Endogenous Angiotensin-Aldosterone-Pressure Relationships During Sodium Restriction

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SUMMARY The effects of moderate restriction of dietary sodium and potassium supplementation on plasma levels of renin, angiotensin II, aldosterone, and cortisol and on arterial pressure were studied in 12 patients with mild essential hypertension. To define hormone-blood pressure relationships, venous hormone levels were measured hourly and intra-arterial pressure continuously for 24 hours after 4 to 6 weeks of sodium restriction, 4 to 6 weeks of potassium supplementation, and a similar period of control diet. Our results show that compared with the control diet, moderate sodium restriction was associated with increased levels of aldosterone but no overall change in renin, angiotensin II, or cortisol levels. Further, slopes of regression lines relating log renin and log angiotensin II to aldosterone were increased, as were log cortisol/aldosterone regression lines. On the contrary, regression lines of log renin and log angiotensin II versus arterial pressure were unaltered by sodium restriction. Hormone and blood pressure relationships were not changed by the potassium supplemented diet. Although confirmatory data are needed, our findings suggest that moderate sodium restriction enhances aldosterone responsiveness to endogenous angiotensin II and adrenocorticotropic hormone without diminishing the pressor activity of endogenous angiotensin II. These results may explain in part the disappointingly small hypotensive effect of modest sodium restriction in mild essential hypertension. (Hypertension 7: 681–687, 1985)

KEY WORDS • essential hypertension • renin • potassium

RESTRICTION of sodium and increased potassium content of Western diets has been advocated widely for lowering arterial pressure.1-3 Because marked reductions of sodium intake are unpalatable to many, programs of modest salt restriction are seen as more realistic long-term goals. Whereas severe sodium restriction usually lowers blood pressure and alters the aldosterone and pressor responses to infused angiotensin II,4,5 little is known of the effects of milder degrees of sodium restriction or of potassium supplementation on hormone–blood pressure relationships. Such information is desirable before recommendations concerning dietary electrolyte intake can be made. Therefore, we assessed blood pressure and hormone responses to moderate sodium restriction and to potassium supplementation in 12 patients with mild essential hypertension.

Subjects and Methods

The protocol was approved by the hospital ethical committee, and informed consent was obtained from each patient. Eight men and four women, aged 19 to 52 years, with essential hypertension were studied. Inclusion required that the subject’s untreated blood pressure was between 140/90 and 180/105 mm Hg (taking phase V as the diastolic reading) after resting supine for 15 minutes on two visits to the outpatient department at least 10 days apart. The subjects were otherwise well and free of clinical or laboratory evidence of secondary hypertension. Chest roentgenograms were normal. The electrocardiogram showed no abnormality in seven patients, and the other five had voltage criteria of left ventricular hypertrophy.

The patients underwent control (180 mmol sodium and 60 mmol potassium daily), sodium-restricted (80...
mmol sodium and 60 mmol potassium daily), and potassium-supplemented (180 mmol sodium and 200 mmol potassium daily) dietary regimens in randomized order; each diet lasted 4 to 6 weeks. A flavored potassium chloride elixir was taken to achieve the required intake for the potassium-supplemented phase. Detailed instructions on the selection and preparation of food were given by our special-project dietitian. A constant caloric intake was encouraged. For the outpatient phase of each diet, the patients attended clinic twice weekly and brought a 24-hour urine collection for measurement of sodium, potassium, and creatinine as a check on dietary adherence. At each outpatient visit, the previous 24-hour urine electrolyte results were discussed with the patient. Sixteen patients started the study, but four were withdrawn because of their inability to collect urine accurately or adhere to the diets.

On completion of each outpatient phase, the patients were admitted to a metabolic ward for 4 days where they received a diet of constant sodium (80 mmol/day) and potassium (60 mmol/day) content. For the control phase this diet was supplemented with sodium chloride capsules to achieve a total sodium intake of 180 mmol/day, and the potassium chloride elixir was given to achieve an intake of 200 mmol/day during the potassium-supplemented diet. In the sodium-restricted regimen no supplements were taken. Daily 24-hour urine collections were analyzed for sodium, potassium, and creatinine excretion.

On the morning of the fourth day in hospital, a cannula was inserted percutaneously into the brachial artery for continuous blood pressure recordings, and an intravenous line was placed for hourly hormone sampling. After catheter insertion and a rest period (0900–1000 hr), the patients were upright, walking or standing from 1000 to 2100 hours, except for the first 15 minutes of each hour when they were resting supine in bed. Meals were taken at 1000 to 1015 hours, 1300 to 1315 hours, and 1800 to 1815 hours. The direct arterial pressure signal together with the electrocardiogram from chest leads was recorded on a miniaturized tape recorder (Oxford Medical Systems, Hayes, Middlesex, England). The method and its validation have been described.

