How Does Angiotensin II Cause Renal Injury?

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Based on several important clinical trials, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 (JNC 7) approves the use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) in the first-line treatment for hypertension in subjects with chronic renal insufficiency, in diabetic subjects with proteinuria, and in black subjects with renal insufficiency and proteinuria, because these agents appear to provide renoprotection in these conditions. The observation that agents that interfere with the renin-angiotensin system (RAS) might be useful in subjects with renal insufficiency seems at first to be counterintuitive, because many subjects with chronic renal insufficiency are volume-expanded, which acts to inhibit the RAS. However, in renal insufficiency, other mechanisms that stimulate renin may be involved, including intrarenal microvascular disease causing ischemia, hyperuricemia, and low 1,25-dihydroxyvitamin D levels. Renal injury will also activate renal afferent nerves to stimulate β-adrenergic output from the central nervous system that can stimulate renin release. Activation of the local RAS has also been shown in renal injury, indicated by upregulation of ACE and the infiltration of leukocytes expressing angiotensin II.

A variety of mechanisms has been suggested by which angiotensin II causes renal injury. Angiotensin II may cause pressure-induced renal injury via its ability to induce systemic and glomerular hypertension or cause ischemia-induced renal injury secondary to intrarenal vasoconstriction and decreased renal blood flow. Angiotensin may also cause tubular injury secondary to angiotensin-induced proteinuria. Angiotensin II also activates renin fibroblasts to become myofibroblasts, stimulates the production of the profibrotic cytokine TGF-β, induces oxidative stress, stimulates chemokines and osteopontin that may cause local inflammation, and stimulates vascular and mesangial cell proliferation and hypertrophy. Taken together, these data provide an excellent rationale for blocking the RAS in subjects with renal disease, because angiotensin II has hemodynamic and nonhemodynamic mechanisms by which it can cause renal damage.

Nevertheless, the mechanism by which blocking the RAS is protective remains controversial. Substantial data, primarily in studies of diabetic subjects and/or subjects with renal insufficiency, suggest that blocking the RAS slows renal injury via blood pressure (BP)-dependent and BP-independent pathways. In contrast, studies in several experimental models of renal disease suggest that the greater protection of ACE inhibitors is caused by better continuous BP control, which is not evident by single daily BP measurements. In the remnant kidney model of progressive renal disease, for example, renoprotection correlates directly with continuous 24-hour systolic BP measurements, regardless of whether agents that block the RAS are used. Several clinical studies, including the recent ALLHAT trial, are consistent with a critical, if not major, role for strict BP control in slowing renal disease.

To better understand what component of renal injury is caused by the hypertensive effects of angiotensin II, we previously examined the histologic changes occurring in the kidneys of the 1-clip 2-kidney model of hypertension. In this model in which circulating angiotensin II levels are known to be elevated, we found that renal injury was observed almost exclusively in the hypertensive kidney (lacking the clip), whereas the clipped kidney showed minimal changes. These studies were consistent with the hypothesis that the renal damage induced by exogenous angiotensin II was primarily caused by its ability to induce systemic hypertension. Although the latter study supported a pressor mechanism as the primary means by which angiotensin II causes renal damage, the degree of BP distal to the clip was not determined.

The elegant study in this issue of Hypertension by Mori and Cowley has addressed whether the main cause of the renal injury induced by exogenous angiotensin II is an elevation in BP. The authors infused angiotensin II into rats and then used a servo-control technique to maintain BP continuously in the normal range so that they could be compared with sham and angiotensin II-infused controls. Rats administered angiotensin II exhibited juxtamedullary glomerular injury, tubular necrosis, and interstitial fibrosis in the outer medullary region of the kidney. Animals whose pressure was controlled had a lesser (10% to 15%) degree of injury because of the nonpressor actions of angiotensin II. In animals infused with angiotensin II, there was also mild glomerular injury in the outer cortex, which was not prevented by controlling BP by the servo-control method.

The results presented in this study emphasize the importance of lowering systemic BP as a means to protect the kidney. This is likely to be most important in conditions in which renal autoregulation is impaired. Normally, an increase
in systemic BP is countered by vasoconstriction of the afferent arteriole and interlobular artery, which prevents transmission of the increased systemic pressures to the glomerular and peritubular capillary beds. However, renal autoregulation is relatively ineffective in the outer medulla, which accounts for why this area is particularly susceptible to pressure-induced injury and suggests why this was the major site of injury in angiotensin II-infused rats in the study by Mori and Cowley. Aff erent arteriolar vasoconstriction in response to increases in systemic BP also appears to be impaired in subjects with chronic renal disease, in blacks with hypertension and renal insufficiency, and in diabetic subjects. The ability of ACE inhibitors and ARBs to lower systolic pressure was reduced to normal levels, might have been statistically, than the sham-operated control. Second, the design of the study, in which blocking the RAS has been shown to be protective. A few caveats are worth considering in relation to the study. First, it is possible that some of the nonpressor-mediated renal injuries were also induced by pressure-dependent mechanisms, because the servo-control was not started until 18 hours after infusing the angiotensin II, and the renal perfusion pressure was higher (7 mm Hg), although not statistically, than the sham-operated control. Second, the design of the study, in which the renal artery perfusion pressure was reduced to normal levels, might have been expected to augment any renal ischemia induced by angiotensin II. Finally, it is important to recognize that the assessment of renal injury in the study by Mori and Cowley involved the measurement of gross lesions only. It is known that angiotensin II can also induce subtle changes in the renal vasculature, glomeruli, and tubulointerstitial areas, and measurements of arteriolar hypertrophy, intrarenal inflammation, and endothelial turnover were not performed. It has also been reported that angiotensin II-dependent preglomerular thickening occurs independently of BP in a model of mild hyperuricemia. In turn, recent studies have suggested that the development of these preglomerular vascular lesions may lead to the development of salt-sensitive hypertension. Therefore, while renal progression may largely depend on the pressor-dependent mechanisms of angiotensin II, other nonpressor mechanisms by which angiotensin II affects the kidney could have important long-term consequences on BP and cardiovascular disease.

References

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