Chapter

The Role of Renin Angiotensin Aldosterone System in the Progression of Cognitive Dysfunction in Chronic Kidney Disease Patients with Alzheimer's Disease

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Abstract

Renin angiotensin aldosterone (RAAS) is very well established as a regulator of blood pressure (BP) and a determinant of target organ injury. It controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and kidneys. The main effector of RAAS is angiotensin II (Ang II), which exerts its vasoconstrictor effect primarily on the postglomerular arterioles, thereby raising the glomerular hydraulic pressure and ultrafiltration of plasma proteins, which may lead to the initiation and progression of chronic kidney disease (CKD). RAAS also plays a, key role in hypertension and cerebrovascular disease. Enhanced Ang II levels accelerate the initiation and progression of cell senescence by fostering inflammation and oxidative stress. Sustained activation of RAAS facilitates aging-related CKD and results in cognitive dysfunction and Alzheimer's disease (AD). However, in many hypertension treatment studies, the frequency of fatal and nonfatal stroke has been greatly reduced, and this is very important since a history of stroke doubles the risk of dementia in both patients without CKD and hemodialysis. In CKD patients with AD, anemia has also been identified as a risk factor for cognitive impairment, and correction of anemia with recombinant erythropoietin treatment has been shown to enhance cognition measures, such as AD markers and neuropsychological tests.

Keywords: Angiotensin converting enzyme, Chronic Kidney Disease, Cognitive Dysfunction, Alzheimer's disease, Amyloid β, Tau

1. Introduction

The renin angiotensin aldosterone (RAAS) system is a hormone system in the body that is responsible for controlling the balance of fluid and blood pressure. The system consists primarily of three hormones, namely renin, angiotensin II and aldosterone. It is controlled mainly by the rate of renal blood flow. The main effector of RAAS is angiotensin II (Ang II), Rising glomerular hydraulic pressure

and ultra-filtration of plasma proteins, which can contribute to the initiation and progression of chronic kidney disease (CKD), as well as key molecules in hypertension and cerebrovascular disease, exerts its vasoconstrictor effect primarily on postglomerular arterioles. Enhanced Ang II levels speed up the initiation and progression of cell senescence by encouraging inflammation and oxidative stress. Sustained RAAS activation facilitates aging-related CKD and results in cognitive decline and Alzheimer's disease (AD). The risk of cognitive dysfunction in CKD patients with AD is significantly greater than in patients without CKD [1], not only in aged patients with CKD, but also in young patients with CKD [2]. It has been believed for a long time that kidney function is associated with brain activity. Our recent clinical studies indicate that CKD patients are more vulnerable to cognitive dysfunction and AD, and the severity of cognitive dysfunction is closely linked to the development of CKD and kidney failure [3–5].

2. RAAS: pathogenic mechanism of chronic kidney disease

RAAS is the best known blood pressure regulator (BP) and the determinant of hypertension damage to the target organs. It also regulates the balance of fluids and electrolytes by coordinated impacts on the heart, blood vessels, and kidneys. The main effector of the RAAS is Ang II [6]. Renin is secreted from the juxtaglomerular apparatus of the kidney in the classic RAAS pathway and acts on the circulating precursor angiotensinogen to create angiotensin I. Angiotensin I has few effects on BP, and in the lungs, ACE is transformed to Ang II. Ang II operates on the heart and kidneys by binding to type 1 (AT1) and type 2 (AT2) G-protein coupled receptors [7]. The more deleterious effects of Ang II, vasoconstriction and heart and vessel hypertrophy are mediated by the AT1 receptor. In addition the vasodilator peptide bradykininin is inactivated by the angiotensin-converting enzyme (ACE)