A minicomputer was used to calculate systolic, diastolic, and mean arterial pressures for every 10 heartbeats, as well as mean pressures and heart rate at 5-minute intervals for the 24 hours of monitoring. Venous samples (10 ml each) for hormone measurements were drawn on the hour, after 45 minutes of upright posture between 1000 to 2100 hours, and while in bed (2200–0900 hr). Blood was taken into chilled containers and centrifuged at 4 °C, and plasma was stored at −20 °C until hormone measurements were done. Plasma angiotensin II, aldosterone, and cortisol (by radioimmunoassay using kits from Diagnostic Products Inc., Los Angeles, CA, USA) were measured as previously described. Plasma renin activity (PRA) was measured by radioimmunoassay using the method of Haber et al. but modified so that pH was stabilized at pH 7.4 during the 37 °C incubation.

Statistical analyses were performed using the BMDP software package and included the t test for paired data, product moment correlation coefficients, and analysis of variance. For the calculation of hormone–blood pressure correlation coefficients, we used integrated arterial pressure readings taken over 5 minutes immediately before the time of venous hormone sampling (n = 24 for each patient). Analysis of variance was carried out with order of diet as a grouping factor and diet and hour of day as repeated measures. Both chi-square and t tests were used to test for the significance of changes in slopes of regression lines.

Results

The study was completed without incident. Plasma angiotensin II measurements were obtained from only 10 of the 12 patients during studies in the control and sodium-restricted phases. Details of the blood pressure and urine electrolyte excretion during the three regimens have been published previously and are summarized in Table 1.

Intra-arterial pressures on the sodium-restricted and potassium-supplemented diets were not significantly different overall from those on the control diet (see Table 1). The PRA, angiotensin II, and cortisol levels were altered little by moderate sodium restriction or by potassium loading. In contrast, plasma aldosterone levels were clearly higher on both modified diets compared with control (p < 0.01; see Table 1).

Effects of Sodium Restriction on Hormone and Arterial Pressure Relationships

For the control diet, PRA-aldosterone correlation coefficients were positive in all subjects and statistically significant in 9 of the 12 (r = 0.476–0.693, n = 24 in each patient), whereas sodium restriction was associated with significant correlations in 11 patients (r = 0.459–0.763, n = 24). A similar trend was seen with angiotensin II–aldosterone relationships, where significant correlation coefficients were seen in four of 10 subjects on the control diet (r = 0.461–0.662), and in seven of 10 patients during sodium restriction (r = 0.442–0.702).

In an attempt to compare tissue responses to endogenous hormone levels, log dose-response regression lines were calculated for each subject and slopes of these regression lines compared for the three diets. Log PRA/aldosterone regression lines (constructed from hourly venous sampling during 24 hr) were steeper in 11 of 12 patients during sodium restriction than during the control diet (Figure 1). This difference was highly significant overall (p < 0.001) and in three subjects (p < 0.05). Similar changes were observed for log angiotensin II/aldosterone relationships (see Figure 1), where regression lines were steepened with sodium restriction for the group as a whole (p < 0.01) and in eight of 10 subjects (p < 0.05 in 5).

