Oral renin inhibitors

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Use of drugs that inhibit the renin-angiotensin system is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders. The idea of blocking the renin system at its origin by inhibition of renin has existed for more than 30 years. Renin inhibition suppresses the generation of the active peptide angiotensin II. The first generation of orally active renin inhibitors were never used clinically because of low bioavailability and weak blood-pressure-lowering activity. At present, aliskiren is the first non-peptide orally active renin inhibitor to progress to phase-III clinical trials. It might become the first renin inhibitor with indications for the treatment of hypertension and cardiovascular and renal disorders. Novel compounds with improved oral bioavailability, specificity, and efficacy are now in preclinical development. This Review summarises the development of oral renin inhibitors and their pharmacokinetic and pharmacodynamic properties, with a focus on aliskiren.

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Inhibition of the renin-angiotensin system is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders.[1] Renin controls the first rate-limiting step of the system (figure 1) and cleaves angiotensinogen to the inactive decapeptide angiotensin I. The active octapeptide angiotensin II is formed from angiotensin I by the angiotensin-converting enzyme. Angiotensin II acts via type-1 angiotensin II receptors (AT1) to increase arterial tone, adrenal aldosterone secretion, renal sodium reabsorption, sympathetic neurotransmission, and cellular growth.[2]

The renin system can be inhibited at various points (figure 1). Bühler and colleagues[3] first showed that β blockers reduce the release of renin from the juxtaglomerular apparatus and lower blood pressure. Inhibitors of angiotensin-converting-enzyme (ACE) reduce the conversion of angiotensin I to angiotensin II.[4] ACE inhibitors also inhibit the inactivation of bradykinin and substance P. These peptides mediate some of the side-effects of ACE inhibitors, such as cough[5] and angio-oedema.[6] Angiotensin-receptor blockers specifically interfere with the interaction of angiotensin II with the AT1 receptor, but do not oppose stimulation of the angiotensin II type-2 receptor.[7] Inhibition of renin activity blocks the renin system at its very origin.[8,9]

ACE inhibitors, angiotensin-receptor blockers, and renin inhibitors interrupt the normal feedback suppression of renin secretion from the kidneys (figure 1). The reactive rise in circulating active renin leads to greater generation of angiotensin I (table 1), which in turn increases the formation of angiotensin II via pathways dependent or independent of the ACE (figure 1).[10] Such escape processes do not occur with β blockers (table 1). Renin inhibitors do not block renin-like enzymes, such as cathepsin D or tonins, which are present in the vascular wall and which release angiotensin I from angiotensinogen (figure 1). Renin has a unique specificity for its only known physiological substrate, angiotensinogen. By 1957, Skeggs[11] had already outlined the potential benefits of specific inhibition of the renin system by diminishing renin activity without interference with other metabolic pathways.

Development of oral renin inhibitors

The sequence of renin differs between species, so that preclinical studies of renin inhibitors must be done in primates, such as marmosets, or in rat models transgenic for human renin and angiotensinogen.[12] The earliest attempts to block the renin system relied on antibodies raised against renin.[13,14] Immunological inhibition of renin reduced blood pressure in volume-depleted normotensive marmosets[15] and provided the proof of concept of renin inhibition.

The first synthetic renin inhibitor was pepstatin.[16] First-generation renin inhibitors were peptide analogues of the prosegment of renin[17] or substrate analogues of the amino-terminal sequence of angiotensinogen containing the renin cleavage site.[18–20] They had to be given parenterally, but were effective at inhibiting renin activity and reducing blood pressure in animals[19] and in people.[21] Further chemical modification led to the development of compounds, such as CGP29287 (Ciba-Geigy, Basel, Switzerland), that had greater stability and longer duration of action. CGP29287 was the first renin inhibitor to show activity when given orally; it was orally active in marmosets at high doses.[22] In the second half of the 1980s, several drug companies developed renin inhibitors that had a molecular weight of a tetrapeptide. These molecules (figure 2) included enalkiren (A 64662; Abbott, Abbott Park, IL, USA), CGP38560A (Ciba-Geigy,

Search strategy

We searched the PubMed and MEDLINE databases (1980–2005), using "renin inhibitor" as an initial search term. We then focused our search, using the terms: "aliskiren", "A 62095", "A 62918", "A 65317", "A 74273", "CGP 29287", "CGP 38560", "CGP 44099", "CGP 60536", "ciprokiren", "CP 71362", "CP 80794", "CP 81282", "CP 85339", "enalkiren", "KRI 1177", "KRI 1230", "KRI 1314", "SPP100", "remikiren", "renin inhibitory peptides", and "zankiren". We preferentially selected articles published in 2000 or later, but we also included older papers to track the historical perspective of the development of renin inhibitors, which spans more than 20 years. We excluded from table 3 any exploratory studies with an open design. We searched the reference lists of review articles by hand for additional information. We visited the websites of the pharmaceutical companies known to be active in the development of renin inhibitors. We also requested and obtained further information from Actelion, Hoffmann-Laroche, Novartis, Pfizer, and Speedel.

