REVIEW

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The renin-angiotensin system and aging in the kidney

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Aging is associated with progressive functional deterioration and structural changes in the kidney. Changes in the activity or responsiveness of the renin-angiotensin system (RAS) occur with aging. RAS changes predispose the elderly to various fluid and electrolyte imbalances as well as acute kidney injury and chronic kidney disease. Among the multiple pathways involved in renal aging, the RAS plays a central role. This review summarizes the association of the RAS with structural and functional changes in the aging kidney and age-related renal injury, and describes the underlying mechanisms of RAS-related renal aging. An improved understanding of the renal aging process may lead to better individualized care of the elderly and improved renal survival in age-related diseases.

Keywords: Aging; Kidney; Renin-angiotensin system

INTRODUCTION

Aging is associated with progressive functional deterioration and structural changes in the kidney. The glomerular filtration rate (GFR) declines by ~0.40 to 1.02 mL/min per year [1], which is attributed to a reduction in the number of functioning glomeruli and an increase in the number of sclerotic glomeruli [2]. The renal plasma flow is maintained at ~600 mL/min until the fourth decade of life and then declines by ~10% per decade [3]. Age-related glomerular hemodynamic changes occur including reductions in the glomerular capillary plasma flow rate, glomerular capillary ultrafiltration coefficient and afferent arteriolar resistance [4]. Structural changes occur along with functional changes: the renal mass regresses progressively with aging [5], the percentage of glomerulosclerosis and tubulointerstitial fibrosis increases [6] and hyalinization of afferent arterioles may develop [7]. In addition, changes in the activity or responsiveness of hormonal systems occur with aging, altering homeostatic mechanisms in the elderly [8]. The renin-angiotensin system (RAS) is particularly important, as changes in the RAS predispose the elderly to acute kidney injury and chronic kidney disease (CKD). This review focuses on RAS changes in normal aging and aging-related kidney disease, as well as the molecular mechanisms underlying the RAS-associated renal aging process.

INVOLVEMENT OF THE SYSTEMIC RAS IN AGING

Previous reports have shown that the systemic RAS is suppressed with age. Compared to younger groups, older populations have lower levels of plasma renin and aldosterone at baseline [9] and show an impaired ability to trigger appropriate responses to RAS stimuli such as upright posture, sodium depletion or potassium infusion [10,11]. Studies in aging animals showed that both

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renal renin formation and release are reduced, which results in a decrease in plasma renin concentration [12]. In addition, the change in RAS activity leads to an altered response to RAS blockade. The effects of angiotensin-converting enzyme (ACE) inhibitors on blood pressure, renal function and proteinuria are blunted in aging animals [13,14]. In addition, elderly populations exhibit a decreased antihypertensive response to ACE inhibitors than younger groups [15].

These age-related decreases in plasma renin and aldosterone may lead to various fluid and electrolyte abnormalities. Elderly populations on a salt-restricted diet have a decreased ability to conserve sodium and are likely to develop hyponatremia [16]. Decreased angiotensin II (Ang II) secretion impairs the tubular concentrating ability and predisposes the elderly to develop volume depletion and hyponatremia [17]. The risk of hyperkalemia increases as the transtubular potassium gradient is reduced in the elderly [18]. In addition, potassium levels can be critically elevated after potassium-loading conditions such as gastrointestinal bleeding, blood transfusion or administration of potassium. The tendency towards hyperkalemia can be enhanced by the reduction in GFR, metabolic acidosis or medications that inhibit renal tubular potassium excretion, such as ACE inhibitors, Ang II type 1 (AT1) receptor antagonists ($AT1_RA$), nonsteroidal anti-inflammatory drugs and potassium-sparing diuretics [12,17].

INVOLVEMENT OF THE INTRARENAL RAS IN AGING

The age-related changes in the RAS are also observed in the kidney. In aging rats, renal mRNA expression was reduced prior to a decline in plasma renin, and renal ACE levels were reduced before the decline in plasma ACE levels [12]. Aging animals show an altered renal response to systemic RAS activation, such as exogenous Ang II. Reductions in GFR and renal plasma flow were exaggerated in older rats with the administration of Ang II, whereas responsiveness to Ang II blockade was preserved but not enhanced [19]. Therefore, the enhanced renal hypersensitivity to Ang II may lead to further reductions in GFR when the elderly kidney is exposed to RAS stimuli such as hypovolemia, hypotension or sodium restriction.

THE RAS AND AGE-RELATED RENAL INJURY

Animal studies have shown increased glomerular capillary pressure due to a reduction in afferent arteriolar resistance, urinary protein excretion, and focal and segmental glomerular sclerosis in the aging kidney. In addition, ACE inhibitors lowered the glomerular capillary pressure and proteinuria, and reduced focal and segmental glomerular sclerosis [13,14] and interstitial sclerosis, whereas calcium-channel blockers did not [20]. These results suggest that the RAS is involved in glomerular and tubular damage during the aging process [21].

