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The renin-angiotensin system, hypertension and cognitive dysfunction in Alzheimer's disease: new therapeutic potential

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1. ABSTRACT

Alzheimer's disease, which is the most common cause of dementia, is traditionally thought to be a neurodegenerative disorder and not of vascular origin. However, there is a growing body of evidence suggesting an association between vascular risk factors and Alzheimer's disease. Several epidemiological studies have shown that high mid-life blood pressure is related to the development of Alzheimer's disease in later life. Furthermore, the use of some kinds of antihypertensive medication has been suggested to reduce the incidence of dementia including Alzheimer's disease. Recent findings indicate that the brain has its own renin-angiotensin system, which mediates several physiological and pathological brain functions. The neurobiological links between the renin-angiotensin system and Alzheimer's disease have been investigated and become a source of interest in the pathogenesis of the disease. This review describes the relation between the renin-angiotensin system, hypertension and Alzheimer's disease, and also discusses the potential use of antihypertensive drugs acting via the renin-angiotensin system in the treatment and prevention of the disease.

2. INTRODUCTION

Hypertension is the most significant predisposing factor for cerebrovascular disease (stroke, ischemic white matter lesions, silent infarcts) and coronary heart disease (myocardial infarction, angina), which are leading causes of morbidity and mortality worldwide (1). Hypertension is currently defined as systolic blood pressure of 140 mmHg or above or diastolic blood pressure of 90 mmHg or above, but the threshold for the diagnosis of hypertension has decreased in recent years. The incidence of hypertension correlates with advancing age, with an estimated prevalence of 50% in people older than 70 years (1). Numerous multicenter randomized clinical trials have been performed, and the benefits of antihypertensive therapy for most categories of hypertensive patients seem well proven. However, until recently, many elderly people with hypertension were left untreated (2).

The renin-angiotensin system (RAS) plays a key role in the regulation of cardiovascular homeostasis, such as controlling sodium balance, body fluid volume and arterial blood pressure. Manipulation of this system has emerged as a new therapeutic approach to the management

of hypertension. Recent clinical trial evidence suggests that blockade of RAS by angiotensin-converting enzyme inhibition or by angiotensin receptor blockade may influence large vessel atherosclerosis and cardiovascular morbidity and mortality independent of blood pressure lowering.

Dementia is also a common disorder in elderly adults. This debilitating condition is characterized by loss of various cognitive function (memory impairment, disorientation, aphasia, or other cortical dysfunctions), with subsequent loss in motor and physical function on a daily basis. Estimates indicate that 5-10% of elderly in the 65-74 year age range are affected, and this figure increases to 25-50% in the over 85 age group. This distressing condition is a major cause of disability and care burden in the elderly, and the economic and social pressures are enormous. More severe behavioral and cognitive impairment in a patient is associated with higher levels of burden and distress. Caregivers provide an unpaid service to society and their family members, at substantial personal cost. They tend to experience higher rates of stress-related illness and neglect their own healthcare, resulting in greater severity of disorders and higher costs.

Alzheimer's disease (AD) is the most common cause of dementia, accounting for about 50-60% of all cases of dementia. The major risk factor for AD is advancing age, and its prevalence doubles every 5 years after age 65 and approaches 50% by age 85 (3). Diagnosis of this disorder is mainly based on clinical symptoms (memory loss with insidious onset, progressive impairment of higher brain function, mood or personality changes) and findings of neuroimaging studies (CT, MRI, SPECT, PET). Autopsy of AD patients reveals considerable atrophy of the brain and abundant intracellular neurofibrillary tangles and extracellular senile plaques. Post-mortem diagnosis of AD is based on these pathological features. Although the etiology of AD remains unresolved, beta-amyloid, which is a major component of senile plaques, is believed to play an important role in disease initiation and progression. The generation of beta-amyloid is the result of sequential cleavage of its precursor, amyloid precursor protein (APP), by several enzyme systems (cleavage by beta/gamma-secretase). Reducing beta-amyloid deposition through inhibition or modulation of these enzymes is one of the main strategies in current drug development for AD.

Traditionally, AD has been thought to be a neurodegenerative disorder and not of vascular origin. However, several epidemiological studies have reported that the vascular risk factors, such as hypertension, atherosclerosis, diabetes mellitus and hypercholesterolemia, might be involved in AD. These vascular factors have strong association with cerebrovascular disease and related vascular dementia (VaD), which is the second most common cause of dementia (3). On clinical grounds, in fact, differentiation between AD and VaD can be difficult. Furthermore the prevalence of mixed dementia, AD with cerebrovascular disease, has been underestimated, particularly in older populations (4). The use of increasingly sophisticated clinical diagnostic tools has demonstrated such an underestimate in figures relating to mixed type of dementia. In addition to simple coexistence, significant associations might exist between these two types of dementias.

