Intra-Renal Angiotensin II/AT₁ Receptor, Oxidative Stress, Inflammation, and Progressive Injury in Renal Mass Reduction

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ABSTRACT

Significant reduction of renal mass triggers a chain of events that result in glomerular hypertension/hyperfiltration, proteinuria, glomerulosclerosis, tubulointerstitial injury, and end-stage renal disease. These events are mediated by a constellation of hemodynamic, oxidative, and inflammatory reactions that are, in part, driven by local AT₁ receptor (AT₁r) activation by angiotensin II (Ang II). Here we explored the effects of 5/6 nephrectomy with and without AT₁r blockade (losartan for 8 weeks) on oxidative stress and inflammation [NAD(P)H oxidase, nuclear factor κB (NF-κB), 12-lipoxygenase, cyclooxygenase (COX)-1, COX-2, monocyte chemoattractant protein (MCP)-1, plasminogen activator inhibitor (PAI)-1, renal T cell, and macrophage infiltration] as well as renal function and structure. The untreated group exhibited hypertension, deterioration of renal function and structure, reduced or unchanged plasma renin activity, aldosterone concentration, marked up-regulations of AT₁r (250%), Ang II-expressing cell count (>20-fold), NAD(P)H oxidase subunits (gp91phox, p22phox, and P47phox, 20–40%), COX-2 (250%), 12-lipoxygenase (100%), MCP-1 (400%), and PAI-1 (20-fold), activation of NFκB, and interstitial infiltrations of T cells and macrophages in the remnant kidneys. AT₁r blockade attenuated the biochemical and histological abnormalities, prevented hypertension, and decelerated deterioration of renal function and structure. Thus, the study demonstrated a link between up-regulation of Ang II/AT₁r system and oxidative stress, inflammation, hypertension, and progression of renal disease in rats with renal mass reduction.

Significant reduction in renal mass by subtotal nephrectomy or by various disease processes triggers a chain of events that culminate in progressive glomerulosclerosis, tubulointerstitial injury, and end-stage renal disease (Remuzzi et al., 2006). Progressive deterioration of the remnant/diseased kidney function and structure is associated with and largely mediated by profound alteration of renal hemodynamics, inflammation, and oxidative stress (Mackenzie et al., 2000). In this context, renal mass reduction results in glomerular capillary hypertension and glomerular hyperfiltration, which play a major role in the pathogenesis of proteinuria and glomerulosclerosis (Hostetter et al., 2001). This assertion is supported by the observations that prevention/alleviation of the maladaptive hemodynamic alterations by lowering dietary protein or blocking renin-angiotensin system (RAS) decelerates progression of renal disease (Nickenig and Harrison, 1994; Mackenzie et al., 2000). In addition to the hemodynamic factors, accumulation of the inflammatory cells plays a major part in progression of renal disease (Chow et al., 2004; Rodriguez-Iturbe et al., 2004b). This supposition is consistent with the demonstration that inhibition of leukocyte recruitment by chemokine receptor antagonists and treatment with immunosuppressive/anti-inflammatory drugs slows progression of renal disease in experimental animals (Fujihara et al., 1998; Romero et al., 1999; Anders et al., 2006). Finally, significant reduction of renal mass results in up-regulation of NAD(P)H oxidase and oxidative stress in the kidney and cardiovascular tissues, which can advance renal injury and compound hemodynamic abnormalities (Vaziri et al., 2003).

Numerous clinical and experimental animal studies have provided compelling evidence for up-regulation of renin-angiotensin system and its role in progression of renal disease (Mackenzie et al., 2000; Gonçalves et al., 2004). In this context, a maladaptive increase in RAS activity in the remnant/
diseased kidney seems to participate in the pathogenesis of the associated renal hemodynamic abnormalities by promoting glomerular hypertension and hyperfiltration (Hostetter et al., 2001). In addition, activation of AT₁R by Ang II can account for up-regulation/activation of NADPH oxidase and oxidative stress in the kidney and cardiovascular tissues (Taniyama and Griendling, 2003). Finally, Ang II promotes activation of NF-κB and production of pro-inflammatory cytokines, chemokines, growth factors, and adhesion molecules, which cause inflammation and fibrosis (Ruiz-Ortega et al., 2000; Nahmod et al., 2003).

