Collecting Duct Renin Is Upregulated in Both Kidneys of 2-Kidney, 1-Clip Goldblatt Hypertensive Rats


Abstract—Renin in collecting duct cells is upregulated in chronic angiotensin II–infused rats via angiotensin II type 1 receptors. To determine whether stimulation of collecting duct renin is a blood pressure–dependent effect; changes in collecting duct renin and associated parameters were assessed in both kidneys of 2-kidney, 1-clip Goldblatt hypertensive (2K1C) rats. Renal medullary tissues were used to avoid the contribution of renin from juxtaglomerular cells. Systolic blood pressure increased to 184±9 mm Hg in 2K1C rats (n=19) compared with sham rats (121±6 mm Hg; n=12). Although renin immunoreactivity markedly decreased in juxtaglomerular cells of nonclipped kidneys (NCK: 0.2±0.0 versus 1.0±0.0 relative ratio) and was augmented in clipped kidneys (CK: 1.7±1.0 versus 1.0±0.0 relative ratio), its immunoreactivity increased in cortical and medullary collecting ducts of both kidneys of 2K1C rats (CK: 2.8±1.0 cortex; 2.1±1.0 medulla; NCK: 4.6±2.0 cortex; 3.2±1.0 medulla versus 1.0±0.0 in sham kidneys). Renal medullary tissues of 2K1C rats showed greater levels of renin protein (CK: 1.4±0.2; NCK: 1.5±0.3), renin mRNA (CK: 5.8±2.0; NCK: 4.9±2.0), angiotensin I (CK: 120±18 pg/g; NCK: 129±13 pg/g versus sham: 67±6 pg/g), angiotensin II (CK: 150±32 pg/g; NCK: 123±21 pg/g versus sham: 91±12 pg/g; P<0.05), and renin activity (CK: 8.6 μg of angiotensin I per microgram of protein; NCK: 8.3 μg of angiotensin I per microgram of protein; sham: 3.4 μg of angiotensin I per microgram of protein) than sham rats. These data indicate that enhanced collecting duct renin in 2K1C rats occurs independently of blood pressure. Upregulation of distal tubular renin helps to explain how sustained intrarenal angiotensin II formation occurs even during juxtaglomerular renin suppression, thus allowing maintained effects on tubular sodium reabsorption that contribute to the hypertension. (Hypertension. 2008;51:1590-1596.)

Key Words: tubular renin ■ prorenin ■ Ang II–dependent hypertension ■ angiotensin II ■ renin mRNA ■ renin Western blot ■ renin immunostaining

The renin-angiotensin system regulates blood pressure, renal hemodynamics, and tubular sodium reabsorption. During angiotensin II (Ang II)–dependent hypertension, there is an augmentation of intrarenal Ang II levels that is greater than can be explained on the basis of the plasma Ang II concentrations.1–4 Increased Ang II kidney content results from the combination of uptake of circulating Ang II and local formation of Ang II from enhanced angiotensinogen (AGT) production and secreted by proximal tubule cells.5–6 Chronic Ang II infusion stimulates proximal tubule AGT production and tubular secretion leading to increased urinary AGT excretion, indicating that the secreted AGT traverses the distal nephron segments.6,7

In addition to juxtaglomerular (JG) cells, renin is expressed in the principal cells of connecting tubules and cortical and medullary collecting ducts, suggesting angiotensin peptide formation in the distal nephron segments.8–10 The upregulation of renin in the collecting ducts (CDs) of Ang II–infused hypertensive rats, along with substantial angiotensin-converting enzyme activity in the late distal tubular fluid and in urine,11 further support the hypothesis that, in Ang II–dependent hypertension, there is an increased spillover of proximally produced AGT into distal nephron segments leading to augmented Ang II formation and enhanced distal Na+ reabsorption.12,13

