



Renin inhibitors – mechanisms of action

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Summary

Renin inhibitors are antihypertensive drugs which block the first step in the renin-angiotensin system. Their mechanism of action differs from that of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, but like these drugs, renin inhibitors interrupt the negative feedback effects of angiotensin II on renin secretion. This increases renin concentrations which may attenuate the inhibition of the renin-angiotensin system by these therapies. Renin inhibitors may interfere with measurements of renin in plasma.

Key words: aliskiren, antihypertensives, hypertension.

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Introduction

Drugs that inhibit the renin-angiotensin system, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, have proven value for the treatment of hypertension, heart failure and renal disease. They reduce the rates of death, myocardial infarction and stroke in a broad range of patients at high risk, but do not control the blood pressure in all cases. This led to research into inhibiting the renin-angiotensin system at its first step – the production of angiotensin I.

Physiology

Renin is an enzyme produced from the inactive protein, prorenin. The release of renin from the juxtaglomerular cells of the kidney is controlled by several mechanisms. These include the sympathetic nervous system, salt and fluid balance, blood pressure, and negative feedback by angiotensin II. Renin cleaves circulating angiotensinogen to form angiotensin I (Fig. 1). This inactive decapeptide is subsequently cleaved by ACE to produce the octapeptide angiotensin II. Although other bioactive angiotensin peptides are produced from angiotensin I and II, angiotensin II is the main bioactive angiotensin peptide.

Two different receptors mediate the actions of angiotensin II. These are the type 1 (AT₁) and the type 2 (AT₂) receptors (Fig. 1). Stimulation of the AT₁ receptor increases arterial tone and

aldosterone secretion. Angiotensin II therefore plays an essential role in blood pressure, and fluid and electrolyte homeostasis. However, this role is much diminished in people consuming a Western diet with an excessive salt content. In these people, even 'normal' concentrations of angiotensin II may play a role in hypertension and in cardiovascular and renal disease.

Angiotensin-(1-7), a heptapeptide, is a metabolite of angiotensins I and II. Both angiotensin-(1-7), acting through its own receptor, and angiotensin II, acting on the AT₂ receptor, may counterbalance some of the effects of angiotensin II stimulating the AT₁ receptor.

The kidney is not the only organ which produces prorenin, and a receptor which binds renin and prorenin has been discovered. The physiological roles of the (pro)renin receptor are unknown, but high concentrations of prorenin predict microvascular complications of diabetes.

Inhibitors of the renin-angiotensin system

The therapeutic benefits of inhibiting the renin-angiotensin system are attributed primarily to reduced stimulation of the AT₁ receptor. This can be achieved by either reducing angiotensin II concentrations or blocking the AT₁ receptor, although other mechanisms may contribute (Table 1).

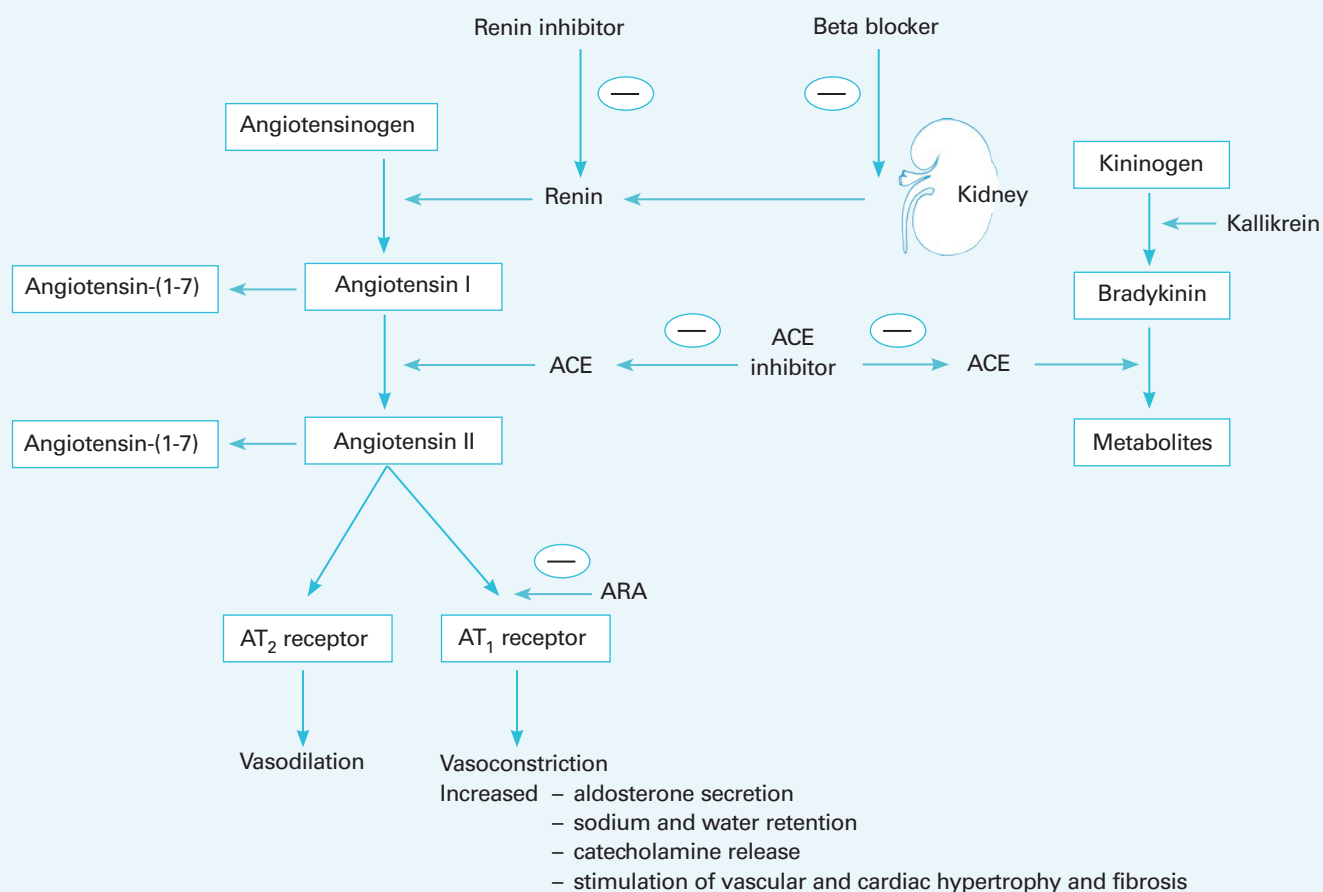
Beta blockers inhibit renin release from the kidney and were the original renin-angiotensin system inhibitors. Reduced renin release leads to reduced concentrations of angiotensin I and II, which may contribute to the benefits of beta blockade in heart failure.¹

