# The Role of the Renin-Angiotensin System in Amyloid Metabolism of Alzheimer's Disease

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The etiology of Alzheimer's disease (AD) remains unclear. Epidemiologic studies suggest hypertension plays a contributing role to AD. Recently, several experimental and observational studies showed interaction between the renin-angiotensin system and amyloid-β, a key pathologic feature of AD, with diverse results. This article reviews molecular, genetic, experimental and clinical data to clarify the impact on an AD patient with angiotensin converting enzyme inhibitor and angiotensin II receptor blocker therapy, with some guidance for the direction of possible future research.

**Key Words:**   Alzheimer's disease ● Amyloid-β ● Renin angiotensin system

## INTRODUCTION

Alzheimer's disease (AD) is well-known to be the most common form of dementia in developed countries.[1] It is a complex and heterogeneous disease, characterized by progressive episodic memory deficit and personality changes, accompanied by specific structural abnormalities in the brain.[2] The main pathological features of AD are extracellular deposits of amyloid-β (Aβ) in the form of senile plaques, and intracellular inclusions of hyperphosphorylated tau in the form of neurofibrillary tangles (NFT). Importantly, there is growing evidence indicating an association between vascular risk factors, for example, hypertension, and AD. Several epidemiological studies have shown that hypertension is related to the development of AD.[3] Since the renin-angiotensin system (RAS) plays a crucial role in the pathogenesis of hypertension, it is not surprising that

RAS is also related to the development of AD.[4] However, the exact impact and mechanisms involved remain largely unknown. On the other hand, clinical differentiation between AD and vascular dementia (VaD), the two most common forms of dementia, can often be confusing. Unlike memory impairment as the earliest symptom of AD, the main problem of VaD was executive function, speed of information processing and attention. Besides, the course of AD was slowly progressive but stepwise in VaD. To provide greater focus, this review only summarizes the updated knowledge of the influence of RAS on the pathogenesis of AD in cell culture systems, animals, and humans.

## EPIDEMIOLOGY AND CLINICAL STUDIES

Previous studies revealed that high midlife blood pressure is a risk factor for dementia[5] and plays a role in AD progression.[6] A report from Taiwan also showed that hypertension, especially diastolic blood pressure (DBP), is a significant risk for AD.[7] However, some adverse results have indicated that low DBP ($\leq$ 70 mm Hg) in older adults is related to an increased dementia risk.[8] Since blood pressure, especially hypertension, plays a role in AD, clinical anti-hypertensive therapy trials have

addressed the issue. Two large studies covering stroke incidence and antihypertensive therapy all mentioned dementia. The Systolic Hypertension in Europe (SYST-EUR) trial[9] was a double-blind placebo-controlled trial that was early terminated in just two years due to a significant reduction of stroke. In two years of follow-up, the study showed a 50% reduced incidence of AD and VaD, regardless of stroke. Similarly, results from The Perindopril Protection Against Recurrent Stroke (PROGRESS) Study, a randomised, double-blind, placebo-controlled trial with previous cerebrovascular accident (CVA) patients[10] suggested angiotensin converting enzyme inhibitor (ACEI) reduced the risk of dementia in stroke patients, and calcium channel blocker (CCB) also had some benefit. Khachaturian et al.[11] found that diuretics provided a benefit for AD but ACEI had no significant influence (hazard ratio 1.08, 95% CI 0.53-1.99). Ohrui et al.[12] stated a new concept that "brain penetrating ACEI", not mentioned in the Khachaturian study, was more effective for slowing cognitive decline in AD patient compared with non-brain penetrating ACEI and CCB. The finding suggested that ACEI may have some potential effect for slowing AD progression beyond a blood pressure-lowing effect. Recently, two large cohort studies[13,14] and one small randomized clinical trial (RCT)[15] also found that angiotensin II receptor blocker (ARB) has protective effect for AD (Table 1). However, another two RCT studies revealed no difference in AD incidence between ARB treatment group and control.[16,17] One study based on the Taiwan National Health Insurance database also found no protective effect of ARB.[18]

In Summary, although low blood pressure in later life may be associated with dementia, almost all studies showed that anti-hypertensive therapy can reduce the incidence and progression of AD. However, the effect of ACEI and ARB was inconclusive and controversial. To date, large-scale clinical trials of ARB and ACEI in AD are lacking and previous studies were too small, having short follow-up periods with some confounding factors such as stroke or other uncontrolled metabolic factors. In addition, the dementia type of AD and VaD was not clearly separated. Further trials addressed a head-to-head comparison of ARB and ACEI, and other anti-hypertensive drugs were needed.

