Divergent effects of dietary chloride restriction on aldosterone biosynthesis and the renin-angiotensin system in rats

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Abstract. The effects of dietary chloride restriction – alone or combined with sodium and postassium restriction – on aldosterone biosynthesis and the renin-angiotensin system were studied in rats. Treatment with a chloride-deficient diet led to a temporary decrease in the capsular adrenal conversions of corticosterone to 18-hydroxycorticosterone and aldosterone (manifest after 2 weeks but not longer apparent after 3 weeks), which was accompanied by a progressive rise in plasma renin activity and a moderate fall in plasma potassium. Combined restriction of sodium, potassium and chloride elicited a decreased activity of the enzyme(s) involved in late steps in aldosterone biosynthesis, an elevation of plasma renin activity to excessively high levels and a substantial hypokalaemia. Chloride repletion of these rats by the addition of NH₄Cl or CaCl₂ to their drinking fluid stimulated aldosterone biosynthesis while lowering plasma renin activity and raising plasma potassium. According to these observations, dietary chloride deficiency is another example of an experimental situation in which a high activity of the renin-angiotensin system contrasts with an unchanged or suppressed aldosterone biosynthesis. Most likely, this divergence is at least partly due to hypokalaemia which is induced during long-term chloride deficiency by a yet unknown mechanism.

Late steps in aldosterone biosynthesis are markedly influenced by changes in sodium and potassium intake. Thus, sodium restriction or potassium loading of rats lead to an increased conversion of corticosterone to 18-hydroxycorticosterone and aldosterone by incubated zona glomerulosa tissue or mitochondria (Marusic & Mulrow 1967; Boyd et al. 1971; Baumann & Müller 1972). Whereas these effects of dietary monovalent cations have been extensively studied, experiments investigating a possible influence of the major dietary anion, i.e. chloride, on aldosterone biosynthesis have to my knowledge never been reported. A dependence of aldosterone biosynthesis on chloride intake would be important to know for a correct interpretation of experiments in which alterations in sodium or potassium intake are combined with alterations in chloride intake. The existence of at least an indirect relationship between aldosterone biosynthesis and chloride intake seems likely in view of two different lines of experimental evidence, one of them pointing to an essential role of the renin-angiotensin system in mediating the effects of sodium intake on late steps in aldosterone biosynthesis (Aguilera & Catt 1978; Aguilera et al. 1980), the other one showing a substantial influence of chloride intake on the activity of the renin-angiotensin system (Kotchen et al. 1976, 1978). In the following experiments, the long-term effects of chloride restriction – alone or combined with sodium and potassium restriction – and of chloride repletion on late steps of aldosterone biosynthesis and on plasma renin activity were studied in rats.
**Materials and Methods**

**Rats and diets**

Groups of 10 pure-bred male Osborne-Mendel rats (Zbz: CARA) weighing between 230 and 280 g were kept for periods of 1 to 3 weeks on semisynthetic diets and demineralized water. The diets, with appropriate modifications, were made up to the specifications of Hartroft & Eisenstein (1957) and had the following sodium, potassium and chloride contents:
- ‘complete’: Na⁺ 230 mmol/kg, K⁺ 230 mmol/kg, Cl⁻ 600 mmol/kg;
- ‘chloride-deficient’: Na⁺ 230 mmol/kg (Na₂SO₄), K⁺ 230 mmol/kg (K₂HPO₄), Cl⁻ traces;
- ‘sodium- and potassium-deficient’: Na⁺ 5 mmol/kg, K⁺ 0.7 mmol/kg, Cl⁻ 140 mmol/kg;
- ‘sodium-, potassium- and chloride-deficient’: Na⁺ 5 mmol/kg, K⁺ 0.7 mmol/kg, Cl⁻ traces.

In one series of experiments, the drinking fluid given to rats for a week consisted of an aqueous solution of sucrose (50 g/l) and one of the following salts: NH₄Cl, NH₄-acetate, KCl, KHCO₃, NaCl, NaHCO₃ (154 mmol/ l) or CaCl₂ (77 mmol/l).

