Effects of Antihypertensive Agents on Experimental Kidney Injury

Five separate studies. In these studies, rats with experimental renal disease were given similar antihypertensive agents. Studies were conducted in several different animal models of hypertension and renal disease, including the following: uninephrectomized spontaneously hypertensive rats (Unx SHR); rats with a remnant kidney given either relatively high-dose (remnant-HD) or low-dose (remnant-LD) drug therapy; rats with desoxycorticosterone-salt–induced hypertension (Doc-salt); and rats with nephrotoxic serum nephritis (NSN), an immune-mediated form of glomerular disease (NSN) [1–5]. In all these studies, untreated rats were compared with those receiving a combination of three antihypertensive agents (triple therapy), including hydralazine, reserpine, and a thiazide diuretic. In rats with remnant kidneys, separate studies examined the effects of low or high doses of these agents. A close correlation was revealed between the degree of reduction in glomerular capillary pressure produced by triple therapy and subsequent development of glomerular sclerosis. The data are consistent with the hypothesis that antihypertensive agents lessen glomerular injury by reducing glomerular capillary pressure. In the studies in rats with remnant kidneys, only a relatively high dose of the drugs was effective in reducing pressure and injury, suggesting that aggressive antihypertensive therapy is more likely to slow progression of renal disease. This finding is particularly true for antihypertensive combinations that include direct vasodilators, such as the triple-therapy regimen. By dilating the afferent arteriolo, regimens such as these tend to further impair autoregulation of glomerular pressure in the setting of chronic renal disease. (From Weir and Dworkin [6]; with permission.)

Correlation between systolic blood pressure and glomerular injury in rats with remnant kidneys. In these rats, blood pressure was continuously monitored by implanting a blood pressure sensor in the abdominal aorta connected telemetrically to a receiver. The time-averaged blood pressure in rats with remnant kidneys that were untreated or given the angiotensin-converting enzyme inhibitor enalapril or triple therapy (combination of hydralazine, reserpine, and a thiazide diuretic) was correlated with morphologic evidence of glomerular injury. A close correlation was found between the average blood pressure and extent of glomerular injury that developed in these rats. It is proposed that, because of impaired autoregulation in chronic renal disease, elevations in systemic blood pressure are associated with glomerular hypertension in these rats. The higher the systemic pressure, the higher the glomerular pressure is predicted to be and the more glomerular injury is observed. These data provide additional evidence that systemic hypertension produces glomerular injury by causing elevation in glomerular pressure, and that antihypertensive therapy reduces injury by reducing glomerular capillary pressure. (From Griffen and coworkers [7]; with permission.)
The role of hypertension in progression of chronic renal disease.

After a partial loss of kidney function, compensatory adaptations within surviving nephrons include renal vasodilation. Vasodilation leads to an increase in glomerular capillary pressure and compensatory renal growth associated with an increase in the radius of the glomerular capillaries. According to the LaPlace equation, wall tension in a blood vessel is equal to the product of the transmural pressure and the radius of the vessel. In a surviving glomerular capillary of a damaged kidney, therefore, wall tension increases not only because of the increase in glomerular pressure but also because of an increase in capillary radius. Elevations in wall tension contribute to progressive renal disease by damaging the endothelial and epithelial cells lining the glomerular capillaries. By reducing wall tension, maneuvers that decrease either glomerular pressure or glomerular capillary radius are predicted to be beneficial. \( P_{GC} \)—glomerular capillary hydraulic pressure; \( R_{GC} \)—glomerular capillary radius; \( T \)—tension. (From Dworkin and Benstein [8]; with permission.)

Scanning electron micrographs of vascular casts of glomeruli from normal or uninephrectomized rats. A, A glomerulus from a rat having had a sham operation, showing a uniform capillary pattern. (Panels B–D display casts from uninephrectomized rats.) B, A uniform pattern with most capillaries being approximately the same size. C and D, Nonuniform patterns in which individual capillary loops (indicated by asterisks) are markedly dilated. In dilated capillary loops, wall tension is elevated and capillary wall damage is most likely to occur. The segmental nature of the capillary dilation may explain why glomerular sclerosis that eventually develops in remnant kidneys is also focal in early stages of the disease process. (Panels A–D \( \times 320 \).) (From Nagata and coworkers [9]; with permission.)
Role of the Renin Angiotensin System

FIGURE 6-9
The central role of angiotensin II (AII) in promoting progressive kidney failure. Based on studies in which the renin-angiotensin system has been blocked and renal injury ameliorated, it has been suggested that activation of this system is a crucial factor promoting progressive kidney failure. Increased activity of the renin-angiotensin system also may help explain the association between hypertension and progression of renal disease. AII may promote renal injury by several mechanisms. Activation of the renin-angiotensin system is one mechanism leading to an increase in systemic blood pressure, the result of peripheral vasoconstriction. Glomerular hypertension results not only from the increase in systemic blood pressure but also because of the ability of AII to constrict efferent arterioles, contributing to an increase in glomerular pressure. Glomerular hypertension damages the glomerular capillary wall and promotes injury by multiple mechanisms (see Fig. 6-1). An increase in glomerular pressure tends to increase protein filtration directly. In addition, evidence suggests that AII alters the permeability of the glomerular capillary wall to macromolecules, directly increasing protein filtration. By activating mesangial and epithelial cells, proteinuria itself is a factor promoting progressive kidney failure. Evidence also exists that AII directly stimulates production of various growth factors and cytokines by kidney cells, including fibrogenic cytokines such as transforming growth factor-beta and platelet-derived growth factor. Release of these factors has been linked to the development of glomerular sclerosis and interstitial fibrosis. AII also stimulates proliferation and growth of kidney cells that contribute to progression of renal disease.

FIGURE 6-10
Angiotensin-converting enzyme (ACE) inhibitors and low-dose triple therapy. The effects of ACE inhibitors are compared with those of low-dose triple therapy on systemic and glomerular pressure, proteinuria, and morphologic evidence of glomerular injury in rats with remnant kidneys. Both ACE inhibitors and triple therapy caused similar reductions in mean arterial pressure in rats with remnant kidneys; however, glomerular pressure declined only in the group treated with ACE inhibitors, by approximately 10 mm Hg. ACE inhibitor—induced reductions in systemic and glomerular pressure were associated with a reduction in proteinuria and morphologic evidence of glomerular injury. The data suggest that ACE inhibitors are superior to low-dose triple therapy in preventing glomerular injury in chronic renal disease. The data support the importance of increased glomerular pressure as a determinant of glomerular injury. ACE inhibitors may be more effective than are other agents, specifically because of their ability to reduce glomerular pressure. It should be noted, however, that significant reductions in glomerular pressure and injury may be achieved even with the triple-therapy regimen when significantly higher doses than those used in the current study are administered (see Figs. 6-5 and 6-6). A asterisk indicates P < 0.05 versus remnant. (Data from Anderson and coworkers [10].)