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Augmented intrarenal and urinary angiotensinogen in hypertension and chronic kidney disease

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Abstract

Activated intrarenal renin–angiotensin system plays a cardinal role in the pathogenesis of hypertension and chronic kidney disease. Angiotensinogen is the only known substrate for renin, which is the rate-limiting enzyme of the renin–angiotensin system. Because the levels of angiotensinogen are close to the Michaelis–Menten constant values for renin, angiotensinogen levels as well as renin levels can control the renin–angiotensin system activity, and thus, upregulation of angiotensinogen leads to an increase in the angiotensin II levels and ultimately increases blood pressure. Recent studies using experimental animal models have documented the involvement of angiotensinogen in the intrarenal renin–angiotensin system activation and development of hypertension. Enhanced intrarenal angiotensinogen mRNA and/or protein levels were observed in experimental models of hypertension and chronic kidney disease, supporting the important roles of angiotensinogen in the development and the progression of hypertension and chronic kidney disease. Urinary excretion rates of angiotensinogen provide a specific index of the intrarenal renin–angiotensin system status in angiotensin II-infused rats. Also, a direct quantitative method has been developed recently to measure urinary angiotensinogen using human angiotensinogen enzyme-linked immunosorbent assay. These data prompted us to measure urinary angiotensinogen in patients with hypertension and chronic kidney disease, and investigate correlations with clinical parameters. This short article will focus on the role of the augmented intrarenal angiotensinogen in the pathophysiology of hypertension and chronic kidney disease. In addition, the potential of urinary angiotensinogen as a novel biomarker of the intrarenal renin–angiotensin system status in hypertension and chronic kidney disease will be also discussed.

Keywords

Angiotensinogen; Renin–angiotensin system; Kidney; Hypertension; Chronic kidney disease

Introduction

Activation of the renin–angiotensin system (RAS) plays a crucial role in the pathogenesis of hypertension and chronic kidney disease (CKD) [54]. In recent years, there has been increased emphasis on the role of the local/tissue RAS in specific tissues [15]. Emerging evidence has demonstrated the importance of the tissue RAS in the brain [4], heart [13], adrenal glands [78], vasculature [10, 20], and kidneys [54, 88]. Angiotensinogen (AGT) is the only known substrate for renin, which is the rate-limiting enzyme of the RAS. Although most of the circulating AGT is produced and secreted by the liver, the kidneys also produce AGT [28]. Intrarenal AGT mRNA and protein have been found to be localized to proximal

tubular cells [29, 49, 100, 119]. The major fraction of angiotensin II present in renal tissues is generated locally from the AGT delivered to the kidney as well as from the AGT locally produced by proximal tubular cells [12, 28]. The AGT produced in proximal tubular cells appears to be secreted directly into the tubular lumen in addition to producing its metabolites intracellularly and secreting them into the tubular lumen [71, 101]. Because of its molecular size and protein binding, it seems unlikely that much of the plasma AGT filters across the glomerular membrane, further supporting the concept that proximal tubular cells secrete AGT directly into the tubular lumen [54]. Renin secreted by the juxtaglomerular apparatus cells into the renal interstitium and vascular compartment also provides a pathway for the local generation of angiotensin I [83]. Angiotensin-converting enzyme (ACE) is abundant in the kidneys and is present in proximal tubules, distal tubules, and collecting ducts [8]. Angiotensin I delivered to the kidney can also be converted to angiotensin II [66]. Therefore, all components enabling the generation of intrarenal angiotensin II are present along the nephron [54, 88].

Because the levels of AGT are close to the Michaelis–Menten constant values for renin, AGT levels can also control the activity of the RAS, and upregulation of AGT levels may lead to elevated angiotensin peptide levels and increases in blood pressure [6, 19]. 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 [5, 14, 16, 44, 59, 72, 80, 102, 114]. Genetic manipulations that lead to overexpression of AGT have consistently been shown to cause hypertension [42, 115]. In human genetic studies, a linkage has been established between the AGT gene and hypertension [3, 30, 31, 35, 127]. Enhanced intrarenal AGT mRNA and/or protein levels have also been observed in multiple experimental models of hypertension including angiotensin II-dependent hypertensive rats [48–50, 57, 62, 110], Dahl salt-sensitive (DS) hypertensive rats [55, 56], and spontaneously hypertensive rats [60] as well as in kidney diseases including diabetic nephropathy [1, 74, 82, 85, 113, 116], IgA nephropathy [53, 117], and radiation nephropathy [61]. Thus, AGT upregulation plays an important role in the development and progression of hypertension and kidney diseases [54, 88].