In Ang II–infused rats, JG and CD renin are differentially regulated.11 Treatment with Ang II type 1 (AT1) receptor blockers prevents the stimulation of distal nephron renin mRNA and protein in Ang II–infused rats,13 a response opposite from the well-known effect of AT1 receptor blockade on JG renin. Because AT1 receptor blocker treatment of Ang II–infused rats also prevents the Ang II–mediated increases in arterial blood pressure, an alternative possibility is that the restoration of normal arterial blood pressure was responsible for the reduced responses in CD renin. The present study was performed to elucidate whether the stimu-
lation of CD renin is independent of the effect of elevated arterial blood pressure or primarily associated with high intrarenal Ang II content. Our hypothesis is that increased intrarenal Ang II content or some downstream consequence stimulates renin in CD cells independent of blood pressure. To test this hypothesis, we used the 2-kidney, 1-clip Goldblatt hypertensive (2K1C) rat model in which the nonclipped kidney (NCK) JG cells are renin depleted, whereas the clipped kidney (CK) JG cells have high or normal renin content.1,14,15 Although both kidneys have increased intrarenal Ang II levels,14 the NCK is exposed to high blood pressure, whereas the CK is perfused with low to normal blood pressure beyond the stenosis caused by the clip, thus allowing differentiation between the effects of intrarenal Ang II versus effects secondary to elevations in blood pressure. In this investigation, we focused our assessments on renal medullary tissues from both CK and NCK of 2K1C rats to avoid the contribution of JG renin to the renin responses.

Methods

Experimental Animals
All of the experimental protocols were approved by the Tulane Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (150 to 175 g; Charles River Laboratories, Wilmington, MA) were cage housed and maintained in a temperature-controlled room with 12-hour light/dark cycles, with free access to tap water and standard rat chow (Ralston Purina) for 4 weeks. After a training period, the systolic blood pressure was monitored by tail-cuff plethysmography (Visitech, BP-2000) 1 day before placement of the clip on the left renal artery, and at the end of weeks 1, 2, and 3 of the study. The surgery (n=16) was performed using inhalation anesthe-sia with Isoflurane (IsoSol, Abbot Laboratories) to implant a clip on the left renal artery, and at the end of weeks 1, 2, and 3 of the experiment. The surgery (n=14) was performed. As a control group, sham operation (n=14) was performed.

Sample Collection, Tissue Preparation, and Evaluation
On day 25 after unilateral renal clip placement, rats were subjected to conscious decapitation, and blood samples and kidney tissues were harvested. After decapsulation, kidneys were weighted and cross-sectioned. Renal cortices were dissected from inner medullas under stereomicroscopy and RNA-free conditions. Our technique for dissecting the renal medullas from the cortices has been shown to allow preservation of renal function in the CK.16 As a control group, sham operation (n=14) was performed.

PRA and Plasma Ang II Samples
For PRA, tubes containing 5.0 mmol/L of EDTA were centrifuged at 4000 rpm for 30 minutes at 4°C, and the plasma fractions were removed and assayed as described previously.17 PRA was expressed as nanograms per milliliter per hour of generated angiotensin I (Ang I). For plasma Ang II levels, tubes contained a mixed inhibitor solution (5 mmol/L of EDTA, 22 μmol/L of pepstatin, 20 μmol/L of enalapril, 1.25 mmol/L of 1,10-phenanthroline, and 10 μmol/L of PMSF) to avoid in vitro formation of angiotensin peptides. The blood samples were immediately centrifuged at 4°C for 10 minutes at 1000g to separate the plasma fractions. Ang II was extracted by adsorption using 1 mL-100 mg phenyl SPE Bond Elut columns (Varian) and levels determined by radioimmunoanalysis, as has been validated and described previously by Zou et al.4

Total Renin, Active Renin, and Prorenin
Active and inactive renin (prorenin) contents were measured by D.E.C. by determining the amount of Ang I generated in the medullary homogenates measured by high-performance liquid chromatography (HPLC), as described previously.18 Total renin content included active renin and inactive prorenin. Prorenin was activated by adding 50 μg/mL of trypsin for 16 to 18 hours at 37°C to 0.9 μg of tissue protein homogenates. The chromatographic profile of each sample was compared with that obtained for standard samples containing AGT and Ang I at an absorbance of 240 nm. Peptide fragments were identified by elution position and quantified by integration of area using repeated injections of standard peptide solution to correct for small differences in retention time (<6%) and peak height (<5%).

Ang I and Ang II Kidney Contents
Renal cortical and medullary levels of Ang I and Ang II were analyzed by HPLC (D.E.C.).18 Angiotensin peptides were extracted from kidney sample homogenates and purified in Sep-Pak-C18 columns (Waters Corporation). One-hundred microliters of each sample were filtered and injected into the HPLC system. Angiotensin peptides were analyzed by reverse-phase HPLC, as described earlier. The chromatographic profile of each sample was compared with that obtained for standard intact and fragmented peptides (Sigma Co) of the renin-angiotensin system at 214-nm absorbance. Peptides were identified according to retention time (<6%) and peak height (<5%). The identity of eluted Ang I and Ang II peptides separated by HPLC was confirmed by direct sequencing (protein sequencer PPSQ-23, Shimadzu Corp).

