Hypertension Research (2009) 32, 738–740
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REVIEW

Effects of angiotensin II receptor blockers on dementia

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The renin–angiotensin system (RAS) is involved in pathological mechanisms of target organ damage as well as the induction of hypertension; therefore, blockade of the RAS has been expected to prevent cardiovascular and cerebrovascular diseases beyond its antihypertensive effects. In spite of the well-characterized role of angiotensin (Ang) II receptor blockers (ARBs) in preventing the onset and recurrence of stroke, the clinical evidence for an effect of ARBs on dementia has not been definitive. However, preliminary experiments raise the possibility that treatment using ARBs may prevent ischemic brain damage and cognitive impairment. Moreover, recent reports have shown that some ARBs prevent amyloid β deposition in the brain and attenuate cognitive impairment in Alzheimer disease models. Furthermore, recent cohort studies indicate that lower incidence of Alzheimer disease is observed in elderly individuals treated with ARBs. These results indicate a beneficial role for ARBs in cognitive impairment associated with vascular disease, Alzheimer disease, metabolic syndrome and other neurodegenerative diseases. Here, we review the effects of ARBs on the brain with a focus on dementia and future therapeutic approaches for elderly people suffering from disabilities.
Hypertension Research (2009) **32,** 738–740; doi:10.1038/hr.2009.110

Keywords: dementia; neuroinflammation; neuroprotective; renin–angiotensin system; stroke

INTRODUCTION

Dementia is a common but serious health problem. An estimated 33 million elderly persons around the world suffer from dementia, and this number is expected to reach 81.1 million by 2040.[1] Dementia impairs quality of life and is associated with a profound disease burden, morbidity and mortality, not only in patients but also in caregivers.[2,3] Therefore, prevention of dementia is a critical need for advanced countries to address. Life style-related disorders, such as hypertension, diabetes mellitus and obesity have been reported to be related to dementia. For example, large prospective cohort studies indicate that midlife hypertension increases the risk of dementia,[4] suggesting that the blood pressure-lowering effects of antihypertensive drugs may reduce the incidence of dementia. Moreover, recent clinical studies and basic research have suggested several ways in which antihypertensive drugs can prevent target organ damage independently of their antihypertensive effect. In particular, the tissue renin–angiotensin system (RAS) (the so-called local RAS) is involved not only in the vasculature but also in the brain. Accumulating evidence from large clinical trials suggests that blockade of the RAS by angiotensin (Ang) II type 1 (AT_1) receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors is more effective at inhibiting target organ (such as heart and kidney) damage than other hypertensive agents.[5] Here, we overview the accumulating evidence and suggest possible mechanisms by which ARBs prevent brain damage and dementia.

STROKE PREVENTION

Recently, there has been a focus on the local RAS in the brain.[6] Although it is thought that Ang II does not cross the blood–brain barrier, it has been reported that all RAS components exist in the central nervous system, suggesting that Ang II is produced and functions in the central nervous system. There is no doubt that lowering blood pressure is one of the most recommended therapeutic approaches for the prevention of stroke. Recent large clinical trials, such as the Losartan Intervention For Endpoint reduction in hypertension (LIFE)[7] study, and the MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES)[8] study indicated that blockade of the RAS helps prevent first and recurrent strokes independently of its blood pressure-lowering effects. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study showed lower mortality at 12 months after stroke in two groups treated with candesartan 7 days after stroke compared with the placebo group (even in individuals with similar blood pressure), suggesting that RAS inhibition in the acute phase of stroke also leads to brain protection irrespective of its hypotensive effect.[9] Furthermore, in the Jikei Heart Study, the addition of valsartan to conventional treatment prevented more cardiovascular events (especially stroke) than supplementary conventional treatment, and did so with no significant change in blood pressure.[10] The MOSES study also showed that the primary end point—a composite of total mortality and all cardiovascular and cerebrovascular events—

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Received 22 June 2009; revised 24 June 2009; accepted 25 June 2009

