Role of prostaglandin in the antihypertensive mechanism of captopril in low renin hypertension

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Summary
1. The role of endogenous prostaglandins in the antihypertensive mechanism of the angiotensin converting enzyme inhibitor, captopril, was investigated.
2. An unequivocal reduction in blood pressure and significant increase in plasma renin activity and urinary prostaglandin E excretion were found after the captopril administration.
3. The changes in blood pressure, plasma renin activity and urinary prostaglandin E excretion induced by captopril were reversed after the inhibition of endogenous prostaglandin synthesis by indomethacin. However, the responses in low renin hypertension were different from those in normal renin hypertension.
4. In low renin hypertensive patients who responded to captopril, the hypotensive effect was abolished after the addition of indomethacin, whereas no marked change in blood pressure was induced by indomethacin in normal renin hypertensive patients. In contrast, plasma renin activity was markedly increased after captopril administration in normal renin hypertension, and no significant change was found in low renin hypertension.
5. Potentiation of the prostaglandin system seems to be a principal factor in the antihypertensive mechanism of captopril in low renin hypertension, and inhibition of the renin–angiotensin system is important in normal renin hypertensives.
6. The increase in renin release after the administration of captopril was inhibited by indomethacin, suggesting that an endogenous prostaglandin system may contribute to the short feedback mechanism of renin release.

Key words: antihypertensive mechanism, captopril, indomethacin, low renin hypertension, prostaglandin, renin.

Introduction
An orally active inhibitor of angiotensin converting enzyme, captopril (Ondetti, Rubin & Cushman, 1977), is effective in reducing blood pressure in hypertensive patients by the inhibition of the conversion of angiotensin I into angiotensin II (Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978; Gavras, Brunner, Turini, Kershaw, Tifft, Cuttelod, Gavras & Vukovich, 1978; Brunner, Gavras, Waeber, Kershaw, Turini, Vukovich, McKinstry & Gavras, 1979). However, there is documented evidence that captopril lowers blood pressure in some patients with low renin hypertension (Gavras et al., 1978; Brunner et al., 1979). Captopril is known to potentiate the biological action of kinin (Murthy, Waldron, Goldberg & Vollmer, 1977; Rubin, Laffan, Kotler, O'Keefe, Demiao & Goldberg, 1977), which also stimulates the release of prostaglandins (McGiff, Itskovitz & Terragno, 1975). Thus there is a possibility that the kinin–prostaglandin system may contribute to the hypotensive action of captopril in low renin hypertension. To investigate this possibility, the influence of indomethacin on the antihypertensive effect of captopril was examined in low renin hypertension and in normal renin hypertension.

Patients and methods
Studies were conducted in 19 hypertensive patients who responded to captopril by 10 mmHg or greater lowering of blood pressure. The
Patients comprised 12 with essential hypertension, four with chronic glomerulonephritis, two with chronic pyelonephritis and one with renovascular hypertension (nine with low renin hypertension and ten with normal renin hypertension). Their age averaged 37.1 ± 3.1 years; 13 were males and six were females. All patients were hospitalized during this study and were given a diet containing 200 mmol of sodium daily. Antihypertensive drugs had been discontinued at least for 2 weeks before the study.

Placebo was given three times daily for 2 weeks and then captopril was administered. After the administration of the effective doses of captopril (75–300 mg/day) for 1 week, indomethacin (75–150 mg/day) was added for the additional 3 days. Blood pressure was measured four times daily in the supine position and averaged. The sampling of blood was done to measure plasma renin activity (PRA) from the fasting subjects lying in bed for 1 h, and urine was collected for 24 h in a bottle kept in a refrigerator at the control period and at the end of each period of medication.

Urinary prostaglandin E (PGE) was measured by radioimmunoassay with a commercial kit. After the conversion of PGE into prostaglandin B (PGB) by alkaline treatment, the sample was acidified to pH 3.4 and extracted with ethyl acetate. The PGB fraction was then purified by silicic acid column chromatography and measured by radioimmunoassay with PGB antiserum. The overall recovery rate of added PGE was 54.8 ± 0.7% and the estimated value was corrected for this loss (Abe, Yasujima, Chiba, Irokawa, Ito, Yoshinaga, & Saito, 1977).

Urinary kallikrein was measured in terms of kininogenase activity. Urine (0.05–0.1 ml) was incubated with 4 μg of bovine serum low-molecular-weight kininogen at 37°C for 20 min. After the incubation, the samples were heated at 80°C for 20 min to terminate the enzymatic reaction and the generated kinin was measured by radioimmunoassay with kallidin antiserum (Abe, Seino, Sakurai, Irokawa, & Miyazaki, 1977).

PRA was determined by a modification of Haber’s method (Abe, Otsuka, Saito, Chin, Aoyagi, Miyazaki, Irokawa, Seino, & Yoshinaga, 1972). Urinary aldosterone extracted by the procedure reported by Langen, Jackson, Adlin & Channick (1974) was measured by radioimmunoassay with a commercial kit (Cer Ire Sorin). Urinary Na⁺ and K⁺ were measured by Auto-analyzer. The results were expressed as means ± SEM. The difference between mean values was tested by paired t-test.