There is accumulating evidence that the brain has its own renin-angiotensin system, which mediates several physiological and pathological brain functions (5). Brain angiotensin receptors and its endogenous angiotensin peptides have been implicated in neural plasticity and cognitive function such as memory and learning. On the other hand, the neurobiological links between RAS and AD have been investigated and become a source of interest in the pathogenesis of this disease.

This review initially focuses on clinical evidence supporting the association between vascular risk factors, especially hypertension, and dementia. This is followed by an account of the role of RAS in the brain and its involvement in the pathophysiology of AD. Finally, the therapeutic potential of manipulating RAS for the treatment or prevention of AD is discussed.

3. HYPERTENSION AND DEMENTIA

Hypertension is a major risk factor for cerebrovascular disease including stroke, and may also contribute to the development of vascular dementia (VaD) (2, 6, 7, 8, 9). The cognitive complications of hypertension and the influence of antihypertensive treatment were underestimated until recently (6), and many older people with hypertension have been left untreated. This is, in part, due to the presumption that high blood pressure constitutes a physiological adaptation to increased arterial resistance, and that lowering blood pressure may increase the risk of ischemic complications, especially in elderly people. However, many epidemiological/clinical studies have confirmed that elevated blood pressure plays an important role in the development of cognitive dysfunction. Randomized controlled trials using antihypertensive agents have provided evidence that safe and effective reduction of hypertension decreases morbidity and mortality and the cognitive complications of hypertension, including dementia (6). The subsequent sections summarize the evidence from population-based observational studies and randomized clinical trials assessing the relations of blood pressure and antihypertensive therapy to cognitive function and dementia.

3.1. Hypertension and cognitive function

Long-term high blood pressure starting in middle age can cause severe atherosclerosis and large-artery stiffness in later life (10, 11). Neuropathological investigations have shown that people with hypertension more often have large areas of white matter hyperintensity, ventricular enlargement and silent infarcts compared to normotensive individuals, which could promote cognitive impairment and clinical expression of dementia (12, 13, 14, 15, 16, 17, 18).

Several epidemiological studies have evaluated the link between hypertension and cognitive decline and

Table 1 Randomized clinical trial of antihypertensive therapy in relation to dementia

Study name	n	Mean age at baseline	Follow-up (years)	Treatment	Main results
SHEP (1991)	4736	72	4.5	(Diuretic ± beta-blocker ± centrally-acting antihypertensive) or placebo	No significant effect of treatment
MRC (1996)	2584	69	3.9	Diuretic or beta-blocker or placebo	No significant effect of treatment
Syst-Eur (1998)	2902	68	2 (4 including open follow-up)	(Calcium channel blocker ± ACE inhibitor ± diuretic) or placebo	Reduced dementia risk by 55% (AD+VaD)
PROGRESS (2001)	6105	64	3.9	(ACE inhibitor ± diuretic) or placebo	Dementia rates were lower in the actively treated patients with concurrent stroke
SCOPE (2003)	4964	76	4.5	AT1 receptor antagonist or placebo	Cognitive function declined significantly less in the treated group with low cognitive function at baseline

SHEP : Systolic Hypertension in the Elderly Program; MRC : Medical Research Council; Syst-Eur : Systolic Hypertension in Europe trial; PROGRESS : Perindopril Protection against Recurrent Stroke Study; SCOPE : Study on Cognitive and Prognosis in the Elderly; AT1 : angiotensin II type1

dementia. The Framingham study provided probably the first main evidence of a relation between blood pressure and cognitive function in elderly people, concluding that elevated blood pressure was associated with modest impairment of cognitive function after a follow-up of 12-15 years (19, 20). Prolongation of follow-up to 20 years showed a stronger association between cognitive impairment and hypertension in non-treated subjects compared with those taking antihypertensive drugs (21). The Honolulu-Asia Aging Study consisting of a 25-year observational analysis also assessed medication use, and found that untreated subjects were at increased risk of cognitive dysfunction (22). These findings are supported by other studies including the Epidemiology of Vascular Aging study (23), the Kungsholmen study (24, 25) and the Rotterdam study (8).

