Differential Regulation of Elevated Renal Angiotensin II in Chronic Renal Ischemia

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Abstract — The present study was undertaken to clarify the role of intrarenal angiotensin (Ang) II and its generating pathways in clipped and nonclipped kidneys of 4-week unilateral renal artery stenosis in anesthetized dogs. After 4 weeks, renal plasma flow (RPF) decreased in clipped and nonclipped kidneys (baseline, 59 ± 3; clipped, 16 ± 1; nonclipped, 44 ± 2 mL/min; P < 0.01, n = 22). Renal Ang I levels increased only in clipped, whereas intrarenal Ang II contents were elevated in both clipped (from 0.7 ± 0.1 to 2.0 ± 0.2 pg/mg tissue) and nonclipped kidneys (from 0.6 ± 0.1 to 2.5 ± 0.3 pg/mg tissue). Intrarenal ACE activity was increased in nonclipped kidneys but was unaltered in clipped kidneys. An angiotensin receptor antagonist (olmesartan medoxomil) given into the renal artery markedly restored RPF, and dilated both afferent and efferent arterioles (using intravital videomicroscopy). Furthermore, in clipped kidneys, the elevated Ang II was suppressed by a chymase inhibitor, chymostatin (from 2.1 ± 0.6 to 0.8 ± 0.1 pg/mg tissue; P < 0.05), but not by cilazaprilat. In nonclipped kidneys, in contrast, cilazaprilat, but not chymostatin, potently inhibited the intrarenal Ang II generation (from 2.4 ± 0.3 to 1.5 ± 0.2 pg/mg tissue; P < 0.05). Finally, [Pro11-D-Ala12]Ang I (an inactive precursor that yields Ang II by chymase but not by ACE; 1 to 50 nmol/kg) markedly elevated intrarenal Ang II in clipped, but not in nonclipped, kidneys. In conclusion, renal Ang II contents were elevated in both clipped and nonclipped kidneys, which contributed to the altered renal hemodynamics and microvascular tone. Furthermore, the mechanisms for intrarenal Ang II generation differ, and chymase activity is enhanced in clipped kidneys, whereas ACE-mediated Ang II generation is possibly responsible for elevated Ang II contents in nonclipped kidneys.

Key Words: angiotensin II ■ chymase ■ angiotensin-converting enzyme ■ ischemia ■ nephropathy

Although renin-angiotensin system participates importantly in the homeostasis of renal physiology, it also is closely associated with the renal pathological milieu, including the progression of renal disease.1 Furthermore, intrarenal renin-angiotensin system constitutes a pivotal determinant of systemic hypertension in renal artery stenosis.2 Within the kidney, there have been substantial reports demonstrating an important contribution of intrarenal renin-angiotensin system to the altered renal hemodynamics in stenotic kidneys of unilateral renal artery stenosis. In contrast, in the nonclipped kidneys of 2-kidney, 1-clip hypertensive rats, renal angiotensin (Ang) II levels are demonstrated to remain elevated3–6 or unchanged,7 despite the suppression of renal renin and renin mRNA content. There remains a matter of controversy as to why the nonclipped kidney fails to suppress intrarenal Ang II levels in response to renin depletion. Furthermore, the role of intrarenal Ang II in mediating the altered renal hemodynamics in chronic ischemic nephropathy has not been fully investigated.

Chymase is a serine protease contained in the secretory granules of mast cells that has been thought to contribute to Ang II production as a pathway independent of ACE.8 Previous studies have demonstrated a substantial involvement of chymase in the cardiac9 and vascular Ang II formation.10 Furthermore, chymase-mediated Ang II formation is demonstrated to contribute to vascular remodeling11 and neointimal formation after balloon injury.12 In contrast, Jin et al13 noted that vascular Ang II formation by ACE, but not by chymase, plays an important role in maintaining systemic hypertension in a 2-kidney, 1-clip hypertensive model. In the kidney, we previously demonstrated that the contribution of intrarenal chymase activity to renal Ang II generation and renal hemodynamics is modest in canine kidneys with normal renal function.14 Nevertheless, there have been no investigations demonstrating the intrarenal chymase activity and the contribution of chymase to renal Ang II generation in situ in chronic renal ischemia.

