affecting up to 50% of elderly persons aged 85 or older, with functional dependence, poor quality of life, institutionalization and mortality. Advanced age is the main risk factor of AD, that is why population ageing, due to life expectancy improvements, increases AD incidence and prevalence, as well as the economic, social, and emotional costs associated with this illness. Existing anti-AD drugs present some limitations, as they target specific downstream neurochemical abnormalities while the upstream underlying pathology continues unchecked. Chronic hypertension has been suggested as one of the largest modifiable risk factors for developing AD. At least 25% of all adults and more than 50% of those over 60 years of age have hypertension. Epidemiological studies have shown that hypertension is a risk factor for dementia and AD, but the association is complex. Some studies have demonstrated that antihypertensive drugs can reduce the risk of AD. This review focuses on current knowledge about the relationship between chronic hypertension and AD as well as antihypertensive treatment effect on AD pathogenesis and its clinical outcomes.

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Dementia has many etiologies, but the most common are Alzheimer's disease (AD) and vascular dementia (VD). VD has traditionally been considered secondary to vascular disease and distinguished from AD, considered to be a purely neurodegenerative form of dementia. However, these two conditions often coexist and there is strong evidence for a continuous spectrum of disease, suggesting an association between vascular risk factors and dementia, including AD.[1]

AD is a slowly progressing chronic neurodegenerative disease that is increasing in prevalence worldwide. AD typically affect short-term memory at onset, and advances to impair all cognitive domains. Key pathological features of AD are amyloid-β (Aβ) and tau proteins misfolding in the brain. Aβ accumulates extracellularly in the form of densely packed fibrils called β-amyloid plaques. Hyperphosphorylated tau protein accumulates intracellularly in the form of tightly packed filaments, called neurofibrillary tangles. β-amyloid plaques and neurofibrillary tangles are the two hallmarks of AD. Current treatment of AD is based on acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) and N-methyl-D-aspartate (NMDA) type glutamate receptor antagonist (memantine), which are widely used for the cognitive dysfunction, but cannot halt AD deterioration.[2] Although much effort has been made to develop disease-modifying treatments, the lack of promising results in human clinical trials has shift the

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attention into trying to identify preventive measures that may delay AD incidence and slow down its progression.

Hypertension, which is the most prevalent vascular risk factor worldwide, is a major modifiable risk factor for developing cerebrovascular disease such as stroke, ischemic white matter lesions, silent infarcts, microbleeds, and also VD.[3, 4] There is strong evidence of a deleterious influence of midlife hypertension on late-life cognitive function, but the cognitive impact of late-life hypertension is less clear.[5] Observational studies demonstrated a cumulative effect of hypertension on cerebrovascular damage, but evidence from clinical trials that antihypertensive treatment improves cognition is not conclusive.[3, 4] It has increasingly been seen as an important contributor to the development of AD as well,[5, 6] but to date antihypertensive drugs have had little effect on AD prevention or slowing its clinical curse.

Relationship between hypertension and Alzheimer disease

Several epidemiological and clinical pathological studies have reported a link between hypertension and AD.[5] However, the chronopathology of the relationship between high BP and the development of AD is not fully clarified, and this could lead to think that this link could be just a spurious association.

Epidemiological aspects

Several forms of cardiovascular disease (CV) have been identified as risk factors for both AD and VD.[3, 6] AD, cerebrovascular disease, and CV have shared genetic contributions,[6] and approximately 50% of individuals diagnosed with AD show significant cerebrovascular pathology on autopsy.[7, 8] These findings suggest that CV, AD, and VD may have an overlapping pathophysiology.[6, 9] Hypertension and AD-type pathophysiology appear to share a common pathogenesis in several imaging features: white matter lesions, cerebral microbleeds, and brain atrophy.[5]

It is known that hypertension is the most prevalent CV risk factor, and the main risk factor for developing cerebrovascular disease, and CV disease as well.[3, 4]

Chronic hypertension, particularly midlife high BP, has been associated with an increased risk for cognitive decline, VD, and AD.[10, 11] Some studies have reported an increased incidence of dementia and AD in people with low diastolic or systolic BP, especially in people aged ≤80 years.[10] The severity of atherosclerosis increases with age, resulting in high SBP and low DBP in later life. Severe atherosclerosis in the very-elderly, as well as episodic or sustained hypotension and, possibly, excessive treatment of hypertension, may induce cerebral hypoperfusion, ischemia, and hypoxia in this age group.