**Blood collection and tissue incubation**

Rats were decapitated with a guillotine between 08.00 and 09.00 h. Blood was collected from the trunk into polyethylene beakers kept on crushed ice and containing a drop of EDTA solution. According to the recommendations by Düsterdieck & McElwee (1971), a mixture of EDTA and o-phenanthroline was added to the blood collected for angiotensin II assays. Only the blood collected during the first 15 seconds after touching the animals was used for the assay of plasma renin activity and angiotensin II, the rest of the collected blood for plasma steroid analysis. For determination of plasma electrolytes and the blood parameters shown in Table 2, blood was collected into heparinized syringes by aortic puncture under ether anaesthesia from separate but identically treated rats.

The excised adrenal glands of 10 decapitated rats were bisected and decapsulated by the method of Giroud et al. (1956). The capsular portions were evenly distributed into 4 homogeneous pools. Ten capsular hemiadrenals were incubated without pre-incubation in 6 ml modified Krebs-Ringer bicarbonate buffer con-

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![Graph](image-url)  
**Fig. 1.**

Effects of a chloride-deficient diet on capsular adrenal conversion of tritiated corticosterone ([³H]B) to aldosterone (Aldo) and 18-hydroxycorticosterone (18-OH-B) and on plasma renin activity in rats. Mean values ± SEM of n observations. Asterisks denote statistical significance of differences from rats on a complete diet according to t-tests: ***P < 0.001, *P < 0.05.
taining 3.6 mmol/l potassium and 2 g/l glucose. [1,2,6,7-3H] corticosterone (New England Nuclear, Boston, MA, USA; 2 μCi and 300 nmol/flask) was added in 0.06 ml ethanol (96%). Incubation was carried out for 120 min at 37°C in an atmosphere of 95% O₂ and 5% CO₂.

Analytical methods
[3H]aldosterone and [3H]18-hydroxycorticosterone were measured by previously described and evaluated double isotope dilution and paper chromatography procedures (Bauman & Müller 1972). Plasma aldosterone concentration was determined by radioimmunoassay after paper chromatography, according to Underwood & Williams (1972). Plasma corticosterone concentration was measured by a previously described and evaluated radioimmunoassay without chromatography (Komor & Müller 1979). Plasma renin activity was assayed by the method of Haber et al (1969) using a commercially available angiotensin I radioimmunoassay kit (New England Nuclear). Plasma angiotensin II concentration was measured by radioimmunoassay according to a previously evaluated modification (Biollaz et al. 1981) of the procedure of Düsterdieck & McElwee (1971).

Results

Chloride restriction
Capsular adrenal conversions of corticosterone to aldosterone and 18-hydroxycorticosterone were unaltered after 1 week, significantly decreased after 2 weeks and normal again after 3 weeks of dietary chloride restriction (Fig. 1). Plasma renin activity was significantly elevated after 1 week of chloride restriction and rose progressively during the following 2 weeks. A small but statistically significant decrease in the plasma chloride concentration was measured after 1 week (Table 1). This parameter fell further during the second week, but remained unaltered during the third week. After 2 and 3 weeks, there were a minor decrease in plasma sodium, a moderate decrease in plasma potassium and small but significant increases in the plasma and blood total CO₂ contents without any change in pH (Tables 1 and 2). After 3 weeks of chloride restriction, a 20-fold increase in plasma renin activity was associated with a 2-fold increase in the plasma angiotensin II concentration and unaltered plasma aldosterone and corticosterone concentrations (Table 3).

Combined sodium, potassium and chloride restriction
After 1 week of combined sodium, potassium and chloride restriction, the capsular adrenal conversions of corticosterone to aldosterone and 18-hydroxycorticosterone (Fig. 2) were the same as those of rats on a complete diet (Fig. 1) and were not significantly different from the conversions by tissue of rats that had been kept on a sodium- and potassium-deficient diet for 3 weeks (Fig. 2). After 2 weeks of combined restriction, a small fall in the conversion of corticosterone to aldosterone

