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COMMENTARY

Intrarenal renin-angiotensin system activation in end-stage renal disease

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The role of the renin-angiotensin system (RAS) in maintaining renal hemodynamics is well recognized.[1] The RAS regulates several components of renal sodium transport in both normal physiological states and pathological conditions, including renal cortical and medullary circulations, glomerular hemodynamics, and glomerular filtration.[2] The RAS was initially presumed to mediate renal damage (Figure 1),[1] and as such, RAS blockades are often administered to patients with chronic kidney disease (CKD). Their efficacy suggests that factors other than angiotensin II (Ang II) are involved in renal disease progression.[3] While evidence suggests that local RAS in various tissues, including the brain, heart and vasculature are regulated independently of the systemic RAS,[1] most current research focuses on analyzing the role of tissue RAS in the kidneys.[4]

The renal RAS is unique because all of the components necessary to generate intrarenal Ang II are present along the nephron both in the interstitial and intratubular components.[4] There is substantial evidence indicating that the Ang II in renal tissues is generated from angiotensinogen (AGT), produced by the proximal tubule cells, and subsequently released into the kidneys.[4] Ang I can also be converted to Ang II in the kidneys,[4] and renin mRNA and renin-like activity have been observed in cultured proximal tubular cells.[5] The brush border membranes of human proximal kidney tubules also express abundant angiotensin-converting enzyme (ACE) mRNA and protein.[4] ACE has been detected in proximal and distal tubular fluids, with higher concentrations observed in proximal tubule fluid.[4]

All major components required to generate Ang II are expressed within the kidneys,[1,3] but it is difficult to distinguish the influences of the intrarenal RAS from those of circulating Ang II.[2] There are circumstances in which the intrarenal RAS and circulating Ang II act together, such as during variations in salt intake.[2] In other situations, such as certain types of hypertension and diabetes mellitus, alterations in the intrarenal RAS are independent of changes in systemic renin and Ang II.[2] Although every organ system in the body has elements of the RAS, the kidneys compartmentalize every RAS component within the nephrons and interstitial networks. Intracellular Ang II accumulation has been observed in the kidneys, creating tissue concentrations much greater than by arterial blood flow alone.[4] Ang II concentrations in the tubular fluid from the other segments of the nephron remain unknown. Several studies support an important role for Ang II in regulating the re-absorptive function in the distal nephron and collecting duct segments, as well as in the proximal tubule segments, which activate the Ang II receptors on the luminal borders.[4] A direct action of Ang II on the luminal amiloride-sensitive epithelial sodium channel has been reported. These data indicate that augmentation of Ang II concentrations in the luminal distal nephron contributes directly to the regulation of sodium re-absorption in the distal tubule and collecting duct.[4]

Although most circulating AGT is produced and secreted by the liver, it is also produced by the kidneys.[4] AGT mRNA and protein have been identified in proximal tubular cells, and intratubular Ang II has been isolated from formed and secreted AGT.[6] Proximal tubule cells produce their own intracellular metabolites and AGT, and secrete both into the tubular lumen.[7] Urinary AGT excretion rates were recently used to create a specific index of the intrarenal RAS in studies.[1] A direct quantitative method of measuring urinary AGT using human AGT enzyme-linked immunosorbent assays has been developed,[8] and clinical studies have indicated that urinary AGT represents a novel biomarker of the activated intrarenal RAS in patients with hypertension, CKD, diabetes,[1] acute kidney injury and organogenesis.[3] Investigation of intrarenal RAS in animal models with end-stage renal disease (ESRD) has proven difficult, however. These animals require dialysis to live, and as such do not excrete urine; it is therefore impossible to evaluate intrarenal RAS activation in dialysis patients using urinary AGT excretion measurements.

In the current issue of *Hypertension Research*, Ohashi *et al.*[9] incorporate several of these concepts and considerations related to activation of the intrarenal RAS and the chymase-dependent pathway after initiation of dialysis. They recruited 19 CKD patients (10 without dialysis and 9 with dialysis) who underwent heminephrectomy, and quantified intrarenal RAS components, and chymase-positive cells in samples from the removed kidney using radioimmunoassay or immunoblot analysis. There were no significant differences between non-dialysis and dialysis patients in plasma renin activity and Ang II levels in the primary analysis. Intrarenal Ang II expression and the extent of tubulointerstitial fibrosis in dialysis patients were significantly increased compared to those in non-dialysis patients. These findings indicate that the local RAS in the kidneys is regulated independently of the systemic RAS in dialysis patients. Consequently, intrarenal