The role of RAS as a driving force in the progression of renal disease is supported by numerous studies that have demonstrated the protective action of blockade of this system in humans and experimental animals (Nickenig and Harrison, 1994; Mackenzie et al., 2000; Remuzzi et al., 2006). It is noteworthy that all components of RAS are present in the kidney and that intrarenal RAS operates independently of factors that regulate plasma RAS activity (Navar, 2004). Most of the deleterious actions of RAS are mediated by AT₁R. The present study was designed to test the hypothesis that imbalance in intrarenal AT₁R/AT₂R contributes to oxidative stress, inflammation, and progressive deterioration of remnant kidney function, and structure in 5/6 nephrectomized rats. To this end, protein expressions of AT₁R, AT₂R, NADPH oxidase, cyclooxygenase, lipooxygenase (LO), MCP-1, and PAI-1, as well as Ang II-positive cell count, NF-κB activation, renal function, structure, and immune cell infiltration were determined in untreated and losartan-treated 5/6 nephrectomized rats.

Materials and Methods

Study Groups. Male Sprague-Dawley rats with an average body weight of 270 g (Harlan Sprague-Dawley Inc., Indianapolis, IN) were used in this study. Animals were housed in a climate-controlled vivarium with 12-h day and night cycles and were fed a standard laboratory diet (Purina Rat Chow; Purina Mills, Brentwood, MO) and water ad libitum. The animals were randomly assigned to the CRF and sham-operated control groups. The CRF group underwent 5/6 nephrectomy and that intrarenal RAS operates independently of factors that regulate plasma RAS activity (Navar, 2004). Most of the deleterious actions of RAS are mediated by AT₁R. The present study was designed to test the hypothesis that imbalance in intrarenal AT₁R/AT₂R contributes to oxidative stress, inflammation, and progressive deterioration of remnant kidney function, and structure in 5/6 nephrectomized rats. To this end, protein expressions of AT₁R, AT₂R, NADPH oxidase, cyclooxygenase, lipooxygenase (LO), MCP-1, and PAI-1, as well as Ang II-positive cell count, NF-κB activation, renal function, structure, and immune cell infiltration were determined in untreated and losartan-treated 5/6 nephrectomized rats.

Measurement of Arterial Pressure. Arterial pressure was determined by tail plethysmography (Harvard Apparatus, Natick, MA). In brief, the conscious animal was placed in a restrainer and permitted to rest for 10 to 15 min. The cuff was then placed on the tail and was inflated and released several times to condition the animal to the procedure. After stabilization, blood pressure was measured three times, and the average of these values was used.

Tissue Preparation. Kidney cortex was separated and homogenized in 10 mM HEPES buffer, pH 7.4, containing 320 mM sucrose, 1 mM EDTA, 1 mM diethiothreitol, 10 mg/ml leupeptin, 2 mg/ml aprotinin, and 1 mM phenylmethylsulfonyl fluoride at 0–4°C. A Polytron tissue mixing and blending device was used to blend the supernatant into a smooth homogenate. Homogenates were centrifuged at 12,000g for 10 min at 4°C to precipitate tissue debris. The supernatant was used to perform Western analyses. Total protein concentration was determined with the use of a Bio-Rad kit (Bio-Rad Laboratories, Hercules, CA).

Western Blot Analyses. Protein abundance of AT₁R, AT₂R, COX-1, COX-2, 12-lipoxygenase, MCP-1, PAI-1, and NADPH oxidase subunits (p91phox, p67phox, p47phox, and p22phox) were measured by Western blot technique. Polyclonal antibodies against COX-1, COX-2, and 12-lipoxygenase were purchased from Cayman Chemical (Ann Arbor, MI). Anti-MCP-1 antibody was purchased from Abcam Inc. (Cambridge, MA). Antibodies against p47phox and PAI-1 were purchased from BD Biosciences (San Diego, CA). AT₁R and AT₂R antibodies were obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Polyclonal antibodies against p91phox and p67phox were purchased from Upstate Inc. (Charlottesville, VA). Antibody against p22phox was generously provided by Dr. A. J. Jesaitis (Montana State University, Bozeman, MT). Actin monoclonal antibody was purchased from Sigma-Aldrich (St. Louis, MO). The polyclonal rabbit antibody against phospho-p42/p44 was purchased from Cell Signaling Technology Inc. (Denver, CO). Peroxidase-conjugated immunopure goat anti-rabbit IgG (H+L) antibodies were purchased from Pierce Biotechnology (Rockford, IL). Western blot analyses for the given proteins were carried out as described in our earlier studies (Zhan et al., 2004; Xu et al., 2005). On each occasion, the gels and membranes were tested with Western blot blue stain (PerkinElmer Life and Analytical Sciences, Boston, MA) to verify the uniformity of protein load and transfer efficiency across the test samples. Experiments failing this test were discarded. Optical densities of protein bands were determined by a laser densitometer (GE Healthcare, Little Chalfont, Buckinghamshire, UK) and expressed as arbitrary units.