<table>
<thead>
<tr>
<th>Experiment group</th>
<th>Treatment</th>
<th>n</th>
<th>Sodium (mmol/l)</th>
<th>Potassium (mmol/l)</th>
<th>Chloride (mmol/l)</th>
<th>CO₂ (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Complete diet</td>
<td>3 weeks</td>
<td>18</td>
<td>142 ± 2</td>
<td>4.0 ± 0.3</td>
<td>106 ± 2</td>
</tr>
<tr>
<td>B</td>
<td>Cl⁻-deficient diet</td>
<td>1 week</td>
<td>10</td>
<td>142 ± 3</td>
<td>4.0 ± 0.4</td>
<td>98 ± 2a</td>
</tr>
<tr>
<td>C</td>
<td>Cl⁻-deficient diet</td>
<td>2 weeks</td>
<td>10</td>
<td>139 ± 2b</td>
<td>3.2 ± 0.3a</td>
<td>92 ± 2a</td>
</tr>
<tr>
<td>D</td>
<td>Cl⁻-deficient diet</td>
<td>3 weeks</td>
<td>10</td>
<td>140 ± 1c</td>
<td>3.3 ± 0.2a</td>
<td>92 ± 1a</td>
</tr>
<tr>
<td>E</td>
<td>Na⁺- and K⁺-deficient diet</td>
<td>3 weeks</td>
<td>10</td>
<td>137 ± 5a</td>
<td>2.6 ± 0.2a</td>
<td>100 ± 3a</td>
</tr>
<tr>
<td>F</td>
<td>Na⁺-, K⁺-, and Cl⁻-deficient diet</td>
<td>1 week</td>
<td>8</td>
<td>157 ± 2</td>
<td>2.4 ± 0.3</td>
<td>97 ± 2d</td>
</tr>
<tr>
<td>G</td>
<td>Na⁺-, K⁺-, and Cl⁻-deficient diet</td>
<td>2 weeks</td>
<td>10</td>
<td>135 ± 3</td>
<td>2.6 ± 0.4</td>
<td>93 ± 3c</td>
</tr>
<tr>
<td>H</td>
<td>Na⁺-, K⁺-, and Cl⁻-deficient diet</td>
<td>3 weeks</td>
<td>10</td>
<td>136 ± 3</td>
<td>2.0 ± 0.4c</td>
<td>79 ± 6e</td>
</tr>
</tbody>
</table>

Mean values of n rats ± SD. Statistical significance of differences from group A: a P < 0.001; b P < 0.01; c P < 0.05 and from group E, respectively; d P < 0.05, e P < 0.001 according to t-tests.
reached statistical significance. After 3 weeks of combined restriction, both conversions were significantly suppressed and were about three times lower than the conversions by capsular adrenals of sodium- and potassium-restricted rats. Plasma renin activity rose to an excessively elevated value within 1 week of combined sodium, potassium and chloride restriction and remained in this range for the following 2 weeks. After 1 and 2 weeks of combined restriction, there was a moderate fall in plasma chloride concentration, similar to the one seen in simple chloride restriction (Table 1). However, plasma chloride was lower after 3 weeks of combined sodium, potassium and chloride restriction than after 3 weeks of simple chloride restriction. Also, the plasma potassium concentration was lower after 3 weeks of combined sodium, potassium and chloride restriction than after either simple chloride restriction or sodium and potassium restriction. The response in plasma CO₂ concentration to treatment with the sodium-, potassium- and chloride-deficient diet was biphasic, with a decrease after week 1 and an increase after week 3. There was no change in blood pH (Table 2). Significant increases in the blood haemoglobin content (indicative of a decreased plasma volume) were observed after 3 weeks of sodium, potassium and chloride restriction as well as after sodium and potassium restriction. In rats treated for 3 weeks with the sodium-, potassium- and chloride-deficient diet, a 5000-fold increase in plasma renin activity contrasted with a 10-fold increase in the plasma angiotensin II concentration (Table 3). Plasma concentrations of aldosterone (+180%) and corticosterone (+500%) were also significantly elevated.

Table 2.
Effects of diets on arterial blood parameters of rats.