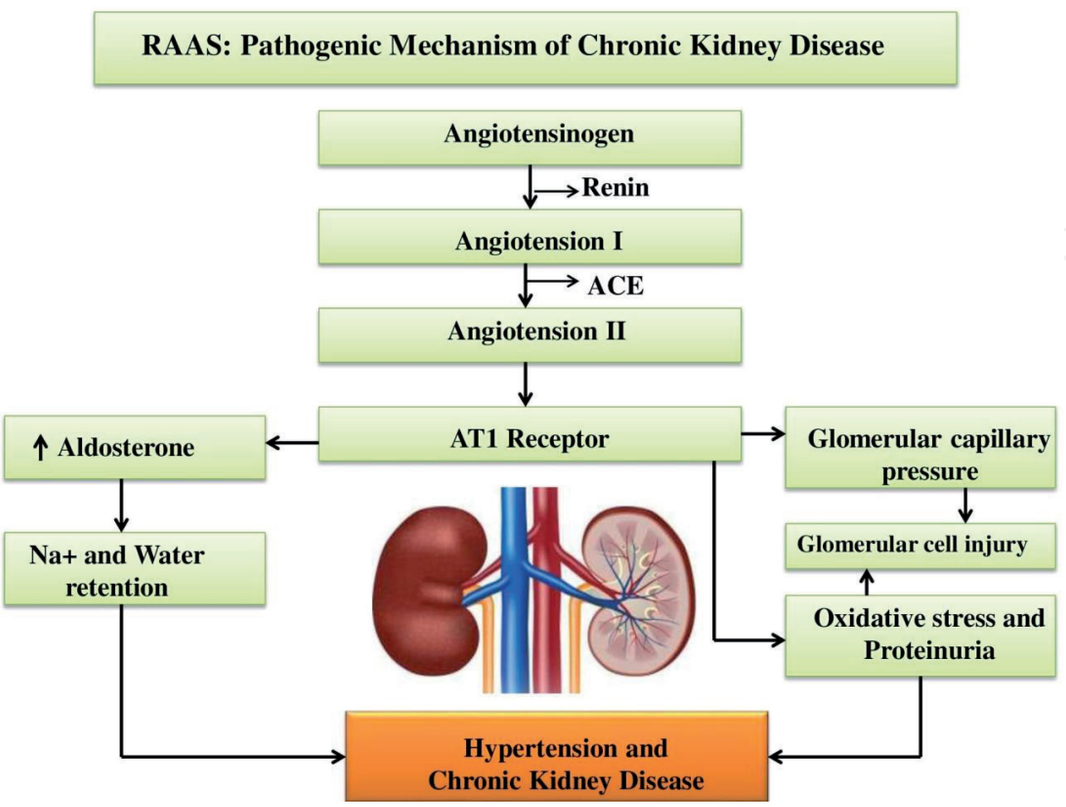

Figure 1.
The pathogenic mechanism of chronic kidney disease in the renin angiotensin aldosterone system.

in addition to the conversion of angiotensin I to Ang II [7]. Recently, ACE type 2 (ACE2) has been found to cleave angiotensin I into inactive angiotensin1–9, transformed by ACE into vasodilator and antiproliferative angiotensin1–7, respectively [8, 9]. While ACE2 in the human kidney is known to be present, there was no evidence on the distribution of tissues in kidney disease [8]. Kidney biopsies from patients with different kidney disorders, including transplant patients, were studied in a recent review. ACE2 was present in the tubular and glomerular epithelium and in the vascular smooth muscle cells and the interlobular artery endothelium in the control kidneys [10]. Neo-expression of ACE2 has been observed in the glomerular and peritubular capillary endothelium in all kidney diseases. Treatment with ACE inhibitors did not change ACE2 expression [10]. In vivo, Ang II increases the vascular tone of both afferent and efferent glomerular arterioles and modulates capillary intraglomerular pressure and glomerular filtration rate (GFR). Ang II primarily exerts its vasoconstrictor effect on the postglomerular arterioles, thereby raising the glomerular hydraulic pressure and filtration fraction, and impairing the glomerular barrier's selective size role for macromolecules, such as plasma proteins [11]. Intra capillary hypertension and increased plasma protein ultrafiltration can lead to the onset and progression of CKD [12]. Angiotensin non-hemodynamic effect may also be relevant in the progression of kidney disease [6].

A diagrammatic sketch of the pathogenic role of RAAS in chronic kidney disease is shown in **Figure 1**.

