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Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension

L Gabriel Navar, **Minolfa C Prieto**, **Ryousuke Satou**, and **Hiroyuki Kobori**
Department of Physiology and the Hypertension and Renal Center of Excellence, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, LA, USA

Abstract

The increased activity of intrarenal renin–angiotensin system (RAS) in a setting of elevated arterial pressure elicits renal vasoconstriction, increased sodium reabsorption, proliferation, fibrosis and renal injury. Increases in intrarenal and interstitial angiotensin (Ang) II levels are due to increased AT_1 receptor mediated Ang II uptake and stimulation of renal angiotensinogen (AGT) mRNA and protein expression. Augmented proximal tubule AGT production increases tubular AGT secretion and spillover of AGT into the distal nephron and urine. Increased renin formation by principal cells of the collecting ducts forms Ang I from AGT thus increasing Ang II. The catalytic actions of renin and prorenin are enhanced by prorenin receptors (PRRs) on the intercalated cells. The resultant increased intrarenal Ang II levels contribute to the genesis of chronic hypertension.

Introduction

The intrarenal renin–angiotensin system (RAS) regulates a diversity of renal hemodynamic and transport processes which contribute to sodium balance and blood pressure homeostasis [1]. Angiotensin II (Ang II), the most potent component of the RAS, exerts pleotropic actions on the renal microvasculature, the tubular network and the interstitium. Although there are two major receptor subtypes responsive to Ang II (AT_1 and AT_2), the AT_1 receptor is primarily responsible for the hypertensinogenic actions of the RAS. Through its effects on AT_1 receptors, Ang II regulates vascular tone of the afferent and efferent arterioles and the glomerular filtration coefficient [2]. It also exerts major influences on several tubule transporters including the Na^+/H^+ exchanger and the Na^+/HCO_3^- co-transporter in proximal tubules and the amiloride sensitive sodium channel ($E_{Na}C$) and Na^+/Cl^- co-transporter in distal nephron segments [3]. Ang II modulates the sensitivity of the tubuloglomerular feedback mechanism and regulates the medullary microvasculature by directly constricting the pericytes in the vasa recta [2,4]. These multiple actions of Ang II act in a synergistic manner to increase the capability of the kidneys to conserve sodium and maintain blood pressure under conditions of sodium depletion, loss of extracellular fluid volume and hypotension. When inappropriately activated, however, the intrarenal RAS leads to excessive sodium retention coupled with increased pressor activity and the development of Ang II dependent hypertension [1,5].

Angiotensin dependent hypertension

There are many models of Ang II dependent hypertension including the 2-kidney, 1-clip (2K1C) Goldblatt model [6], the chronic Ang II infusion model [7] and transgenic rat and

Corresponding author: Navar, L Gabriel (navar@tulane.edu).

mouse models of hypertension [5,8–10]. In these Ang II dependent hypertensive models, intrarenal Ang II content increases progressively to levels that cannot be explained on the basis of simple equilibration with plasma Ang II concentrations [11]. The increased intrarenal Ang II content results from both AT_1 receptor mediated uptake of circulating Ang II and de novo intrarenal Ang II generation as a consequence of local augmentation of intrarenal angiotensinogen (AGT) produced and secreted by proximal tubule cells [12,13]. These mechanisms lead to increased intrarenal, interstitial, and intratubular Ang II concentrations even under conditions where plasma renin activity (PRA) is markedly suppressed [14–17].

Intrarenal angiotensinogen

Chronic Ang II infusions resulting in moderate increases in circulating Ang II stimulate intrarenal AGT mRNA and protein in proximal tubule cells [1,12]. Ang II infusion increases intrarenal NF-κB activity [18]. Activation of NF-κB plays an important role in the stimulation of AGT expression in cultured proximal tubule cells [19]. Moreover, as shown in Figure 1, Ang II elicits intrarenal pro-inflammatory cytokine expression such as interleukin-6 (IL-6) [20••,21••]. As indicated in Figure 2, IL-6 contributes to the increase in AGT expression via activation of a JAK-STAT pathway [19]. These results indicate that Ang II stimulates AGT expression via both direct and indirect mechanisms mediated by NF-κB and cytokines in renal proximal tubular cells. IL-6 knockout reduces the activation of intrarenal JAK-STAT pathway and the severity of the hypertension [22•,23•]. In contrast, tumor necrosis factor α, which is also an Ang II-induced pro-inflammatory factor in the kidney, suppresses AGT expression through the formation of p50/p50 complex (Figure 2) in cultured renal proximal tubular cells [24]. This action serves to counteract or limit Ang II-induced AGT augmentation in renal proximal tubular cells which may explain how higher Ang II doses into mice fail to stimulate intrarenal AGT levels [7]. Interestingly, while chronic Ang II infusions tend to downregulate AT_1 receptors in vascular smooth muscle cells, the AT_1 receptors in tubular cells are either upregulated or maintained [1,25], thus allowing sustained actions on proximal tubule AGT as well as stimulation of sodium reabsorption. In Ang II dependent hypertension, there are associated increases in Ang II levels in the renal interstitial fluid which can contribute to increased renal microvascular tone and increased tubular reabsorption [15].