<table>
<thead>
<tr>
<th>Diet (3 weeks)</th>
<th>n</th>
<th>Haemoglobin (g/l)</th>
<th>P-CO₂ (kPa)</th>
<th>CO₂ total (mmol/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>10</td>
<td>158 ± 8</td>
<td>5.8 ± 0.7</td>
<td>28.5 ± 1.0</td>
<td>7.40 ± 0.05</td>
</tr>
<tr>
<td>Sodium- and potassium-deficient</td>
<td>9</td>
<td>177 ± 12a</td>
<td>4.8 ± 0.7b</td>
<td>24.0 ± 1.9a</td>
<td>7.41 ± 0.03</td>
</tr>
<tr>
<td>Chloride-deficient</td>
<td>10</td>
<td>151 ± 4c</td>
<td>6.1 ± 0.5</td>
<td>30.8 ± 1.8b</td>
<td>7.41 ± 0.03</td>
</tr>
<tr>
<td>Sodium-, potassium- and chloride-deficient</td>
<td>9</td>
<td>170 ± 8b</td>
<td>5.6 ± 0.4</td>
<td>30.5 ± 2.7c</td>
<td>7.41 ± 0.04</td>
</tr>
</tbody>
</table>

Mean values ± SD of n rats. Statistical significance of differences from rats on complete diet according to t-tests: aP < 0.001, bP < 0.01, cP < 0.05.

Table 3.
Effects of diets on plasma hormone concentrations of rats.

<table>
<thead>
<tr>
<th>Diet (3 weeks)</th>
<th>Renin activity (nmol · l⁻¹ · h⁻¹)</th>
<th>Angiotensin II (pmol/l)</th>
<th>Aldosterone (pmol/l)</th>
<th>Corticosterone (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>1.5 ± 0.8 (27)</td>
<td>31 ± 16 (6)</td>
<td>111 ± 92 (9)</td>
<td>49 ± 14 (10)</td>
</tr>
<tr>
<td>Sodium- and potassium-deficient</td>
<td>23.7 ± 6.1a (19)</td>
<td>152 ± 41a (5)</td>
<td>216 ± 133 (8)</td>
<td>84 ± 38 (10)</td>
</tr>
<tr>
<td>Chloride-deficient</td>
<td>31.6 ± 22.5a (10)</td>
<td>63 ± 14c (6)</td>
<td>117 ± 88 (10)</td>
<td>43 ± 14 (10)</td>
</tr>
<tr>
<td>Sodium-, potassium- and chloride-deficient</td>
<td>7320 ± 3290a (15)</td>
<td>299 ± 72a (6)</td>
<td>311 ± 169b (7)</td>
<td>292 ± 61b (10)</td>
</tr>
</tbody>
</table>

Mean values ± SD. Number of observations in brackets. Statistical significance of differences from rats on complete diet according to t-tests: aP < 0.001, bP < 0.01, cP < 0.05.
Effects of a sodium-, potassium- and chloride-deficient diet on capsular adrenal conversions of tritiated corticosterone ([^3]H)B) to aldosterone (Aldo) and 18-hydroxycorticosterone (18-OH-B) and on plasma renin activity in rats. Mean values ± SEM of n observations. Asterisks denote statistical significance of differences from rats on a sodium- and potassium-deficient diet (containing chloride) according to t-tests: *** P < 0.001, * P < 0.05.

Table 4.

Effects of electrolytes in drinking fluid on plasma parameters of previously sodium-, potassium- and chloride-depleted rats.

<table>
<thead>
<tr>
<th>Addition to drinking fluid 3rd week</th>
<th>n</th>
<th>Plasma concentration (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sodium</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>136 ± 3</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>10</td>
<td>137 ± 2</td>
</tr>
<tr>
<td>NH₄-acetate</td>
<td>10</td>
<td>133 ± 9ᵇ</td>
</tr>
<tr>
<td>CaCl₂</td>
<td>9</td>
<td>139 ± 3</td>
</tr>
<tr>
<td>KCl</td>
<td>8</td>
<td>136 ± 3</td>
</tr>
<tr>
<td>KHCO₃</td>
<td>9</td>
<td>132 ± 3ᵇ</td>
</tr>
<tr>
<td>NaCl</td>
<td>10</td>
<td>143 ± 1ᵃ</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>10</td>
<td>140 ± 2ᵃ</td>
</tr>
</tbody>
</table>