Clinical and pathological aspects

The association between hypertension and AD is still not well understood. Previous findings suggest that the combination of high blood pressure (BP) in midlife followed by low BP in late-life may place individuals at especially high risk of developing AD.

Midlife hypertension (age 40-64 years) increases the risk for AD later in life (≥65 years), and hypertension has been associated with increased amyloid deposition and neurofibrillary tangles, both neuropathologic hallmarks of AD.[12] Hypotension in the elderly has also been associated to a higher risk of AD.[12]

Some autopsy studies have showed that the probability of manifesting dementia for a given level of AD pathology is increased by the presence of cerebrovascular pathology, which is strongly linked to hypertension.[13] It is true that an increased incidence of dementia in individuals with hypertension could be due merely to its impact on cerebrovascular pathology. However, uncontrolled hypertension appears to predict the level of neurofibrillary tangles and neuritic plaques in the brain, which could be a direct effect of hypertension on AD.[13]

Compared to the brains of normotensive subjects, the brains of subjects with a history of hypertension show greater levels of β-amyloid plaques, atrophy, and neurofibrillary tangles.[6, 14] In the same way, hypertension has been identified as a risk factor for cortical fibrillar β-amyloid deposits, and reduced glucose metabolism in AD specific brain regions using positron emission tomography in the brains of cognitively normal middle-aged and older adults.[6, 15]

By promoting endothelial dysfunction, hypertension is believed to disrupt the coordinated coupling among neurons, glia, and cerebral blood flow in the microvasculature.[16] Hypertension-induced vascular remodeling and hypoxia trigger inflammation by activating

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microglia that release proinflammatory cytokines such as tumoral necrosis factor α (TNF-α) and interleukin 6 (IL-6). This inflammation increases reactive oxygen species (ROS) that can damage cerebral blood vessels, deteriorates the blood-brain barrier, and glial function. ROS lead to protein misfolding, synaptic degradation and amyloid deposition. TNF-α down regulates the synthesis of nitric oxide and increases endotheline-1 production, leading to vasoconstriction an incremental vascular injury. This inflammatory state contributes to amyloid deposition and formation of neurofibrillary tangles (Figure 1). [17-19]

In normal conditions, autoregulatory mechanisms maintain a constant cerebral blood flow over a wide range of mean arterial pressures. However cerebral regulation is better adapted to compensate for sudden increases rather than for decreases in BP. Hypertension alters the cerebrovascular autoregulation capacity by increasing myogenic tone, vascular remodeling, and hypertrophy, necessitating higher perfusion pressures to maintain the same level of cerebral blood flow. This increases the susceptibility of the brain to ischemic and hypoxic injury when systemic BP drops, due to its inability to compensate. Therefore, brain hypoperfusion and hypoxia is a complication of chronic uncontrolled hypertension.[20, 21] In animal models of AD with mutations in the amyloid precursor protein (APP), regulation of cerebral blood flow is impaired, and episodes of hypotension or hypertension result in undesired fluctuations in cerebral blood flow that may contribute to neuronal dysfunction.[22]

Chronic hypertension precipitates age-induced vascular abnormalities in the brain, such as increased vascular stiffness, and decreased vessel wall pulsatility. Increased vessel stiffness alters arterial pulsations, disturbing the glymphatic system and leading to a significant increase of β-amyloid deposition in the brain parenchyma. Several amyloid-degrading enzymes destroy Aβ peptides, including Neprilysin, angiotensin converting enzyme (ACE), endothelin converting enzyme and insulin degrading enzyme. Neprilysin is the most potent Aβ-degrading enzyme in the brain and can degrade not only monomeric forms of Aβ but also its more toxic oligomers. Neprylisin is localized on the pre- and postsynaptic neuronal cell cleave. Neprylisin levels and activity decrease with aging and after hypoxia and ischemic events. That is to say, brain hipoperfusion, a chronic hypertension complication, can lead to a lower degradation of Aβ by neprilysin, resulting in its accumulation in the central nervous system parenchyma (Figure 2).