Five main randomized placebo-controlled clinical trials have evaluated the protective effect of antihypertensive medication against cognitive impairment or dementia (Table 1).

The Systolic Hypertension in the Elderly Program (SHEP) trial investigated the influence of antihypertensive treatment (diuretic and beta-adrenoceptor antagonist) versus placebo over a 5-year follow-up period, and found no significant effect of treatment on cognitive function (26). It was suggested that the lack of significant difference between the two groups might, in part, have been due to the high discontinuation rate in the placebo group in this trial.

The Medical Research Council (MRC) trial of hypertension selected a subset of 2584 patients aged 65 to 74 years from more than 4000 subjects who were randomized to receive diuretic, beta-blocker or placebo (27, 28). The initial conclusion was that there was no significant benefit of treatment on cognitive function. However, further follow-up of the remaining 387 patients 9 to 12 years later found that poorer cognitive function was associated with a smaller decline in systolic blood pressure, which indicates that lowering blood pressure could protect against cognitive deterioration later in life.

The Systolic Hypertension in Europe (Syst-Eur) study, involving more than 2000 participants, examined whether or not treatment of older patients with isolated systolic hypertension was able to reduce the incidence of VaD (29, 30). Active treatment was with the calcium channel blocker nitrendipine, possibly together with the angiotensin-converting enzyme (ACE) inhibitor enalapril, with or without the diuretic hydrochlorothiazide. The trial follow-up was limited to only 2 years because there was early evidence of a reduction in stroke, the primary outcome. The main conclusion was that antihypertensive treatment was associated with a lower incidence of dementia (both VaD and AD). A further 2-year follow-up after the double-blind controlled period also showed reduced risk for both types of dementia.

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) was also a randomized, double-blind, placebo-controlled trial involving more than 6000 patients with a previous stroke or ischemic attack (31). Participants were treated with an ACE inhibitor (perindopril), to which a diuretic (indapamide) was added if necessary. Dementia rate was lower in the actively treated group, but only in patients with concurrent stroke during the study.

In the Study on Cognitive and Prognosis in the Elderly (SCOPE) trial, which included elderly hypertensive subjects aged 70-89 years with an Mini-Mental State Examination (MMSE) score of 24 or more, the potential effect of treatment with an angiotensin-receptor blocker (candesartan) on cognitive function was assessed (32). In patients with slightly low cognitive function at baseline (MMSE score 24-28), the score declined significantly less in the candesartan group (33).

These studies reviewed above are not easily comparable because of differences in study design (study population, mean age at baseline, follow-up period, cognitive function tests) and the different degrees of blood pressure decrease caused by various treatments. However, some hypotheses can be advanced based on these findings. Because the classes of drugs used were different, one can speculate on a possible class effect for prevention of cognitive decline; that is, calcium channel blockers and ACE inhibitors could be effective and probably better than diuretics and beta-blockers for cognitive function in patients with hypertension. More extensive clinical investigation and laboratory-based findings will probably confirm the data of these trials.

In summary, despite all the limitations and methodological differences, these reports show that hypertension in midlife, especially if not treated, negatively affects cognitive function and contributes to the development of dementia, both VaD and AD, in late life, and suggest a protective effect of antihypertensive treatment against cognitive decline and dementia.

3.2. Hypertension and Alzheimer's disease

Much epidemiological evidence points to a link between high mid-life blood pressure, risk factors for atherosclerotic vascular disease, and AD (25, 34, 35, 36). In these studies, blood pressure was measured 20-30 years before cognitive assessment. Skoog and colleagues reported in their longitudinal study that high blood pressure (both systolic and diastolic) preceded the onset of clinical manifestation of AD by 10-15 years, and the risk of developing dementia increased with increasing blood pressure at baseline (1, 34). In the Kuopio and Joensuu studies, the investigators found that the risk effects of mid-life elevated blood pressure on late-life development of AD was independent of *APOE* genotype, which is the major genetic risk factor for this disease, and that high blood pressure combined with hypercholesterolemia had a higher risk of AD than did either of them alone (36, 37).

The association between late-life blood pressure and risk of AD is unclear. There is no strong evidence to suggest that high blood pressure in later life is a risk factor for AD (38, 39, 40, 41, 42, 43, 44, 45). Some cross-sectional or short follow-up studies have shown a risk effect of low blood pressure in later life on the development of AD (46, 47, 48).