Renin Immunohistochemical Analysis
Paraffin-embedded kidney sections (3 μm) were immunostained by the immunoperoxidase technique using an automatic robot system (DAKO Corp), which allowed identical incubation time of all of the slides to reagents and an antibody. Mounted tissue sections were sequentially incubated with normal blocking rabbit serum, primary antibody (rabbit renin polyclonal antibody generously provided by Dr Tadashi Inagami, Vanderbilt University, Nashville, TN) at 1:8000 concentration, biotin-conjugated rabbit antimouse secondary anti-body, and avidin-biotinylated horseradish peroxidase H complex (ABC Elite Vectastain, Vector Laboratories Inc), followed by 0.1% 3,3’-diaminobenzidine tetrahydrochloride (DAB, Sigma) to visualize peroxidase activity. Intensity of renin immunoreactivity (ratio of the sum of density of positive cells:area) was determined separately in JG and CD cells from both kidneys of the 2K1C rats and kidneys from sham rats using Image-Pro Plus Software (version 4.5.1 for Windows 2000 XP, Media Cybernetics, Inc), as described previously.19 Ten different microscopic fields per tissue section per animal were analyzed. The results are expressed in arbitrary units of the relative intensity normalized to the renin immunostaining average of the sham group.

Protein Expression Levels of Renin by Western Blot
Proteins were extracted from renal medullas dissected from the NCK, CK, and sham rats. Renin Western blot analysis using 10 μg of protein against rat renin antibody at a concentration of 1:4000 was performed under a standard protocol as described previously.8 Protein loading was controlled by reprobing the membranes with β-actin.

mRNA Levels of Renin by Real-Time Quantitative RT-PCR
Fifty nanograms per well of total RNA were used as described previously.8 Amplification of the rat renin 1c gene was performed using specific the following set of primers: sense: 5'-AGT ATG GTG AGA TCG GCA TT-3', antisense: 5'-AGA TTC ACA ATC TTT GAC CAC GGG TTC AG-3', in addition to coamplification of the GAPDH gene labeled with 5’-HEX and 3’-black hole quencher-2.
Kidney Ang I and Ang II Concentrations

The kidney tissue concentrations of Ang I and Ang II were measured after 3 weeks of clipping the left renal artery and are shown in Figure 2. Levels of Ang I were higher in the renal medulla than in the renal cortex in all of the groups of rats; however, renal medullary levels of Ang II were significantly greater than cortical content only in the CK and NCK of the 2K1C rats. Medullary Ang I levels were higher in both CK and NCK kidneys of 2K1C rats compared with sham rats (CK: 120±18 pg/g; NCK: 129±13 pg/g versus sham: 67±6 pg/g; P<0.05). Medullary Ang II levels were maintained or slightly greater in the CK and NCK compared with the sham rats (CK: 150±32 pg/g; NCK: 123±21 pg/g versus sham: 90±12 pg/g).

Kidney Renin and Prorenin Content

Figure 3 shows the renin content of the active and inactive renin forms determined by measuring the amount of Ang I generated per hour from added substrate corrected by total protein in the tissue kidney lysates. In cortex, the renin activity for free renin and prorenin was higher in all of the time periods (1, 2, 8, and 24 hours of incubation with the tetradecapeptide; data not shown) in the CK but not in the NCK. After 2 hours of incubation with the tetradecapeptide, the peak renin values were 5.9±0.2 μg of Ang I per microgram of protein in CK and 3.5±0.2 μg of Ang I per
microgram of protein in NCK compared with the values in sham rats of 2.2±0.8 µg of Ang I per microgram of protein (P<0.05); the prorenin values were 4.0±0.5 µg of Ang I per microgram of protein in CK and 2.4±0.3 µg of Ang I per microgram of protein in NCK compared with 1.7±0.6 µg of Ang I per microgram of protein (P<0.05) in sham rats. Medullary tissue renin activities were similar in both the CK and NCK of 2K1C rats and were significantly higher than in sham rats after either 2 or 8 hours of incubation with the tetradecapeptide, with the greatest difference being at 2 hours (CK: 8.6±0.1µg of Ang I per microgram of protein; NCK: 8.3±0.3µg of Ang I per microgram of protein; sham: 4.1±1.6 µg of Ang I per microgram of protein; P<0.05).