3. RAAS: pathogenic mechanism of Alzheimer's disease

Alzheimer disease (AD) is the most common neurodegenerative disease associated with dementia in the elderly. Various mechanisms, including DNA damage, lysosomal dysfunction, epigenetic modulation, and immune dysregulation, have been involved in neurodegenerative pathogenesis. Importantly, the homeostasis between protein synthesis, folding, and clearance of unfolded proteins, called proteostasis, is disrupted in AD and other neurodegenerative diseases. This contributes to an accumulation of proteins that are oligomerized and aggregated (Intracellular Tau (Neurofibrillary tangles [NFT]), and extracellular amyloid β (Aβ) (Senile plaques)) that ultimately induce protein toxicity. In many neurodegenerative disorders, including AD, oxidative stress are frequently found. In AD, Aβ accumulation, tau hyperphosphorylation, and the resulting degradation of synapses and neurons may be promoted by oxidative stress. In several target cells, Ang II has been shown to induce mitochondrial dysfunction through angiotensin II type 1 receptor (AT1R). Mechanistically, Ang II increases mitochondrial reactive oxygen species (ROS) [13]. Several studies indicate that ROS is involved in the development of Aβ fibrillation and NFT in AD and increases the pathology of Aβ and NFT in AD [14, 15].

The hyperactivity of the RAAS classical axis, mediated by AT1R, is implicated in the pathogenesis of AD. Ang II intracerebroventricular infusion increased both of the amyloid-β (Aβ) [16] and tau pathology, and also reduced cognitive performance [17], in aged normal rats. In most but not all AD mouse models, angiotensin II type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) minimize the amount of AD-like pathology and increase cognitive efficiency [18, 19]. Clinical studies have also identified ACE2 and ACE as brain RAAS factors, not only in the regulation of blood pressure, but also in the conversion of Aβ43 to Aβ40, which may decrease Aβ accumulation associated with AD and decrease serum ACE-2 activity in AD patients compared to control subjects [20].

A diagrammatic sketch of the pathogenic role of RAAS in Alzheimer's disease is shown in **Figure 2**.

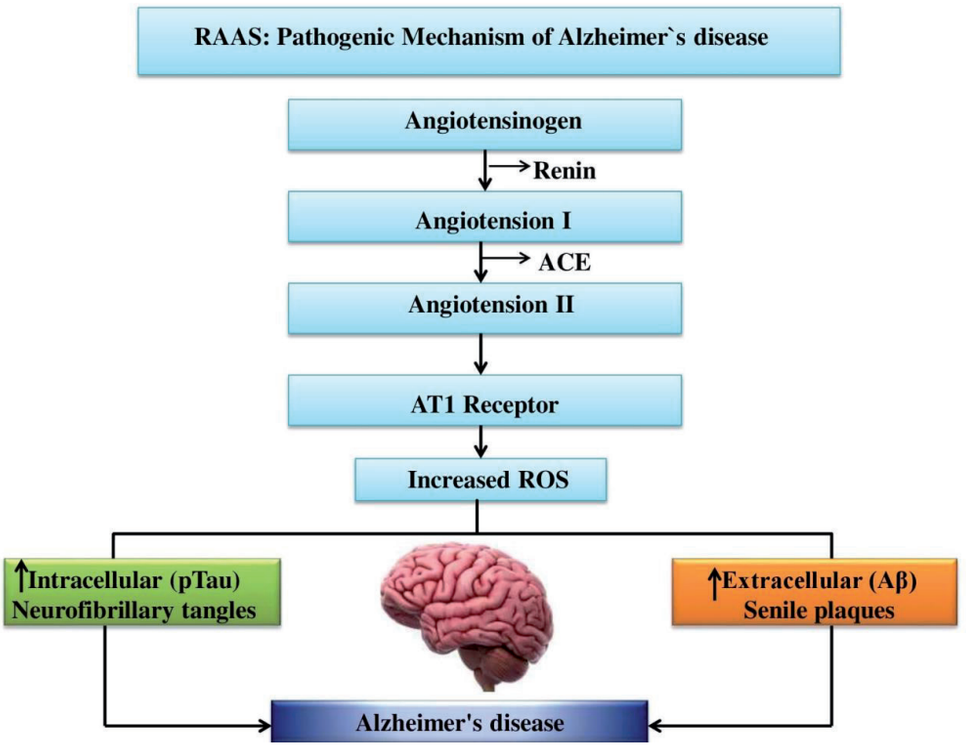

Figure 2.
Pathogenic Alzheimer's disease pathway of the renin angiotensin aldosterone system.