Previous studies emphasized the role of renal sirtuins in protecting the kidney against aging. Sertuins are a family of NAD^+-dependent histone deacetylases that act on forkhead homeobox type O (FoxO) transcription factors, peroxisome proliferator-activated receptor γ and nuclear factor-κB [22,23]. Among seven mammalian sirtuins, sirtuin 1 (Sirt1), and sirtuin 3 (Sirt3) are considered antiaging molecules in the kidney [24]. Sirt1 activation protected the mouse renal medulla from oxidative injury and provided antiapoptotic and antifibrotic effects in the obstructed mouse kidney [25]. Recently, we demonstrated decreased renal Sirt1 expression and increased oxidative stress in the kidneys of aging mice [26]. These findings suggest a role for Sirt1 in regulation of oxidative stress in the aging kidney. Several reports have suggested the role of Sirt1 as a negative regulator of AT1 receptor expression. Overexpression of Sirt1 or treatment with resveratrol, an activator of Sirt1, suppressed AT1 receptor expression in cultured smooth muscle cells, and resveratrol improved Ang II-induced hypertension in mice [27]. Sirt1 overexpression decreased Ang II-increased binding of nuclear factor-κB to its specific binding sites and inhibited Ang II-induced vascular remodeling in mice [28]. Ang 1–7, a derivative from the cleavage of Ang II by ACE, has counteractive effects of Ang II [29,30]. Ang 1–7 reduced renal lipotoxicity through the regulation of the Sirt1-FoxO1 pathway in diabetic nephropathy [31]. Sirt3 may also be involved in renal aging in association with the RAS. Mice with disrupted $AT1_A$ receptor genes live longer

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and have lower levels of oxidative stress and increased expression of Sirt3 compared with aged wild-type mice [32]. In addition, Sirt3 mRNA expression was downregulated by Ang II, which was inhibited by $AT1_RA$ in tubular epithelial cells [32]. These prosurvival effects of RAS blockade are related to the preservation of renal mitochondria. $AT1_A$ receptor-deficient mice showed an increased number of mitochondria in the proximal renal tubular cells [32]. Moreover, the treatment with ACE inhibitor or $AT1_RA$ attenuated the age-associated mitochondrial dysfunction [33]. These findings suggest the association of the RAS with oxidative stress in the aging process in the kidney.

KLOTHO AND RAS IN THE KIDNEY

Genetics play an important role in aging-associated renal impairment [34]. In 1997, the *klotho* gene was found to be involved in the suppression of aging phenotypes [35]. The discovery of *klotho* led to further insight into the role of genetics in aging-related renal changes. The *klotho* gene is expressed predominantly in the kidney in a transmembrane form [36], and the expression of *klotho* was reduced markedly in the kidney of patients with CKD [37]. Previously, we demonstrated increased renal fibrosis and oxidative stress with decreased renal expression of *klotho* in aging mice [26]. The secreted *klotho* functions as a regulator of multiple glycoproteins, including insulin/insulin-like growth factor-1 receptors, and possess antiapoptotic and antioxidant effects [36,38]. Increasing evidence has shown the association between *klotho* and the RAS. Long-term infusion of Ang II downregulated renal *klotho* gene expression, and *in vivo klotho* gene transfer ameliorated Ang II-induced renal damage [39]. Another study showed that the Ang II-induced reduction in renal *klotho* expression was mediated by promoting intrarenal iron deposition and induction of oxidative stress [40]. Moreover, diabetic patients with CKD treated with $AT1_RA$ showed elevated plasma soluble Klotho levels compared to those who were not treated with $AT1_RA$ [41]. We reported previously that the intrarenal RAS is upregulated and renal expression of *klotho* is downregulated in chronic cyclosporine-induced nephropathy, and that $AT1_RA$ upregulated the expression of renal *klotho* and attenuated renal fibrosis and oxidative stress [42]. Characteristics of chronic cyclosporine-induced nephropathy include progressive renal failure with striped interstitial fibrosis, tubular atrophy, inflammatory cell infiltration and hyalinosis of the afferent arterioles [43], and are similar to the alterations in the aging kidney. These findings suggest that the RAS is involved in renal senescence at the genetic level.

CONCLUSIONS

Aging disrupts the activity and responsiveness of the RAS. The altered systemic and intrarenal RAS may predispose the elderly population to kidney damage or fluid and electrolyte imbalances. Therefore, understanding the association between renal aging and the RAS is crucial for providing individualized care in the elderly. Moreover, the RAS is involved in the age-associated structural and functional renal impairment, and RAS inhibition has a protective role against renal aging. The underlying mechanisms of renal aging involve the regulation of renal sirtuins, oxidative stress and mitochondrial dysfunction, and the antiaging gene *klotho*. As changes in renal aging overlap with the structural and functional manifestation of CKD, understanding the role of the RAS in age-related changes in the kidney may help to elucidate the pathogenesis of CKD.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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