Mean values of n rats ± SD. All animals were kept on a sodium-, potassium- and chloride-deficient diet for 3 weeks and received demineralized water as drinking fluid for the first 2 weeks. One group received water as drinking fluid also for the third week. For the other groups, the drinking fluid given during the third week contained sucrose (50 g/l) and one of the salts listed in the first column in a concentration of 154 mmol/l. The concentration of CaCl₂ was 77 mmol/l. Statistical significance of differences from rats drinking water according to t-tests: ᵇ P < 0.001, ᵉ P < 0.01, ᵇ P < 0.05.
Effects of the addition of various salts to the drinking fluid for 1 week to sodium-, potassium- and chloride-depleted rats on the capsular adrenal conversion of tritiated corticosterone ([3H]B) to aldosterone (Aldo) and on the plasma renin activity. See legend to Table 4 for experimental details. Mean values ± SEM of n observations. Asterisks denote statistical significance of differences from rats drinking water according to t-tests: *** P < 0.001, * P < 0.05.

Repletion experiments
Potassium or chloride repletion of previously sodium-, potassium- and chloride-depleted rats by the addition of NH₄Cl, CaCl₂, KCl or KHCO₃ to the drinking fluid for 1 week restored the activity of the final steps of aldosterone to normal and brought back plasma renin activity into the upper physiological range (Fig. 3). NH₄Cl stimulated aldosterone biosynthesis to a somewhat greater extent than the other three salts. Ammonium acetate did not affect aldosterone biosynthesis but had a minor suppressive effect on plasma renin activity. NaCl and NaHCO₃ further suppressed aldosterone biosynthesis while also strikingly lowering plasma renin activity. NH₄Cl and CaCl₂ significantly raised the plasma potassium concentration; however, only to still subnormal values (Table 4). An elevated and a normal plasma potassium concentration were observed after drinking KCl and KHCO₃, respectively. NaCl and NaHCO₃ drinking caused an additional fall in plasma potassium. The plasma total CO₂ content was lowered to subnormal values by NH₄Cl and KCl, normalized by CaCl₂ and additionally raised by KHCO₃ and NaHCO₃.
Discussion

Many investigators, among them Davis (1975) and Fraser et al. (1979), consider the renin-angiotensin system the most important physiological regulator of aldosterone secretion. In particular, increases in aldosterone biosynthesis in response to sodium deficiency appear to be mediated mainly by elevated levels of circulating angiotensin II (Aguilera & Catt 1983). In a review on the control of aldosterone secretion, Coghlan et al. (1979) confirmed that there was an excellent correlation between renin-angiotensin and aldosterone under numerous circumstances, but they also listed 11 different experimental and clinical situations in which the nexus between aldosterone and angiotensin was broken. According to the present observations, chloride deficiency is another example of an experimental situation in which there is an obvious divergence between the activity of the renin-angiotensin system and the biosynthesis of aldosterone. Thus, dietary chloride restriction of rats induced a progressive rise in plasma renin activity but a temporary decrease in the activity of the final steps in aldosterone biosynthesis. After 3 weeks of simple chloride restriction, a 20-fold increase in plasma renin activity and a 2-fold increase in the plasma angiotensin II concentration were accompanied by an unaltered plasma aldosterone concentration and normal capsular adrenal conversion of corticosterone to 18-hydroxycorticosterone and aldosterone. After combined sodium-, potassium- and chloride restriction, there was an even greater disparity between an excessively raised plasma renin activity and a suppressed aldosterone biosynthesis. A similar discrepancy was observed during chloride repletion of previously sodium-, potassium- and chloride-depleted rats, when striking falls in plasma renin activity contrasted with significant increases in the conversion of corticosterone to aldosterone.

The extracellular potassium concentration is another well-established regulator of the aldosterone secretion. On the one hand, this factor can directly influence aldosterone biosynthesis on its own, independently of the renin-angiotensin system (for a review see Müller 1971). On the other hand, the extracellular potassium level can also modify the steroidogenic action of angiotensin II on the zona glomerulosa cell (Fredlund et al. 1977; Douglas 1980a,b). It seems likely that the decreases in plasma potassium observed in the present experiments accounted at least for some of the discrepancies between a high plasma renin activity and a low activity of the final steps in aldosterone biosynthesis. In reverse, the enhanced conversion of corticosterone to aldosterone induced by the addition of NH₄Cl or CaCl₂ to the drinking fluid of sodium-, potassium- and chloride-depleted rats could have been partly due to increases in plasma potassium. However, the decreases in plasma potassium caused by chloride restriction were moderate although statistically significant, and the stimulation of the final steps of aldosterone biosynthesis by chloride or potassium repletion was not proportional to the increases in plasma potassium.

