The renin–angiotensin–aldosterone system in the maintenance of blood pressure, aldosterone secretion and sodium balance in normotensive subjects

G. A. MACGREGOR, N. D. MARKANDU, J. E. ROULSTON, J. C. JONES AND J. J. MORTON*

Department of Medicine, Charing Cross Hospital Medical School, London, and *MRC Blood Pressure Unit, Glasgow, Scotland, U.K.

Summary

1. Captopril given for 5 days caused a fall in blood pressure in normotensive subjects. The percentage fall in mean supine pressure was greatest on a low sodium diet (10 mmol/day), 19.6%, least on a high sodium diet (350 mmol/day), 11%, and in between on a normal sodium diet (120 mmol/day), 16.5%.

2. Captopril caused a marked fall in plasma aldosterone in normal subjects on all three sodium intakes.

3. Captopril caused an increase in sodium excretion on the normal (120 mmol/day) and low (10 mmol/day) sodium diet but not the high sodium diet.

4. These results suggest that the renin–angiotensin–aldosterone system is a normal mechanism for maintaining blood pressure and aldosterone secretion in normotensive man. The system may also be involved in the maintenance of sodium balance.

5. These results may lead to a better understanding of the role of the renin–angiotensin–aldosterone system in the maintenance or causation of high blood pressure in essential hypertension.

Key words: aldosterone, angiotensin, captopril, normotensive subjects, renin, sodium.

Introduction

The renin–angiotensin–aldosterone system has been regarded as a defence mechanism to maintain blood pressure in normal man only after volume depletion (e.g. blood loss) or sodium depletion or restriction (Haber, 1976). With the recent development of a specific oral inhibitor of angiotensin converting enzyme (captopril, SQ 14 225) long-term inhibition of the formation of angiotensin II is now possible (Ondetti, Rubin & Cushman, 1977). In this study we have looked at the effect of captopril given for 5 days on blood pressure, aldosterone and sodium balance in normotensive volunteer subjects on three different sodium intakes: low (10 mmol/day), normal (120 mmol/day), high (350 mmol/day).

The results suggest that the renin–angiotensin–aldosterone system, like the sympathetic nervous system, is not only a defence mechanism but a normal mechanism for maintaining blood pressure. This may help to explain some of the recent controversy over the importance of the renin–angiotensin system in the maintenance or causation of blood pressure in essential hypertension (Case, Wallace, Keim, Weber, Drayer, White, Sealey & Laragh, 1976).

Methods

Normotensive, healthy, male subjects whose diastolic pressure was less than 80 mmHg after a 2 month observation period were included in the study. All subjects gave their informed consent. Mean age of subjects was 22 years (range 21–26 years). The subjects were studied on three sodium balances, on each balance for 3 weeks, with a gap between each balance period when they ate their normal diet. The low sodium intake was 10 mmol/day, the normal sodium intake was 120 mmol/day and the high sodium intake was 350 mmol/day. The high sodium diet was achieved by supplementing the diet with slow sodium (CIBA). The potassium intake was kept constant at 115
mmol/day for all three diets. All food and drink apart from water was provided by the metabolic ward kitchen. During the 3 weeks of each diet continuous 24 h urine collections were made. The normotensive subjects were allowed to go about their normal activities throughout the study and were not admitted to hospital. They were discouraged from vigorous exercise. Captopril was started on day 8 of the balance, measurements being made 2 h after the first dose of 25 mg. The subjects were allowed to pursue their usual activities during this 2 h period. The dose of captopril was 25 mg three times on day 1, increasing to three doses of 50 mg on day 2 and 100 mg thrice daily for the next 2 days and one dose of 100 mg on the morning of day 5. Daily measurements of blood pressure and 24 h urinary sodium were made. All blood pressures were measured by nurses using semi-automatic ultrasound sphygmomanometers (Arteriosonde 1217) (George, Lewis & Petrie, 1975). The mean value of five readings at 1–2 min intervals, supine, sitting and standing, were taken as the blood pressure in that position. Blood pressure measurements were made at the same time of day between 10.00 and 12.00 hours in the same room, by the same nurse, on the same arm. Pulse rate was measured on a Cambridge 3048 pulse monitor with ECG display and recording. Urinary aldosterone was measured 2–4 days before the start of captopril, during the 5 days of captopril and for 4 days after captopril was stopped. Plasma angiotensin II, plasma renin activity and plasma aldosterone, blood urea, electrolytes and plasma creatinine were measured on days 5 and 8 of the balances before captopril, 2 h after the first dose of captopril and on days 4 and 5 during treatment with captopril. All blood was taken without stasis after sitting upright for 5–10 min between 10.00 and 12.00 hours. Plasma renin activity, plasma aldosterone and plasma angiotensin II were measured by radio-immunoassay (Düsterdieck & McElwee 1971; James & Wilson, 1976; Roulston & MacGregor, 1978). Statistical analysis was done using Student's t-test (for hormone measurements log values were used) or, for correlations, the method of least squares. Mean blood pressures were calculated as diastolic pressure + (\(\frac{1}{3}\) x pulse pressure). Results are reported as the mean ± SEM.

