Renin Inhibition
New Potential for an Old Therapeutic Target

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E
xperimental and clinical studies have highlighted the importance of the local renin-angiotensin system (RAS) as a pathogenetic factor in various tissues, including the kidney, heart, and eye. These studies have indicated that blockade of the RAS is an important therapeutic strategy in reducing cardiovascular and renal disease. However, the therapeutic response achieved with current blockers of the RAS—angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)—although efficacious, is limited. This may be partly because of the reactive rise in renin that these agents induce with the resultant increase in angiotensin peptides. Other, more effective strategies to block the RAS have, therefore, been sought.

Angiotensin II, the major effector molecule of this system, is synthesized in a multistep process in which angiotensinogen is cleaved by the aspartic peptidase, renin, produced mainly in the juxtaglomerular cells of the kidney, to give to rise to angiotensin I. This biologically inactive decapeptide is then converted to the active octapeptide angiotensin II by ACE or by a range of other proteases.

Renin was first isolated from extracts of renal cortex, where its pressor effect was noted following intravenous injection. More than a century later the physiological and pathological significance of renin is still being unraveled. For instance, a renin receptor in the kidney and vasculature has recently been identified. Binding of renin to this receptor not only increases its catalytic efficiency in angiotensin I formation, but also converts the otherwise inert prorenin into an active moiety. Moreover, the interaction between renin or prorenin with its receptor leads to activation of the potentially pathogenetic mitogen-activated protein kinase pathway in the absence of angiotensin peptide formation.

Together these findings raise the possibility that additional advantages of renin inhibition beyond those of conventional RAS blockade are also possible. Indeed, renin not only catalyzes the rate-limiting step in angiotensin II formation but also has remarkable substrate specificity for angiotensinogen, making it an attractive target for drug development. The first low weight inhibitor to block the action of renin was reported back in 1980, however this substrate analogue was not very potent and although hypotensive at higher doses, it exhibited a lack of specificity. Despite the success of early renin inhibitors in validating the potential therapeutic targets, further drug development was hampered by issues mainly relating to potency, bioavailability, and duration. More recently, newer technologies have enabled the active site of renin to be modeled at higher resolution and a series of novel renin inhibitors have been synthesized. Aliskiren [2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamid hemifumarate, SPP100, Speedel/Novartis] is the most advanced of the new class of orally active, nonpeptide, low-molecular-weight renin inhibitors. In healthy volunteers, aliskiren (40 to 640 mg/d) is orally well tolerated and induces a dose-dependent decrease in plasma renin activity and active angiotensin peptide concentrations as well as providing a dose-dependent reduction in ambulatory blood pressure of patients with essential hypertension (aliskiren, 37.5 to 300 mg/d). More recently, 652 hypertensive subjects were randomized to receive either the ARB irbesartan or aliskiren. At a dose of 150 mg, aliskiren was as effective as irbesartan (150 mg) in lowering blood pressure with similar safety and tolerability over the short term. In the study reported in this issue of Hypertension, Pilz et al demonstrated attenuation of renal and cardiac end organ damage by aliskiren at an equi-antihypertensive dose to the ARB, valsartan, in double renin transgenic rats. The potential to actively inhibit the rate-limiting step of the RAS cascade is an important advance in the field, and these findings suggest that renin inhibitors will at least provide an alternative to ACE inhibitors and ARBs with respect to blood pressure control and end organ damage. However, what remains to be seen is whether they will also provide superior organ protection when used as single agents or more likely as “add-on” therapy to conventional RAS blockade.

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References

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