Augmented intratubular renin and prorenin expression in the medullary collecting ducts of the kidney as a novel mechanism of angiotensin II-induced hypertension

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THE RENIN-ANGIOTENSIN SYSTEM (RAS) is arguably one of the most important humoral factors in the regulation of blood pressure and body salt and fluid balance both in health and diseases through the classic renin/angiotensin-converting enzyme (ACE)/angiotensin (ANG) II/ANG II receptor axis. Although still debatable, the roles of the RAS in the blood pressure and body salt and fluid regulation are largely mediated through the actions of this axis on the kidney (1). All key components of the RAS, including the precursor angiotensinogen, enzymes renin and ACE, and G protein-coupled receptors for ANG II, AT1 and AT2, have been demonstrated in various structures in the kidney, especially in the renal tubular segments (5, 10, 17). However, circulating renin is almost exclusively derived from the juxtaglomerular (JGA) cells in the afferent arterioles of the kidneys (2, 6, 15). Classically, there is a close inverse relationship between blood pressure, body sodium and fluid balance, and the activity of the RAS in the circulation and the expression and release of renin from JGA (2, 6). This unique relationship dictates that in the presence of moderate to severe sodium and fluid depletion, volume contraction, and a fall in systemic blood pressure, the RAS is immediately activated through increased renin expression and release of active renin from the JGA, followed by increased production of ANG II in the circulation and tissues. Conversely, the expression and release of renin from the JGA and subsequent ANG II formation will be suppressed in the events of high circulating ANG II levels, sodium retention, and persistent hypertension (2, 6). The intrarenal RAS is also supposed to respond reciprocally to the activity of the circulating RAS. Low circulating ANG II levels as occurred during ACE inhibition and high-salt intake would lead to increased renin expression in the JGA. By contrast, high circulating ANG II levels as elicited by sodium depletion or acute ANG II infusion are expected to suppress renin expression and/or release from the JGA (2, 6). Under physiological conditions, most active renin in the kidney is localized in JGA, which may be extended into interlobular arteries during sodium depletion (15). While this reciprocal relationship between circulating ANG II and intrarenal RAS may remain largely true under physiological conditions, accumulating evidence suggests that it may no longer be applicable to long-term ANG II-induced hypertension (4, 5, 10, 12, 16).

It has been consistently shown that high blood pressure induced by long-term systemic infusion of ANG II is associated with augmented ANG II levels in the kidney to a greater extent than can be explained on the basis of the circulating ANG II levels (4, 7, 8, 10, 16, 18, 19). Despite marked suppression of plasma renin activity and renin release from the JGA, the levels of ANG II in the kidney are much higher than expected during chronic ANG II infusion. One of the well-recognized mechanisms is that the kidney, proximal tubules by implication specifically, has the capacity to accumulate circulating and/or extracellular ANG II via AT1 (AT1a) receptor-mediated uptake (7, 8, 16, 18, 19). The second potential mechanism is that Navar and Kobori’s group (4, 5, 10) consistently demonstrated that intrarenal angiotensinogen expression is markedly increased in ANG II-induced hypertension. Instead of undergoing reciprocal suppression by long-term ANG II infusion, increased angiotensinogen mRNA and protein expression was demonstrated in the proximal tubules of the kidney and urine (4, 5, 10). Thus, it is not surprising that increased angiotensinogen expression will provide abundant substrates for ANG II production in the kidney. In an issue of the American Journal of Physiology-Renal Physiology, Liu et al. (9) provide evidence for a novel mechanism, which is that increased expression or secretion of renin and prorenin from the medullary collecting ducts may contribute to augmented intratubular and urinary ANG II levels in chronic ANG II-infused hypertensive rats. This study further adds to the even more complexity of the intrarenal and/or intratubular RAS in the kidney.

The same group of investigators have been instrumental in demonstrating that ANG II-induced hypertension is associated with increased proximal tubular expression and urinary excretion of angiotensinogen and the expression of prorenin and renin in the inner medulla of the kidney (3–5, 10–14). It is not quite clear from those earlier studies whether increased expression of prorenin and renin in the medulla would lead to increased urinary ANG II formation and excretion. In the current study, Liu et al. further expanded the same line of research by showing for the first time that increased renin expression and excretion in the medullary collecting ducts are indeed associated with augmented levels of urinary ANG II excretion in chronic ANG II-infused hypertensive rats. To test their hypothesis, the authors treated Sprague-Dawley rats with infusion of a sham or a highly pressor dose of ANG II for 14 days with or without concurrent treatment with a high-salt diet to maximally suppress the endogenous circulating and intrarenal ANG II formation. Additionally, an AT1 receptor blocker was used to test whether AT1 receptors are involved. The authors then carefully compared the plasma, cortical, and medullar and urinary levels of prorenin, renin, angiotensino-
gen, and ANG II expression or excretion. The most significant finding of this study appears to be the augmented angiotensinogen, prorenin, and renin proteins, renin activity, and ANG II in the urine of the chronic ANG II-infused rats compared with control rats. Second, this study employed innovative renin assays to determine the renin content and/or renin activity in the rat renal medulla, and it demonstrated remarkably higher levels of prorenin and renin in the medulla compared with plasma renin content/activity under basal conditions and during chronic ANG II infusion. Although these results remain to be confirmed, the authors provide the evidence to support a potential role for the intracollecting duct prorenin/renin and ANG II in the regulation of sodium and fluid reabsorption in the distal nephron and blood pressure.

The findings of Liu et al. (9) that intratubular and urinary angiotensinogen, prorenin/renin, and ANG II levels are augmented rather than suppressed by ANG II during chronic ANG II infusion may be physiologically and therapeutically significant. The study may provide further opportunities for others to study why and how, unlike renin in the JGA, intratubular RAS is differentially regulated in hypertensive diseases, where the circulating and tissue RAS is activated. Although Liu et al. may have provided indirect evidence of augmented renin secretion into the collecting duct tubular fluid, which in turn implies that ANG II may be generated in urine of ANG II-infused hypertensive rats, the study was not designed to directly measure renin secretion into the collecting duct tubular fluid. Thus, microperfusion collection of the tubular fluid directly from the collecting duct lumen of the rat kidney in vivo or from microperfused medullary collecting ducts in vitro for direct renin measurements may be necessary. Finally, the studies of Prieto and Navar’s group (3, 9, 11–14) strongly suggested that increased collecting duct prorenin and renin expression and (Pro)renin receptors (PRR) may contribute to the ANG II-induced hypertension. It may be tempting for the authors and others to study whether blockade of PRR and therefore prorenin activation selectively in the collecting ducts of the kidney or inhibition of renin with renin inhibitors can significantly attenuate ANG II-induced hypertension and kidney injury. These new studies may provide further new insights and perspectives into the potential roles of intratubular RAS in the regulation of renal transport physiology and the development of ANG II-dependent hypertension.

REFERENCES