The present study was conducted to clarify the role of intrarenal Ang II in mediating the renal hemodynamic changes in chronic unilateral renal ischemia. Whether ACE or non-ACE activity contributed to the intrarenal Ang II generation in ischemic and nonischemic kidneys was also examined.
Role of Intrarenal Ang II
To clarify the role of intrarenal Ang II in altered renal hemodynamics in unilateral chronic renal ischemia, the effect of an Ang receptor antagonist, olmesartan medoxomil (CS866; Sankyo), on renal hemodynamics and microvascular tone was evaluated in 4-week chronic renal ischemia. After the evaluation of baseline renal hemodynamics, CS866 (30 μg/kg) was infused into the renal artery at a bolus. The effect of this agent was reassessed after 30 minutes of the CS866 infusion.

Chymase- and ACE-Dependent Ang II Formation
The mechanisms for the intrarenal Ang II formation in 4-week chronic renal ischemia were examined. After the evaluation of baseline hemodynamics and intrarenal Ang II contents, either an ACE inhibitor, cilazaprilat (30 μg/kg; Eisai), or a chymase inhibitor, chymostatin (1 mg/kg; Sigma) was infused into the renal artery at a bolus, and the effects of these agents on RPF were assessed by clearance study. Thereafter, the renal tissue was obtained with a biopsy needle for measurements of intrarenal Ang II contents.

Role of Chymase in Ang II Formation
The role of chymase in intrarenal Ang II production was assessed with the use of [Pro^{11}-D-Ala^{12}]Ang I (Peptide Institute). This substrate is converted to Ang II by chymase, which is released from secretory granules of mast cells and then activated by degranulation, but not by ACE. Ang II generated with this agent therefore should represent its production in situ within the kidney. After the evaluation of baseline hemodynamics and renal Ang II contents, [Pro^{11}-D-Ala^{12}]Ang I (0.1 to 50 nmol/kg)–induced changes in these parameters and the effect of each dose of this agent on RPF and urinary sodium excretion (UNaV) was assessed with the renal clearance study. Furthermore, to evaluate the changes in renal Ang II contents, renal biopsy was conducted 10 minutes after the infusion of each dose of the agent. Finally, whether a chymase inhibitor, chymostatin (1 mg/kg), prevented the [Pro^{11}-D-Ala^{12}]Ang I (0.1 to 50 nmol/kg)–induced changes in these parameters was also assessed.

Statistics
Results are expressed as mean±SEM. Data were analyzed by 2-way ANOVA with repeated measures, followed by Bonferroni’s post hoc test. P<0.05 was considered statistically significant.

Results
Changes in Renal Hemodynamics
Left renal artery clipping caused mild elevation in MAP at week 4 (from 111±2 to 128±2 mm Hg; P<0.01, n=22). Plasma renin activity was elevated after 4 weeks of renal artery clipping (from 1.7±0.2 to 7.8±0.8 ng/mL per hour; P<0.01, n=22).

After 4 weeks of renal artery clipping, both RPF and GFR decreased in clipped kidneys (RPF, from 59±3 to 16±1 periods were allocated for assessment of baseline renal function. The control values are evaluated based on the samples collected from both kidneys. Renal biopsy was conducted for evaluation of intrarenal renin-angiotensin system.

After evaluation of renal hemodynamics and intrarenal parameters, chronic renal ischemia was induced by clipping the left renal artery. An electromagnetic flow probe was placed around the left renal artery. Thereafter, a silver clip was placed around the renal artery. The internal diameter of the clip was adjusted to reduce renal blood flow of the ipsilateral kidney to 10% of the prestenotic level by monitoring renal blood flow with an electromagnetic flow probe.