Previous reports have demonstrated that urinary excretion rates of AGT provide a specific index of intrarenal RAS status in angiotensin II-infused rats [48–50, 57, 62]. Also, a direct quantitative method has been developed recently to measure urinary AGT using human AGT enzyme-linked immunosorbent assay (ELISA) [40]. The ELISA has facilitated the measurements of urinary AGT in patients with hypertension and CKD, and has encouraged us to investigate the correlations with clinical parameters. This brief review will address the role of the augmented intrarenal AGT in the pathophysiology of hypertension and CKD. In addition, the potential of urinary AGT as a novel biomarker of the intrarenal RAS status in hypertension and CKD will be also discussed.

Intratubular localization of AGT

Using in situ hybridization, Ingelfinger et al. [29] demonstrated that the AGT gene was specifically present in the proximal tubules. Terada et al. [119] reported that AGT mRNA was expressed largely in the proximal convoluted tubules and proximal straight tubules, and in small amounts in glomeruli and vasa recta as revealed by reverse transcription and polymerase chain reaction. Richoux et al. [100] and Darby et al. [11, 12] showed that renal AGT protein was specifically located in the proximal convoluted tubules by immunohistochemistry. Kobori et al. [49] also showed that there was strong positive immunostaining for AGT protein in proximal convoluted tubules and proximal straight tubules, and weak positive staining in glomeruli and vasa recta; however, there was no staining in distal tubules or collecting ducts. The origin of AGT mRNA as well as AGT

protein in the kidney is still controversial [57, 77, 86, 90, 99]. The localization and regulation of intrarenal AGT mRNA/protein are more complicated than they seem [95, 105–108]. Recently, Kamiyama et al. [37] have established a novel method to isolate the three segments of the proximal tubular cells and to culture them separately (S1 segment: the pars convoluta, S2 segment: the end of the pars convoluta, and S3 segment: the pars recta). In the near future, these methods may be useful to investigate the segmental regulation of AGT mRNA and protein expression in physiological and pathological conditions.

Augmented intrarenal AGT in hypertension and CKD

Angiotensin II-dependent hypertension

The feedback loop of AGT by angiotensin II is demonstrated in various tissues including the liver [6, 46], heart [25, 118], adipose tissue [21, 75], and kidney [27, 110]. In more recent studies, Kobori et al. [48–50, 57, 62] have evaluated the effects of angiotensin II infusions on AGT and angiotensin II levels in the kidney and the relationship between urinary excretion of AGT and kidney angiotensin II or AGT levels in several models of hypertension. They reported that angiotensin II-infused rats have increases in renal AGT mRNA [49] and protein [48], and an enhancement of urinary excretion rate of AGT [50]. Chronic angiotensin II infusion to normal rats significantly increased urinary excretion rate of AGT in a time- and dose-dependent manner. Urinary excretion rate of AGT was closely correlated with systolic blood pressure and kidney angiotensin II content, but not with plasma angiotensin II concentration. Urinary protein excretion in volume-dependent hypertensive rats was significantly increased more than in angiotensin II-dependent hypertensive rats; however, urinary AGT excretion was significantly lower in volume-dependent hypertensive rats than in angiotensin II-dependent hypertensive rats [57]. Rat AGT was detected in plasma and urine before and after an acute injection of exogenous human AGT. Human AGT, however, was detected only in the plasma collected after the acute administration of human AGT but was not detected in the urine in angiotensin II-dependent hypertensive or sham-operated normotensive rats. The failure to detect human AGT in the urine suggests limited glomerular permeability and/or tubular degradation. This suggests that urinary AGT originates from the kidneys and not from plasma in rats [57, 86]. Chronic angiotensin II type 1 receptor blocker (ARB) treatment offsets the augmented intrarenal/urinary AGT by angiotensin II infusions in rats [62].