However, after activating prorenin, the Ang I formation rate was increased only in the medulla of NCK but not in the CK compared with sham rats (CK: 1.7±0.2 µg of Ang I per microgram of protein; NCK: 3.6±0.6 µg of Ang I per microgram of protein; sham: 1.2±0.3 µg of Ang I per microgram of protein).

**Renin Immunohistochemistry in JG Cells and Cortical and Medullary CDs**

Figure 4A through 4F depicts the renin immunostaining in rat kidney sections using an immunoperoxidase technique. Renin-specific immunoreactivity is shown in JG cells of sham (Figure 4A) and CK (Figure 4B) and NCK (Figure 4C) of 2K1C rats. In addition, renin immunostaining was observed in cortical CD cells of 2K1C rat kidneys (Figure 4B and 4C) and medullary CD cells (Figure 4E and 4F) but rarely in sham rats (Figure 4A and 4D). Figure 4G through 4I shows the semiquantitative analysis of intensity of renin immunoreactivity in the kidneys of all of the groups of rats. The integrated densitometric values of renin immunoreactivity increased in the cortical CD (Figure 4H) and medullary (Figure 4I) of CK and NCK of 2K1C rats compared with kidneys from sham rats (CK: 2.8±1 cortex, 2.1±1 medulla; NCK: 4.6±2 cortex, 3.2±1 medulla versus 1.0±0.0 DU; P<0.05; Figure 4). These findings contrast with the renin immunoreactivity quantitated in JG cells, which was increased in the CK and suppressed in the NCK of the 2K1C rats as compared with sham rats (CK: 1.7±1; NCK: 0.2±0.0 versus 1.0±0.0 DU relative to sham rats; P<0.001; Figure 4G).

**Renin Protein Expression in Rat Kidney Medullas**

Analysis of integrated densitometric values showed that the ratios for renin protein were significantly augmented in renal medullary tissue of both kidneys of 2K1C rats compared with the average observed in sham rats (CK: 1.4±0.2; NCK: 1.5±0.3 versus 1.0±0.0 relative ratio; P<0.05; Figure 5A). As a control study to assess for equal loading, integrated densitometric value levels in membranes reprobed with β-actin were unaltered among the groups.

**Quantitative RT-PCR for Renin in Rat Kidney Medulla**

Expression of renin mRNA in renal medullary tissues is shown in Figure 5B. Medullary tissue samples from both CK and NCK of 2K1C rats showed significantly higher renin mRNA levels compared with sham-operated rat kidneys (CK: 5.8±2; NCK: 4.9±2 versus 1.0±0.0 relative ratio; P<0.05). There was no significant difference in renin mRNA levels between the CK and NCK from 2K1C rats. Similar levels of GAPDH mRNA were found in all 3 of the groups of rat samples. These results indicate that both kidneys of 2K1C rats have stimulation of medullary renin mRNA, which reflects the renin transcript level in the CD cells.

**Discussion**

In addition to localization in JG cells, renin has been demonstrated in proximal tubule cells, connecting tubules and cortical and medullary CDs in rat, mouse, and human kidneys.8–10 In connecting tubules and CDs, renin is selectively colocalized with aquaporin 2, indicating that it is specifically present in principal cells.8 Our previous demonstration that CD renin transcript and protein levels are upregulated in the renal medulla of chronic Ang II-infused rats suggests that Ang II stimulates renin expression in the distal nephron segments,8 which contrasts with the inhibitory effect of Ang II on JG renin. This independent regulation of tubular renin has been also suggested by Rohrwasser et al,10 who showed in mice that the combination of a high-sodium diet plus administration of an epithelial sodium channel inhibitor (amiloride) increased renin immunoreactivity in connecting tubule cells although there were decreases in JG renin. Furthermore, connecting tubule cell renin immunoregulation...
activity in mice did not exhibit significant variation in response to changes in dietary sodium. In the present study, the renin upregulation in CD cells of 2K1C rats, another model of Ang II-dependent hypertension, suggests a close association between increased intrarenal Ang II and increased gene expression of CD renin.