After 4 weeks of renal arterial clipping, initially, 7F catheters were implanted in both ureters for collection of urine. After a 180-minute equilibration period, systemic (MAP and HR) and renal parameters (RPF and GFR) and intrarenal renin-angiotensin system were evaluated.

Renal Hemodynamic Studies
Measurements of Systemic and Renal Hemodynamics
All experimental procedures in this study were conducted according to the guidelines of the Animal Care Committee of Keio University. Adult male mongrel dogs (11 to 13 kg; Nihon-Shizen-Kagaku, Fukushima, Japan) were fed a standard diet (Oriental Yeast Co) and were anesthetized with sodium pentobarbital (30 mg/kg). After intratracheal intubation, each animal was ventilated with an artificial respirator and placed on a heating blanket to maintain body temperature at 37°C. A 7F catheter was inserted through the right femoral artery to measure mean arterial pressure (MAP) and heart rate (HR), and the left radial vein was catheterized for infusion of drug. A 7F catheter (Create Medic) was placed in the bladder for clearance study. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured with the use of inulin and p-aminohippuric acid, respectively.

Chymase- and ACE-Dependent Ang II Formation
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After 4 weeks of renal artery clipping, both RPF and GFR decreased in clipped kidneys (RPF, from 59±3 to 16±1
Changes in Renal Renin-Angiotensin System

Intrarenal Ang I levels increased in clipped (from 48.3 ± 2.3 to 69.5 ± 2.4 pg/mg tissue; *P < 0.01, n = 22), but not in nonclipped kidneys (from 48.0 ± 2.2 to 48.7 ± 3.3 pg/mg tissue; *P > 0.5, n = 22) (Figure 3). In contrast, intrarenal Ang II contents were elevated in both clipped (from 0.7 ± 0.1 to 2.3 ± 0.4 pg/mg tissue; † † † P < 0.001, n = 22) and nonclipped kidneys (from 0.6 ± 0.1 to 2.5 ± 0.3 pg/mg tissue; *P < 0.01, n = 22). Intrarenal ACE activity was unaltered in clipped kidneys but was enhanced in nonclipped kidneys (from 478 ± 41 to 1088 ± 72 nmol/min/g tissue; † † † P < 0.01, n = 22).

These hemodynamic changes were attributed to afferent and efferent arteriolar responses to this agent. Thus, in clipped kidneys, ACE inhibition did not alter MAP (from 127 ± 3 mm Hg, *P > 0.1, n = 4) but had no effect on GFR (from 17 ± 1 to 18 ± 1 mL/min; *P > 0.2, n = 4) (Figure 4). In nonclipped kidneys, ACE inhibition markedly increased RPF (from 19 ± 2 to 21 ± 2 mL/min; † † † P < 0.01, n = 4) and GFR (from 15 ± 1 to 21 ± 2 mL/min; † † † P < 0.01, n = 4), with a reduction in filtration fraction (from 0.38 ± 0.01 to 0.33 ± 0.02; † † † P < 0.01). Furthermore, more pronounced dilator responses to ACE inhibition were observed in afferent arterioles compared to efferent arterioles.
We assessed the effects of intrarenally administered [Pro^{11}-D-Ala^{12}] Ang I on renal Ang II contents and renal hemodynamics at 4 weeks after clipping. MAP was elevated modestly with 10 nmol/kg (3 ± 2%, P < 0.05, n = 6) and 50 nmol/kg [Pro^{11}-D-Ala^{12}] Ang I (9 ± 1%, P < 0.01, n = 6). In clipped kidneys, intrarenal Ang II contents tended to be increased by 0.1 nmol/kg [Pro^{11}-D-Ala^{12}] Ang I, and a significant elevation was observed at 1 nmol/kg (5.6 ± 1.7 pg/mg tissue; P < 0.05) (Figure 6). Further increases in [Pro^{11}-D-Ala^{12}] Ang I infusion caused dose-dependent elevations in intrarenal Ang II levels, producing a 4-fold increase at 50 nmol/kg (8.5 ± 1.7 pg/mg tissue; P < 0.01). Similarly, the injection of 0.1 nmol/kg [Pro^{11}-D-Ala^{12}] Ang I elicited marked changes in intrarenal Ang II generation (upper), RPF (middle), and UNaV (lower) in clipped kidneys, but had modest effect on these parameters in nonclipped kidneys (Figure 6). Further increasing doses of [Pro^{11}-D-Ala^{12}] Ang I produced dose-dependent reductions in RPF and UNaV. When pretreated with chymostatin, the clipped kidneys manifested markedly blunted the responses of these renal parameters to [Pro^{11}-D-Ala^{12}] Ang I infusion (n = 4) (Figure 6). In nonclipped kidneys, however, [Pro^{11}-D-Ala^{12}] Ang I had no effect on these parameters.