Plasma Renin Activity Assay. Plasma renin activity (PRA) was determined by measuring the amount of angiotensin I produced from endogenous substrate after incubation at 37°C. To this end, plasma angiotensin I concentration in each specimen was measured before and after incubation at 37°C for 1 h. Angiotensin I concentration was quantified by radioimmunoassay using 125I-angiotensin I and anti-angiotensin I antibody. PRA was determined by subtracting pre-existing angiotensin I from that found after incubation and expressed as nanogram of angiotensin I generated per milliliter of plasma per hour. The sensitivity of the assay was 0.1 ng/ml/h. The interassay variation was less than 12%.

Aldosterone Assay. Aldosterone was quantitated by liquid chromatography with tandem mass spectrometry using deuterated internal standard. The assay was specific for aldosterone and had no cross-reactivity with aldosterone metabolites. The assay sensitivity was 1 ng/dl. The interassay variation was less than 10%.

Histology and Immunohistochemistry. Light microscopy was done in the formalin-fixed sections stained with periodic acid Schiff and hematoxylin and eosin. Glomerulosclerosis was graded by a score index used in our previous studies (Rodriguez-Iiturbe et al., 2005b); glomeruli were graded from 0 to +4 (grade 0 = normal, grade 1 = <25% involvement of the glomerular tuft, grade 2 = 25–50% involvement of the glomerular tuft, grade 3 = 50–75% involvement of the glomerular tuft, and grade 4 = sclerosis occupying >75% of the glomerular tuft, grade 5 = sclerosis occupying 100% of the glomerular tuft).
glomerular tuft. The glomerulosclerosis score was obtained as follows: [1 × number of glomeruli with +1] + [2 × number of glomeruli with +2] + [3 × number of glomeruli with +3] + [4 × number of glomeruli with +4] × 100/total number of glomeruli examined.

Tubulointerstitial damage was scored as described previously (Rodríguez-Iturbe et al., 2005b) using a 0 to 5 scale depending on the extent of areas with tubular dilatation, interstitial infiltration, and fibrosis (0 = no changes, grade 1 = <10%, grade 2 = 10–25%, grade 3 = 25–50%, grade 4 = 50–75%, and grade 5 = 75–100%). To this end, successive fields were examined at 20× magnification in the entire cortical and juxta-medullary areas of each specimen, and areas with tubulointerstitial damage were identified and related to the total area under examination using computer-assisted image analysis (Olympus BX51 System Microscope and DP70 microscope digital camera with software; Sigma Pro, Leesburgh, VA) (Rodríguez-Iturbe et al., 2005a). Lymphocytes (CD5-positive cells) and macrophages (ED1-positive cells) were identified using avidin-biotin-peroxidase methodology, as described previously (Rodríguez-Iturbe et al., 2005b). Immune cell infiltration was evaluated in glomeruli (positive cells/glomerular cross-section) and in tubulointerstitial areas (positive cells/mm²). All histological examinations were done in a blinded fashion.

**Antisera.** Lymphocytes and macrophages were identified with monoclonal anti-CD5 and anti-ED1 antibodies (Biosource Inc., Camarillo, CA), respectively. Rabbit anti-human angiotensin II anti-serum with cross-reactivity to rat angiotensin II (Peninsula Laboratories Inc., San Carlos, CA) was used to identify angiotensin II-positive cells; specificity of the staining was tested by preincubating serum with cross-reactivity to rat angiotensin II (Peninsula Laboratories). Secondary biotin-conjugated affinity-pure antibodies with minimal reactivity to rat serum proteins were purchased from Accurate Chemical and Scientific Inc. (Westbury, NY). Nonrelevant antibodies were used for negative control studies.

**Statistical Analysis.** Student’s t test, analysis of variance, and Tukey post-tests were used in statistical analysis of the data as appropriate. P values equal to or less than P < 0.05 were considered significant. Data are presented as mean ± S.E.M. unless specified otherwise.