Salt-sensitive hypertension

DS rats have been used as a model of human salt-sensitive hypertension because salt loading exaggerates the development of hypertension in strains that are genetically predisposed to hypertension [32]. It is well-known that mature DS rats have low plasma renin activity levels [32], and few studies have addressed intrarenal angiotensin II and AGT regulation in DS rats because it has been assumed that the RAS is suppressed in DS rats fed high-salt (HS) diet. However, recent studies suggest that treatment with ACE inhibitors or ARBs reduces cardiac and/or renal dysfunction in DS rats made hypertensive by HS diet [23, 24, 64, 91, 96, 104]. Furthermore, Nakaya et al. [87] reported that prepubertal treatment with an ARB causes partial attenuation of hypertension and ameliorates the renal damage in adult DS rats fed HS. These data suggest that the local RAS may contribute to the development of hypertension and renal dysfunction in this model.

Kobori et al. [56] reported that DS rats on HS diet have inappropriate augmentation of intrarenal AGT that is not reflected in the plasma levels of RAS components. This enhancement of AGT may contribute to the impaired sodium excretion during HS and the development of hypertension in this strain. However, the mechanisms responsible for the inappropriate augmentation of intrarenal AGT by HS have been incompletely elucidated in

that study. Recent studies reported that augmented oxidative stress or superoxide anion formation plays an important role in this animal model of hypertension [79, 120, 126]. Recently, Kobori et al. [55] demonstrated that inappropriate augmentation of intrarenal AGT by HS is associated with augmented reactive oxygen species in DS rats. In that study, systolic blood pressure was significantly increased by HS in DS rats, and was equally suppressed by a superoxide dismutase mimetic, tempol, and a nonspecific vasodilator, hydralazine. HS has been shown to suppress plasma and intrarenal expression of AGT in Sprague-Dawley [111] and Wistar-Kyoto [28] rats. Similarly, in that study, plasma AGT levels are also suppressed by HS. However, kidney AGT levels are enhanced by HS, and tempol treatment prevents this augmentation but hydralazine does not in DS rats. This paradoxical enhancement of intrarenal AGT by HS is observed in DS rats but not in Dahl salt-resistant rats [56]. Thus, these studies provide evidence that inappropriate augmentation of intrarenal AGT by HS is associated with the augmented reactive oxygen species in DS rats. The oxidative stress-induced RAS activation via AGT is also supported by a recent structural biology study [128]. The protein AGT must undergo conformational changes to be cleaved into a precursor of the hormone angiotensin, which increases blood pressure. Oxidative stress seems to mediate this structural alteration [112, 128].

Chronic glomerulonephritis

Chronic glomerulonephritis that results in substantial renal damage is frequently characterized by relentless progression to end-stage renal disease. Renal angiotensin II, the production of which is enhanced in chronic glomerulonephritis, can elevate the intraglomerular pressure, increase glomerular cell hypertrophy, and augmented extracellular matrix accumulation [7, 65]. RAS blockades markedly decelerate, and can even prevent, renal deterioration in glomerular disease [18, 70]. This may be an indication that factors other than angiotensin II play an important role in the progression of renal disease. There are several studies for renal expression of AGT in IgA nephropathy [17, 53, 117]. Most studies have shown an increased expression of AGT in the kidney of IgA nephropathy.

Glomerular crescents are defined as the presence of two or more layers of cells in the Bowman's space. Monocyte/macrophages and parietal epithelial cells are the principal mediators of crescents formation. Monocyte chemoattractant protein 1/CC chemokine receptor 2 signaling pathway is involved in the pathogenesis of crescentic glomerulonephritis. The presence of crescents in glomeruli is a marker of severe injury [26]. After a single injection of antiglomerular basement membrane antibodies, marked crescent formations were observed in almost all glomeruli as a result of severe glomerular damage. CC chemokine receptor 2 antagonist or ARB alone moderately normalized the crescent formation [123]. Their combination significantly blocked the development of crescent formation, preventing the infiltration of macrophages. Consistently, the combination therapy markedly reduced proteinuria. In this glomerulonephritis model, the glomerular expression levels of AGT, angiotensin II and angiotensin II type 1 receptors were increased compared with control rats. While CC chemokine receptor 2 antagonist or ARB treatment moderately reduced the increase of these components in glomeruli, CC chemokine receptor 2 antagonist plus ARB treated further prevented these increases. Urinary AGT levels were paralleled with the expression levels of RAS components in glomeruli. These indicate that blocking the RAS is a key target and that AGT expression reflects intrarenal RAS activation in treatment of crescentic glomerulonephritis (Fig. 1) [121].