Skoog and co-workers also noted that there was a decline in blood pressure in the years just preceding AD onset. They suggest that the low blood pressure observed prior to the diagnosis of AD is a result of the brain lesions of the disease itself (1). Several of the brain regions involved in central blood pressure regulation (hypothalamus, amygdala, insular cortex, medial prefrontal cortex, locus ceruleus, parabrachial nucleus, pons, and medulla oblongata) are affected in AD (49, 50). Impairment of cerebral blood flow regulation and cerebral hypoperfusion might contribute to the development of AD (1, 17, 18).

Neuropathological studies have linked atherosclerotic burden in the brain to pathological changes in AD (51, 52, 53, 54). Increased amyloid plaques and neurofiblillary tangles, the key neuropathological features of AD, have been found in hypertensive subjects. On the other hand, vascular pathology (microinfarctions, lacunae and cerebral hemorrhages) have been found to be associated with AD (55, 56, 57, 58).

These findings support the idea that vascular factors such as hypertension that cause damage to the cerebral vasculature may also be involved in the pathogenesis of AD. Reducing the burden of such risk factors by antihypertensive therapy may have a positive effect of reducing the incidence of AD.

3.3. Antihypertensive drugs and risk of AD

In Syst-Eur study, active therapy with calcium channel blocker reduced the incidence of AD in addition to that of VaD and mixed dementia. One possible explanation for the decreased incidence of AD could involve a specific neuroprotective action conferred by calcium channel blockade. Some laboratory-based findings have suggested that disruption of calcium homeostasis may be the molecular basis for the pathogenesis of AD (59, 60, 61, 62, 63). This dysregulation of intracellular calcium signaling may be linked to the formation of amyloid plaques and neurofibrillary tangles and cell death. However, there is no sufficient evidence to clearly explain the mechanisms that calcium channel blockers could improve the pathological processes of AD. More findings will be required to rationalize use of calcium channel blockers for prevention and treatment of AD.

Ohrui and colleagues investigated the incidence of AD in elderly Japanese patients with hypertension who were treated with either an ACE inhibitor or other antihypertensive medication over a 10-year period (64). They reported that brain-penetrating ACE inhibitors had a beneficial effect on the rate of AD development. Furthermore, they performed a randomized, prospective, parallel group trial with one-year exposure to antihypertensive medication (65). In this study, mild-to-moderate AD patients with hypertension were treated with either a brain-penetrating ACE inhibitor (perindopril or captopril), a non-brain-penetrating ACE inhibitor (enalapril or imidapril), or a calcium channel blocker (nifedipine or nilvadipine). Stable use of cholinesterase inhibitor (donepezil), statin, or low-dose aspirin was allowed. After one-year follow-up, treatment with brain-penetrating ACE inhibitors was shown to slow the rate of cognitive decline in mild to moderate AD patients in comparison to other antihypertensive medication. Since no significant difference was found in the level of blood pressure among the three groups, this beneficial effect might be due to a direct effect of ACE inhibitors on the brain renin-angiotensin system. They also speculated that an increased level of brain substance P by ACE inhibitors, which is reported to augment the activity of neprilysin, a major beta-amyloid-degrading enzyme in the brain, might be another possible mechanism of this favorable effect.

Some other observational studies support these findings. Rozzini and colleagues reported that individuals with mild cognitive impairment (MCI), which is a preclinical state of AD, treated with ACE inhibitors showed less memory decline (did not convert to AD) after a year of follow-up (66).

It is suggested that drugs acting via the renin-angiotensin system may produce their effects via mechanisms other than their antihypertensive actions. Although the mechanisms of these favorable effects are not known, there is some biological rationale to support these findings. It is reported that RAS might be activated in the AD brain (67), and this would be reduced by ACE inhibitors, especially by brain-penetrating ones. Another possible explanation is that decreased angiotensin II could prevent the inhibition of potassium-mediated release of acetylcholine, which is a major neurotransmitter in memory and learning (68). The biological association between the brain RAS and AD is discussed in section 5.

4. BRAIN RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is widely recognized as the most powerful signaling system for controlling cardiovascular homeostasis. Synthesis of angiotensins begins with the conversion of angiotensinogen to angiotensin I by the enzyme renin. Angiotensin II is then synthesized from angiotensin I by the action of angiotensin-converting enzyme (ACE), which is present in the endothelium of most blood vessels but has the highest concentration within the pulmonary vasculature. Angiotensin II is then metabolized to angiotensin III, angiotensin IV and to inactive peptide fragments by the activity of ACE and several other peptidases. Although angiotensin II is well known for its hypertensive effect and its ability to stimulate cardiac remodeling, other angiotensin peptides are also pharmacologically active with markedly different potencies (69, 70, 71).

