6.7 The Role of Hypertension in Progression of Chronic Renal Disease

FIGURE 6-11
Effect of renal vein constriction on glomerular protein filtration. The role of angiotensin II (AII) in modulating macromolecular clearance across the glomerular capillary wall has been examined by Yoshioka and coworkers [11]. These authors used a model of renal vein constriction to increase glomerular pressure and markedly increase protein filtration. They calculated the volume flux through the small selective pores (effective pore radius, 40–50 Å) within the glomerular capillary wall and through the large nonselective pores. A, Volume fluxes under control conditions (hatched bars) and during renal vein constriction (open bars). Renal vein constriction causes an increase in filtration through large nonselective pores, which accounts for increased protein filtration. B, Effects of renal vein constriction were again examined, alone (open bars) and during administration of the AII receptor antagonist saralasin (hatched bars). Saralasin reduced volume flux through the large pores, indicating that increased endogenous AII action was largely responsible for proteinuria during renal vein constriction. (From Yoshioka and coworkers [11]; with permission.)

FIGURE 6-12 (see Color Plate)
Local activation of the renin-angiotensin system and production of fibrogenic cytokines in experimental chronic renal disease. In situ reverse transcriptase was performed in rats with remnant kidneys to examine the level of gene expression for angiotensinogen and transforming growth factor-beta (TGF-beta). Rats still had not developed widespread morphologic evidence of glomerular injury 24 days after subtotal nephrectomy. A. At this point in time (arrows), staining for angiotensinogen messenger RNA (mRNA) was observed along the wall of a dilated capillary loop (CL) and in an adjacent cluster of mesangial cells. B. TGF-beta mRNA was present in an identical pattern in a contiguous section (arrows). C and D. Staining for angiotensinogen (panel C) and TGF-beta (panel D) is examined in kidneys from rats treated with the angiotensin receptor antagonist losartan from the time of nephrectomy. Administration of losartan markedly reduced expression of both factors in remnant kidneys. The findings are consistent with the hypothesis that endothelial injury is associated with increased angiotensinogen production and local activation of the renin-angiotensin system, leading to increased expression of TGF-beta and progressive glomerular fibrosis. (From Lee and coworkers [12]; with permission.)
Angiotensin II (AII) may be a proinflammatory molecule. The effect of AII on production of the chemokine RANTES was examined in cultured glomerular endothelial cells. **A**, Effects of AII on secretion of RANTES by cultured glomerular endothelial cells. AII markedly stimulated RANTES secretion. Of note is that AII-induced RANTES secretion was prevented by incubation with the AT2 receptor antagonists SCP-42112A (CGP) or PD 1231777 (PD) but not by the AT1 receptor antagonist losartan (los). These findings suggest AT2 receptors mediate the increase in secretion of RANTES. **B**, Results of a chemotactic assay for human monocytes. Migration of monocytes was assessed using a modified Boyden chamber. Migration of monocytes was stimulated by conditioned medium from glomerular endothelial cells that were exposed to AII. This effect was blocked by incubation of the medium with an anti-RANTES antibody but not by control serum. The anti-RANTES antibody alone was also without effect, as was AII in the absence of conditioned media. The findings are consistent with the hypothesis that AII promotes glomerular inflammation by binding to AT2 receptors, promoting RANTES secretion and infiltration of inflammatory monocytes and macrophages. fg—femtograms. (From Wolf and coworkers [13]; with permission.)

**FIGURE 6-14**
Renin-angiotensin systems. For many reasons the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) type 1 AT1 receptor antagonists on the progression of chronic renal disease may not be identical. In the classic pathway, renin cleaves angiotensinogen to form AI, which is further cleaved by ACE to form biologically active AII. ACE inhibitors inhibit the renin-angiotensin system by reducing the activity of ACE and decreasing AII formation. ACE also catalyzes other important pathways, however, including the breakdown of vasodilator substances such as bradykinin, substance P, and enkephalin. Increased levels of these substances might account for some of the biologic effects of ACE inhibition. Levels of these substances would not increase after administration of an AT1 receptor antagonist. In contrast, inhibition of the renin-angiotensin system by ACE inhibitors may be incomplete because other proteases may catalyze to conversion of angiotensinogen to AII (on the right). CAGE—chymostatin-sensitive angiotensin II–generating enzyme; t-PA—tissue plasminogen activator. (Adapted from Dzau and coworkers [14].)
### FIGURE 6-15
Subclasses of angiotensin receptors. Another theoretical reason the actions of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor antagonists may differ. All of the AII receptor antagonists currently available for clinical use selectively block the AT1 receptor. This receptor appears to transduce most of the well-known effects of AII, including vasoconstriction, stimulation of cell growth, and secretion of aldosterone. Increasingly, however, potentially important actions of other angiotensin receptors are being discovered. For example, AT2 receptors may be involved in regulation of apoptosis and modulation of inflammation by way of secretion of RANTES (see Fig. 6-13) [13,15]. AT4 receptors bind other angiotensins preferentially and may promote endothelially mediated vasodilation [16]. Activity of all pathways is reduced after administration of ACE inhibitors, whereas only AT1 receptor–mediated events are blocked by drugs currently available. Whether these differences will have important consequences for progression of renal disease is currently unknown.

### FIGURE 6-16
Shown are results of studies comparing the effects of angiotensin II (AII) receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors on experimental renal injury. AII receptor antagonists were as effective as were ACE inhibitors in the remnant kidney model; streptozocin-induced diabetic rats; the puromycin aminonucleoside model of progressive glomerular sclerosis, preventing interstitial fibrosis associated with obstructive uropathy; and an inherited model of glomerular sclerosis, the Munich-Wistar Furth/Ztm rat [17–21]. In contrast, AII receptor antagonists were somewhat less effective than were ACE inhibitors in several other animal models of chronic renal disease, including uninephrectomized spontaneously hypertensive rats, obese Zucker rats, and the passive Heymann nephritis model of membranous glomerulonephritis [22–24]. Clinical trials are necessary to determine whether these classes of drugs will be equally effective in preventing progressive renal disease in humans.

### FIGURE 6-17
Three calcium channel blockers and their effects in experimental animals. The results of several studies examining the effects of three different dihydropyridine calcium channel blockers on hemodynamics and injury in the uninephrectomized spontaneously hypertensive rat model of progressive glomerular sclerosis are summarized. The three drugs produced graded declines in mean arterial pressure (MAP), with nifedipine causing the greatest and amlodipine the least reduction in systemic pressure. Micropuncture determinations of glomerular capillary hydraulic pressure (P_GC) revealed that only nifedipine and felodipine caused glomerular pressure to decline significantly. These drugs reduced both the protein excretion rate (PROT) and morphologic evidence of glomerular injury (SCLER). The data are consistent with the hypothesis that antihypertensive agents ameliorate renal damage by reducing glomerular pressure and that, for calcium channel blockers, significant reductions in P_GC occur only when drug administration causes a marked decline in systemic pressure. (From Dworkin [25,26]; with permission.)