**Results**

**Normal sodium intake (120 mmol/day)**

Eight normal subjects were studied on a sodium intake of 120 mmol/day. Captopril caused a significant fall in blood pressure within 2 h of the first dose and this was greater by day 5 (Table 1). The percentage fall in mean supine blood pressure with captopril by day 5 was 16.5±9%. Blood pressure returned to similar levels to the pre-captopril values in the 7 days after stopping captopril. Plasma angiotensin II and plasma aldosterone fell with captopril and plasma renin activity rose with captopril (Table 1). Mean 24 h urinary sodium excretion 4 days before captopril was 107±4.3 mmol, and during the 5 days of captopril was 135±10.0 mmol. Net loss of sodium during the 5 days of captopril was 142 mmol. All normal subjects lost weight and by day 5 of captopril the mean weight loss was 1.1±1.5 kg. Urinary aldosterone excretion fell during captopril. Mean urinary aldosterone in the 4 days before captopril was 50±2.5 mmol/24 h and during the 5 days of captopril was 36.5±3.6 mmol/24 h.

**High sodium intake (350 mmol/day)**

Seven normal subjects were studied. By day 8 of the high sodium diet in the seven normal subjects, mean 24 h urinary sodium excretion was 334±21 mmol. There was no significant change in weight with the high sodium diet. Plasma angiotensin II, renin activity and aldosterone had fallen (Table 1). Captopril caused a significant fall in blood pressure (Table 1). The fall was less than on the normal sodium diet but the difference was not significant. The percentage fall in mean supine blood pressure was 11.0±1%. With captopril, plasma angiotensin II and plasma aldosterone fell; plasma renin activity rose (Table 1). There was no detectable change in sodium balance with captopril. Mean urinary sodium excretion in the 4 days before captopril was 324±5.9 mmol and during captopril was 323±7.8 mmol. There was no significant change in mean weight with captopril (71.55–71.40 kg). Mean urinary aldosterone in the 4 days before captopril was 18.7±5.9 mmol/24 h, and during the 5 days of captopril was 16.3±1.1 mmol/24 h.

**Low sodium intake (10 mmol/day)**

Five normal subjects were studied. By day 8 of the low sodium diet the five normal subjects had lost 150.6 mmol of sodium and 1.5±0.5 kg. The mean 24 h urinary sodium was 8.6±2.0 mmol. Plasma angiotensin II, renin and aldosterone had risen (Table 1). Blood pressure fell with captopril (Table 1). The fall in blood pressure was significantly greater than the fall on the high sodium diet (P < 0.005). The percentage
fall in mean supine blood pressure was 19.6%. There was no evidence of postural hypotension on the low sodium diet. With captopril plasma angiotensin II and aldosterone fell, plasma renin activity rose. Mean urinary sodium excretion in the 4 days before captopril was 10.85 ± 0.86 mmol and during the 5 days of captopril was 18.2 ± 2.4 mmol. The net loss of sodium during captopril was 43.6 mmol. There was no significant change in weight with captopril (68.0 ± 2.4 mmol/24 h and during the 5 days of captopril was 84 ± 13.0 mmol/24 h).