4. Hypertension is a risk factor for cognitive dysfunction in chronic kidney disease patients with Alzheimer's disease

The most common neurodegenerative disorders associated with CKD in the elderly are AD and dementia. Ang II represents a central molecule in cerebrovascular pathology and hypertension. Enhanced Ang II levels speed up the initiation and progression of cell senescence by encouraging inflammation and oxidative stress. Sustained RAAS activation causes aging related end stage organ damage and results in cognitive decline and dementia [21]. Studies also show that hypertension is the most important factor that adversely affects cerebral aging modalities and is related to cognitive compromise in people who are aging [22, 23]. This discovery has contributed to the belief that hypertension, up to the point of AD and dementia, is one of the factors responsible for the compromise of cognitive function in the elderly. It is therefore hypothesized that aging contributes to systemic and tissue RAAS hyperactivity and a rise in neurogenic hypertension, whereas evidence that connects brain RAAS with AD, memory, and learning develops cognitive functions [24]. In this regard, one of the long-term hypertension complications is clinically defined as dementia (for example AD) or vascular dementia, associated with diseases of the degenerative central nervous system (CNS). The temporal association between dementia and broad cerebrovascular pathology indicates that there is a pattern of sudden initiation and progressive development of cognitive impairment in the onset of dementia within three months of the diagnosis of stroke. It is understood that hypertension raises the risks of the target organ, such as cardiomegaly, progressive hypertensive retinopathy, nephropathy and stroke. In addition to repeated episodes of stroke or acute ischemic attacks, chronic hypertension, which results in a reduction in cerebral blood flow, is associated with vascular dementia and results in cognitive impairment [25].

A diagrammatic sketch of the role of RAAS in the induction and mediation of high blood pressure and cognitive impairment in CKD patients with AD is shown in **Figure 3**.