Linking possible beneficial effects of antihypertensive therapy on Alzheimer disease

In healthy brain, A*β* levels are regulated by a dynamic equilibrium between A*β* release from the APP and its removal by perivascular drainage or by amyloid-degrading enzymes. Aβ hydrophobic plaques are toxic not

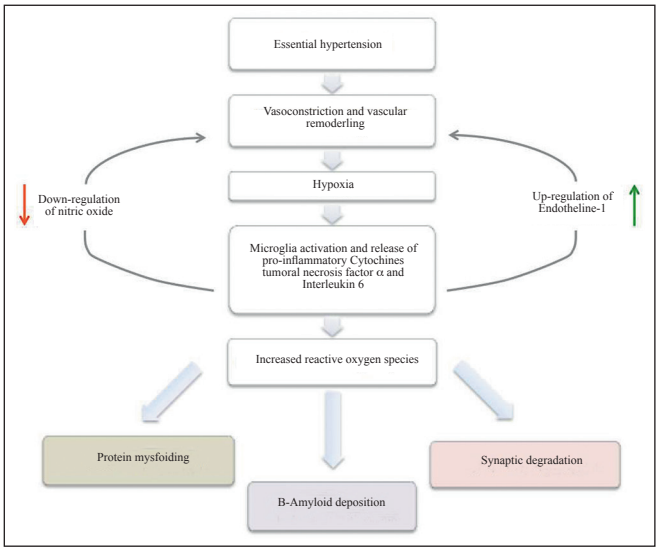

Figure 1.—Hypertension-induced inflammation increases amyloid deposition.

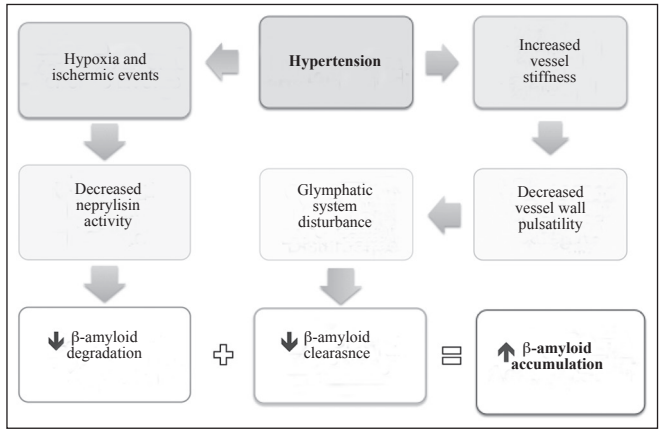

Figure 2.—Hypertension alters β-amyloid clearance and β-amyloid physiological elimination.

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only to neurons, which end up inducing their apoptosis, but also to brain endothelial cells, whose impairment weakens brain blood vessel walls and increases the risk of hemorrhage and rupture, in what is called amyloid angiopathy.[19] Cerebral amyloid angiopathy occurs in more than 90% of patients with AD, and to a lesser extent in about 30% of non-demented elderly people.[23] Two main hypotheses have been described to explain the pathophysiology linking hypertension/antihypertensive-treatment and AD. The amyloid hypothesis suggests that high ACE activity decreases the risk of AD by reducing accumulation of amyloid-beta (Aβ) protein. In addition, some studies have shown that patients with altered genotypes of the ACE gene, were associated with lower serum ACE levels, and had an increased risk of developing AD and brain atrophy.[24]

The vascular hypothesis suggests that high ACE activity increases the risk of AD by altering cerebral vasculature through angiotensin II. Chronic hypertension may alter the movement of Aβ into and out of the brain across the blood brain-barrier, or along the perivascular extracellular matrix. This may in turn contribute to development of amyloid angiopathy in blood vessels of the brain, which is a common occurrence in AD.[24, 25]