The present results demonstrate that stimulation of CD renin in Ang II-dependent hypertension is independent of blood pressure. Our previous observation that increases in CD renin transcript and protein levels in chronic Ang II-infused rats are prevented by AT1 receptor blocker suggests an AT1 receptor–mediated mechanism. However, these data did not distinguish between the stimulatory effects of Ang II versus those because of the associated increases in arterial blood pressure. To address this question, we evaluated the renin responses from CK and NCK of 2K1C rats. This model allowed us to dissect the effects of high Ang II levels, which are present in both kidneys of 2K1C rats, from the effects of exposure to elevated arterial pressure, which is restricted to the NCK. During 2K1C Goldblatt hypertension, a cascade of events initiated by the increases of renin secretion from the CK is followed by early increases in circulating Ang II, which ultimately inhibit JG renin synthesis and release in the NCK. High circulating Ang II levels return back toward normal after 2 to 3 weeks of renal unilateral clipping. Our present findings of increased renin immunoreactivity and protein levels in the CD cells with augmented mRNA renin levels in the renal medullary tissues of both CK and NCK of 2K1C rats support enhanced local synthesis and stimulation of renin in the distal nephron segments independent of blood pressure.

Although the specific localization of renin in the principal cells and not in the intercalated cells indicates selective renin cell-type expression in the distal nephron segments, it is also possible that some renin protein uptake by the CD cells contributes to the increased CD renin as well. The recently cloned prorenin receptor (PRR), demonstrated in brain, placenta, lung, and in mesangial cells, cortical renal arteries, and distal tubules of the kidney, may also be responsible for renin or prorenin uptake by CD cells. By binding renin or prorenin, the PRR increases Ang II tissue generation, and its overexpression has been linked to high blood pressure and to

**Figure 4.** Renin protein expression in JG cells and cortical and medullary CD cells: renin immunoreactivity by using the immunoperoxidase technique in kidney cortex and medulla. A through C, cortex of kidney sections (3 µm) with specific renin immunostaining in sham rats (A), and CK (B) and NCK (C) of Goldblatt rats. Arrows show positive specific JG renin immunoreactivity (DAB chromogen) in a sham (A) and in the CK (B) and NCK (C) from Goldblatt rats. Higher renin immunoreactivity (*DAB chromogen) are shown in the CDs of the renal cortexes of both CKs (B) and NCKs (panel C) relative to the sham kidney section (A). D and E, Renin immunoreactivity (*DAB chromogen) in the collecting ducts of the renal medulla of sham (D), CK (E), and NCK (F) sections. In addition, we show the densitometric analyses of the renin intensity immunoreactivity in JG cells (JG renin; G) and cortical (H) and medullary (I) CDs of sham rats and CKs and NCKs of Goldblatt rats performed in 4 kidney sections per animal (10 microscopic fields per kidney section at the renal cortex and medulla regions) and compared with sham kidneys. Sham rats, n=5; Goldblatt rats, n=6. Glom indicates glomerulus; IDV, integrated densitometric values. Values are means±SEs; *P<0.0001 vs sham rats. Renin antibody concentration is 1:4000. *P<0.05 vs sham rats; #P<0.05 CK vs NCK.
cardiac and glomerular fibrosis by stimulation of mitogen-activated protein kinases and profibrotic molecules. The present study does not allow the quantification of either the amount of renin taken up by PRR or the amount of renin generated de novo by the enhanced CD renin mRNA. Alternatively, renin synthesized by principal cells might be secreted into the lumen and then anchored by the PRR, thus contributing to higher Ang I formation. Data from Rohrwasser et al suggest in vitro renin secretion by isolated CD cells compared with JG cells. Moreover, the increased renin activity in the medullary tissues from both kidneys of 2K1C rats indicates that renin predominantly existing in the renal medulla of 2K1C rats is in the active form and suggests that, in Goldblatt hypertension, there is a continued capability to maintain of hypertension in this model.