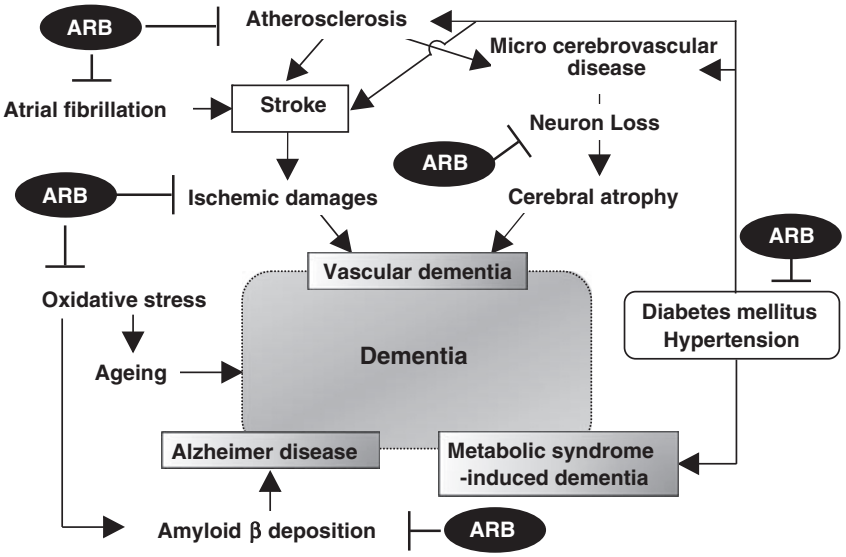

Figure 1 Renin–angiotensin system (RAS) Inhibition by angiotensin II receptor blockers (ARBs) in dementia. ARBs may prevent dementia through stroke prevention, neural protection from ischemic damage, inhibition of neural loss and/or amyloid β deposition.

was significantly lower with treatment with an ARB (eprosartan) without a change in blood pressure.[8] However, these and other large clinical trials also indicate that ARBs prevent the onset of diabetes mellitus[11] and atrial fibrillation,[12] which are strong risk factors for stroke.

PROTECTION FROM ISCHEMIC BRAIN DAMAGE

The brain RAS is involved in ischemic brain damage after stroke. An experimental brain injury model with middle cerebral artery occlusion using genetically modified mice showed that AT_1 receptor signaling enhances brain damage owing, partly, to an increase in oxidative stress in the ischemic brain and a decrease in cerebral blood flow in the penumbral region of the middle cerebral artery territory; therefore, pretreatment with ARBs prevents ischemic brain damage. Our recent study indicates that activation of the human RAS in chimeric transgenic mice with human renin and human angiotensinogen genes exaggerates ischemic brain damage mainly through stimulation of the AT_1 receptor.[13] In contrast, activation of the angiotensin II type 2 (AT_2) receptor attenuated brain injury[14] with counter-regulatory effects on the AT_1 receptor. ARBs stimulate AT_2 receptor signaling with unbound Ang II by blocking AT_1 receptor signaling. Therefore, we could expect that ARBs would be more effective than angiotensin-converting enzyme inhibitors at preventing ischemic brain damage. However, no meta-analyses have concluded that ARBs are better than angiotensin-converting enzyme inhibitors in terms of stroke prevention.

Interestingly, the Trial Of Preventing Hypertension (TROPHY) recently showed that treatment of prehypertension with the ARB, candesartan, reduced the incidence of clinical hypertension even after cessation of ARB administration,[15] suggesting that some factors might be imprinted by ARB treatment and that it can last for an extended period. We have also reported that temporary treatment with the ARB, valsartan, can protect against ischemic brain damage even after its cessation, at least in part, because of an increase in capillary density.[16] Therefore, pretreatment with ARBs is expected to prevent ischemic brain damage after stroke, even after cessation of the treatment.