Antihypertensive treatment and Alzheimer disease

Observational and epidemiological studies have shown that antihypertensive therapy could have protective effects on cognitive impairment and dementia.[3] Indeed, in this kind of studies it has been shown that antihypertensive therapy may decrease the incidence and progression of cognitive decline and dementia, not only VD but also AD. However few large BP-lowering trials have incorporated cognitive assessment or a diagnosis of dementia and the results are controversial. To date, evidence from large placebo-controlled, randomized clinical trials has been conflicting. It could be due to the design of the studies (most of them considering cognitive function as a secondary objective), patient populations, outcomes, brief study durations and insufficient power to detect effects. In addition, most of these studies used the Mini-Mental State Examination, which is notoriously incentive to cognitive change, especially in domains of executive functioning and processing speed. Meta-analyses of these trials neither prove nor disprove the efficacy of antihypertensive treatment on dementia risk.[3] A recent systematic review of observational studies, randomized clinical trials (RCT) and meta-analysis showed:[1] 1) with relation to the effect of antihypertensive therapy on cognitive impairment there were 7 longitudinal studies showing beneficial effect in all of them, and 7 RCT with positive effect in 2 of them (HOPE[25], PROGRESS[26]); 2) with relation to the effect of antihypertensive therapy on incidence of any dementia there were 11 longitudinal studies with beneficial effects in 8 of them, and 7 RCT with beneficial effects in 3 of them (Syst-Eur I-II[27, 28], PROGRESS[26]).

Cognitive decline, even in the course of neurodegenerative disease, is a relatively gradual process, and elevated BP in midlife may be the most important determinant of risk for subsequent cognitive decline and dementia. Thus, midlife may be the most critical window during which BP control must begin. Some studies showed that calcium channel blockers (CCB) and renin-angiotensin-aldosterone-system (RAAS) blockers would be the most beneficial. They could reduce the risk for and progression of cognitive impairment and dementia by lowering BP and through a neuroprotective specific effect.[1] In support of this idea, one of the last meta-analysis of RCT performed that compared the neuroprotective properties of different antihypertensive drug classes found angiotensin receptor blockers (ARB) to be superior to β-blockers, diuretics, and ACE inhibitors for preventing cognitive decline.[29]

Pharmacological therapy strategies

Thiazide diuretics

The Ginkgo Evaluation of Memory Study found that diuretics were associated with at least a 50% decreased risk of developing AD dementia. They found a similar decreased risk of AD dementia among potassium-sparing diuretics and nonsparing Diuretics.[30] The HYVET-COG Study with indapamide, a diuretic thiazide, failed to prove a significant difference in the rate of dementia between treatment and placebo in patients aged 80 years or older.[31] The SHEP Trial did not confirm that antihypertensive treatment starting with the thiazide diuretic chlorthalidone with the possible addition of atenolol or reserpine, protects against cognitive impairment.[32] The CACHE County Study found that dementia risk was no changed with thiazide diuretics and loop diuretics (Table I).[33]

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TABLE I.—*Summary of hypothesized mechanism linking antihypertensive treatment and cognitive outcome and its effect on AD.*

Antihypertensive drug	Hypothesized mechanism of cognitive outcome	AD effect
β-blockers	Blunt adrenergic pathways if centrally active	Negative
Potassium sparing diuretics	Raise and maintain potassium levels	Positive
Thiazide diuretics	None	Neutral
Dihydropiridines calcium channel blockers	– Maintain intracellular calcium homeostasis – Decrease amyloidogenic pathway	Positive
Renin inhibitors	Attenuate NADPH oxidase mediated oxidative stress	Not clarified
Angiotensin-converting enzyme inhibitors	– Improve brain hypoperfusion, acetylcholine release and boost neprylisin anti-amyloidogenic activity – Increase long-term burden of toxic brain β-amyloid	Neutral
Angiotensin II receptor blockers	– Enhance β-amyloid elimination – Reduce glutamate excitotoxicity – Reduce tau hyper-phosphorylation	Positive
Neprilysin inhibitors	Increase long-term burden of toxic brain β-amyloid	Not clarified

POTASSIUM SPARING DIURETICS

The CACHE County Study found that potassium sparing diuretics are associated with the greatest reduction in AD risk, among other antihypertensive medications tested. They suggested that increased potassium levels might be associated with a reduced risk of dementia. Consistent with this idea, they mention observations that low potassium concentrations are associated with oxidative stress, inflammation, platelet aggregation, and vasoconstriction, all of which are possible contributors to AD pathogenesis.[33]