Recent findings suggest that there is an independent brain RAS separate from blood-borne angiotensins, and it contributes to neural plasticity and some cognitive function. Subsequent sections discuss the components of the brain RAS and then its association with cognitive function, especially memory and learning.

4.1. The AT1 and AT2 receptor subtypes

The cardiovascular and other actions of angiotensin II are mediated by AT1 and AT2 receptors, which are seven transmembrane glycoproteins with 30% sequence identity (71). The most prevalent angiotensin receptor is the angiotensin type 1 (AT1) receptor.

The AT1 receptor is a G-protein-coupled receptor with signaling via phospholipase-C and calcium in its downstream. Binding of the angiotensin peptide to this receptor induces a conformational change in the receptor protein that activates G proteins that, in turn, mediate signal transduction. This transduction includes several plasma membrane mechanisms including some types of calcium channels (71, 72). This receptor subtype is also coupled to intracellular signaling cascades that regulate gene transcription and the expression of proteins that mediate cellular proliferation and growth in many target tissues (5). AT1 receptor mediates almost all of the known physiological actions of angiotensin II in target organs, which include the heart and vascular tissue, kidney, liver, uterus, ovary, testis, adrenal grand and brain (5, 71, 73).

The AT2 receptor protein also exhibits a seven-transmembrane domain characteristic of G-protein-coupled receptors. The signal transduction mechanism varies but commonly involves potassium and calcium ion channels and growth factor stimulation. It is also known that the AT2 receptor counteracts several of the growth responses initiated by the AT1 and growth factor receptors. This receptor is expressed ubiquitously in the fetus and has been implicated in fetal development (74). Although the density of this receptor declines rapidly after birth, expression is maintained in the heart, nonpregnant uterus, adrenal grand, ovary, and brain (5, 71, 73). It is also associated with vascular growth during development (75) and the regulation of cerebral blood flow (76, 77).

4.2. The AT4 receptor subtype

Angiotensin peptides shorter than angiotensin III were traditionally considered biologically inactive and of little physiological importance; however, these assumptions have now changed with the identification of angiotensin IV and its putative receptor, the AT4 receptor (5). The AT4 receptor has been identified in a variety of tissues including the adrenal gland, heart, thymus, kidney, bladder, aorta and brain (73). Angiotensin IV has a wide range of physiological effects, and its facilitatory role in memory processing is of great interest (78, 79, 80, 81, 82, 83, 84). The pharmacological profile of this receptor subtype deviates significantly from those of the AT1 and AT2 receptors, as it only displays very low affinity for angiotensin II. Although the signal transduction mechanisms are unknown, AT4 receptor stimulation may oppose the effect of AT1 receptor activation in the same way as does AT2 receptor stimulation (85). The receptor has been identified as an insulin-related amino peptidase, although other transduction mechanisms may exist (73).

4.3. Cerebral distribution of angiotensin peptide and its receptors

Almost all components of RAS have been identified in the brain, and it is believed that endogenous angiotensin peptides are associated with its receptors. The brain has a high concentration of angiotensinogen, especially in the choroid plexus and astrocytes. Angiotensin II has been identified within synaptic vesicles in nerve terminals in those areas with high angiotensin receptor concentrations. Renin and ACE are also widely distributed throughout the brain (73).

The brain has high concentrations of angiotensin receptors in several regions. Binding sites for angiotensin II have been identified within the circumventricular organs (CVO), specifically in the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), area postrema (AP), median eminence, and anterior pituitary gland (86, 87, 88).

The AT1 subtype is localized with high densities in the following brain regions: anterior pituitary, lateral geniculate, anterior ventral third ventricle region, subfornical organ, paraventricular, supraoptic, and ventral medial nuclei, median eminence, and preoptic region of the hypothalamus, the nucleus of the solitary tract, dorsal motor nucleus of the vagus, and the inferior olivary nucleus of the medulla (5). High densities of AT2 receptors are found in the amygdala, medial geniculate, hypoglossal nucleus, inferior olivary nucleus, lateral habenula, caudate putamen, globus pallidus, locus ceruleus, thalamus, inferior colliculus, and ventral tegmental area (5). The AT4 receptor has been found in high concentrations in the neocortex, piriform cortex, hippocampus, caudate putamen, nucleus accumbens, medial habenula, periaquaductal gray, nucleus basilis of Meynert, ventral tegmental area, and cerebellum (5), some of which are involved in cognitive processing (91).