In contrast to these findings, renin–arterial pressure relationships were not altered by sodium restriction. Correlations between PRA and diastolic arterial pressure were statistically significant in seven of 12 patients on the control diet (r = 0.496–0.810, n = 24)
TABLE 1. Clinical, Arterial Pressure, and Biochemical Data in 12 Essential Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control diet</th>
<th>Na-restricted diet</th>
<th>K-supplemented diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>74.5 ± 5.5</td>
<td>74.3 ± 5.7</td>
<td>75.1 ± 5.6</td>
</tr>
<tr>
<td>Urinary electrolytes (mmol/24 hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Sodium</td>
<td>202 ± 13</td>
<td>97 ± 9†</td>
<td>209 ± 9</td>
</tr>
<tr>
<td>Potassium</td>
<td>62 ± 6</td>
<td>70 ± 5</td>
<td>193 ± 14†</td>
</tr>
<tr>
<td>Creatinine</td>
<td>12.9 ± 1.0</td>
<td>14.7 ± 1.4</td>
<td>13.9 ± 1.2</td>
</tr>
<tr>
<td>Inpatient Sodium</td>
<td>152 ± 9</td>
<td>65 ± 6†</td>
<td>146 ± 9.6</td>
</tr>
<tr>
<td>Potassium</td>
<td>55 ± 3</td>
<td>56 ± 4</td>
<td>170 ± 7†</td>
</tr>
<tr>
<td>Creatinine</td>
<td>15.5 ± 0.9</td>
<td>14.2 ± 1.2</td>
<td>13.6 ± 1.2</td>
</tr>
<tr>
<td>Plasma potassium (mmol/L)</td>
<td>3.84 ± .05</td>
<td>3.77 ± .08</td>
<td>3.99 ± 0.12</td>
</tr>
<tr>
<td>Intra-arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136.7 ± 3.9</td>
<td>132.7 ± 4.5</td>
<td>136.6 ± 4.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.9 ± 2.4</td>
<td>82.9 ± 2.9</td>
<td>85.1 ± 2.3</td>
</tr>
<tr>
<td>Plasma renin activity (nmol/L/hr)</td>
<td>1.33 ± 0.25</td>
<td>1.64 ± 0.54</td>
<td>1.64 ± 0.45</td>
</tr>
<tr>
<td>Angiotensin II (pmol/L)*</td>
<td>36 ± 4</td>
<td>36 ± 2</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>299 ± 29</td>
<td>411 ± 22†</td>
<td>406 ± 27†</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>337 ± 17</td>
<td>356 ± 23</td>
<td>330 ± 19</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Body weight and plasma potassium were recorded on admission to hospital. For arterial pressure, 5-minute mean levels were used to calculate the 24-hour mean. Hormone values are from 24 recordings for each patient taken during the day of intra-arterial pressure monitoring. Outpatient 24-hour urinary sodium and potassium values are taken from the levels recorded during Week 3 of the outpatient phase. Inpatient 24-hour urine electrolyte data are from Day 3 of the inpatient phase, the day before intra-arterial recording.

*p < 0.01, †p < 0.001 compared with the control diet.

[Figure 1: Regression lines relating plasma renin activity and angiotensin II (log scale) to plasma aldosterone in 12 patients (n = 10 for angiotensin II) on a control diet and a sodium-restricted diet. Each regression line was constructed from 24 hormone samples drawn hourly for 24 hours. Slopes of regression lines increased significantly with sodium restriction overall (p < 0.001 for plasma renin activity, p < 0.01 for angiotensin II; paired t test).]
and in the same seven subjects during sodium restriction ($r = 0.420–0.819$). There was no significant change in the slope of regression lines (log PRA/diastolic pressure) with sodium restriction in the group as a whole or in any subject (Figure 2). Nor was there a systematic, parallel shift of regression lines to the right during sodium restriction (see Figure 2). Likewise, sodium intake had no effect on angiotensin II–arterial pressure relationships. Correlations between these two indices were statistically significant in two of 10 patients on the control diet ($r = 0.505$ and $0.524$, $n = 24$) and in five of 10 subjects during sodium restriction ($r = 0.450–0.761$). Regression lines relating log angiotensin II to diastolic pressure were neither steepened nor flattened overall, and slope changes in individual subjects were minor (see Figure 2).

We examined adrenocorticotropic hormone (ACTH)–aldosterone relationships assuming that plasma cortisol was an accurate biological marker of ACTH. As already noted, cortisol levels were similar on control and sodium-restricted diets (see Table 1). Cortisol-aldosterone correlation coefficients were significant in eight of 12 patients on the control diet ($r = 0.450–0.773$, $n = 24$) and in 10 of 12 subjects during sodium restriction ($r = 0.465–0.712$). Slopes of regression lines increased with sodium restriction in 11 of 12 patients ($p < 0.05$ in 3) and for the group overall ($p < 0.05$; Figure 3).

To summarize, sodium restriction overall was associated with increased slopes of regression lines relating renin and angiotensin II to aldosterone, and cortisol to aldosterone, but there was no change in renin–blood pressure relationships. Detailed results from one patient are shown in Figure 4.

Effects of Potassium Supplementation on Hormone and Arterial Pressure Relationships

Compared with the control diet, potassium supplementation was not associated with significant changes in slopes of regression lines relating renin and angiotensin II to aldosterone or to arterial pressure. Likewise, cortisol-aldosterone relationships were not altered by the increase in potassium intake.