BETA-BLOCKERS

β-blockers worse cognition decline or are neutral according to whether or not they cross the blood brain barrier (BBB). In general, β-blockers do not impair cognition in normal subjects. It has been shown that central nervous system-active β-blockers could affect delayed memory function in patients with cognitive impairment.[34]

Centrally acting sympatholytic agents have a negative impact on cognition, as BBB-penetrating β-blockers (less liposoluble), probably by blunting the adrenergic pathways.[35]

CALCIUM CHANNEL BLOCKERS

Voltage-gated calcium channel are found in neurons in the brain where calcium regulation is very important in both learning and memory. Aβ peptide causes increases of intracellular calcium via these channels. Intracellular calcium level has also been shown to contribute to the mechanism underlying the formation of neurofibrillary tangles, causing tau protein hyperphosphorylation.[36]

It is thought that certain dihydropyridine CCB, which are more effective at crossing the blood brain barrier, lower Aβ production and facilitate Aβ clearance across the blood brain barrier.[12] Whether the effects observed in cell culture and in animal models translate to humans is less clear. According to the Syst-Eur Trial, a calcium channel blocker, nitrendipine, compared with placebo, decreased the risk of both vascular and degenerative dementia by 55% (2/3 of AD type). The Syst-Eur Trial is the only randomized control trial of hypertension to have found statistically significant positive effects of nitrendipine to reduce the incidence of AD.[27, 28] Diuretic thiazide chlortalidone in the SHEP Trial does not protect against cognitive impairment while BP reduction was comparable with the Syst-Eur Trial (12 mmHg lower SBP in the SHEP *vs.* 10 mmHg lower SBP in the Syst-Eur), suggesting that nitrendipine has a neuroprotective effect beyond its goal to reduce BP.[27, 28, 32]

However, it is not clear whether this benefit resulted solely from vasomodulatory properties of nitrendipine or from other non-vasomodulatory molecular effects of the drug. There have also been more-specific trials with nimodipine in AD patients. In these studies, nimodipine was not found to slow the rate of progression of AD in the overall patient sample but there was some evidence in support of more severe patients receiving some benefit.[36] Several observational studies, which offer more limited interpretation than clinical trial, have suggested that calcium channel blockers reduce the rate at which AD progress, such as the Ginkgo Evaluation of Memory Study.[30] The CACHE County Study found that dementia risk was no changed with CCB.[33]

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ACE-INHIBITORS

In a laboratory study with APP expressing cells, cellular expression of ACE promoted degradation of naturally secreted Aβ, leading to significant clearance of this protein. The inhibition of ACE by captopril, promoted the accumulation of cellderived Aβ in the media.[37] In an animal study, the administration of captopril in transgenic mice with a double mutation in APP gene, promoted Aβ deposition in their brain tissue.[38] In another rat experiment, chronic cerebral hipoperfusion downregulated the relative expression of cholinergic muscarinic receptor and choline acetyltransferase, as well as up-regulated the AT1R expression in hippocampus and elevated the lipid peroxidation level. The treatment with ACE-inhibitor captopril was found to attenuate hypoperfusion-induced cholinergic downregulation and lipid peroxidation-mediated damage in the hippocampus of rats.[39]

In human studies, a French cohort study found that the use of ACE-inhibitor in older adults with AD is associated with a slower rate of cognitive decline independent of hypertension.[40] In the Cardiovascular Health Study it was observed that ACE-inhibitor reported to cross the BBB and deemed to be centrally active, were associated with 65% less cognitive decline per year of exposure. This observational study reported that centrally active ACE-inhibitor reduced cognitive decline more efficiently than non-centrally active ACE-inhibitor.[41] A large randomized trial found that patients treated with the BBB penetrating captopril or perindopril slowed cognitive declines more than did the non-BBB penetrating enalapril or imidapril.[42] The Wisconsin Study found that ramipril therapy inhibited cerebrospinal fluid ACE activity and improved BP, but did not influence cerebrospinal fluid Aβ42. If hypoperfusion and the presence of Aβ lead to neuronal damage, in part through dysregulation of central nervous system ACE activity and elevated BP, then modifying cerebral blood flow and Aβ accumulation through the use of ACE-inhibitor may potentially reduce the risk of developing AD in high-risk individuals.[43]