The mechanism by which dietary chloride restriction caused hypokalaemia is not clear. According to Abboud et al. (1979), acute selective chloride depletion of rats by peritoneal dialysis against isotonic NaHCO₃ or NaNO₃ solution did not lower plasma potassium although resulting in plasma chloride levels below those seen in the present experiments. The combination of a normal pH with a moderately elevated plasma CO₂ concentration indicates compensated metabolic alkalosis. Perhaps, a normal pH was maintained in chloride-restricted rats at the cost of a negative potassium balance. Alternatively, potassium loss may have been the consequence of an unknown renal defense mechanism against urinary chloride losses.

When added to the drinking fluid of sodium-, potassium- and chloride-depleted rats, ammonium chloride stimulated aldosterone biosynthesis more extensively than potassium chloride, although it raised the plasma potassium concentration less markedly. Ammonium chloride has previously been shown to directly stimulate aldosterone output by incubated quartered rat adrenals (Müller 1965) or by autotransplanted sheep adrenal glands (Blair-West et al. 1968). However, ammonium ions exerted this effect only at unphysiologically high concentrations. Since the addition of ammonium acetate to the drinking fluid did not affect aldosterone biosynthesis, the stimulatory effect of ammonium chloride was probably due rather to acidification than to an increased plasma ammonium concentration. Although there are several reports about a stimulation of aldosterone secretion by metabolic acidosis, the available evidence for possible mechanisms of this
phenomenon is rather equivocal. A direct effect of hydrogen ions on the adrenal cortex seems unlikely, since lowering of the pH of the incubation medium from 7.4 to 7.1 or 6.8 as well as raising it to 7.7 resulted in marked decreases in aldosterone production by rat adrenal zona glomerulosa cells (Gilchrist et al. 1983). In patients with diabetic ketoacidosis, elevated plasma aldosterone levels were accompanied by hyperkalaemia and increased plasma renin activity (Christlieb et al. 1975). Short-term infusion of NH₄Cl into sodium-restricted men lowered the plasma renin activity without altering the plasma aldosterone concentration (Kisch et al. 1976). Oral administration of NH₄Cl to normal subjects on a low-sodium diet resulted in a significant rise in plasma aldosterone, which was not accompanied by any change in plasma renin activity, cortisol or potassium concentrations (Perez et al. 1977). Acute increases in plasma aldosterone in response to lactic acid infusion in dogs were probably due to increased ACTH secretion and were prevented by treatment with dexamethasone (Perez et al. 1980). Long-term feeding of sulphuric acid to dogs on a sodium- and chloride-deficient diet led to increases in aldosterone secretion and in plasma renin activity, which were most likely caused by urinary sodium loss (Kraut et al. 1982).

The progressive increase in plasma renin activity in response to chronic chloride restriction confirms the previous experiments by Abboud et al. (1979) in which plasma renin activity was stimulated by acute chloride depletion. Possibly, the increased content of sulphate and phosphate in the chloride-deficient diet may also have contributed to the stimulation of renin release. However, I could find no precedent in the literature for the excessive rise in plasma renin activity observed during combined sodium-, potassium- and chloride restriction. Treatment of men with an electrolyte-free diet for 4 days resulted only in a moderate increase in plasma renin activity (Bauer et al. 1977). Keeping rats on sucrose and water for 2 days did not affect plasma renin activity (Haldy & Müller 1981). However, it must be kept in mind that the sodium-, potassium- and chloride-deficient diet used in the present experiments was not electrolyte-free but contained considerable quantities of calcium, magnesium, iron, copper, phosphate and sulphate. As shown in Fig. 3, sodium, potassium and chloride ions were similarly effective in restoring plasma renin activity to the range usually found in men and animals. Although, the plasma angiotensin II concentration was also very high in sodium-, potassium- and chloride-restricted rats, it was in no way proportional to the level of plasma renin activity. Future investigations will have to show whether this discrepancy was due to impaired or limited converting enzyme activity or rather to increased degradation of angiotensin II in vivo or in vitro.

Acknowledgments

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