Discussion

Our study of subjects with mild hypertension showed that a moderate reduction in sodium intake increased plasma aldosterone levels but did not signifi-

![Figure 2](http://hyper.ahajournals.org/Downloadedfrom)
cantly alter arterial pressure, PRA, or angiotensin II, plasma potassium, or cortisol levels. Previous work in normal subjects has shown that severe sodium restriction (10 mmol/day), without furosemide pretreatment, is associated with increased circulating concentrations of both renin (and angiotensin II) and aldosterone, and in addition, the aldosterone level for any plasma value of angiotensin II is higher than values observed on a normal or high sodium intake. These conclusions were derived from relationships between endogenous hormone values as well as results obtained during exogenous infusions of angiotensin II. Our results, based on endogenous hormone levels, show that a similar augmentation of the aldosterone response occurs during more modest degrees of sodium restriction and without any increase in PRA or angiotensin II. The lack of change in PRA and angiotensin II is not surprising since others have shown that more severe sodium restriction usually is required to elicit a clear-cut rise in renin.\textsuperscript{14, 15}

While the magnitude of change in the slopes of regression lines (log PRA/aldosterone and log angiotensin II/aldosterone) varied among patients, the direc-
tion of change was uniform and highly significant in the group as a whole. Since alterations in dietary sodium intake do not change the metabolic clearance rate of aldosterone, our results are consistent with the view that a "sensitizing factor," independent of change in angiotensin II levels, enhances the aldosterone response when sodium intake is reduced. Others have shown that the aldosterone response to ACTH, like that to angiotensin II, is enhanced by severe sodium restriction. Since slopes of log cortisol/aldosterone regression lines were steepened in our study, it is likely that both effects (ACTH and angiotensin II augmentation) contributed to the increase in plasma aldosterone observed during modest restriction of dietary sodium.

It is interesting that whereas potassium supplementation, like sodium restriction, increased plasma aldosterone, no changes in log PRA/aldosterone or log cortisol/aldosterone relationships were seen. This finding is surprising since previous workers have reported enhanced aldosterone responses to infused angiotensin II or ACTH during high potassium diets. The discrepancies might relate to differences in levels of dietary sodium intake or cumulative sodium balance, the use of dexamethasone before angiotensin II administration, and the fact that normotensive volunteers (rather than persons with essential hypertension) were studied. Plasma potassium concentration was altered little during the high potassium intake in our patients. The results are consistent with a direct effect of potassium, perhaps mediated by increases in intracellular potassium within the adrenal glomerulosa.

In contrast to the changes described for PRA- and angiotensin II–aldosterone relationships, we found no alteration in the relationship between renin-angiotensin activity and arterial pressure during moderate sodium restriction. By infusing angiotensin II in normal volunteers it has long been appreciated that severe sodium restriction is associated with reciprocal changes in the responsiveness of adrenal and vascular tissues: the aldosterone responses are enhanced, whereas the pressor effect of angiotensin II is diminished. Our findings in hypertensive subjects suggest that these changes need not be closely coupled and that the threshold for augmentation in aldosterone responsiveness to endogenous angiotensin II might occur at a higher level of sodium intake than that for the diminution in pressor response. This heightened aldosterone response (with consequent preservation of body sodium content despite the reduced dietary intake), in the absence of a concomitant reduction in pressor action of angiotensin II, may partly explain the lack of overall hypotensive effect of moderate sodium restriction.

When blood pressure responses to mild sodium restriction were analyzed individually in our patients, those showing the greatest fall in pressure exhibited little or no rise in PRA, whereas arterial pressure rose in patients with vigorous increases in PRA. These observations could be explained by the uniform activation of sodium-retaining mechanisms (augmented angiotensin II–aldosterone response) and the continued pressor role of the renin-angiotensin system (failure of angiotensin II–blood pressure response to decline) during moderate restriction of sodium intake. With more severe degrees of sodium restriction, a diminution in angiotensin II–pressor responsiveness will occur and may well contribute to the decline in arterial pressure.

A factor that hampers interpretation of the present results is that control of aldosterone and arterial pressure is multifactorial, thus selection of a single regulatory system (the renin-angiotensin system) for study could lead to misleading conclusions. For example, an important change in endogenous angiotensin II–blood pressure relationships during dietary sodium restriction could conceivably be obscured by alterations in other vasopressor or vasodepressor systems. Since this possibility cannot be excluded, our results require confirmation, for example, using incremental infusions of exogenous angiotensin II at different levels of dietary sodium intake.

We emphasize that our findings in patients with mild essential hypertension cannot be extrapolated to other hypertensive persons (such as elderly persons with hypertension or persons with low-renin or secondary forms of hypertension) or to subjects who are normotensive. Differences in adrenal and pressor responses to infused angiotensin II have been reported in essential hypertensive subjects compared with responses in normotensive controls. Studies on the effects of moderate sodium restriction on hormone-pressor relationships are required in normal subjects before our findings can be applied more generally. Such studies should be undertaken if whole populations are to restrict sodium intake.

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