ROLE OF COLLECTING DUCT RENIN IN BLOOD PRESSURE REGULATION

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Abstract

Numerous studies indicate that renin is synthesized and secreted by the collecting duct. Collecting duct-derived renin may act directly upon intercalated and/or principal cells through direct interaction with prorenin receptors and/or through cleavage of proximal tubule-derived angiotensinogen to ultimately produce angiotensin II and activate AT1 receptors. Preliminary studies suggest that the net effect of CD renin would be to increase distal nephron salt reabsorption and increase blood pressure. Collecting duct renin production is markedly increased in diabetes and angiotensin-II induced hypertension, suggesting that this system may exert pathophysiological effects. In this brief review, we summarize the current literature on synthesis and regulation of CD renin and consider potential mechanisms by which it regulates blood pressure.
Introduction

Components of the renin angiotensin system (RAS) exist in several tissues, however the kidney is the only organ that contains all elements necessary for generation of angiotensin-II (Ang-II). Angiotensinogen (AGT) is synthesized in the proximal tubule and secreted into the tubule lumen. Tubule fluid AGT is potentially hydrolyzed by renin derived from glomerular filtrate or from the distal nephron. Angiotensin-converting enzyme (ACE) is found throughout the nephron; subsequently generated Ang-II may bind apical Ang-II receptors with resultant modulation of sodium transport. Herein, we briefly review the regulation and synthesis of renin derived from the distal nephron and postulate on its effects in modulating blood pressure.

Renin presence in the distal nephron in health and disease

In a seminal publication in 1999, Rohrwasser et al described renin immunostaining in principal cells of the connecting segment in murine and human kidneys (17). They also demonstrated that proximal tubule AGT was luminally secreted and hypothesized that a paracrine RAS operated within the renal tubule. Several ensuing studies have confirmed AGT synthesis in the proximal tubule (5, 6, 9, 18) as well as renin production by the connecting segment and collecting duct (CD) (4, 13, 14). Renin immunostaining or activity has also been described in cultured isolated connecting segment cells (17) and M1 collecting duct cells (4). Of great interest, medullary renin immunostaining and renin levels were elevated in 2-kidney
1-clip Goldblatt hypertensive rats (13) and in a transgenic rat model with inducible extra-renal mouse renin gene (Ren 2) expression (12). In addition, using a novel experimental approach that employs multi-photon confocal fluorescence microscopy \textit{in vivo}, Kang et al found greatly increased renin fluorescence in the principal cells of the CD in streptozotocin-induced diabetic rats (4). They noted that renin granules were present at both the apical and basolateral poles of the principal cells, suggesting access to the tubular lumen and to peritubular capillaries. Taken together, these studies show that CD principal are capable of renin synthesis and that this system may be stimulated during pathological states such as diabetes or hypertension.

\textbf{Regulation of distal nephron renin synthesis}

Ang-II has been implicated as an important stimulant of CD renin synthesis. Ang-II infusion increases renin mRNA and protein levels in the CD while suppressing systemic renin from the juxtaglomerular apparatus (JGA) (14). Further, treatment with an angiotensin receptor blocker (2) reduced CD renin, suggesting the AngII is stimulating CD renin via activation of AT1 receptors (15). Similar attenuation of CD renin fluorescence by an ARB was noted in experimental diabetes (4). Moreover, Ang-II increased renin activity in cell cultured M1 collecting duct cells (4). To elucidate whether the AngII stimulation of CD renin was dependent upon blood pressure, Prieto et al used 2-kidney -clip Goldblatt hypertensive rats wherein both kidneys were exposed to elevated intra-renal Ang-II, but only the non-clipped kidney was exposed to elevated blood pressure (13). Significant increases in cortical and medullary CD renin mRNA, protein and immunoreactivity were observed in both
kidneys in contrast to significantly decreased JGA renin only in the non-clipped kidney. Taken together, these results indicate that CD renin synthesis is stimulated by AngII directly and that this effect may be important in hypertension associated with elevated Ang-II levels.