### Discussion
In the present study, we have demonstrated that 4-week chronic unilateral renal ischemia elicits substantial decreases in RPF in both clipped and nonclipped kidneys (Figure 2). These changes are accompanied by an elevation in filtration fraction, suggestive of enhanced Ang II activity. Indeed, we observed an elevation in intrarenal Ang II levels (Figure 3). Furthermore, CS866 restored RPF and dilated both afferent and efferent arterioles (Figure 4) in dogs with unilateral renal artery clipping, whereas in normal dogs, the same dose of CS866 had modest effects on these renal parameters. In

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**Figure 5.** Differing effects of chymostatin and cilazaprilat on intrarenal Ang II production and RPF in 4-week chronic renal ischemia. Chy indicates chymostatin; cilaz, cilazaprilat. *P < 0.05 vs baseline.

**Figure 6.** Effects of intrarenally administered [Pro^{11}-D-Ala^{12}] Ang I on intrarenal Ang II generation, RPF, and UNaV in 4-week chronic renal ischemia. The infusion of [Pro^{11}-D-Ala^{12}] Ang I elicited marked changes in intrarenal Ang II generation (upper), RPF (middle), and UNaV (lower) in clipped kidneys, but had modest effect on these parameters in nonclipped kidneys (Figure 6). Further increases in [Pro^{11}-D-Ala^{12}] Ang I infusion caused dose-dependent elevations in intrarenal Ang II levels, producing a 4-fold increase at 50 nmol/kg (8.5 ± 1.7 pg/mg tissue; P < 0.01). Similarly, the injection of 0.1 nmol/kg [Pro^{11}-D-Ala^{12}] Ang I elicited marked changes in intrarenal Ang II generation (upper), RPF (middle), and UNaV (lower) in clipped kidneys, but had modest effect on these parameters in nonclipped kidneys (Figure 6). Further increasing doses of [Pro^{11}-D-Ala^{12}] Ang I produced dose-dependent reductions in RPF and UNaV. When pretreated with chymostatin, the clipped kidneys manifested markedly blunted the responses of these renal parameters to [Pro^{11}-D-Ala^{12}] Ang I infusion (n = 4) (Figure 6). In nonclipped kidneys, however, [Pro^{11}-D-Ala^{12}] Ang I had no effect on these parameters.
concert with our recent observation that that unilateral renal artery clipping reduces UNaV in both clipped and nonclipped kidneys, and that this response is restored by CS866. Our current findings indicate an important contribution of intrarenal Ang II to the impaired renal hemodynamics in both clipped and nonclipped kidneys of unilateral renal artery clipping. Of note, in nonclipped kidneys, CS866 completely reversed RPF to the level of control (ie, before clipping). It follows therefore that the decreased RPF in nonclipped kidneys is attributed in large part to the augmented activity of intrarenal Ang II. Chronic renal artery clipping alters several aspects of renal hemodynamics. Thus, the contribution of intrarenal Ang II to renal arteriolar tone might differ in clipped and nonclipped kidneys. The present study shows that the blockade of Ang II action by CS866 elicits smaller vasodilation of afferent and efferent arterioles in clipped kidneys than in nonclipped kidneys (Figure 4). This finding suggests that Ang II–mediated arteriolar tone is diminished in clipped kidneys. Intrarenal Ang II contents, however, increased in a similar magnitude in both kidneys (Figure 3). Of interest, we have recently demonstrated a marked elevation in intrarenal PGE2 levels, and cyclooxygenase inhibition by sulpyrine causes a greater reduction in RPF in clipped than in nonclipped kidneys. Alternatively, renal artery clipping would reduce myogenic (ie, pressure-induced) tone and favor dilation of afferent arterioles, which may modify the renal action of CS866. Indeed, baseline afferent arteriolar diameters in clipped kidneys are greater than those in nonclipped kidneys (Figure 4), a finding in agreement with that by Inscho et al. Speculatively, these humoral and myogenic factors may act in concert to modify the Ang II–mediated renal arteriolar tone in clipped kidneys. Of note, in nonclipped kidneys, despite the dilator responses of both afferent and efferent arterioles, which result in a decrease in filtration fraction, a marked increase in RPF by CS866 would elevate GFR. Indeed, Navar et al showed increases in RPF and GFR by candesartan. In contrast, mechanical arterial clipping and the CS866–induced efferent arteriolar dilation would restrict the RPF-dependent increase in GFR in clipped kidneys.