The three diets, taken together, showed that with captopril, plasma angiotensin II and aldosterone fell to approximately the same level irrespective of the diet or starting level of angiotensin II (Table 1). Plasma aldosterone, although showing large falls with captopril, did not fall to the same level on the different diets (Table 1). Considering all 20 normal subjects who were studied with captopril irrespective of diet, there was a significant correlation between initial log(plasma renin activity) and the fall in blood pressure (r = 0.71, P < 0.001). There was also a significant correlation between the initial log (angiotensin II) and the fall in blood pressure (r = 0.71, P < 0.001), and a significant correlation between the fall in log(angiotensin II) and the fall in blood pressure (r = 0.63, P < 0.001). There was also a significant correlation between the initial plasma renin activity, angiotensin II and the fall in angiotensin II against the fall in aldosterone that occurred with captopril by day 5 (r = 0.66, r = 0.82, r = 0.78 respectively, P < 0.001). These correlations are not strictly statistically justified as five of the same normal subjects were studied on the three different diets and the diets were not achieved by chance. Nevertheless, they indicate the close relationship between the fall in blood pressure and the initial levels of plasma renin activity, angiotensin II and the fall in plasma angiotensin II.

### Table 1. Supine and standing blood pressures, plasma angiotensin II concentration, plasma renin activity and plasma aldosterone concentration on a normal sodium (120 mmol/day), a high sodium (350 mmol/day) and a low sodium (10 mmol/day) intake

<table>
<thead>
<tr>
<th>Diet</th>
<th>Supine Blood Pressure (mmHg)</th>
<th>Standing Blood Pressure (mmHg)</th>
<th>Angiotensin II (pmol/l)</th>
<th>Plasma Aldosterone (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal diet (120 mmol/day, n = 8)</td>
<td>116/72 (±2.2/±1.4)</td>
<td>110/79 (±2.0/±2.3)</td>
<td>34.4 (±3.7)</td>
<td>659 (±99)</td>
</tr>
<tr>
<td>Supine blood pressure</td>
<td>118/69 (±2.3/±1.3)</td>
<td>112/79 (±2.9/±2.4)</td>
<td>25.3 (±2.3)</td>
<td>549 (±64)</td>
</tr>
<tr>
<td>Captopril 2 h after 25 mg</td>
<td>108/64 (±2.4/±2.7)</td>
<td>105/78 (±2.5/±3.1)</td>
<td>15.5 (±1.9)</td>
<td>184 (±26)</td>
</tr>
<tr>
<td>Captopril 5 days after 25 mg</td>
<td>105/53 (±2.6/±3.4)</td>
<td>96/68 (±3.3/±4.4)</td>
<td>11.0 (±1.4)</td>
<td>164 (±21)</td>
</tr>
<tr>
<td>Normal diet (120 mmol/day, n = 8)</td>
<td>116/59 (±2.7/±3.2)</td>
<td>112/81 (±3.3/±3.1)</td>
<td>15.4 (±2.2)</td>
<td>201 (±44)</td>
</tr>
<tr>
<td>Supine blood pressure</td>
<td>118/72 (±3.3/±3.1)</td>
<td>115/79 (±3.2/±2.8)</td>
<td>17.0 (±2.6)</td>
<td>318 (±53)</td>
</tr>
<tr>
<td>Captopril 2 h after 25 mg</td>
<td>115/66 (±2.8/±3.4)</td>
<td>110/76 (±3.3/±3.9)</td>
<td>11.7 (±2.7)</td>
<td>112 (±15)</td>
</tr>
<tr>
<td>Captopril 5 days after 25 mg</td>
<td>111/61 (±2.6/±3.8)</td>
<td>103/71 (±3.5/±2.3)</td>
<td>9.6 (±2.3)</td>
<td>117 (±21)</td>
</tr>
<tr>
<td>Low sodium diet (10 mmol/day, n = 5)</td>
<td>121/70 (±3.4/±1.8)</td>
<td>110/78 (±3.5/±4.0)</td>
<td>59.0 (±11.2)</td>
<td>1235 (±260)</td>
</tr>
<tr>
<td>Supine blood pressure</td>
<td>122/69 (±1.6/±2.5)</td>
<td>109/80 (±1.6/±4.6)</td>
<td>64.4 (±9.3)</td>
<td>1395 (±252)</td>
</tr>
<tr>
<td>Captopril 2 h after 25 mg</td>
<td>110/63 (±3.0/±4.2)</td>
<td>100/68 (±3.3/±6.3)</td>
<td>39.6 (±11.5)</td>
<td>641 (±176)</td>
</tr>
<tr>
<td>Captopril 5 days after 25 mg</td>
<td>100/57 (±4.1/±5.3)</td>
<td>93/61 (±3.2/±6.1)</td>
<td>132 (±4.7)</td>
<td>395 (±138)</td>
</tr>
</tbody>
</table>
Discussion

Captopril in normotensive subjects caused a significant fall in blood pressure on a high, normal or low sodium diet. The fall was greatest on the low sodium diet and was least on the high sodium diet. There is controversy about how captopril might lower blood pressure.