4.4. Angiotensin and long-term potentiation

There is a growing body of evidence that brain angiotensin peptides and their receptors are involved in cognitive function, especially in memory processing. Long-term potentiation (LTP) is thought to serve as the basic

physiological mechanism underlying memory storage. Wayner and co-workers reported that angiotensin II delivered into the CA1 field of the rat hippocampus inhibited LTP. This inhibition could be blocked by losartan, or a non-specific AT1 and AT2 receptor antagonist; however, a specific AT2 receptor antagonist failed to block this angiotensin II-induced inhibition of LTP (90, 91, 92, 93, 94). Kramár and colleagues (79, 95) and other groups (96, 97) have reported angiotension IV-induced enhancement of LTP in hippocampal slices and *in vivo*. This effect could be blocked by the specific AT4 receptor antagonist. These results suggest that angiotensin II and angiotensin IV may have opposing effects on LTP; that is, angiotensin II acts on the AT1 receptor to suppress LTP and, on the other hand, angiotensin IV enhances it through the AT4 receptor.

The molecular mechanisms responsible for angiotensin II-induced suppression and angiotensin IV-induced increase of LTP are not fully understood. Albrecht and co-workers have shown that angiotensin II caused a strong inhibition of NMDA (*N*-methyl-D-aspartate)- or kainate-evoked increases in the discharge rate of dorsal lateral geniculate neurons of rat (98). Recently it is reported that AT4 receptor activation increases calcium influx through postsynaptic calcium channels and induces a non-NMDA dependent form of LTP in area CA1 of rat hippocampus (99). Additional investigation will be required to elucidate these mechanisms.

4.5. Angiotensin and cognitive function

Morgan and co-workers reported that angiotensin II injected directly into the dorsal neostriatum impaired a step-down shock avoidance response (100). Similarly, Lee and colleagues observed that direct injection of angiotensin II into the dentate gyrus disrupted performance of a single trial step-through shock avoidance response (101). These impairments were significantly attenuated by losartan (100, 101). It is also reported that intracerebroventricularly infused renin impaired performance of a passive avoidance task in a dose-dependent manner (102). Although an AT1 receptor antagonist and the ACE inhibitor captopril attenuated this renin-induced deficit, co-application of an AT2 receptor antagonist failed to influence this deficit.

In contrast to these findings, other groups have reported angiotensin II-induced enhancement of cognitive function (103). These observations indicate that angiotensin may exert a bimodal action upon learning, in part, depending on the doses of applied peptides. It is important to recognize that different experimental paradigms have been used to generate these results in different species of animals.

It has been reported that ACE inhibitors and AT1 receptor antagonists have favorable effects on cognitive function. Mondadori and co-workers (104) found that both captopril and enalapril significantly prevented electroshock-induced amnesia in mice. Costall and colleagues (105) administered captopril and ceranapril to mice and found facilitation of the habituatory response, while the cholinergic receptor antagonist scopolamine impaired habituation.

In addition to these animal studies, some clinical studies suggest a positive effect of these drugs on cognition. Croog and colleagues reported, in their randomized double-blind trial with mild to moderate hypertensive male patients, that patients' subjective self-reports indicated improved mental acuity at work in those on captopril, but no change in those treated with a beta-blocker (106). Tedesco and colleagues undertook a clinical trial comparing an AT1 antagonist (losartan) with another antihypertensive agent (diuretic) in matched samples of older and younger patients with mild-to-moderate hypertension (107). They reported that there was an absolute improvement of MMSE score in patients receiving the AT1 antagonist. Similarly, Fogari and colleagues also reported that an AT1 blocker produced a favorable effect on cognition in very elderly hypertensives (108).

Although the precise involvement of the brain RAS in cognitive function is still unclear, several of the studies discussed above suggest a protective effect of drugs acting via RAS on cognitive function. Some investigators speculated that these drugs facilitate cognitive function by reducing the inhibitory influence of angiotensin II upon acetylcholine release, but additional studies will be required to confirm this hypothesis.

5. ALZHEIMER'S DISEASE AND THE RENIN-ANGIOTENSIN SYSTEM

Some researchers have revealed contributory functions of RAS in the process of AD pathology. Savaskan and co-workers investigated the immunohistochemical alternations of ACE, angiotensin II, and AT1 receptor in the parietal cortex in AD, and reported increased immunoreactivity of all three antigens, involving predominantly cortical layer 5 (67). In addition, elevated perivascular ACE and angiotensin II immunoreactivity surrounding some cortical vessels was observed (67). This finding may reflect enhanced brain RAS activity in the disease process. Activation of RAS in the AD brain has also been reported by other groups (109, 110).