Diabetic nephropathy

Diabetes affects 220 million people worldwide, including 24 million Americans, and is the sixth leading cause of death in the USA. It is associated with increased incidence of functional and structural alterations in the kidneys, eventually leading to end-stage renal

failure in many patients. Diabetic nephropathy is the most common cause of end-stage renal failure in the USA, accounting for 45 % of patients starting dialysis [36, 84]. Type 2 diabetes mellitus is the most common type of diabetes accounting for 90–95 % of all diagnosed cases of diabetes and affecting 8 % of the US population. Obesity has been identified as the principal risk factor associated with the rising prevalence of type 2 diabetes. The epidemic proportions of obesity and diabetes justify the enormous effort to identify novel pathways and mechanisms involved in their prevention and treatment. Diabetes is a chronic and debilitating disease that is characterized by progressive albuminuria, declining glomerular filtration rate, functional and structural deterioration of the kidney, and increased risk of cardiovascular disease.

Data concerning intrarenal RAS states in diabetes are inconsistent. Although various studies support an association between RAS and diabetic nephropathy, direct measurements have been unsuccessful in establishing that intrarenal angiotensin II is consistently elevated in diabetes [129]. However, intrarenal AGT levels are elevated in patients with diabetic nephropathy [38]. In rodent diabetic models, renin content varies and ACE expression has been shown to be increased or unchanged in glomeruli and vessels [22, 124]. In the type 2 diabetic mouse kidney, proximal tubule ACE immunostaining is decreased, while ACE2 immunostaining is increased compared to control mice [97]. However, angiotensin II type 1 receptor protein levels were significantly elevated in renal cortex from streptozotocin-induced diabetic rats compared with control rats, associated with the downregulation of angiotensin II type 2 receptors [22, 124]. The cortical collecting ducts of streptozotocin-induced diabetic kidneys displayed a striking increase in angiotensin II type 1 receptor immunostaining intensity compared with control kidneys [22]. Moreover, it was recently shown that prorenin expression is elevated in the cortical collecting ducts of type 1 diabetic rats [39]. Furthermore, studies in models of type 2 diabetes show increased intrarenal angiotensin II levels and AGT mRNA levels, which are prevented by treatment with an ARB [85, 93]. Finally, increases in renal cortical AGT and angiotensin II levels associated with increased reactive oxygen species and renal injury have been observed in Zucker diabetic fatty obese rats compared to control lean rats [82, 116].

Urinary AGT as a novel biomarker of intrarenal RAS in hypertension and CKD

Development of human AGT ELISA

As discussed above, there is a quantitative relationship between urinary AGT and intrarenal production of AGT and angiotensin II. Urinary AGT excretion rates may provide a useful tool to identify angiotensin II-dependent hypertension in human hypertensive subjects. Recently, AGT ELISA systems have been established in humans [40] as well as in mice and rats [52]. Using these methods, evidence has been accumulated from clinical studies indicating that urinary AGT can be a novel biomarker of the activated intrarenal RAS in hypertension [47, 63, 67], in diabetic nephropathy [94, 103, 109], and in CKD [33, 34, 41, 43, 58, 68, 69, 73, 76, 81, 92, 122].

Urinary AGT in hypertension

The important role of the activated intrarenal RAS in the pathogenesis of hypertension is extensively discussed in a recent review article [89]. In a cross-sectional study, Kobori et al. reported that urinary AGT levels were significantly greater in hypertensive patients not treated with RAS blockers compared with normotensive subjects [47]. Moreover, patients treated with RAS blockers exhibited a marked attenuation of this augmentation. These data suggest that the efficacy of RAS blockade to reduce the intrarenal RAS activity can be assessed by measurements of urinary AGT [47].

In a population study, Kobori et al. demonstrated that activated intrarenal RAS is correlated with high blood pressure in humans [63]. They recruited 251 subjects and collected a single random spot urine sample from each subject. Because urinary AGT levels are significantly increased in patients with diabetes [58] and the use of antihypertensive drugs affects urinary AGT levels [47], they excluded patients who had diabetes and/or were receiving antihypertensive treatment. Consequently, 190 samples were included in this analysis. Urinary AGT levels did not differ between the races or the genders, but were significantly correlated with systolic and diastolic blood pressure. Moreover, this correlation was high in men, especially in Black men [63]. These data suggest that urinary AGT provides a novel reflection of the intrarenal RAS status in hypertension.