Results

An unequivocal reduction in blood pressure was found after captopril administration in all patients. Blood pressure fell significantly from 166.4 ± 5.2 to 133.4 ± 3.2 mmHg (P < 0.0001) systolic and from 104.2 ± 3.6 to 82.9 ± 1.6 mmHg (P < 0.001) diastolic after the administration of captopril, and PRA increased significantly from 1.33 ± 0.16 to 4.37 ± 0.73 ng of angiotensin 1 h⁻¹ ml⁻¹ (P < 0.001). Urinary excretion of aldosterone was significantly decreased from 12.0 ± 3.6 to 3.8 ± 0.9 µg/day (P < 0.05).

The changes in blood pressure and PRA induced by the captopril administration were reversed after the inhibition of prostaglandin synthesis by indomethacin. PRA decreased significantly from 4.37 ± 0.73 to 1.57 ± 0.24 ng h⁻¹ ml⁻¹ (P < 0.0001), and blood pressure rose from 133.4 ± 3.2 to 147.2 ± 6.66 mmHg (P < 0.05) systolic and from 82.9 ± 1.9 to 90.6 ± 3.2 mmHg (P < 0.02) diastolic. However, the responses of blood pressure and PRA after the addition of indomethacin were different in low renin hypertension and in normal renin hypertension. Blood pressure was elevated and the hypotensive effect of captopril was abolished after the administration of indomethacin in captopril-responders with low renin hypertension, whereas no marked change was found in captopril-responders with normal renin hypertension (Fig. 1). In contrast, PRA was increased markedly after the administration of captopril and decreased significantly after the addition of indomethacin in normal renin hypertension, whereas no significant change was found in low renin hypertension. Urinary excretion of PGE was measured in 15 patients (eight normal renin and seven low renin hypertension). The estimated values were significantly increased from 315 ± 74 to 599 ± 101 ng/day (P < 0.05) after captopril administration and significantly decreased to 225 ± 42 ng/day (P < 0.05) after the addition of indomethacin. In normal renin hypertension, similar significant change was found, with no significant change in low renin hypertension. Urinary kallikrein excretion was significantly decreased from 9.76 ± 3.18 to 4.43 ± 1.42 µg/day (P < 0.05) after the captopril administration.

Urinary Na⁺ excretion did not change significantly, from 182 ± 9 to 193 ± 12 mmol/day after the administration of captopril, although it was significantly decreased to 127 ± 12 mmol/day (P < 0.0001) after the addition of indomethacin. However, there was no significant
Captopril and low renin hypertension

Fig. 1. Effects of captopril and indomethacin on (a) systolic (●) and diastolic (○) blood pressure, (b) urinary Na+ (●) and K+ (○) excretion, (c) plasma renin activity (●) and (d) urinary PGE (●) and kallikrein (○) excretion in normal renin hypertension (n = 10) and low renin hypertension (n = 9). Asterisks indicate significant differences: **P < 0.05; *P < 0.01.

difference in urinary Na⁺ excretion between low renin hypertension and normal renin hypertension. Urinary K⁺ excretion was not significantly changed after the administration of captopril and indomethacin.

Discussion

In the present study, captopril lowered blood pressure in the patients with low renin hypertension as in other studies (Gavras et al., 1978; Brunner et al., 1979). The mechanism of the antihypertensive effect of captopril in these patients may be unrelated to the inhibition of the renin–angiotensin system, since their hypertension is not renin-dependent. In the present study, urinary PGE excretion was increased after the administration of captopril and the antihypertensive effect of captopril was abolished after the inhibition of prostaglandin synthesis with indomethacin in captopril-responders with low renin hypertension. These results indicate that chronic administration of captopril augments the release of endogenous vasodilating prostaglandins and this contributes to the antihypertensive mechanisms of captopril in low renin hypertension. On the other hand, the antihypertensive effect was maintained after the addition of indomethacin in normal renin hypertension. These results indicate that the inhibition of the renin–angiotensin system may be the prime antihypertensive mechanism of captopril in normal renin hypertension. Augmented renin release after the administration of captopril seems to be due to the suppression of the negative short feedback mechanism for renin release. The fact that enhanced PRA induced by captopril was reduced towards normal by indomethacin suggests that the prostaglandin system may be an important factor in the renin release in this situation. In the present study, urinary kallikrein excretion was significantly decreased after captopril administration. Therefore there was no evidence that captopril potentiates kinin-mediated prostaglandin synthesis. Dusting & Doyle (1979) reported that angiotensin I stimulated the release of prostaglandin I₂-like substance from the rat mesenteric artery and captopril enhanced this substance by augmented angiotensin I. In low renin hypertension, however, captopril may be unable to cause accumulation of angiotensin I. Thus the mechanism of the augmentation of endogenous prostaglandin system by captopril remains unknown.

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References