In contrast to beta blockers, ACE inhibitors, angiotensin receptor antagonists and renin inhibitors cause an increase in renin release. This is because by reducing AT₁ receptor stimulation they interrupt the negative feedback-mediated regulation of renin release. The combination of an ACE inhibitor, angiotensin receptor antagonist or renin inhibitor with another drug from these groups, or with a diuretic, markedly amplifies the increase in renin concentrations. The increase in renin concentrations may be as much as 100-fold, which then offsets the inhibition of the renin-angiotensin system by these antihypertensive drugs. This may attenuate any reduction in blood pressure.

ACE inhibitors, angiotensin receptor antagonists and renin inhibitors have different effects on the concentrations of angiotensin peptides and bradykinin (a vasodilator) (Table 1).

Fig. 1

Mechanisms of action of renin inhibitors



The renin-angiotensin system can be inhibited by angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor antagonists (ARA), renin inhibitors and beta blockers. Also shown is the role of ACE in bradykinin metabolism. ACE also metabolises angiotensin-(1-7).

— inhibitory action

Table 1

Effects of renin-angiotensin system inhibitors on renin, angiotensin and bradykinin concentrations, and on AT₁ and AT₂ receptor stimulation

	Beta blocker	ACE inhibitor	ARA	Renin inhibitor
Renin concentrations	↓	↑	↑	↑
Renin activity	↓	↑	↑	↓
Angiotensin II concentrations	↓	↓	↑	↓
Angiotensin I concentrations	↓	↑	↑	↓
Angiotensin-(1-7) concentrations	↓	↑	→	↓
Bradykinin concentrations	?	↑	↑	?
AT ₁ receptor stimulation	↓	↓	↓	↓
AT ₂ receptor stimulation	↓	↓	↑	↓

ACE angiotensin converting enzyme ↑ increase → no change
ARA angiotensin II type 1 receptor antagonist ↓ decrease ? uncertain

Renin inhibitors reduce the concentrations of all angiotensin peptides, and their effect on bradykinin concentrations is under investigation.

ACE inhibitors block the conversion of angiotensin I to angiotensin II and the metabolism of angiotensin-(1-7). They reduce angiotensin II concentrations and increase the concentrations of angiotensin I and angiotensin-(1-7). In addition, because ACE contributes to bradykinin metabolism, ACE inhibitors increase bradykinin concentrations², which may contribute to the therapeutic benefits of ACE inhibition.

Angiotensin receptor antagonist therapies block AT₁, but not AT₂, receptors. This blockade leads to increased renin concentrations and consequently increased angiotensin II concentrations. This causes increased stimulation of the AT₂ receptor. Angiotensin receptor antagonists also increase bradykinin concentrations.³ Stimulation of the AT₂ receptor and increased bradykinin concentrations may contribute to the clinical effects of angiotensin receptor antagonist therapy.

Renin inhibition differs from ACE inhibitor therapy because it reduces angiotensin I and angiotensin-(1-7) concentrations. It differs from angiotensin receptor antagonist therapy because there is reduced stimulation of the AT₂ receptor.

Clinical pharmacology of renin inhibitors

Several renin inhibitors were abandoned because of problems in development. Aliskiren is the first renin inhibitor for which we have extensive information about clinical pharmacology. Other renin inhibitors in clinical development are likely to have different pharmacologies.