Another potential regulator of renin synthesis in the CD is tubular sodium delivery. Rohrwasser et al noted augmented renin expression in the microdissected connecting segment taken from animals during sodium restriction (17). Further, overnight sodium restriction in mice led to a marked increase in renin immunostaining in the connecting segment, while sodium restriction with furosemide decreased this effect. Conversely, mice exhibited minimal renin immunostaining with high sodium intake; addition of amiloride during high salt intake markedly increased connecting segment renin immunostaining. Thus, these initial studies suggested that distal nephron renin synthesis was stimulated by low Na delivery and that the epithelial sodium channel was involved in mediating this effect. However, a subsequent study found that high sodium intake increased urinary renin excretion as compared to that observed during sodium restriction (6). A recent study also noted augmented urinary renin content in rats with Ang-II infusion that increased even more when these animals were subjected to a high sodium diet (7). Interpretation of these findings is confounded by the lack of information on the sources of urinary renin; it is possible that both distal nephron-derived and filtered renin appear in the urine. In addition, how a high Na diet affects filtered renin appearance in the urine needs to be determined since this relationship is not obvious: high Na intake may increase distal nephron renin delivery by increasing
GFR and reducing proximal tubule uptake of filtered renin, however it would also suppress systemic renin levels. Clearly, further studies are needed to establish the role of sodium intake in regulating CD renin synthesis.

**Functional significance**

While the presence of CD renin has clearly been established, its functional significance remains unknown. Using gene targeting, we have developed a mouse model with renin overexpression selectively in the CD (16). Preliminary studies show a 5-fold increase in medullary renin mRNA levels and 2.5-fold increase in urinary renin excretion in the gene targeted mice compared to control mice. These mice exhibit salt-sensitive hypertension and have reduced plasma renin concentration, suggesting that CD renin has the potential to modulate blood pressure.

Although direct evidence is lacking, potential mechanisms by which CD renin modulates blood pressure have been reported (Figure 1). The recent discovery of the prorenin receptor (PRR) in CD intercalated cells suggests one possible mechanism of action for CD renin (1). Binding of renin to intercalated cell PRR induces activation of ERK1/2 leading to up-regulation of cyclooxygenase 2 and other signaling pathways (3). Another interesting possibility is that CD renin, via PRR binding or AT1 receptor activation, might modulate intercalated cell chloride transport by pendrin. In this regard, it is relevant to note that AngII can increase cortical CD pendrin-mediated chloride transport, albeit only basolateral AngII effects on this system have been assessed (10). In addition to modulation of cell signaling, binding of CD-derived renin
to the PRR, either on the surface of intercalated cells or to the soluble PRR within tubule fluid, would increase the catalytic efficiency of the conversion of AGT to angiotensin I. Finally, luminal Ang-II binding to AT1 receptors potently stimulates CD Na transport via activation of the epithelial sodium channel (8, 11). Further studies are needed to delineate the exact mechanisms by which CD renin modulates renal transport and blood pressure.

**Conclusion**

In summary, there is considerable evidence for synthesis and regulation of renin in the CD. CD renin production can occur under normal physiologic conditions, and may be markedly increased during pathological states such as diabetes and hypertension. CD renin has the potential to modulate distal nephron solute reabsorption and blood pressure through interaction with apical PRR and AT1 receptors. Much research remains to be done in this area; amongst other studies examination of blood pressure and renal function during health and disease in mice with CD-specific renin knockout may shed light on this area.
References


Figure 1. Possible mechanisms of blood pressure regulation by collecting duct renin.

AGT: angiotensinogen; Ang: angiotensin; ACE: Angiotensin converting enzyme; AT-1: angiotensin receptor type 1; PRR: Prorenin receptor; ENaC: epithelial sodium channel; ERK 1/2: extracellular regulated kinases 1 and 2; COX-2: Cyclooxygenase 2; sPRR: soluble PRR
Figure 1