Diabetic nephropathy, the most common cause of end-stage renal disease (ESRD) in the Western world, is characterized by suppression of the systemic but activation of the intrarenal tissue renin-angiotensin system (RAS). Blockade of the RAS with angiotensin converting enzyme (ACE) inhibitors or angiotensin type-1 receptor blockers (ARBs) retards but does not eliminate the progression of diabetic nephropathy to ESRD in prospective, randomized, controlled clinical trials. Studies have demonstrated that a major component of tissue protection from RAS blockers derives from reduction in blood pressure. However, a possibility for failure to prevent completely the decline in renal function attributable to tissue damage is that the activity of the intrarenal RAS may be inadequately suppressed by these drugs.

Renin, an aspartyl protease cleaving angiotensinogen (Agt) at the origin of the angiotensin peptide cascade, has been a logical target for RAS inhibition. Since 1982, when the first peptide analogues of Agt were designed to block its catalytic cleavage by renin, multiple attempts have been made to inhibit renin, first by dipeptide transition-state analogue inhibitors of the renin active site and most recently by nonpeptide compounds, of which aliskiren is the most successful example. Aliskiren, approved for the treatment of hypertension in 2007, decreases plasma renin activity, angiotensin I and angiotensin II concentrations, and blood pressure in hypertensive patients. The blood pressure reduction of aliskiren is additive to that of ACE inhibitors, ARBs, and diuretics by preventing the increase in plasma renin activity accompanying the use of these agents. In spite of its inhibition of the enzymatic activity of renin, however, aliskiren increases the biosynthesis and secretion of renin and prorenin, which are available to activate the (pro)renin receptor, originally discovered by Nguyen et al in 1996. Because (pro)renin receptor activation stimulates the mitogen activated protein kinase pathway, particularly extracellular signal-related kinases, and increases transforming growth factor-β, plasminogen activator inhibitor-1, fibronectin, and type I collagen in renal mesangial cells, concern has been raised that treatment with aliskiren, as well as with ACE inhibitors and ARBs, might induce renal tissue damage by activating the (pro)renin receptor.

Feldman et al11 in this issue of Hypertension report the renal distribution, protective properties, and mechanisms of action of aliskiren in streptozotocin-induced diabetic, hypertensive TG(mRen-2)27 rats, providing a wealth of important information on several of the recently discovered components of the RAS. Similar to other classes of RAS blockers, aliskiren induced a dose-dependent decrease in blood pressure and prevented progressive microalbuminuria in diabetic rats. It will be important to compare the renal protective actions of ACE inhibitors, ARBs, and aliskiren and to determine any additive/synergistic attributes of combinations in future studies. Whether renin inhibition results in better target organ protection than that afforded by ACE inhibitors or ARBs remains to be proven.

Aliskiren reduced renal cortical transforming growth factor-β and collagen-I gene expression, which can be stimulated by activation of mesangial cell (pro)renin receptors.9,10 For this reason, the relationships of aliskiren with prorenin and the (pro)renin receptor were explored in this study. Interestingly, aliskiren exhibited specific binding to the active site of (pro)renin. Prorenin exists in 2 structurally distinct forms: a catalytically “inactive state” in which the prosegment covers the active site, preventing Agt access, and an “active state”, wherein the prosegment is displaced allowing Agt access to the active site for cleavage (Figure). Highaffinity aliskiren binding to the active site of prorenin would be expected to prevent access of Agt substrate to the enzyme and, consequently, decrease downstream angiotensin peptide formation (Figure). Although aliskiren binding to prorenin occurred, aliskiren did not alter prorenin binding to the (pro)renin receptor, in accord with earlier observations.12 Strikingly, however, aliskiren significantly reduced (pro)renin receptor gene expression in renal glomeruli and tubules of hypertensive diabetic animals in vivo. Because aliskiren did not alter (pro)renin receptor expression in cultured mesangial cells, the in vivo results suggest that aliskiren may have suppressed (pro)renin receptor gene expression by indirect mechanisms yet to be determined. Therefore, aliskiren likely inhibits the activity of the RAS by at least 2 mechanisms: (1) binding to the active site of (pro)renin and renin and (2) reducing the expression of the (pro)renin receptor, activation of which normally increases the catalytic conversion of Agt by approximately 5-fold.12

Drug localization in the kidney is potentially important for blockers of the RAS in diabetes.1 The study by Feldman and coworkers11 demonstrated a high degree of distribution of aliskiren in renal glomeruli and small cortical blood vessels, but the specific vascular/glomerular cell type(s) could not be
determined. In future studies, it will be important to demonstrate the specific renal cellular localization of aliskiren. If aliskiren were distributed intracellularly in juxtaglomerular cells, the renin inhibitor would have the potential to inhibit prorenin and renin within their cells of origin. This possibility might convey a therapeutic advantage in disease states associated with increased RAS activity.

In summary, this informative study demonstrates the potential for renin inhibition with aliskiren to prevent renal damage in hypertension and diabetes by lowering blood pressure and possibly by selectively inhibiting the activity of the intrarenal RAS. These observations suggest that aliskiren binding to the active site of prorenin prevents prorenin activation and additionally that aliskiren reduces (pro)renin receptor gene expression. The precise role of aliskiren in preventing target organ damage awaits future studies in experimental animals and humans.

Disclosures
None.

References