There are some possible explanations to support the observations of ACE-inhibitor cognition improvement. ACE inhibitors can prevent brain hypoperfusion and its complications. Through prevention of angiotensin II formation, they help to stop inhibition of potassium-mediated release of acetylcholine in human and rat entorhinal cortex slices.[23] The cholinergic system is involved in memory acquisition and its dysfunction leads to memory impairment in AD.[39] Another possible explanation for the benefits of ACE inhibitors is that they increase brain substance P (normally degraded by ACE), which in turn is reported to increase Neprilysin activity, a recognized amyloid-β degrading enzyme.[42] In contrast, a retrospective cohort study recently assessed the effect of centrally *versus* non-centrally acting ACE-inhibitor on the incidence of AD in a large study population and reported no difference between the two groups.[44] The PROGRESS Study did not show a clear effect of perindopril and thiazide diuretic indapamide in degenerative dementias or cognitive decline in the absence of recurrent stroke.[26] The CACHE County Study found that dementia risk was no changed with ACE-inhibitors.[33] The Amsterdam Dementia Cohort Study found that higher cerebrospinal fluid ACE activity is associated with a reduced risk of global brain atrophy. This result suggest that high ACE might have protective effects on the brain, and that ACE inhibitors, which may lower cerebrospinal ACE levels, are not preferred as an antihypertensive treatment in patients at risk of AD.[24] Another retrospective cohort study showed that ACE-inhibitor were associated with increased risk of mortality in AD patients. This observation is consistent with the evidence from laboratory-based studies that interference with ACE catalytic function may have an adverse effect on Aβ pathophysiology.[45]

ACE-inhibitor have an ambiguous influence in brain cognition, as on one hand, brain ACE inhibition may improve brain hypoperfusion, acetylcholine release and boost Neprylisin antiamyloidogenic activity, but on the other hand, may increase long-term burden of toxic brain beta-amyloid.[46]

ANGIOTENSIN II RECEPTORS BLOCKERS

Angiotensin II receptors blockers (ARBs) may confer cognitive benefits activating AT2R with unbound endogenous angiotensin II, which may have a hypotensive and protective vascular remodeling benefit that leads to memoryenhancing effects. Blocking AT1R may also increase processing of the excess of angiotensin II to angiotensin III and in turn angiotensin IV, which activates AT4R involved in memory acquisition and recall.[29, 47] That's why ARBs have been proposed to have better cognitive outcome than other medications for BP control. In mouse models, ARB treatment was associated with reduced Al-

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zheimer's neuropathology and improved performance in learning and memory tests.[29] In human studies, results are more controversial. On one hand, the SCOPE Study did not show a significant effect of candesartan on prevention of AD.[48] The PRoFESS Study with telmisartan described no significant change in MMSE score and no difference in the numbers of demented patients.[49] In a Taiwan nationwide cohort study ARB treatment in a 5-year follow-up was not associated with a reduction of risk of AD in Asian patients with essential hypertension.[50] In the SCOPE Trial, candesartan did not decrease the risk of all dementia when compared to a false placebo, since due to changes in treatment guidelines and for ethical reasons, other antihypertensive drugs (diuretics, β-blockers, CCB, ACE inhibitor, ARBs) were added in patients whose BP remained high, in a higher frequency in the placebo group. As a result, the trial actually compared a candesartan based regimen with a usual treatment regimen not containing candesartan. The addition of possible dementia protective antihypersive drugs (dihydropyridine) to placebo could have mitigated the relative cognitive effect of candesartan.[48] On the other hand, the use of ARBs appear also quite promising since in the MOSES Trial (performed in patients with a history of stroke or transient ischemic attacks), eprosartan was found as protective against cognition decline as nitrendipine.[51] In addition, the neuroprotective effect of AT1R blockers is found in the OSCAR cohort Study, where eprosartan was associated with an increase of 1.5 within 12 months in the MMSE Score.[52] A network meta-analysis in 2013 revealed that the benefits on cognition were greater with ARBs than with placebo, β-blockers, diuretics and ACE-inhibitors in rank order.[29] ARBs reduced the incidence of AD by as much as 50%, compared with non-RAAS-targeting antihypertensives, independent of their effect on BP reduction.[47] In a small clinical trial, telmisartan was compared to amlodipine for 6months in elderly patients with probable AD and essential hypertension. Both groups had a similar significant reduction in systolic and diastolic BP after treatment, but the telmisartan group showed significantly higher cognitive scores. In addition, imaging tests shown that telmisartan has an increased regional cerebral blood flow than the amlodipine group. These findings suggest that telmisartan may have additional benefits and may be useful for the treatment of elderly hypertensive patients with AD.[53]