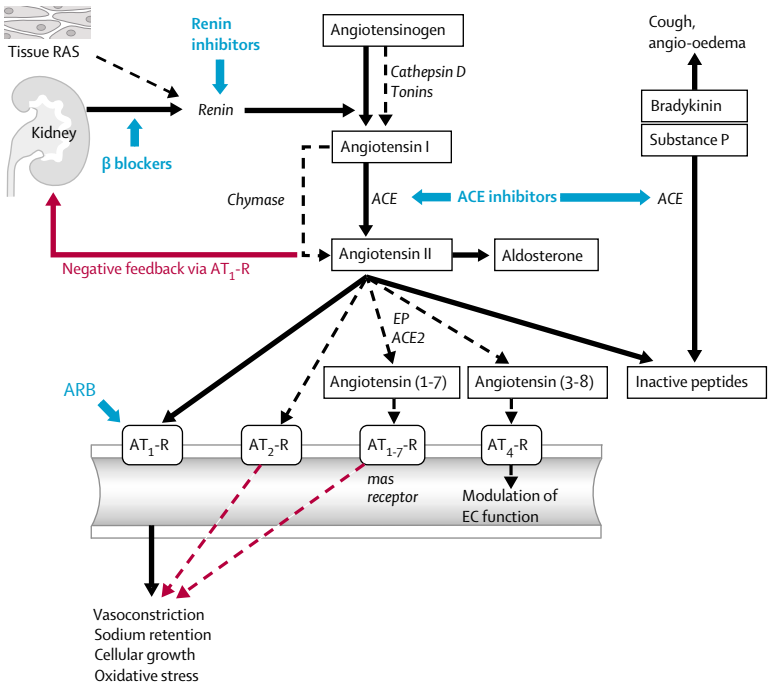

Figure 1: **The renin-angiotensin-aldosterone system**
Black arrows show stimulation and red arrows show inhibition. Dotted lines show alternative pathways mainly documented in experimental studies. β blockers, renin inhibitors, inhibitors of angiotensin-converting enzyme (ACE) and angiotensin II type-1 receptor blockers (ARB) reduce the activity of the renin-angiotensin system (RAS). AT-R=angiotensin receptor; EP=endopeptidases; EC=endothelial cells.

Basel, Switzerland, [not shown in figure 2]), remikiren (Ro 425892; Hoffmann-La Roche, Basel, Switzerland), and zankiren (A 72517; Abbott).[9,23,24] When given orally, they had a bioavailability of less than 2%, a short half-life, and weak blood-pressure-lowering activity[9] (table 2[25–29]).

By means of crystallography and computational molecular modelling starting from a corporate compound library, Hoffmann-La Roche subsequently developed and optimised substituted piperidine renin inhibitors, which were abandoned after tests in preclinical studies.[30] At about the same time, Ciba-Geigy (now Novartis, Basel, Switzerland) discovered the orally active compound aliskiren (CGP 60536B, figure 2).[31] However, the pathway for its synthesis, patented in 1995, had many steps and was not suitable for industrial manufacture. In 1999, aliskiren was out-licensed to Speedel AG (Basel, Switzerland), who succeeded in designing a cost-effective method of production.[23,32] After successful preclinical and clinical testing of aliskiren (SPP 100) by Speedel, Novartis exercised its call-back option for the further development of aliskiren in phase-III clinical trials.[33]

In 2001, Hoffmann-La Roche copied this strategy by out-licensing to Speedel a new subclass of renin inhibitors, which are known as the SPP 600 series and are now under preclinical investigation.[23] In April, 2003, Speedel joined forces with Locus Pharmaceuticals (Blue Bell, PA, USA), who used their proprietary computational technologies to identify novel leads. In June, 2005, Speedel announced the discovery of new compounds (SSP 800 series), which have entered pharmacological profiling in animal models, with the goal of selecting a preclinical candidate in 2006.

Studies of the first generation of oral renin inhibitors

Haemodynamic and endocrine effects

In normotensive primates[24,34–38] and human beings,[29,39–51] renin inhibitors given intravenously or orally lead to acute and dose-dependent decreases in plasma renin activity, plasma concentrations of angiotensin I and angiotensin II, (table 1) and blood pressure, without inducing reflex tachycardia.

Table 3 summarises the effects of oral remikiren[28,41,43–48] and zankiren[29,42] on blood pressure and plasma renin activity in randomised clinical trials, excluding two exploratory studies with an open design.[26,52] In general, the blood-pressure-lowering activity has been small. Because normal feedback inhibition is interrupted by angiotensin II (table 1), renin inhibition consistently elicits a rise in circulating active renin. This escape process, which also occurs during treatment with ACE inhibitors and angiotensin-receptor blockers, explains why these three drug classes behave as incomplete

	Enzymes		Substrates			End-products	
	PRA	PRC	Angiotensinogen	Angiotensin I	Bradykinin	Angiotensin II	Aldosterone
β blockers	↓	↓	NA	NA	NA	NA	NA
Renin inhibitors	↓	↑	NA	↓	NA	↓	↓
ACE inhibitors	↑	↑	↓	↑	↑	↓	↓
ARB	↑	↑	↓	↑	NA	↑	↓
ACE inhibitors plus ARB	↑↑	↑↑	↓↓	↑↑	↑	NA	↓
Renin inhibitors plus ARB	↓	↑↑	NA	NA	NA	NA	↓↓

PRA=enzymatic activity of plasma renin—ie, the rate of generation of angiotensin I. PRC=the plasma concentration of renin, not including prorenin; PRC is also referred to as circulating active renin. NA=data not available.

Table 1: **Effects of inhibitors of the renin system on enzymes, substrates, and end-products**