Acute reduction in inactive renin after stimulation of active renin by converting enzyme inhibition (CEI) in man

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Summary
1. Administration of a single dose of captopril, 50 mg, to normal man \( (n = 7) \) on a low salt intake induced a 12.5 ± 0.9-fold rise in active renin. The rise in active renin was associated with a reciprocal decrease in circulating inactive renin to 10% or less of control levels.
2. Repeated administration of captopril (50 mg p.o. q 6 h x 3 days) to normal man resulted in increases in both active and inactive renin concentration in plasma.
3. When a single dose of captopril was administered to three patients with hyporeninaemic hypoaldosteronism, no changes in their circulating levels of active or inactive renin occurred.
4. These observations suggest that renal conversion of inactive to active renin may be important in active renin production.

Key words: active renin, captopril, converting enzyme, hypoaldosteronism.

Introduction
Inactive renin may be a precursor of active renin. Several investigators have demonstrated that plasma levels of inactive renin change with perturbations of the renin–angiotensin system [1–8], suggesting a renal source of inactive renin in man. In general, changes in inactive renin parallel changes in active renin and are apparent only after chronic stimulation or suppression [9]. Since converting enzyme inhibition is a potent stimulus to active renin secretion via reduction in angiotensin II negative feedback, we studied acute and chronic changes in active and inactive renin after captopril administration.

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Methods
Active renin was measured as the generation of angiotensin I with time following incubation of plasma with sheep angiotensin [10]. Inactive renin was measured following dialysis of plasma to pH 3.3 and then to pH 7.4 [11]. Captopril, when added to normal plasma to a final concentration of 1.6 µg/ml, did not interfere with the renin assay or with renin activation. All samples from a single subject were measured in the same assay. The interassay coefficient of variation is 6% determined for plasma samples with a renin concentration of 20 to 200 ng h⁻¹ ml⁻¹.

Seven normal volunteers were placed on 4–5 days of a 25 mmol/day sodium and 100 mmol/day potassium diet. At the end of this period, blood was sampled for renin determinations at 07.00 and 07.30 hours following overnight recumbency, and then captopril, 50 mg p.o., was given. Bloods were then sampled hourly for up to 7 h after captopril. Blood pressure was also monitored hourly. Following this acute phase of the study, captopril, 50 mg, was administered every 6 h for the next 3 days, and blood was sampled 3 h following each dose. Three diabetic subjects with hyporeninaemic hypoaldosteronism were studied under the same protocol conditions of the acute phase.

Results
Mean blood pressure in the seven subjects decreased by 12.1 ± 2.0 (mean ± SEM) mmHg following a single dose of captopril and remained at 70.8 ± 1.1 mmHg during the second phase of the study. At the time when the initial dose of captopril was administered, the 24 h urinary sodium was 24.9 ± 2.2 mmol and potassium was 94.7 ± 5.9 mmol.

Baseline levels of active renin were 13.2 ± 2.4
ng h⁻¹ ml⁻¹. After a single dose of captopril, active renin peaked at 176.7 ± 45.3 ng h⁻¹ ml⁻¹ (P < 0.02) at 2 to 4 h. Baseline inactive renin was 49.4 ± 6.8 ng h⁻¹ ml⁻¹. After captopril, inactive renin levels plummeted to 10% or less of control values. In each subject the peak of active renin was increased at 128.4 ± 18.5 ng h⁻¹ ml⁻¹.

In the three diabetic patients with hyporeninaemic hypoaldosteronism, baseline active renin was 6.0 ± 1.5 ng h⁻¹ ml⁻¹ and inactive renin was increased at 128.4 ± 17.1 ng h⁻¹ ml⁻¹. No significant change occurred in these values during administration of a single dose of captopril, despite a blood pressure drop of 10.7 ± 0.8 mmHg.

Discussion

During profound stimulation of active renin secretion, as during removal of angiotensin II negative feedback, we have detected marked decreases in circulating levels of inactive renin. These reciprocal changes in active and inactive renin suggest that conversion of inactive to active renin may play a physiological role in active renin production in man.

These results are in agreement with the observations of Goto et al. [11], who administered captopril to hypertensive patients and measured inactive renin by cryoactivation. In those patients who demonstrated a rise in active renin, inactive renin decreased by 85%. These studies could be challenged because cold exposure activates only about 30% of the inactive renin in plasma [12]. Two other groups of investigators, using trypsin to activate plasma renin, failed to demonstrate a change in inactive renin after a single dose of captopril. Sealey et al. [13] sampled plasma of hypertensives on normal salt intake at 1 h, so the maximum changes in active and inactive renin could have been missed. Millar et al. [14] sampled plasma from normals on low salt diet and chlorothiazide at 2 h post dose. Chronic diuretic treatment is known to increase both active and inactive renin secretion [9], so a drop in inactive renin following captopril might have been obscured by the chlorothiazide.

In order to determine whether the acute effects of captopril on renin occurred in plasma or kidney, captopril was administered to three patients with diabetic nephropathy and hyporeninaemic hypoaldosteronism. There was no change in the high levels of inactive renin and no increase in active renin in response to captopril, so the kidney is implicated as the site of renin activation. Thus, acute reduction in angiotensin II negative feedback appears to augment active renin production by enhanced renal conversion of inactive to active renin.

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References