### Results

**General Data.** Results are summarized in Table 1 and Fig. 1. Compared to the control group, the untreated CRF group exhibited significant elevations of arterial pressure, plasma creatinine, and urinary protein excretion and reduced creatinine clearance. Although the mean PRA in the CRF group (0.1 ± 0.00 ng/h) was lower than that in the control group (0.4 ± 0.17 ng/h), the difference did not reach statistical significance. This was primarily due to wide variability in values found in the control animals. Likewise, no significant difference was found in plasma aldosterone concentration between the CRF (6.7 ± 1.2 ng/dl) and the control group (5.3 ± 1.1 ng/dl). AT1r blockade prevented hypertension, reduced proteinuria, and attenuated the rise in plasma creatinine and the fall in creatinine clearance.

**AT1r and AT2r Data.** Data are depicted in Fig. 2. The untreated CRF rats exhibited a greater than 2.5-fold rise in AT1r protein abundance in the remnant kidney tissue compared with the corresponding value found in the sham-operated controls. AT1r abundance was lowered to less than 50% by losartan administration. AT1r abundance was unchanged in the remnant kidney and was unaffected by losartan administration.

**NAD(P)H Oxidase Data.** Data are illustrated in Figs. 3 and 4. Compared with the control group, the untreated 5/6 nephrectomized animals showed significant (20–40%) up-regulations of gp91phox, p22phox, and p47phox subunits of NAD(P)H oxidase in the remnant kidneys. AT1r blockade significantly attenuated the up-regulation of p22phox and p47phox subunits of NAD(P)H oxidase but did not alter gp91phox or p67phox abundance in the treated animals.

**COX-1, COX-2, and 12-Lipoxygenase Data.** Data are illustrated in Figs. 5 and 6. Compared with the sham-operated controls, the untreated 5/6 nephrectomized group had significant increases in the remnant kidney tissue abundance of COX-1 (40%), COX-2 (2.5-fold), and 12-lipooxygenase (2-fold). AT1r blockade prevented the rise in COX-2 and 12-lipooxygenase expression in the treated CRF group. However, COX-1 protein abundance was unaffected by losartan administration.

**MCP-1 and PAI-1 Data.** Data are depicted in Fig. 7. MCP-1 and PAI-1 protein expressions were markedly elevated in the remnant kidneys of the untreated 5/6 nephrectomized animals (4- and 20-fold, respectively) compared with the corresponding values found in the control kidneys. AT1r blockade prevented up-regulations of MCP-1 and PAI-1 in the treated group.

**NFκB Data.** Data are shown in Fig. 8. The untreated CRF group showed a significant increase in the abundance of phospho-IκB in the remnant kidney cortex pointing to enhanced activation of NFκB. Administration of AT1r blocker resulted in significant reduction of phospho-IκB abundance in the treated animals.

**Ang II-Positive Cells.** Data are presented in Fig. 9. The number of Ang II-positive cells was significantly (>20-fold) higher in the remnant kidneys of the untreated CRF group than in the control rats. Losartan administration lowered the number of Ang II-positive cells by 40% in the CRF animals. The Ang II-positive cells in the CRF groups were primarily localized in the tubulointerstitial region of the remnant kidney and primarily consisted of tubular epithelial and inflammatory cells.

**Immune Infiltration Data.** Data are depicted in Fig. 10. The remnant kidney tissues showed significant interstitial macrophage and T cell infiltrations in the untreated 5/6 nephrectomized rats. Administration of losartan significantly reduced interstitial inflammation in the treated group.

**Renal Histology Data.** Data are shown in Fig. 11. The untreated animals exhibited significant glomerulosclerosis, tubular atrophy/dilation, interstitial fibrosis, increased glomerulosclerosis index, and tubulointerstitial damage scores 8 weeks after 5/6 nephrectomy. AT1r blockade with losartan significantly reduced glomerulosclerosis index and tubulointerstitial damage scores in the treated CRF group.

### Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>CRF</th>
<th>CRF + ARB</th>
</tr>
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<tbody>
<tr>
<td><strong>Plasma creatinine (mg/dl)</strong></td>
<td>0.41 ± 0.22</td>
<td>1.85 ± 0.50*</td>
<td>1.07 ± 0.27**</td>
</tr>
<tr>
<td><strong>Creatinine clearance (ml/min)</strong></td>
<td>3.08 ± 0.38</td>
<td>0.85 ± 0.26*</td>
<td>1.61 ± 0.25**</td>
</tr>
<tr>
<td><strong>Proteinuria (mg/24 h)</strong></td>
<td>4.9 ± 3.60</td>
<td>125 ± 11.46*</td>
<td>39.05 ± 29.6*</td>
</tr>
</tbody>
</table>

Data are shown in Fig. 8. The untreated CRF group showed a significant increase in the abundance of phospho-IκB in the remnant kidney cortex pointing to enhanced activation of NFκB. Administration of AT1r blocker resulted in significant reduction of phospho-IκB abundance in the treated animals.
The untreated 5/6 nephrectomized rats, exhibited a marked increase in AT1r but no change in AT2r abundance in the remnant kidney. Up-regulation of AT1r was coupled with a marked increase in the numbers of Ang II-positive cells. Ang II is known to raise arterial pressure, induce renal cell hypertrophy, and promote NFκB activation and matrix protein accumulation, events that are linked to progression of renal disease (Wolf et al., 1992; Ruiz-Ortega et al., 2000; Hoffmann et al., 2004). Most of the hemodynamic and non-hemodynamic actions of Ang II in adult tissues are mediated by AT1r. Consequently, up-regulation of AT1r together with increased numbers of Ang II-positive cells and hypertension can contribute to progression of renal disease. This supposition is supported by favorable response to AT1r blockade in our 5/6 nephrectomized rats and numerous other animal studies and clinical trials (Nickenig and Harrison, 1994; Mackenzie et al., 2000; Remuzzi et al., 2006), which have demonstrated greater renal protection with the use of angiotensin-converting enzyme inhibitors and AT1r antagonists compared with other equally potent antihypertensive regimens.

In an earlier study, Mackie et al. (2001) showed increased angiotensin II level in the peri-infarct region of the remnant kidney despite suppressed plasma renin activity in rats studied 5 weeks after 5/6 nephrectomy. A similar discrepancy between plasma renin activity and remnant kidney tissue Ang II was evident in our rats studied 8 weeks post-resectional 5/6 nephrectomy. Together these observations suggest that production of Ang II in the remnant/diseased tissue may be independent of plasma renin activity.

The remnant kidneys in untreated CRF animals showed increased NFκB activation (elevated phospho-IκB) and macrophage/T lymphocyte infiltration. NFκB is the general transcription factor for numerous proinflammatory cytokines, chemokines, and adhesion molecules that are essential for...
activation and tissue infiltration of immune cells. By activating NFκB, Ang II has been shown to promote inflammation (Ruiz-Ortega et al., 2000). In contrast, inflammation has been shown to promote intrarenal Ang II production by tubular epithelial cells and infiltrating inflammatory cells (Okamura et al., 1999; Rodríguez-Iturbe et al., 2004c) and stimulate angiotensinogen gene expression (Brazier and Li, 1996).

The prototypical phagocytic NAD(P)H oxidase (NOX-II) and its tissue-specific isoforms (NOX-I, NOX-IV, and NOX-V) are the main source of ROS in endothelial cells, vascular smooth muscle cells, and cellular constituents of the kidney (Chabrashvili et al., 2002; Taniyama and Griendling, 2003; Griendling, 2004). Pro-inflammatory cytokines, angiotensin II, and mechanical stress acutely raise ROS production by activating NAD(P)H oxidase. In addition, chronic exposure to
these stimuli leads to up-regulation of constitutively active isoforms of the enzyme and, thereby, sustained increase in ROS production (Lassègue and Clempus, 2003). In confirmation of our earlier study (Vaziri et al., 2003), the untreated CRF rats showed marked up-regulation of NAD(P)H oxidase (gp91phox, p22phox, and p47phox subunits) in the remnant kidney and significant elevation of lipid peroxidation product malondialdehyde in the plasma denoting presence of oxidative. Angiotensin II-induced oxidative stress contributes to renal injury and dysfunction by several mechanisms. Chief among them is the reduction of nitric oxide bioavailability, which has been demonstrated in CRF animals (Vaziri et al., 2002) and can cause endothelial dysfunction, hypertension, inflammation, fibrosis, vascular thrombosis, and tissue injury.