AGT is secreted into the proximal tubular lumen where it gives rise to Ang I and Ang II formation at the level of the proximal tubule thereby stimulating proximal sodium reabsorption rate [26]. Furthermore, the increased AGT expression and secretion in Ang II dependent hypertension lead to spillover into distal nephron segments leading to increased urinary excretion of AGT [27]. Thus, AGT secreted into the lumen of proximal tubules traverses through the distal nephron segments and provides substrate for further downstream Ang I and Ang II generation. Importantly, in the presence of oxidative stress, which exists in hypertension and other vascular diseases, the AGT molecule undergoes a subtle conformational rearrangement to a form that more effectively releases Ang I when exposed to renin [28••], thus facilitating increased generation of Ang II. The increased urinary AGT is derived from the enhanced proximal tubule AGT secretion as well as increased filtration of AGT due to slight increases in glomerular permeability [29,30•]. Nevertheless, several studies have demonstrated that urinary AGT provides an index of the intrarenal Ang II levels in Ang II-infused rats [1,27,31]. To extend these studies to human subjects, an assay was developed to quantitatively measure urinary AGT in humans [32]. Studies using this human AGT ELISA, demonstrated elevated urinary AGT in hypertensive subjects not treated with blockers or inhibitors of the RAS [33] and also found that urinary AGT is correlated with blood pressure in humans participating in the Bogalusa Heart Study [34].

Collecting duct renin and Ang II

Renin from juxtaglomerular apparatus (JGA) cells is released primarily into the interstitium but JGA renin is suppressed in chronic Ang II infused hypertensive rats [17]. Thus, the source of intratubular renin available to act on intratubular AGT has remained unclear. It is now recognized, however, that renin is also expressed by the principal cells of connecting tubules and cortical and medullary collecting ducts (CD) from rat, mouse and human kidneys [13,35••,36]. In distal nephron segments, renin resides in principal cells co-localizing with aquaporin 2 [36]. Importantly, renin in distal nephron segments is differentially regulated from renin in JGA cells. In response to chronic Ang II infusions, renin mRNA and protein levels in principal cells are stimulated leading to increased distal nephron renin expression during Ang II-dependent hypertension [36]. This effect is an AT_1 receptor-mediated process since treatment with an AT_1 receptor blocker prevents the stimulation of distal nephron renin mRNA and protein levels [37], a response distinct from the well known effect of AT_1 receptor blockade to stimulate JGA renin levels. These results indicate that the regulation of renin in principal cells of the CD is different from that of JGA cells, and help to explain the marked reduction in sodium excretion and impairment in pressure natriuresis that occurs with chronic Ang II infusions [8,38,39].

The augmentation of CD renin in chronic Ang II-infused rats does not distinguish between the direct effects of Ang II *versus* those possibly due to the effects of chronic elevations in arterial blood pressure. To distinguish between these effects, renin gene expression in the CD of clipped and non-clipped kidneys from 2K1C Goldblatt hypertensive rats was measured three weeks after clipping one renal artery [40]. We observed increases in distal nephron renin expression in both clipped and non-clipped kidneys indicating that the stimulation occurs independently of blood pressure [40]. The results suggest that in 2K1C Goldblatt hypertensive rats, there is a direct positive effect exerted by intrarenal Ang II to stimulate renin expression in CD cells. In further studies, we observed enhancement of ACE and inhibition of ACE2 in both kidneys associated with substantial decreases in intrarenal Ang 1–7 levels suggesting that reductions in ACE2 activity provide another mechanism for increased Ang II levels [41]. Collectively, the results provide further support to the hypothesis that the increased AGT spillover into distal nephron segments leads to increased distal intratubular Ang I formation and subsequent conversion to Ang II, which increases CD Ang II concentration. Increases in Ang II concentrations in CD, as reflected by increases in urinary Ang II concentrations, have been shown in studies in rats [16,17] and mice [39,42•]. In particular, rats infused chronically with Val^5-Ang II show a progressive increase in urinary concentration of endogenous Ang II (Ile^5-Ang) indicating increased tubular production of Ang II [17]. Furthermore, AT_1 receptor blockers prevented this progressive increase indicating that chronic augmentation requires AT_1 receptor activation [16].