Traditionally, long-term unilateral impairment in renal function is associated with functional and histological compensation of the contralateral kidney. The contralateral kidney in various forms of unilateral renal disease, including unilateral ureteral obstruction and unilateral nephrectomy, is capable of rapidly increasing its filtration rate in response to the reduction in function of the affected kidney. In unilateral renal artery stenosis, Truong et al indicated that the contralateral kidney manifested hypertrophy and hyperfiltration. In contrast to this observation, several investigations also demonstrated that the nonclipped kidney failed to compensate for the impaired function of the affected kidney. Our present observations therefore agree with these reports, and further clarify the role of Ang II in mediating the impairment in renal function of nonclipped kidneys. Although the discrepant effects of unilateral clipping on the renal function of the contralateral kidney remain unclear, different experimental settings may affect the renal function of the nonstenotic kidney. In our chronic renal ischemic model, the severity of renal artery stenosis is quantified by measuring renal blood flow with electromagnetic flow probe to reduce renal blood flow to 10% of the prestenotic level. Because MAP is elevated only modestly in our model, the observed effects appear to be attributed mainly to renal ischemia per se, rather than systemic hypertension. These differences may modify the intrarenal humoral factors and would play a distinct role in the impaired renal function in the nonclipped kidney. Of course, this controversy requires further investigations.

Although the mechanism for the elevated intrarenal Ang II remains fully undetermined, several lines of studies indicate multiple pathways for generation of intrarenal Ang II in nonclipped kidneys. In the present study, we have demonstrated that intrarenal Ang II contents in nonclipped kidneys are increased without changes in the Ang I levels (Figure 3). Furthermore, these changes are accompanied by simultaneous augmentation of ACE activity. Finally, an ACE inhibitor, cilazaprilat, reduced the intrarenal Ang II contents and restored RPF (Figure 5), whereas plasma renin activity was unaltered by this agent. In concert, these observations clearly indicate that intrarenal ACE contributes importantly to the intra-renal generation of Ang II within the nonclipped kidney and plays a substantial role in the impairment in renal hemodynamics. In this regard, Navar et al have demonstrated that intrarenal ACE activity is enhanced in Ang II–infused rats, in which plasma Ang II is chronically elevated, a result consistent with our present finding. Furthermore, Zwe et al have recently found that in Ang II–infused rats, circulating Ang II was internalized after the binding with angiotensin receptors. Finally, the elevated level of intrarenal Ang II in animals treated with chronic Ang II infusion fails to suppress renal angiotensinogen gene expression. It is therefore conceivable that these mechanisms contribute to the augmented intrarenal Ang II activity in nonclipped kidneys. Of note, in clipped kidneys, cilazaprilat failed to reduce intrarenal Ang II contents or alter RPF. The different responsiveness to the ACE inhibitor therefore strongly suggests distinct mechanisms for the elevated intrarenal Ang II level in clipped and nonclipped kidneys.

