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Spotlight on Renin: Therapeutic opportunities for renin inhibitors

Norman K Hollenberg

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Spotlight on Renin

Therapeutic opportunities for renin inhibitors

Norman K Hollenberg (*Departments of Medicine and Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA*)

The key role played by renin in the regulation of blood volume, arterial pressure, and cardiac and vascular function has long been recognised. Skeggs *et al.* first described renin as the initial and rate-limiting step in the renin-angiotensin-aldosterone system (RAAS) cascade in 1957. Therapeutic manipulation of the RAAS with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has become important for treating hypertension, renal injury and heart failure.²⁻¹⁰

Although research has shown that blocking the initial step in the cascade has the potential for additional improvements in therapy, the development of renin inhibitors has been beset with problems. The cost of synthesis, low and variable bioavailability, the lack of appropriate animal models and the success of the ARB class have all impacted development. Efforts to conquer these problems, however, are proving successful and a new era in the development of renin inhibitors has emerged. I provide here a synopsis of my recently published paper (co-authored with Naomi Fisher) that looks at these issues in detail.¹¹ I will focus on three main areas:

- The development of novel agents emerging out of an approach based on X-ray crystallography
- Recent advances in our understanding of the pathophysiology of the RAAS
- The rationale for and efficacy of combination therapy.

Renin inhibitors: rationale and development of novel agents

There are a number of places at which the RAAS can be interrupted (Figure 1). In 1957, Skeggs *et al.* argued that blocking the rate-limiting step – the catalytic effect of renin on its substrate angiotensinogen (AGT) – was the logical first

choice.¹ Renin inhibition is made an even more attractive choice by the fact that renin has a remarkable specificity for its substrate,¹² which reduces the likelihood of unwanted interactions, and thus side-effects. The first therapeutic breakthrough, however, occurred lower down the RAAS cascade with the development of ACE inhibitors; these were discovered as an unanticipated consequence of research into the ability of a pit viper's venom to lower blood pressure.¹³ However, both ACE inhibitors and ARBs also lead to a reactive renin rise and thus to an increase in angiotensin peptides, whereas renin inhibition suppresses formation of all AGT-derived products. Whether a quiescent RAAS provides an advantage, only time and future studies will tell, but it provides an attractive potential.

Proof of principle that blocking the renin step would produce a biologically important response first came from an immunologic approach, which led to the early development of renin inhibitors following two different approaches.¹⁴ One approach was based on the hypothesis that the prosegment of prorenin is capable of inhibiting enzyme activity by preventing access to the substrate; however, this pathway developed only weak inhibitors. The other approach was to synthesise peptidic analogues of the N-terminal amino acid sequence of the substrate AGT. Over time, the sequences were manipulated to produce inhibitors with increased potency. The emphasis then shifted from the development of inhibitors that would retain potency to those that would also be bioavailable. However, the rapid advance of the ARBs was thought to make ultimate commercial success of these renin inhibitors unlikely.

The opportunities afforded by developments in X-ray crystallography and the consequent ability to reconstruct the active site of renin has led to the successful development of some novel agents (Figure 2). Aliskiren (Novartis and Speedel) has been tested in humans^{15,16} and is in Phase III evaluation. The agents developed by Actelion-Merck, Concurrent and Pfizer are earlier in development and little has been reported. No information on the bioavailability of the last

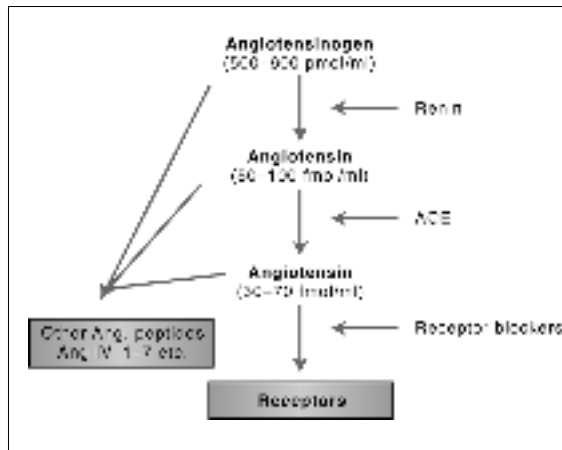


Figure 1 Key steps by which pharmacologic antagonists or blockers interfere with the renin-angiotensin system together with representative plasma concentrations from rats. Reproduced with permission from reference 10.