Prorenin receptor

Recently, a prorenin receptor (PRR), which binds both renin and prorenin and activates prorenin, was cloned and found to be localized to lung, brain, placenta and kidneys [43••, 44••]. In the kidney, the PRR is present in mesangial cells, podocytes, renal arteries and tubules. In particular, the PRR is present on intercalated cells of the CDs [44••]. These results suggest the intriguing hypothesis that prorenin or renin formed by principal cells and secreted into the distal tubular fluid is anchored by the PRR on the apical surface of the intercalated cells thus increasing the catalytic activity for Ang I generation and reducing washout of prorenin or renin into the urine [45,46]. Indeed, we recently showed increases in PRR mRNA levels and specific immunoreactivity in the medullary tissues from clipped kidney (CK) but not in the non-clipped kidneys of 2K1C Goldblatt hypertensive rats (NCK) (Figure 3). In addition, increased levels of the PRR transcript and the soluble form of the

PRR in renal medullary tissues and urine of chronic Ang II-infused rats and Cyp1a1Ren2 transgenic rats with Ang II-dependent malignant hypertension have been reported [47,48]. It is possible that the soluble form of PRR activates prorenin secreted by CD cells and, together with the upregulation of ACE, further enhance the formation of Ang II in the distal nephron segments [41,49]. The increased Ang II directly stimulates sodium reabsorption in CD cells [50] which contributes to the suppression of the pressure-natriuretic response to elevations in arterial blood pressure in Ang II infused rats [38] and the non-clipped kidney of 2K1C Goldblatt rats [51]. As depicted in Figure 4, the presence of prorenin, renin and PRR in distal nephron segments [36,40,48] may provide a critical final mechanism for intratubular Ang I and Ang II formation and, together with the augmentation of proximal tubule AGT expression, play a major role in the genesis and maintenance of chronic hypertension [45].

Conclusion

Experimental findings within recent years have demonstrated the complexity of the mechanisms regulating renal interstitial and tubular Ang II concentrations. An initial inappropriate increase in Ang II can lead to a positive augmentation of intratubular AGT and CD renin activity which exacerbates the hypertension. Thus it is essential to recognize the importance of blocking the intrarenal RAS in order to achieve good blood pressure control and restoration of normal renal function. Toward this end, measurements of urinary AGT provide one means of determining the efficacy of the therapeutic regimen. The available data have identified the key components responsible for the augmented intrarenal RAS activity, but their specific quantitative contributions to the genesis and maintenance of chronic hypertension remain to be determined.

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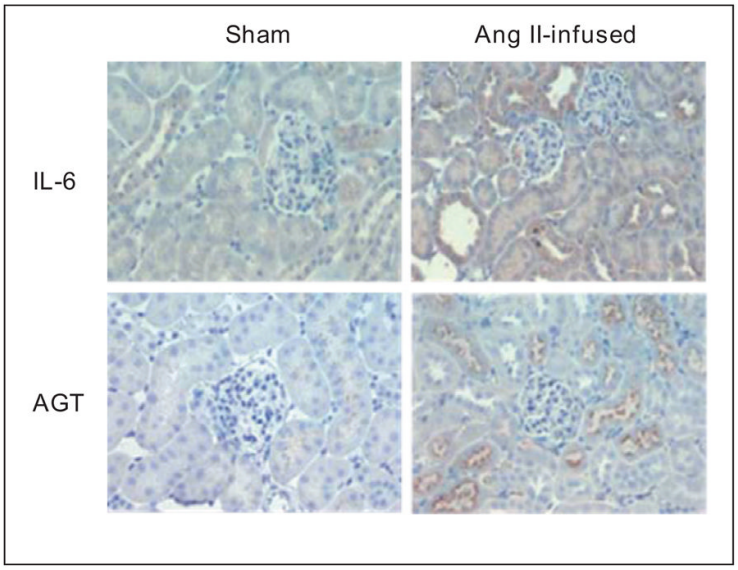

Figure 1.
Stimulation of intrarenal IL-6 and AGT levels in Ang II-infused mice. Chronic Ang II infusion increases the expression of intrarenal IL-6 and AGT in mice. Ang II was infused at a dose of 400 ng/kg/min for two weeks via osmotic minipump.