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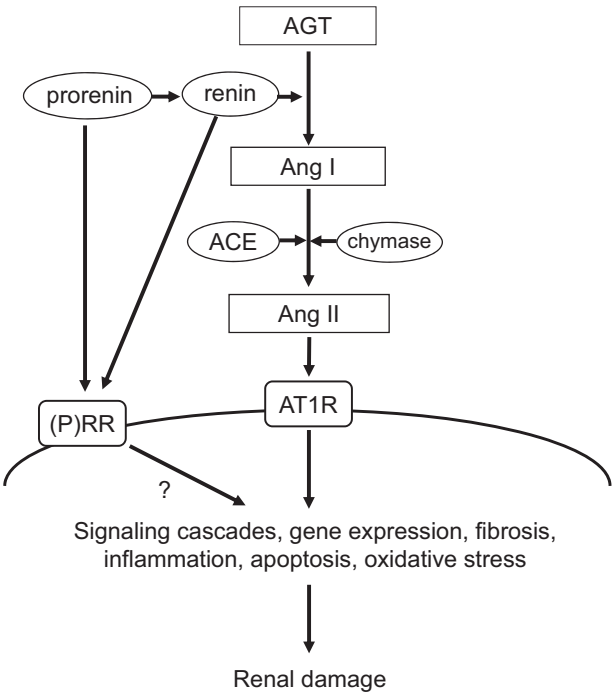

Figure 1 Schematic of the renin-angiotensin system in renal damage. ACE, angiotensin converting enzyme; AGT, angiotensinogen; Ang, angiotensin; AT1R, angiotensin type 1 receptor; (P)RR, (pro)renin receptor.

RAS protein levels were evaluated by immunoblotting and immunostaining. ACE expression was abundant in the proximal tubule brush border in non-dialysis patients, and dramatically decreased in dialysis patients. The number of chymase-positive cells in dialysis patients was significantly greater than in non-dialysis patients. The extent of tubulointerstitial fibrosis was significantly and positively correlated with the number of chymase-positive cells, intensity of Ang II type 1 receptor (AT1R) signals, and intrarenal Ang II levels. The authors suggest that a chymase-dependent pathway may contribute to Ang II generation in place of ACE and contribute to renal damage according to renal dysfunction.[9] They also observed that prorenin expression decreased significantly in proportion to renal damage, indicating proteolytic activation.[9] The study, in addition, used multiple liner regression analyses to measure the extent of interstitial fibrosis, finding significant positive relationships between the extent of interstitial fibrosis and AGT intensity. The paper also reports that intrarenal AGT and AT1R are augmented by intrarenal RAS activation, leading to renal damage such as the tubulointerstitial fibrosis associated with renal dysfunction in dialysis patients. This is not incongruous with prior studies that have reported the relationship between intrarenal RAS activation and renal damages.[1]

Because AGT levels are close to the Michaelis–Menten constant for renin, AGT can also control RAS activity, and upregulation of AGT levels may lead to elevated angiotensin peptide levels and increases in blood pressure.[1] Recent studies using experimental animal models and transgenic mice have documented the involvement of AGT in the activation of the intrarenal RAS and development of hypertension.[1] Genetic manipulations that lead to overexpression of AGT have consistently caused hypertension, and a link has been established between the AGT gene and hypertension in humans.[1] Enhanced intrarenal AGT mRNA and protein levels have also been observed in multiple experimental hypertension models, including Ang II-dependent hypertensive rats, Dahl salt-sensitive hypertensive rats, and spontaneously hypertensive rats as well as in kidney diseases, including diabetic nephropathy, IgA nephropathy, radiation nephropathy and anti-thymocyte serum nephritis rats.[1,10] AGT upregulation thus plays an important role in the development and progression of hypertension and kidney disease.[1] Proximal tubular AGT concentrations range from 300–600 nM in anesthetized rats, which greatly exceeds the concentrations of free Ang I and Ang II in tubular fluid.[3] Given the molecular size (50–60 kDa) of AGT, it seems unlikely that significant amounts of plasma AGT filters across the glomerular membrane, further supporting the concept that proximal tubular cells secrete AGT directly into the tubules.[3] To determine whether circulating AGT is a source of urinary AGT, Nakano *et al.*[11] examined the glomerular permeability of AGT by multiphoton imaging, and found an extremely low glomerular permeability of injected exogenous AGT. In contrast, urinary excretion of endogenous AGT was significantly higher. These results indicate that the majority of urinary AGT originates from the kidneys, rather than from glomerular filtration.

The study by Ohashi *et al.*[9] makes several interesting observations and enhances understanding of the intrarenal RAS activation mechanism in dialysis patients. This should allow for early detection of and preventative or targeted treatments for ESRD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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