Company	Structure	Activity (nM)	Stage
Merck/Schering-Plough		0.8	Phase II
Astellera/Novartis		<100	Phase I (04-04)
Pfizer		0.2	Phase I
Novartis		0.4	Phase I

Figure 2 Structure, activity, and stage of development of renin inhibitors in current evaluation. All were developed on the basis of X-ray crystallography and active site modelling. Reproduced with permission from reference 11.

three groups of agents in humans has yet been reported.

Pathophysiology: advances in our understanding

One recent line of investigation has focused on the potential pathophysiological effects of prorenin, which had long been assumed to be merely the inactive precursor of renin. Multiple studies have shown that the onset of microvascular disease in the patient with diabetes coincides with elevated concentrations of prorenin in plasma.¹⁷⁻²⁵ The onset of microvascular disease and the increase in prorenin are not necessarily associated with hypertension.²⁰ The relationship of prorenin to total renin is different in the patient with diabetes and in other patients in whom the renin system has been activated. In diabetic patients the increase in prorenin substantially exceeds the increase in prorenin in the other conditions.²⁶ Although the increase in plasma prorenin has been attributed to a range of factors, it does not account directly for the association with both retinopathy and nephropathy, and it is not

directly compatible with the documented suppression of renin release in the same patients. The mechanism responsible for the increase of plasma prorenin, as well as the mechanism by which prorenin contributes to the pathogenesis of microvascular injury, has yet to be established.

The potential importance of these results is highlighted in the recent work of Nguyen *et al.*, who reported the identification of a renin receptor in the human kidney.²⁷ This receptor, localised primarily in the mesangium of glomeruli but also in the subendothelium of arteries of the heart and kidney, also engages and is activated by prorenin. The function of the receptor is fascinating; firstly, when renin is bound to the renin receptor its catalytic activity increases four- to five-fold; secondly, prorenin also binds to the same receptor, and when it is bound it is as active as renin; thirdly, both renin and prorenin activate intracellular pathways that are known to be pathological via a sequence that does not require angiotensin generation. These findings are exciting because if prorenin contributes to pathophysiology, and if the renin inhibitors interrupt this sequence, then renin inhibitors could play an important part in the treatment of the patient with diabetic nephropathy or retinopathy – the leading causes of both end-stage renal disease and blindness in the Western world.

Combination therapy: efficacy and rationale

A number of reports have described the combination of an ACE inhibitor with an ARB to be more effective in reducing proteinuria than either agent alone. Ultimately, these studies must consider the issue of dose. As ARBs are far better tolerated than ACE inhibitors, an optimal study for showing the benefits of this combination would involve assessing the influence of the ARB at the top of its dose-response relationship for proteinuria reduction and then ascertaining whether adding an ACE inhibitor improves the therapeutic response.

Although it is clear that renin-system blockade at any step leads to a therapeutic response, we need to work out how best to achieve that goal. In combination therapy, it seems intuitively obvious that one of the steps blocked should be the rate-limiting step. The renin-angiotensin interaction has been defined as the rate-limiting step as it provides the largest step-down in concentration in the renin cascade (Figure 1). Available data suggest that this is true in the plasma compartment, but whether this extends to tissue compartments remains open.

One crucial question for combination therapy is how important, quantitatively, is the reactive renin response to blockade with an ACE inhibitor or ARB? A study in which an ACE inhibitor or an ARB is combined with a renin inhibitor in the

patient with proteinuria will help to answer the question and establish whether blockade at the most sensitive step is likely to provide the best possible therapy.

Efficacy: blood pressure reduction and renal response

Studies reported to date have shown that the more renin-dependent the blood pressure level, the larger the fall induced by renin inhibition.^{16,28,29} The data on renal response strongly suggest that in the case of the kidney, renin inhibition is far more effective than ACE inhibition in blocking angiotensin II formation.^{30,31} These observations clearly could have clinical significance; however, longer-term studies are required to demonstrate the ultimate implications of these agents in therapeutic use.

What is the future for renin inhibition?

The search for a viable orally bioavailable renin inhibitor may finally be nearing its end. Further, as diabetic nephropathy and diabetic retinopathy are the leading cause of end-stage renal disease and blindness in the US and much of the rest of the world, we believe that the potential of renin inhibition in human therapy has been underestimated. If the clues concerning microvascular disease at the level of the kidney and the eye and the possible influence of a renin inhibitor prove to be correct, then this pathway will lead to important advances in treatment.

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