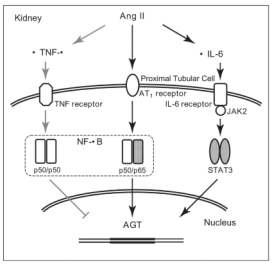

Figure 2.

Schematic summary of regulation of AGT expression in renal proximal tubular cells. The black arrows indicate mechanisms of augmentation of AGT expression. The gray arrows indicate a mechanism of suppression of AGT expression. Derived from Satou *et al*. [19,24].

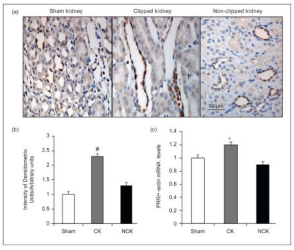

Figure 3.

Prorenin receptor (PRR) immunoreactivity and mRNA in collecting duct cells. **(a)** Specific PRR immunoreactivity (brown, DAB chromogen) is shown in the collecting duct cells of sham (left panel), clipped (middle panel) and non-clipped (right panel) kidney medullary regions. **(b)** Densitometric analysis of PRR intensity immunoreactivity in collecting duct cells of both kidneys (CK and NCK) of Goldblatt hypertensive rats was performed. Sham rats ($n = 5$), 2K1C rats ($n = 6$). **(c)** PRR mRNA levels were quantified in the renal medullary tissues of sham kidneys, and CK and NCK of Goldblatt hypertensive rats by qRT-PCR using samples in triplicate and values expressed relative to β-actin in arbitrary units. Values are mean ± S.E. $^{*}P < 0.05$ *versus* sham rats. PRR (Abcam 5959) antibody dilution used 1:200. CK: clipped kidney; NCK: non-clipped kidney. $^{\#}P < 0.05$ clipped kidney *versus* non-clipped kidney. IDU: integrated densitometric units.

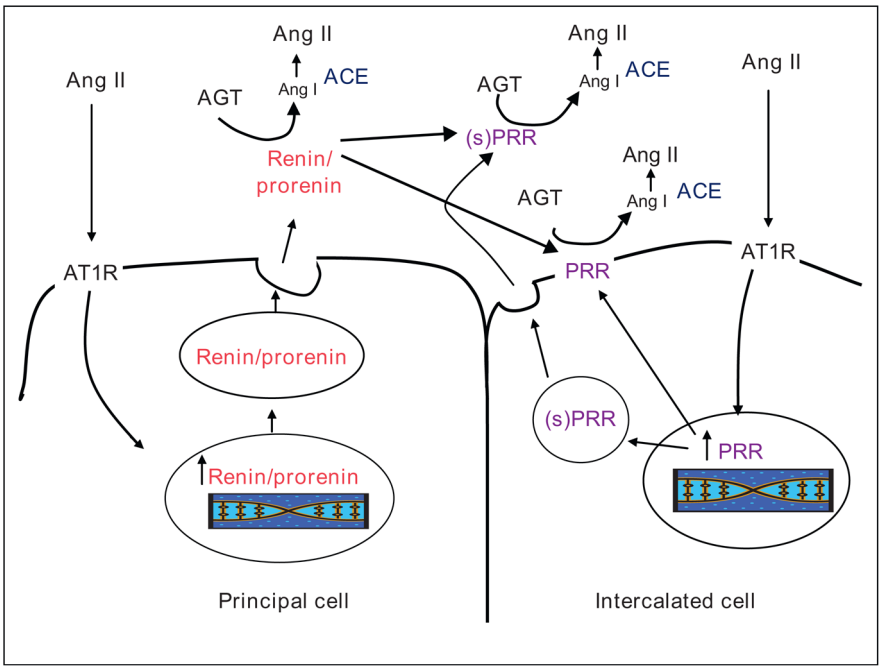

Figure 4.

Renin and prorenin receptor interaction in the collecting duct. Ang II mediated stimulation of renin and prorenin in the principal cells of the collecting ducts may increase intrarenal and intratubular Ang I and consequently Ang II content. The presence of prorenin receptor at the surface of the intercalated cells increases the catalytic activity for Ang I generation and may anchor renin and prorenin secreted by the principal cells to reduce washout into the urine. The availability of ACE in distal nephron segments along with reduction in ACE2 facilitates subsequent enhanced formation of Ang II. Ang: angiotensin; AGT: angiotensinogen; ACE: angiotensin converting enzyme; AT1R: angiotensin II type 1 receptor; PRR: prorenin receptor; (s)PRR: soluble form of the prorenin receptor.