Captopril is known to be a potent inhibitor of angiotensin-converting enzyme. Inhibition of this enzyme leads to a fall in circulating angiotensin II (Atkinson, Brown, Fraser, Leckie, Lever, Morton & Robertson, 1979; Fagard, Amery, Lijnen & Reybrouck, 1979). As this enzyme is also partly responsible for the breakdown of bradykinin, there could be an accumulation of bradykinin, a potential vasodilator. Recent work has not confirmed an increase in bradykinin with captopril (Mathews, McGrath & Johnston, 1979). Significant correlations have been shown between the fall in angiotensin II and the blood pressure fall with captopril in patients with hypertension (Fagard, et al. 1979) and salt-depleted dogs (Morton, Tree, Casais-Stenzel, 1980). Angiotensin II has other actions besides those of direct vasoconstriction of arterioles and these may also contribute to the fall in blood pressure with captopril. The fall in aldosterone that occurs within 2 h of the first dose of captopril may also have a blood-pressure-lowering effect.

Our results showing a close relationship in these normal subjects between the fall in blood pressure with captopril and the initial plasma renin activity, the initial plasma angiotensin II and the fall in angiotensin II with captopril suggest that part of the mechanism whereby captopril lowers blood pressure is through the reduction in angiotensin II that occurs. It might seem surprising that captopril did not have a greater effect on blood pressure on the low sodium diet compared with the high sodium diet. This could be explained by the increased sensitivity of vascular receptors to angiotensin II in salt-loaded normal subjects compared with sodium-restricted normal subjects (Oelkers, Brown, Fraser, Lever, Morton & Robertson, 1974). If part of the mechanism whereby captopril lowers blood pressure is through the fall in angiotensin II our results show that the renin–angiotensin system is a normal mechanism for maintaining blood pressure in normotensive subjects rather than just a defence mechanism to maintain blood pressure after volume depletion (Haber, 1976).

The fall in plasma aldosterone that occurred with captopril on all three diets indicates that angiotensin II is an important mechanism in maintaining aldosterone secretion, irrespective of sodium intake in normotensive man. However, the plasma aldosterone achieved during captopril was lowest on the high sodium diet and highest on the low sodium diet, illustrating that other factors besides the renin–angiotensin system are also involved in the changes of aldosterone secretion with different sodium intakes.

Captopril caused an increase in sodium excretion on the normal diet and on the low sodium diet but no change on the high sodium diet. This may be due to the fall in angiotensin II and/or the fall in aldosterone, and these results provide circumstantial evidence that the renin–angiotensin–aldosterone system may be a factor in the control of sodium balance on a low and normal sodium intake but not on a high sodium intake.

The fact that all drugs that block or inhibit the renin–angiotensin–aldosterone system appear to cause the same percentage change in blood pressure for a given plasma renin activity in both normotensive subjects and patients with essential hypertension (MacGregor, Markandu & Roulston, 1979) does suggest that this system plays no greater role in essential hypertension in the maintenance of blood pressure than in normal subjects for a given value of plasma renin activity. Our results with captopril, suggesting that the renin–angiotensin–aldosterone system is a normal mechanism (analogous to the sympathetic nervous system) for maintaining blood pressure in normotensive subjects on a normal sodium intake, necessarily implies that in essential hypertension the renin–angiotensin system is also a normal mechanism for maintaining the blood pressure, but is not the cause of the high blood pressure. The renin–angiotensin system, therefore, can only be the direct cause of high blood pressure if the level of angiotensin II is inappropriately high for the sodium balance or if there is an increase in sensitivity to the various actions of angiotensin II, as compared with normotensive subjects.

Acknowledgments

This study was supported by the Wellcome Trust, the Medical Research Council and the National Kidney Research Fund.

References

Renin system in maintenance of blood pressure

hypertension; acute and chronic changes in circulating concentrations of renin, angiotensin I and II and aldosterone, and in body composition. Clinical Science, 57 (Suppl. 5), 139s–143s.