Elevated ACE activity in the brain may be directly responsible for the cognitive dysfunction in AD, since enhanced formation of angiotensin II would result in an increased inhibitory effect of angiotensin II on acetylcholine release, as described in the previous section. Another effect of ACE may be based on regulation of neuropeptides, because it has been reported that ACE is involved in the degradation of several neuropeptides such as bradykinin, encephalins, substance P and neurotensin, and abnormalities of these neuropeptides have been implicated in the pathogenesis of AD (111).

Recent *in-vitro* studies have suggested that ACE could play an important role in metabolism of beta-amyloid (112, 113, 114). Hemming and colleagues demonstrated that cellular over-expression of ACE promoted degradation of naturally secreted beta-amyloid and pharmacological inhibition of ACE activity by an ACE inhibitor captopril prevented this effect and resulted in the accumulation of cell-derived beta-amyloid (114). This finding suggests that ACE inhibitors might increase the burden of beta-amyloid, instead of reducing it, in the brain of patients taking this medication. On the other hand, in animal models, there is

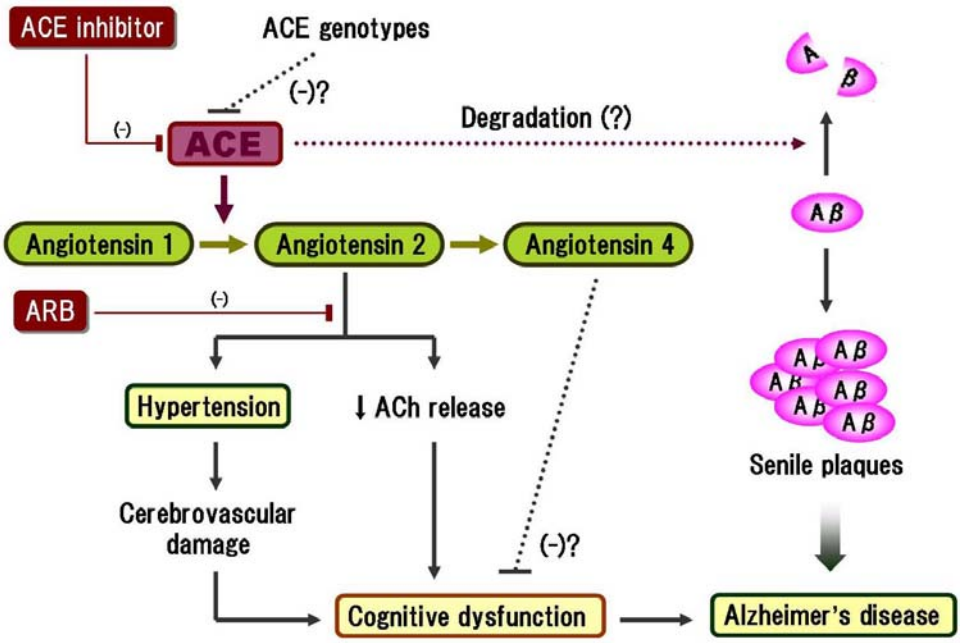

Figure 1. Possible association between renin-angiotensin system and Alzheimer's disease. Angiotensin II, whish is synthesized from angiotensin I by the action of angiotensin-converting enzyme (ACE), is involved in the pathogenesis of hypertension. Hypertension is the most significant risk factor for cerebrovascular disease, and vascular damage of the brain could contribute to cognitive dysfunction. Angiotensin II-mediated inhibition of acetylcholine (ACh) release is also believed to impair cognitive function. These may lead to early clinical presentation of Alzheimer's disease. Angiotensin IV, through its AT4 receptor, could exert some favorable effect upon cognitive function. Although not fully demonstrated, ACE is suggested to be involved in degradation of beta-amyloid, which is the major component of senile plaques. Introduction of an ACE inhibitor could prevent the negative effect of angiotensin II; however, it may reduce the putative beneficial effect of ACE on amyloid metabolism. Angiotensin-receptor blocker (ARB) inhibits the action of angiotensin II more specifically, which might be a more appropriate treatment for hypertension in Alzheimer's disease patients or people at risk of developing the disease.

little evidence to support a role of ACE as a degrading enzyme of beta-amyloid. Eckman and co-workers analyzed beta-amyloid accumulation in brains from ACE-deficient mice and in mice treated with ACE inhibitors, and found that ACE deficiency did not alter steady-state beta-amyloid concentration (115).