Current evidence shows that ARBs may have a neuroprotective effect. In addition, unlike ACE-inhibitor, ARBs preserve and enhance ACE-induced Aβ degradation.

Renin inhibitors

Chronic cerebral hypoperfusion cause a significant activation of renin activity, and high angiotensin II levels, which activate NADPH oxidase and enhances oxidative stress in brain tissue. Direct renin inhibition by aliskiren was found to prevent cognitive impairment blocking angiotensin II formation and attenuating NADPH oxidase-mediated oxidative stress and subsequent inhibition of glial activation. Aliskiren ameliorated brain damage and working memory deficits in a mice model of chronic cerebral ischemia.[54] Rat cortical neurons exposed to Aβ *in vitro* have shown to increase renin expression. Aliskiren blocked Aβ-mediated neuronal induction of renin and carried neuroprotective action against Aβ toxicity.[55] At present, there are no results from clinical trials concerning the potential of the renin inhibitor aliskiren to influence cognition and dementia incidence in humans, due to its newness and low use.[47]

Neprilysin inhibitors

Neprilysin is a zinc-dependent metallopetidase that catalyzes the degradation of various peptides including atrial natriuretic peptide, brain natriuretic peptide, vasoactive peptides (bradykinins and endothelin-1), and neuropeptides (substance P, enkephalins) and contributes to the breakdown of Aβ.[56, 57] Inhibition of neprilysin in order to increase circulating levels of natriuretic peptides has been studied for its therapeutic effect on BP. Although neprilysin inhibition alone has little antihypertensive effect, concomitant inhibition of both neprilysin and RAAS has demonstrated a synergic lowering on BP. LCZ696 (Valsartan/Sacubitril) is a first-in-class angiotensin II-receptor neprilysin inhibitor (NEPi).

While the chronic use of NEPi appears beneficial for the treatment of chronic hypertension and heart failure, it may compromise Aβ peptide degradation in the brain, and may accelerate AD and cerebral amyloid angiopathy progression, in patients at risk of developing AD with genetic factors or vascular factors. Indeed, the crossing of the blood-brain barrier by NEPi is anticipated to be deleterious in patients at risk since in-

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tracerebral infusion of the NEPi provokes AD lesions in animal models.[56] Up-regulation of NEP expression and activity represents a new strategy for therapeutic intervention in AD.[58]

Conclusions

The onset and progression of AD is associated with multiple factors being hypertension one of the main ones. The strongest evidence that hypertension is a risk factor for cognitive impairment and dementia comes from observational studies with midlife measures of BP and late-life measures of the cognitive status. Hypertension is related to cerebrovascular disease and Aβ deposition, which are major pathological factors in dementia.

Consequently, different types of approaches are needed for effective disease-modifying treatment, such as removing amyloid burden, intervening in the amyloid or tau accumulation cascade or repairing vascular pathology, as well as lifestyle correction. Many antihypertensive drugs, besides its potential to reduce BP, have a direct effect on brain structure and function by crossing the brain blood-barrier or by targeting brain endothelial cells. Antihypertensive drugs are not equal in preventing cognitive decline and dementia. ARB may offer the most benefit by interfering in amyloid formation, breakdown and clearance.

In summary, treating hypertension in the early stages at midlife and achieving strict and sustained BP control below 140/90 mmHg is the only armamentarium in the hands of general practitioners to prevent cognitive decline associated with age and AD.

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