Urinary AGT in CKD

The important role of an activated intrarenal RAS in the pathogenesis of CKD is extensively discussed in a recent review article [45]. In order to test the hypothesis that urinary AGT levels are enhanced in CKD patients and correlated with some clinical parameters, 80 patients with CKD (37 women and 43 men, from 18 to 94 years old) and seven healthy volunteers (two women and five men, from 27 to 43 years old) were recruited [58]. Plasma AGT levels showed a normal distribution; however, urinary AGT-creatinine ratios deviated from the normal distribution. When a logarithmic transformation was executed, Log[urinary AGT-creatinine ratio] showed a normal distribution. Therefore, Log[urinary AGT-creatinine ratio] was used for further analyses. Log[urinary AGT-creatinine ratio] was not correlated with age, gender, height, body weight, body mass index, systolic blood pressure, diastolic blood pressure, serum sodium levels, serum potassium levels, urinary sodium-creatinine ratios, plasma renin activity, or plasma AGT levels. However, Log[urinary AGT-creatinine ratio] was significantly correlated positively with urinary albumin-creatinine ratios, fractional excretion of sodium, urinary protein-creatinine ratios, and serum creatinine, and correlated negatively with estimated glomerular filtration rate. Log[urinary AGT-creatinine ratio] was significantly increased in CKD patients compared with control subjects. These data suggest that urinary AGT levels can be a potential biomarker of severity of CKD [58].

In order to test the hypothesis that urinary AGT levels are increased in chronic glomerulonephritis patients, 100 urine samples from 70 chronic glomerulonephritis patients (26 from IgA nephropathy, 24 from purpura nephritis, 8 from lupus nephritis, 7 from focal segmental glomerulosclerosis, and 5 from non-IgA mesangial proliferative glomerulonephritis) and 30 normal control subjects were analyzed [122]. Urinary AGT-creatinine ratio was correlated positively with diastolic blood pressure, urinary albumin-creatinine ratio, urinary protein-creatinine ratio and urinary occult blood. Urinary AGT-creatinine ratio was significantly increased in chronic glomerulonephritis patients not treated with RAS blockers compared with control subjects. Importantly, patients with glomerulonephritis treated with RAS blockers had a marked attenuation of this augmentation. These data indicate that urinary AGT are increased in patients with chronic glomerulonephritis and treatment with RAS blockers suppresses urinary AGT. Thus, the efficacy of RAS blockade to reduce the intrarenal RAS activity can be confirmed by measurements of urinary AGT in chronic glomerulonephritis patients [122].

In order to test the hypothesis that urinary AGT provides a specific index of intrarenal RAS status in patients with IgA nephropathy, an observational study was performed [92]. This paper is a survey of urine specimens from three groups: healthy volunteers, patients with IgA nephropathy, and patients with minor glomerular abnormality. Patients with hypertension, diabetes, reduced glomerular filtration rate, and/or who were under any medication were excluded from this study. Urinary AGT levels were not different between healthy volunteers and patients with minor glomerular abnormality. However, urinary AGT levels, renal tissue AGT expression, and angiotensin II immunoreactivity were significantly

higher in patients with IgA nephropathy than in patients with minor glomerular abnormality. Baseline urinary AGT levels were positively correlated with renal AGT gene expression and angiotensin II immunoreactivity but not with plasma renin activity or the urinary protein excretion rate. In patients with IgA nephropathy, treatment with an ARB significantly increased renal plasma flow and decreased filtration fraction, which were associated with reductions in urinary AGT levels. These data indicate that urinary AGT is a powerful tool for determining intrarenal RAS status and associated renal derangement in patients with IgA nephropathy [92]. These data suggest that urinary AGT levels can be used as a novel biomarker of the intrarenal RAS status in patients with CKD.

Urinary AGT as a new biomarker of intrarenal RAS status in diabetes

The important role of the activated intrarenal RAS in the pathogenesis of diabetic nephropathy is extensively discussed in a recent review article [51]. Clinically, microalbuminuria is the most commonly used early marker of diabetic nephropathy [9]. Diabetic nephropathy is thought to be a unidirectional process from microalbuminuria to end-stage renal failure [2]. However, recent studies demonstrate that a large proportion of diabetic nephropathy patients revert to normoalbuminuria and that one third of them exhibit reduced renal function even in the microalbuminuria stage [98]. It is claimed that urinary inflammatory markers are high in microalbuminuric type 1 diabetes having diminished renal function, but not in microalbuminuric type 1 diabetes patients with stable renal function. However, no single marker has been sufficient to represent the whole panel [125]. Therefore, a more sensitive and more specific marker for activation of the RAS in diabetic nephropathy would be highly advantageous.