ENHANCEMENT OF NEURAL DIFFERENTIATION

Recent basic research has raised the possibility that stimulation of AT_2 receptors may promote cell differentiation and regeneration in neuronal tissue.[17,18] Li *et al.*[19] reported that AT_2 receptor stimulation supported neuronal survival and neurite outgrowth in response to ischemia-induced neuronal injury. Moreover, Gallo-Payet *et al.*[20–22] showed that Ang II induces neural differentiation and neurite outgrowth through mitogen-activated protein kinase or nitric oxide through AT_2 receptor activation, and that it is involved in brain development. This accumulating evidence indicates that AT_2 receptor signaling acts as a crucial cerebroprotective factor after stroke. We also showed that AT_2 receptors enhance neural differentiation and the repair of damaged DNA by induction of the neural differentiating factor MMS2 (methyl methane sulfonate sensitive-2), which is one of the ubiquitin-conjugating enzyme variants.[6]

PREVENTION OF METABOLIC SYNDROME-INDUCED DEMENTIA

Continuous activation of the brain RAS impairs cognitive function through stimulation of the AT_1 receptor.[23] The ARB candesartan ameliorates impaired cognitive function in mice with type 2 diabetes (KKAy), at least partly, because of increased expression of MMS2 and an improvement in glucose intolerance.[24] Interestingly, another ARB, olmesartan, is therapeutically effective at preventing the impairment of cognition in mice fed a high-fat and high-salt diet.[25] RAS has a pathophysiological role in metabolic syndrome, contributing to enhanced levels of oxidative stress and inflammation. Moreover, RAS in cerebral microvessels is involved in cerebral metabolism and hemodynamics, especially in diabetic patients. Recently, Kario *et al.*,[26] using magnetic resonance spectroscopy and phase-contrast magnetic resonance angiography, clearly showed that an ARB (candesartan) significantly improves cerebrovascular reserve in hypertensive patients, and that it does so more markedly in patients with diabetes than in those without diabetes. This indicates that improvement of cerebral microcirculation by ARBs prevents neuronal damage, especially in patients with diabetes. Therefore, blockade of the RAS by ARBs could prevent diabetes- and metabolic syndrome-induced dementia.

PREVENTION OF ALZHEIMER DISEASE

Recently, RAS inhibition by ARBs has been suggested to prevent the onset of Alzheimer disease. An ARB (valsartan) was able to attenuate oligomerization of amyloid β peptides into high molecular weight oligomeric peptides.[27] Moreover, treatment with valsartan also disrupted the development of amyloid β-mediated cognitive impairment in Tg2576 mice, a model to study Alzheimer disease. However, angiotensin-converting enzyme is involved in the decomposition of amyloid β.[28] In a clinical investigation of the relation between antihypertensive medication and the onset of Alzheimer disease in the elderly population, aged 65 years and older, in Cache County (UT, USA),[29] the onset of Alzheimer disease was attenuated by a diuretic agent and a calcium channel blocker; however, treatment with angiotensin-converting enzyme inhibitors failed to prevent Alzheimer disease, indicating the involvement of angiotensin-converting enzyme in amyloid β deposition. However, the amyloid β level in the brain was not altered in angiotensin-converting enzyme-deficient mice, indicating that regardless of whether angiotensin-converting enzyme is actually involved in the decomposition of amyloid β, these issues should be investigated further.[30]

Moreover, according to medical records of more than 5 million patients, people taking ARBs had a 35–40% lower risk of developing Alzheimer disease and similar neurodegenerative disorders.[31] We also showed that the ARB, telmisartan, had a preventive effect on cognitive decline in an Alzheimer disease mouse model that was intracerebroventricularly injected with amyloid β.[32,33] Therefore, ARBs may have a preventive effect on amyloid β deposition in the brain.

CONCLUSION

Although improvement of cognitive function by RAS inhibition has not been confirmed clinically to date, RAS inhibition is expected to prevent dementia induced by vascular disease, Alzheimer disease and metabolic syndrome, with multiple beneficial effects (Figure 1). Further clinical trials should be conducted to test this hypothesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by grants from the Ministry of Education, Science, Sports, Technology, and Culture of Japan to MH and MM, and the Novartis Foundation for Gerontological Research to MM.

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