Products of the main enzymes of arachidonic acid metabolism, i.e., COX-I, COX-II, and LO, exert numerous physiologic and pathologic effects. For instance, 12(S)-hydroxyeicosatetraenoic acid [12(S)-HETE], a byproduct of 12-LO, mediates hyperglycemia-induced (Kang et al., 2001) and Ang II-induced (Reddy et al., 2002) mesangial cell growth and matrix production. In addition, COX-2 participates in the pathogenesis of oxidative stress, inflammation, and hemodynamic disorders (Cheng et al., 2002; Gonçalves et al., 2004; Krämer et al., 2004).

Our untreated CRF rats showed up-regulations of COX-1, COX-2, and 12-LO in the remnant kidneys. As described above, up-regulation of these enzymes can contribute to inflammation, fibrosis/sclerosis, oxidative stress, and hemodynamic disorders associated with renal mass reduction. This supposition is supported by earlier studies (Gonçalves et al., 2004), which showed that COX-2 is heavily induced in the tubulointerstitial region of the remnant kidney and that deterioration of renal function/structure is decelerated by COX-2 inhibition in CRF rats. Up-regulations of renal 12-LO and COX-2 abundance in our CRF rats paralleled those of AT1r and Ang II-positive cells and were reversed by AT1r blockade. These findings point to the causal role of heightened Ang II/AT1r activity in the up-regulation of these enzymes. Ang II-mediated inflam-
Information and oxidative stress may contribute to up-regulation of COX-2 whose expression is induced by reactive oxygen species (Kiritoshi et al., 2003). Interestingly, COX-1 expression remained elevated despite AT1r blockade, suggesting that up-regulation of COX-1 in the remnant kidney is independent of AT1r activity.

Accumulation of inflammatory cells in the remnant kidneys of CRF rats was associated with significant up-regulation of MCP-1, which is essential for monocyte/macrophage recruitment. Amelioration of renal tissue inflammation with AT1r blockade was associated with significant reduction of MCP-1. Likewise, tubulointerstitial fibrosis and glomerulosclerosis in the CRF rats was accompanied by marked up-regulation of the profibrotic metalloproteinase PAI-1. AT1r blockade ameliorated glomerulosclerosis and reduced PAI-1 abundance in the remnant kidney. These observations are consistent with previous studies in rats with renal ablation (Ma et al., 2000; Remuzzi et al., 2002) and in the obese Zucker rats (Xu et al., 2005).

Earlier studies have shown a marked shift in Ang II production and AT1r expression toward tubulointerstitial region with renal mass reduction and other nephropathies (Gonçalves et al., 2004; Rodríguez-Iturbe et al., 2004b). Likewise, expression of COX-2, which is normally confined to macula densa (Harrison-Bernard et al., 1997), heavily shifts to the glomeruli, vessels, and the interstitial regions in 5/6 nephrectomized rats (Fujihara et al., 2003; Gonçalves et al., 2004). The redistribution of Ang II, AT1r, and COX-2 in the remnant/diseased kidney signifies the shift from their normal biological functions to the pathological functions that contribute to inflammation, fibrosis, and tissue damage. It is noteworthy that inflammatory cells in the tubulointerstitial region constitute nearly 20 to 40% of the Ang II-positive cells in the diseased kidney (Rodríguez-Iturbe et al., 2004a,c). Thus,
alleviation of inflammation by AT1r blockade can, in part, account for the reduction of Ang II-positive cells in the remnant kidneys. NFκB activation, the accompanying up-regulation of inflammatory pathways, and favorable response to AT1r blockade observed in 5/6 nephrectomized rats shown here are consistent with findings in obstructive nephropathy (Klahr and Morrissey, 2002).

It is noteworthy that renal protection conferred by RAS blockade, shown in this and other studies, has been invariably accompanied by amelioration of hypertension. Because hypertension is a major cause of renal injury and inflammation (Bidani and Griffin, 2004; Vaziri and Rodríguez-Iturbe, 2006), its amelioration undoubtedly contributes to protective actions of angiotensin system inhibitors. Further studies are required to discern the impact of blood pressure reduction per se on the parameters studied here.

In summary, progressive deterioration of renal function and structure following renal mass reduction was associated with heightened intrarenal (but not plasma) RAS and activation/up-regulation of inflammatory/oxidative pathways in the remnant kidney. AT1r blockade lowered blood pressure, decelerated progression of renal disease, and attenuated up-regulations of the pro-oxidant/proinflammatory systems in the remnant kidney. These observations point to activation of intrarenal Ang II/AT1r system and its potential role in the hemodynamic and nonhemodynamic disorders that contribute to progression of renal disease.

References