To demonstrate that administration of an ARB interferes with the vicious cycle of high glucose-reactive oxygen species-AGT-angiotensin II-angiotensin II type 1 receptor-reactive oxygen species by suppressing reactive oxygen species and inflammation, 13 patients with hypertensive diabetic nephropathy were recruited and evaluated before and at 16 weeks after treatment by ARBs [94]. Urinary AGT, albumin, 8-hydroxydeoxyguanosine, 8-epi-prostaglandin F2 alpha, monocyte chemoattractant protein 1, interleukin-6, and interleukin-10 were assessed. ARB treatment reduced the blood pressure and urinary levels of AGT, albumin, 8-hydroxydeoxyguanosine, 8-epi-prostaglandin F2 alpha, monocyte chemoattractant protein 1, and interleukin-6, while increasing urinary interleukin-10 levels. The reduction of urinary AGT correlated with the reduction of blood pressure and urinary levels of albumin, 8-hydroxydeoxyguanosine, 8-epi-prostaglandin F2 alpha, monocyte chemoattractant protein 1, and interleukin-6 and the increase of urinary interleukin-10 levels. These results suggest that the mechanisms by which ARBs exert their renoprotective effect in patients with type 2 diabetes may involve the suppression of intrarenal AGT levels in association with reduced anti-inflammatory and antioxidant effects [94].

To determine if urinary AGT levels can be dissociated from urinary albumin or protein excretion rates in type 1 diabetes juveniles, early phase studies were performed in control and diabetic juveniles [103]. Of the 55 juveniles recruited, 34 were patients with type 1 diabetes and 21 were gender- and age-matched control subjects. Since the primary focus of the study was comparison between the normoalbuminuric patients with type 1 diabetes and their control subjects, six microalbuminuric patients with type 1 diabetes (urinary albumin-creatinine ratio >30 mg/g) were excluded. Consequently, 49 urine and plasma samples were analyzed. None of them received treatment with RAS blockade. Neither urinary albumin-creatinine ratios nor urinary protein-creatinine ratios were significantly increased in these patients with type 1 diabetes compared to control subjects, suggesting that these patients were in their pre-microalbuminuric phase of diabetic nephropathy. However, urinary AGT-creatinine ratios were significantly increased in these patients compared to control subjects. Importantly, the AGT increase was not observed in plasma. These data indicate that urinary

AGT levels are increased in type 1 diabetes subjects before any increase in urinary albumin levels, suggesting a possibility that urinary AGT levels serve as a very sensitive early marker of intrarenal RAS activation and may be one of the earliest predictors of diabetic nephropathy in patients with diabetes [103].

Conclusions

This brief review discussed the important role of the activated intrarenal RAS in the pathogenesis of hypertension and CKD. In addition, the potential of urinary AGT as a novel biomarker of the intrarenal RAS status in hypertension and CKD was also addressed. The complicated and pleiotropic roles of activated RAS in pathogenesis of hypertension and CKD continue to receive recognition from emerging and ongoing studies. Accordingly, the assessment of urinary AGT as an early biomarker of the status of the intrarenal RAS may be of substantial importance. It may be particularly helpful in serving as a means to determine efficacy of the treatment to reduce intrarenal angiotensin II levels.

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Fig. 1.

Working scheme for the augmented intrarenal and urinary angiotensinogen in hypertension and chronic kidney disease. Intrarenal renin-angiotensin (*Ang*) system in proximal and distal nephron segments was summarized. Because of its molecular size, it seems unlikely that much of the plasma angiotensinogen (*AGT*) filters across the glomerular membrane. In Ang II-dependent hypertension, increased proximal tubular (*PT*) secretion of *AGT*s spills over into the distal nephron and increases Ang II effects on distal tubular (*DT*) reabsorption. *CD*, collecting ducts. *ACE*, Ang-converting enzyme. *AT1*, Ang II type 1 receptors adapted from Kobori, 2007 [54]