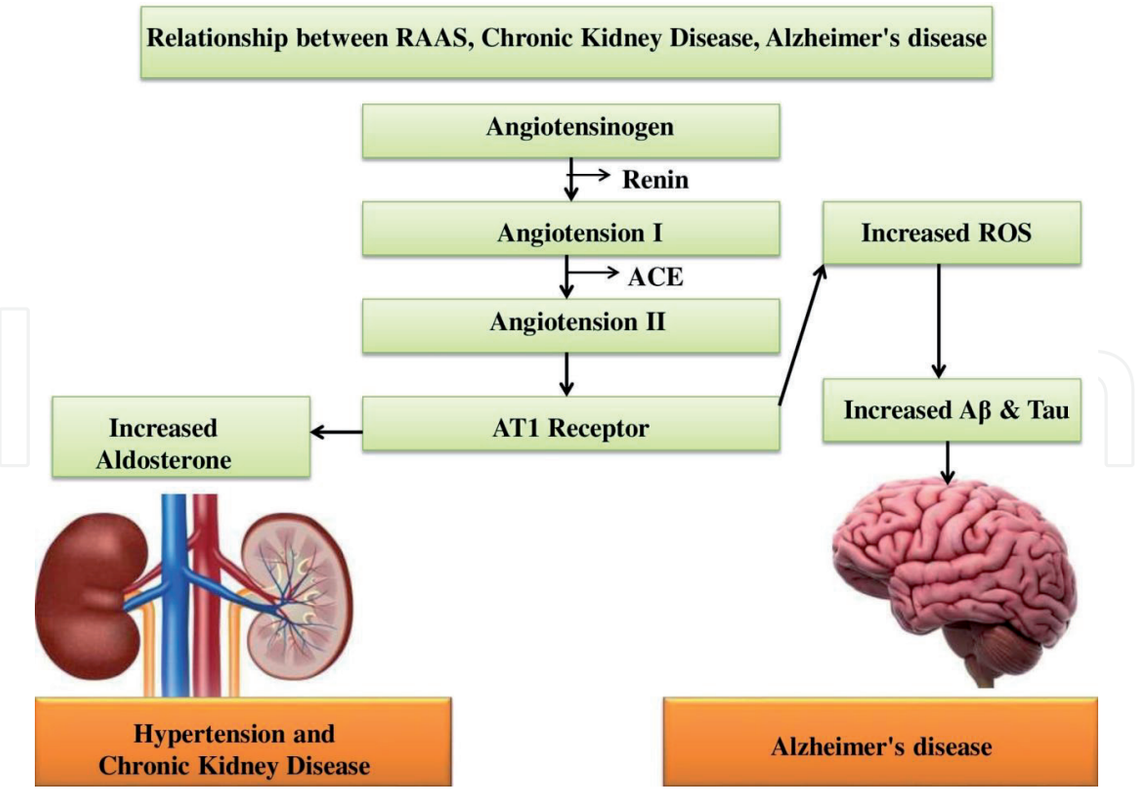

Figure 3.
Chronic kidney disease and alzheimer's associated renin angiotensin aldosterone system share ageing related molecular pathways, including processing of APP, tau phosphorylation, and increased oxidative stress.

5. Treatment of cognitive dysfunction in chronic kidney disease patients with Alzheimer's disease

Cognitive dysfunction is common among patients with CKD and dialysis in the memory, attention, and executive function domains. In our previous study, working memory and executive control, two main areas of cognitive ability, are potentially significant variables in drug compliance [4, 5]. Increased risk for injury, increased health care costs and progression to dementia are also associated with cognitive dysfunction without dementia [26]. Dementia is described by a drop in cognitive performance from a previous higher level along with a behavioral disorder that interferes with everyday function and independence. The brain and kidney vascular beds have identical anatomical and hemodynamic characteristics; these results have contributed to the speculation that cognitive dysfunction and CKD are a reflection of vascular damage in multiple end organs [26]. In addition, most patients with CKD have elevated rates of hypertension, diabetes, high levels of inflammatory receptors and vascular endothelial dysfunction, cardiovascular events like stroke, and carotid atherosclerosis, both leading to vascular cognitive decline and neurodegenerative diseases such as AD [27]. Potential steps to minimize cognitive impairment in CKD patients may include the treatment of cardiovascular risk factors, but, unfortunately, no clinical trials have been performed in CKD patients assessing cardiovascular risk factors for the prevention of cerebrovascular disease or cognitive impairment.

There is a trial showing that treatment with hypertension has a beneficial effect on cognition. In that survey, High blood pressure care with medication not only improves the cardiovascular health of older people, but can also reduce their risk of dementia and AD [27, 28]. The combined risk ratio of dementia preferred care in a meta-analysis of antihypertensive trials [29]. There is no strong evidence from

the trials in a systematic analysis of hypertension research to confirm that decreasing blood pressure prevents the development of dementia or cognitive decline in hypertensive patients with no clear previous CVD [30]. However, the occurrence of fatal and non-fatal stroke has been greatly decreased in many studies of hypertension treatment, and it is very important since a history of stroke doubles the risk of dementia in both patients with non CKD and *hemodialysis*. In CKD patients, Anemia has also been identified as a risk factor for cognitive decline in CKD patients, and our studies have shown correction of anemia with recombinant erythropoietin therapy to improve cognitive measures, such as AD markers and neuropsychological tests [4, 5].

6. Future directions and challenges

This chapter explores the relationship between RAAS, cognitive dysfunction anemic CKD patients and EPO. We then hypothesized that the EPO may inhibit ACE2 interest and likely eventually alter complicated signaling cascades to boost cognition through changes in AD markers. A main aspect of this assessment is that in anemic CKD sufferers with cognitive impairment, the limited molecular effects of the treatment with EPO are crystal-clear. I may conclude by saying that a bright future for the EPO remedy. In order to better understand the mechanisms underlying the effects of EPO in anemic CKD with AD patients, further research into pharmacogenomics and clinical trials is required.

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