Several lines of evidence have indicated the presence of non–ACE-mediated pathways in tissue renin-angiotensin system in normal and pathophysiological conditions. Chymase represents a non–ACE-dependent Ang II–generating pathway, which plays a pathophysiological role in the tissue injury in a variety of disorders, including myocardial infarction and atherosclerosis. In the present study, we have demonstrated that in clipped kidney, chymostatin, a relatively specific inhibitor for chymase, markedly reduces intrarenal Ang II contents, with a concomitant increase in RPF (Figure 5). Furthermore, we assessed the effect of intrarenally administered [Pro<sup>11</sup>-D-Ala<sup>12</sup>]Ang I, a selective substrate for chymase, on the renal contents of Ang II. This in vivo methodology with [Pro<sup>11</sup>-D-Ala<sup>12</sup>]Ang I to elucidate the mechanism of intrarenal Ang II production thus provides advantage because other techniques using tissue homogenates may overestimate the chymase-like activity, with inclusion of chymase within secretory granules. Using our current technique, we demonstrate that the infusion of [Pro<sup>11</sup>-D-Ala<sup>12</sup>]Ang
I increased intrarenal Ang II in clipped kidneys, with simultaneous decreases in RPF and UNaV. In the same setting, only modest changes in intrarenal Ang II levels, RPF, and UNaV were observed in nonclipped kidneys (Figure 6). More importantly, the [Pro^1→D-Ala^2]Ang I–induced changes were markedly blunted by the chymase inhibition with chymostatin. Based on these results, the contribution of chymase to intrarenal Ang II generation differs in clipped and nonclipped kidneys; the elevated intrarenal Ang II level observed in clipped kidneys is attributed to chymase activity, whereas the role of this enzyme in the intrarenal Ang II production appears modest in nonclipped kidneys. In this regard, we previously demonstrated that in normal canine kidneys, chymase-like activity is small, using the same Ang I analogue. It is thus strongly suggested that unilateral renal artery clipping causes activation of intrarenal chymase in clipped, but not in nonclipped, kidneys, and this mechanism would contribute to the augmented intrarenal Ang II production, in concert with stimulated renin activity.

The present findings indicating distinct mechanisms for the intrarenal Ang II production merit comments. It has been established that renal ischemia elicits renin activation, which subsequently augments Ang I production (Figure 3). Furthermore, the present study clearly demonstrates that the augmented intrarenal Ang II production is mediated mainly by chymase rather than ACE in clipped kidneys. In contrast, in nonclipped kidneys, ACE constitutes a key enzyme, converting Ang I to Ang II. These site-specific differences in angiotensin-converting pathways could be relevant to whether the kidney is exposed to ischemia. It has been reported that cardiac chymase activity is upregulated in myocardial infarction. Furthermore, Maruyama et al have demonstrated that the Ang II–dependent norepinephrine release from cardiac tissues under anoxic conditions is inhibited by chymostatin but not by enalaprilat, and they suggested that ischemia augments the chymase activity. Although this form of angiotensin II–dependent pathways in canine kidney.

Perspectives

The present study demonstrates that intrarenal Ang II–generating pathways are regulated differently in clipped and nonclipped kidneys of chronic unilateral renal ischemia. In clipped kidneys, the elevated Ang II level is attributed to stimulated chymase, as well as well-established renin, activity, whereas augmented ACE activity constitutes a major determinant of the elevated intrarenal Ang II contents in nonclipped kidneys. Such elevated Ang II levels would contribute to the amplification of renal impairment in clipped kidneys and the failure of the nonclipped kidneys to compensate for the impaired renal function in clipped kidneys. Finally, suppression of the Ang II production in unilateral renal artery stenosis may offer future tools for the prevention of chronic ischemic nephropathy.

References


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