The augmented gene expression of renin in CD cells of the renal medulla in both CK and NCK from 2K1C rats was associated with elevated intrarenal Ang II content. It is unlikely that circulating Ang II sustains the upregulation of distal nephron renin, because plasma Ang II concentrations in 2K1C hypertensive rats return toward control levels. However, increases in medullary Ang II concentration occur during the early phases after renal unilateral clipping, which could play a role in initiating the increases of Ang II by augmentation of intrarenal AGT and AT$_1$ receptor-mediated uptake. Accordingly, the initial event caused by unilateral renal artery clipping may initiate the cascade responsible for intrarenal Ang II augmentation in the NCK. Furthermore, it is also unlikely that circulating renin or prorenin is the stimulus for the upregulation of renin in the CD cells, because chronic Ang II–infused rats exhibit stimulation of renin in distal nephron segments in a setting of marked suppression of PRA. The results suggest that the local amplification mechanism of intrarenal Ang II on distal nephron renin may allow a moderate increase in Ang II to further augment the intratubular and interstitial Ang II levels to achieve rapid homeostatic regulation of sodium balance as needed in a setting of volume depletion. While appearing to be a positive feedback under pathological conditions, the physiological consequences of this mechanism would be to prevent or minimize the volume depletion by enhancing sodium reabsorption to re-establish sodium balance and allow renin to return to normal levels. Thus, in physiological conditions, this represents a feed-forward mechanism that anticipates and prevents volume depletion. However, during overactivation of the renin-angiotensin system, such as after unilateral renal artery clipping or chronic exogenous infusions of Ang II, this stimulus would be sustained, leading to further increases in local Ang II levels through the coordinated actions of AGT in the proximal tubule cells and renin in the distal nephron segments. Although other possible downstream mediators, such as distal nephron sodium reabsorption, changes in distal sodium delivery, and aldosterone, might also be involved in the regulation of CD renin during Ang II-dependent hypertension, the current data support the hypothesis that stimulation of renin in distal nephron segments is more closely associated with increased intrarenal Ang II content than with increases in renal perfusion pressure.

Our current demonstration of increased medullary renin and prorenin contents in 2K1C rats and, more importantly, that the renal cortex of NCK of 2K1C rats does not exhibit suppression of renin nor prorenin activities support the notion that the distal nephron segments are significant suppliers of active renin and are responsible for counterbalancing the suppression of JG renin during high Ang II states. This effect might be explained by the relative abundance of CD principal cells compared with JG cells. Moreover, the increased renin activity in the medullary tissues from both kidneys of 2K1C rats indicates that renin predominantly existing in the renal medulla of 2K1C rats is in the active form and suggests that, in Goldblatt hypertension, there is a continued capability to form Ang I because of the augmented distal tubular renin. The presence of angiotensin-converting enzyme in renal medullary CD cells supports the further conversion to Ang II, which could thus be contributing to increased Ang II levels observed in both kidneys of 2K1C rats. Furthermore, Ang II directly stimulates epithelial sodium channel activity in cortical CD cells, and there is intraluminal conversion of Ang I to Ang II in cortical CDs. Our results demonstrating renin augmentation in the distal nephron segments along with increases in medullary Ang I content of both kidneys of 2K1C rats support the notion of increased intratubular Ang II formation, which ultimately may stimulate sodium reabsorption in the CD and explain the attenuation of the pressure-natriuretic response to elevations in arterial blood pressure and the development and maintenance of hypertension in this model.
Perspectives
This study indicates that the stimulation of CD renin in Ang II-dependent hypertension is independent of blood pressure. These data help explain how, even during states of JG renin suppression, the NCK can still maintain de novo intrarenal Ang II formation. The demonstration in previous studies of enhanced AGT in urine of Ang II-dependent hypertensive rats reflects spillover of AGT from proximal neprhron segments and substrate availability throughout the nephron. Thus, augmented CD renin mRNA and protein levels in the renal medulla of Ang II-dependent hypertensive rats, along with the increased levels of Ang I, suggest that distal neprhron renin provides a pathway for increased Ang I generation from proximal delivery of AGT. The availability of angiotensin-converting enzyme supports subsequent the formation of Ang II. Accordingly, we propose that the enhancement of renin in the CD augments intrarenal and intratubular Ang II levels and, thus, contributes to the relative sodium retention for any given arterial pressure. The importance of CD renin should not be underestimated in patients with renovascular hypertension, because the activation of renin in the distal neprhron segments may explain why the nonstenotic kidney in unilateral renal vascular hypertension still exerts powerful hypertensinoic influences that contribute to the development and maintenance of hypertension. The development of newer antihypertensive drug therapies specifically targeting renin in tubular segments might be a novel approach to reduce the enhanced intrarenal Ang II levels in patients with renovascular hypertension.

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Disclosures
None.

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