## FINDING OF CELL-BASED EXPERIMENTS AND ANIMAL MODELS

$A\beta$ is a key pathological feature of Alzheimer's disease which consists of 40-42 amino acid peptides.[19] It is commonly known that $A\beta$ accumulation in AD patients reflects imbalance between $A\beta$ production and removal. Transmembrane amyloid precursor protein (APP) was cleavaged by $\beta$- and $\gamma$-secretases (the amyloidogenic

**Table 1.** Clinical trials evaluating the effects of antihypertensive drugs in AD

| Source | Drugs | Study size and members | Length of follow up | outcome |
|---|---|---|---|---|
| SYST-EUR trial (1998) | Placebo vs. nitrendipine (10-40 mg/day) $\pm$ enalapril (5-20 mg/day) $\pm$ hydrochlorothiazide | Age > 60 years HTN p't, n = 2148 | 2 years | ACEI reduced AD and VaD |
| PROGRESS trial (2003) | Placebo vs perindopril $\pm$ indapamide | Prior stroke HRN p't, n = 6105 | 3.9 years | ACEI reduced dementia |
| Ohrui et al. (2004) | Perindopril 2 mg/day vs. enalapril 5 mg/day vs. nifedipine 20 mg/day | Mild to moderate AD p't n = 162 | 1 years | Brain penetrating ACEI slowed cognitive decline |
| Khachaturian et al. (2006) | ACEI vs. $\beta$-blocker vs. CCB vs. diuretics | Age > 65 years HTN p't, n = 3308 | 5 years | ACEI had no influence on AD risk |
| Rozzini (2006) | ACEI vs. $\beta$-blocker vs. CCB | MCI p't, n = 74 | 1 year | ACEI have protect effect for MCI |
| Kazumasa (2012) | Telmisartan 40-80 mg/day vs. amlodipine 5-10 mg/day | AD p't, n = 20 | 6 months | ARB had protective effect for AD |

ACEI, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; HTN, hypertension; MCI, mild cognitive impairment; p't, patient.

pathway)[20] and formed Aβ. Aβ may aggregate and be deposited in the brain, leading to neurotoxicity.[21]

Besides, reduced cholinergic fibers in the brain were another pathological abnormality contributing to the development of AD.[22] Currently, primarily cholinesterase inhibitors such as Donepezil and Rivastigmine have been approved by the Food and Drug Administration for treatment of AD.

There are several in vivo and in vitro studies that showed interaction regarding Aβ and angiotensin-converting enzyme (ACE). Hu et al.[23] first described that human affinity-purified ACE had an inhibitory effect for synthetic Aβ aggregation in vitro by cleavage at the site Asp[7]-Ser[8] of Aβ. Compared with Aβ, the degraded product had reduced aggregation ability and cytotoxicity. They also demonstrated ACE had reduced Aβ toxic effects on rat cell line, and was nullified if the ACEI lisinopril was added to the cultures. Besides, Hemming and Selkoe[24] used cloned ACE from human neuroblastoma cells to demonstrate both the N- and C-domains of ACE were able to degrade Aβ and the properties were inhibited by captopril. According to these in vivo studies, ACE seems to have some measure of protective effects while drugs inhibiting ACE may be harmful.

A review of the prior literature also indicates that there have been varied results in animal studies (Table 2). One study showed that in ACE knockout mice and wild type mice treated with perindopril, the Aβ level was not altered.[25] Similarly, another study demonstrated that in APP transgenic mice, treatment with captopril failed to change the Aβ level.[26] Drugs such as ARB were also tested in these animal studies. Valsartan[27] and telmisartan[28] were tested and showed reduced Aβ level and improvement of mice cognitive function. Since telmisartan also possesses peroxisome proliferator-activated receptor (PPAR-γ) agonist properties, PPAR-γ antagonist was also tested and it reduced the protective effect of telmisartan.[28]

To explore the possible explanations for the conflicting results of ACE and AD in vivo and in vitro studies, we need to review the renin-angiotensin system pathway. Renin acts on angiotensinogen to produce angiotensin I, which in turn is cleaved by ACE to form the active angiotensin II, a potent vasoconstrictor exerting the hypertensive effects by its action on two receptors (AT1 and AT2).[29] Some evidence has showed that angiotensin 2 inhibits potassium-mediated release of acetylcholine,[30] which was also involved in pathophysiology in AD as mentioned previously. Therefore, ACE inhibitors, by reducing the level of both ACE and angiotensin II, caused both beneficial and negative effects for AD. Such an explanation also provides clues as to why the effect can only be seen in vivo but not in vitro (Figure 1). Another possible explanation for the beneficial effects of ACE inhibitors is that they increase brain substance P,[31] which is normally degraded by ACE. Substance P was reported to augment the activity of neprilysin, a recognized Aβ degrading enzyme.[32]