Several studies have examined DNA polymorphism of the ACE gene as an additional risk factor for AD. Currently, more than 70 polymorphisms have been reported in the gene coding for ACE, the most investigated of which is an insertion/deletion polymorphism. Subjects with deletion of a 287 bp repeat at intron 16 of this gene (D-allele) have higher plasma ACE levels than those with an insertion of this repeat (I-allele). Some studies showed that the frequency of the ACE-I allele was significantly increased in patients with AD, but others yielded conflicting results (116, 117, 118, 119, 120, 121, 122, 123, 124). These inconsistencies might be due to a small contribution of the ACE gene to the risk of AD, or to differences in methodology.

Although these findings point to a neurobiological link between AD and RAS, there are some paradoxes in these findings; that is, clinical studies have shown a beneficial effect of ACE inhibitors upon the development of AD; however, *in-vitro* findings have suggested that ACE inhibition might reduce degradation of beta-amyloid. One possible reason for these conflicting results may be the difference of experimental situation. The data derived from the in-vitro laboratory-based findings might not be applicable to the human disease state. In animal models, experiments were done in relatively young animals and therefore the effect of aging upon the metabolism of beta-amyloid and its interaction with ACE inhibitors might be insufficient. We also have to consider the association between mouse ACE and human beta-amyloid. It is not clear that mouse ACE interacts with human beta-amyloid in the same way as in human brain. In clinical situation, ACE inhibitors may have some favorable effects on cognition (prevention of hypertension induced cognitive dysfunction, block of angiotensin II-mediated inhibition of acetylcholine release, and effect on cerebral amyloid angiopathy) and these positive effects might overcome the negative effect on beta-amyloid metabolism. Additional investigation to understand the role of RAS in the brain of AD patients and the effect of its inhibition is needed. The putative association between RAS and AD is summarized in Figure 1.

6. SUMMARY AND PERSPECTIVE

Early and aggressive management of AD can delay symptom progression and help to maintain the quality

of life of both the patient and the caregiver. Although numerous therapies for the treatment of AD are under investigation, at present, cholinesterase inhibitors are the mainstay of symptomatic treatment for this disease. However, since cholinesterase inhibitors confer only modest benefit, additional AD therapies are urgently needed. In view of the increased costs for patients with more severe AD, interventions that would reverse or delay progression may result in significant cost saving.

There is increasing evidence that vascular risk factors, especially hypertension, are involved in the pathogenesis of AD. The identification of cerebrovascular damage as a significant factor in cognitive impairment and progression of AD means that there is considerable potential for antihypertensive drugs for prophylactic use against this neurodegenerative disorder.

RAS, which is recognized as an important factor in the pathogenesis of hypertension, has become an area of great interest in the pathophysiology of AD, and this could be a new therapeutic target in this disease. Some clinical studies have reported a potential benefit of ACE inhibitors for cognitive function in AD patients, although the mechanisms of this favorable effect have not been fully investigated. It should be noted that several laboratory-based findings showed a potentially harmful effect of ACE inhibitors on beta-amyloid metabolism. If ACE were involved in degradation of beta-amyloid in the human brain, ACE inhibition would elevate the concentration of these toxic polypeptides. Angiotensin-receptor blockers, which act on the same biological pathway as ACE inhibitors, are gaining recognition as an alternative antihypertensive medication. This specific blockade of the AT1 receptor could reduce angiotensin-induced inhibition of acetylcholine release and could be more appropriate treatment for AD patients or for people at risk of developing this disease, with hypertension. More recent work with angiotensin-receptor blockers has suggested this potential effect.

Anything that could reduce the incidence of AD would be socially important, and if a reduction in blood pressure via manipulation of RAS can result in such an effect, this might have a huge impact.

7. ACKNOWLEDGMENTS

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Abbreviations : AD: Alzheimer's disease, VaD: vascular dementia, RAS: renin-angiotensin system, ACE: angiotensin-converting enzyme, ARB: angiotensin-receptor blocker, AT1 receptor: angiotensin II type1 receptor, LTP: long-term potentiation, ACh: acetylcholine, NMDA: *N*-methyl-D-aspartate, MMSE: Mini-Mental State Examination

Key Words: Alzheimer's disease, Beta-amyloid, Dementia, Hypertension, Renin-angiotensin system, Angiotensin II, Angiotensin IV, ACE inhibitor, Angiotensin-receptor blocker, Cognitive function, Prevention, Review

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