Aliskiren is a competitive renin inhibitor which binds to the active site of the enzyme. It is a rather hydrophilic molecule with high aqueous solubility.⁴ The distribution volume of intravenously administered aliskiren is 135 L in normal volunteers, indicating extensive tissue uptake of the drug.⁵ The absorbed fraction of orally administered aliskiren is approximately 5%. This low oral bioavailability is compensated for by a long plasma half-life of 34–41 hours, and steady-state plasma aliskiren concentrations are achieved after 5–8 days of daily dosing.⁶ Approximately 90% of the drug is excreted unchanged in the faeces.⁷ The long plasma half-life and very low urinary excretion (< 1%)^{6,7} suggest extensive binding of the drug to plasma proteins.⁵

Protein binding accounts for the discrepancy between the concentration of aliskiren required for 50% inhibition of pure renin and that for inhibition of renin in plasma. The concentration (IC₅₀) required was 0.6 nmol/L for pure renin versus 10–14 nmol/L for renin in human plasma.⁵ This suggests that more than 90% of plasma aliskiren is bound to plasma proteins. Extensive binding of aliskiren to plasma proteins reduces the 'free' concentration of aliskiren available to inhibit

renin. This, together with the several-fold increase in renin concentrations, accounts for the modest and transient reduction of plasma angiotensin concentrations during aliskiren therapy.⁶ Long-term therapy failed to significantly reduce plasma aldosterone concentrations, although aliskiren did reduce urinary aldosterone excretion.⁶

Effect of renin inhibitors on renin measurement

Renin is measured in the investigation of hypertension. There are two methods – activity assays and immunoassays.⁵ Activity assays measure angiotensin I produced by renin cleavage of plasma angiotensinogen. Immunoassays measure renin concentrations in plasma. Renin inhibitors have different effects on the two methods of renin measurement. Renin inhibitors reduce plasma renin activity, although the reduction in plasma renin activity is attenuated by the rise in renin concentrations. By contrast, renin immunoassay measures both active renin molecules and renin molecules that are inhibited by the renin inhibitor. Consequently, renin immunoassay shows increased renin concentrations because of the increased release of renin that occurs during treatment with a renin inhibitor.

Renin inhibitor therapy can interfere with renin activity assays and immunoassays in other ways. The renin activity assay may overestimate renin inhibition because displacement of the inhibitor from plasma proteins during the assay causes greater inhibition of renin activity *in vitro* than was present *in vivo*. During immunoassay, renin inhibitors may cause an artefactual increase in the amount of renin molecules measured as the drug binds to, and causes unfolding of, the prosegment of plasma prorenin. This unfolding causes prorenin to be recognised by the renin immunoassay.

The clinician who wishes to screen for primary aldosteronism or who wishes to investigate hypertensive conditions with high renin concentrations such as renal artery stenosis, in a patient receiving renin inhibitor therapy, needs to cease this therapy for at least two weeks. This allows for clearance of the renin inhibitor before samples are taken for measurement by either activity assay or immunoassay.

Conclusion

Renin inhibitors represent an alternative strategy for inhibiting the renin-angiotensin system. They have a mechanism of action different from that of ACE inhibitors and angiotensin receptor antagonists. Whether renin inhibitors offer therapeutic benefits beyond those provided by ACE inhibitor and angiotensin receptor antagonist therapies will require their direct comparison in clinical outcome studies.

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Self-test questions

The following statements are either true or false (answers on page 143)

- Renin inhibitors act at angiotensin II receptors.
- Renin inhibitors increase the plasma concentration of renin.



Experimental and clinical pharmacology

Clinical implications of renin inhibitors

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Summary

Direct renin inhibition lowers blood pressure by an effective blockade of the renin-angiotensin system. Aliskiren is the first renin inhibitor to be marketed for the treatment of hypertension. At currently available doses it lowers blood pressure to a similar degree as other antihypertensive drugs. Used in combination with thiazides, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or calcium channel blockers, aliskiren has improved blood pressure control with no appreciable increase in adverse events. Aliskiren has an adverse effect profile comparable to placebo, but its long-term effects are unknown.

Key words: aliskiren, antihypertensives, hypertension.

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Introduction

Hypertension is one of the commonest reasons for general practitioner attendances. Less than 25% of those who are diagnosed attain their recommended blood pressure targets, while some studies place this figure as low as 7%. Although much of this failure to control blood pressure can be attributed to therapeutic inertia, the adverse effects of antihypertensive drugs also contribute. These adverse effects often limit the doses at which antihypertensive drugs can be used. This problem has prompted the ongoing search for more efficacious drugs with fewer adverse effects. One such group of drugs is the direct renin inhibitors which are currently undergoing clinical trials. The first of the drugs to be marketed is aliskiren.

Prorenin and the renin receptor

The discovery of the renin receptor provided a new role for renin, that of a profibrotic agent in its own right. It was subsequently found that the renin receptor also binds