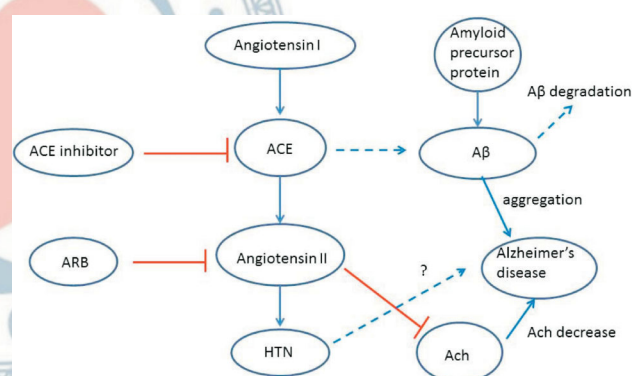Besides, it is important to clarify that the data



**Figure 1.** Potential interaction of renin-angiotensin system (RAS) system and amyloid-β (Aβ) metabolism. Angiotensin converting enzyme (ACE) has positive effects for Aβ degradation (dotted line) and angiotensin II has inhibitory effects on acetylcholine release (red line). Therefore, ACE inhibitors, by reducing the level of both ACE and angiotensin II, generate both beneficial and negative effects for AD. Ach, acetylcholine; ARB, angiotensin II receptor blocker; HTN, hypertension.

**Table 2.** Effects of ACEI and ARB on animal serum Aβ level

| Animal models | Tested drugs | Results |
|---|---|---|
| Tg 2576 (3-4 weeks) | Perindopril (0.2 mg/kg/ day) | ACEI not affect Aβ level[25] |
| 3*TG (3 months) | Captopril (2 g/l-28 days) | ACEI not affect Aβ level[26] |
| Tg2576 (6 months) | Valsartan (10 mg/kg-5 months) | ARB reduced serum Aβ level and improved cognitive function[27] |
| ddY (8 weeks) | Telmisartan (100 mg/kg-28 days) | ARB reduced serum Aβ level and improved cognitive function[28] |

Aβ, amyloid-β; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

derived from the animal models might not apply to its human-equivalent disease. Moreover, the animals used in AD studies were too young (only 3 and 4 weeks of age) such that age-related metabolic abnormalities as seen in older humans might not exist. Finally, It is not clear whether mouse ACE acted on Aβ in the same way as that seen in humans. Consequently, additional studies focusing on these issues are needed.

## THE HUMAN GENE AND BRAIN TISSUE FINDINGS

One post-mortem brain tissue study from AD patients[33] showed elevated ACE activity in the medial hippocampus and parahippocampal gyrus, frontal cortex and caudate nucleus correlated with Aβ plaque load. Another study[34] using ACE radioligand [3H] ceranapril to assess the binding density in brain tissue showed increased ACE in the temporal cortex in patients with AD. On the other hand, studies of ACE level and activity in the CSF have yielded equivocal results, with reports of reduced,[35] no difference[36] or elevated[37] ACE level. However, these studies were small in sample size and therefore required further evaluation. It is not clear why ACE activity is increased in the brain and how alternation of brain ACE contributes to blood flow change in the AD patients.

In human genetic studies, Kehoe et al.[38] first found AD was associated with insertion (I)/deletion (D) polymorphism within intron 16 of the ACE gene. Later, multiple case-control studies were published with variable results. A meta-analysis[39] supports a modest contribution (OR: 1.27, 95% CI, 1.10 to 1.47; p < 0.001) of ACE gene variation to the risk of developing late onset AD. In recent years, genome-wide association studies (GWASs) of single nucleotide polymorphisms (SNPs) found evidence to support the involvement of ACE in AD,[40,41] which possibly work through interaction with LRRTM3 gene[42] and A2M gene.[43] However, it is still a question how genetic variations in ACE affect risk of AD.

## CONCLUSIONS

There are several controversial results concerning the connection between RAS and AD. Fortunately, no human clinical data showed harmful effects of using an ACE inhibitor in AD patients. Besides, whether angiotensin-receptor blockers are appropriate drugs for hypertension control in AD patients remain unclear. To answer these questions, future prospective studies monitoring the effects of ACEI and ARB on cognitive performance and blood pressure as well as post-mortem assessment of pathology in the AD patients are required.

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