Salt, frusemide and renin in severe experimental renal hypertension

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Summary

1. Sodium-deficient diet failed to alter development and maintenance of severe renal hypertension produced in the rat by ligation of the aorta between the renal arteries.
2. High sodium diet did not alter the early phase of this hypertension, but significantly decreased blood pressure elevation in the late phases.
3. The decrease in blood pressure produced by high sodium intake does not appear to be mediated by renin suppression.
4. Frusemide effectively reduced blood pressure and renin at all phases.

Key words: blood pressure, frusemide, renal hypertension, renin, salt.

Introduction

The role of salt in the pathophysiology of hypertension has been extensively studied. In addition to the importance of salt per se, Dahl and co-workers established that a genetic factor is responsible for the susceptibility of the rat to develop hypertension in response to increased salt intake (Knudsen, Iwai & Dahl, 1973).

In hypertension induced by mineralocorticoids or loss of renal mass, administration of salt is a sine qua non for the production of blood pressure elevation (Selye, Hall & Rowley, 1943; Koletsky & Goodsitt, 1960). In contrast, low salt intake exerts different effects on different models of experimental renal hypertension (Grollman & Harrison, 1945; Redleaf & Tobian, 1958; Fischer & Klein, 1963; Conway, 1969; Miksche, Miksche & Gross, 1970; Swales & Tange, 1971).

In some models of renal hypertension renin has been implicated. As salt balance is one of the determinants of renin secretion, the role of salt should be examined in relationship to renin. Dauda and co-workers reported that sodium supplementation may prevent the development of signs of malignant hypertension in the rat. The renin-suppressive effect of sodium administration was considered an important factor in determining this effect (Dauda, Mörhing, Hofsauer, Homys, Miksche, Orth & Gross, 1973).

The purpose of the present study was to assess the effects of variations of salt intake and of the administration of frusemide on blood pressure and plasma renin, during the onset and maintenance of severe hypertension secondary to ligation of the aorta between the renal arteries in the rat. This model was selected because of the precise reproducibility of blood pressure and renin measurements at successive phases (Fernandes, Onesti, Weder, Dykyj, Gould, Kim & Swartz, 1976).

Methods

Male Sprague-Dawley rats weighing 270–310 g were divided into four groups: (1) rats on standard Purina Chow and tap water; (2) rats on standard Purina Chow and NaCl (10 g/l) drinking solution ad libitum; (3) rats on a sodium-deficient diet (Nutritional Biochemicals Corp., Cleveland, Ohio, U.S.A.: sodium content = trace) and distilled water ad libitum; (4) rats on standard Purina Chow and tap water containing frusemide. The frusemide solution was calculated to give a dose of 36 mg day⁻¹ kg⁻¹. Diets and frusemide were initiated 2 weeks before
the induction of hypertension and continued through the observations. Hypertension was produced by ligation of the aorta between the renal arteries immediately below the superior mesenteric arteries (Fernandes et al., 1976).

Arterial pressures were recorded directly through an indwelling Teflon-Tygon catheter inserted in the left common carotid artery and exteriorized at the nuchal region. Blood samples (1 ml) for renin determination (Gould, Skeggs & Kahn, 1966) were obtained from the same catheter. All observations were conducted in the conscious unrestrained animal. After aortic ligation the rats were allocated to designated periods (days 3, 5, 12, 20 and 30). Cannulations were performed 24 h before blood pressure and renin determinations were made.

Results

Ligation of the aorta between the renal arteries resulted in equally severe blood pressure elevation in the two groups of rats on standard diet and on sodium-deficient diet for the duration of the experimental observations.

In the group of rats on high sodium diet hypertension was equally as severe as in the standard diet group on days 3 and 5. On days 12, 20 and 30, however, rats on high sodium diet exhibited a significantly lower mean arterial pressure.

Ligation of the aorta in the frusemide-treated group resulted also in sustained increase in blood pressure. This increase, however, was significantly less at all phases than that observed in the untreated animals on standard diet (Table I).

After aortic ligation, peripheral plasma renin concentration was equally elevated in the groups on standard diet and on sodium-deficient diet on days 3, 5 and 12. In the sodium-deficient group, peripheral plasma renin concentration was significantly higher than in the control group on standard diet on days

Table 1. Mean arterial pressure and plasma renin concentration in conscious rats with renal hypertension

Results are shown as mean values ± sd. MAP = mean arterial pressure (mmHg); PRC = plasma renin concentration (Goldblatt units; results x 10^-4). (P values = significance of difference from standard diet group.)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3 days</th>
<th>5 days</th>
<th>12 days</th>
<th>20 days</th>
<th>25 days</th>
<th>30 days</th>
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<tbody>
<tr>
<td><strong>Standard diet</strong> (n = 134)</td>
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<tr>
<td>MAP</td>
<td>115 ± 8.8</td>
<td>157 ± 18.7</td>
<td>182 ± 14.4</td>
<td>166 ± 20.2</td>
<td>161 ± 10.9</td>
<td>161 ± 10.6</td>
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<tr>
<td>PRC</td>
<td>0.66 ± 0.37</td>
<td>3.68 ± 0.75</td>
<td>8.68 ± 6.10</td>
<td>3.02 ± 2.0</td>
<td>1.68 ± 0.82</td>
<td>0.95 ± 0.40</td>
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<tr>
<td><strong>Sodium-deficient diet</strong> (n = 118)</td>
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<tr>
<td>MAP</td>
<td>114 ± 6.6</td>
<td>156 ± 16.3</td>
<td>175 ± 6.9</td>
<td>163 ± 13.2</td>
<td>160 ± 19.6</td>
<td>159 ± 17.26</td>
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<tr>
<td>PRC</td>
<td>0.96 ± 0.30</td>
<td>3.70 ± 1.70</td>
<td>8.69 ± 3.28</td>
<td>2.42 ± 1.43</td>
<td>2.26 ± 1.17</td>
<td>2.55 ± 0.96</td>
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<tr>
<td><strong>High Na diet</strong> (n = 141)</td>
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<tr>
<td>MAP</td>
<td>114 ± 5.3</td>
<td>155 ± 11.7</td>
<td>178 ± 12.9</td>
<td>148 ± 10.1</td>
<td>152 ± 5.6</td>
<td>149 ± 5.16</td>
<td>140 ± 6.1</td>
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<tr>
<td>PRC</td>
<td>0.34 ± 0.19</td>
<td>5.56 ± 2.95</td>
<td>6.28 ± 2.07</td>
<td>2.7 ± 2.4</td>
<td>1.73 ± 2.1</td>
<td>0.72 ± 0.45</td>
<td>0.80 ± 2.26</td>
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<tr>
<td><strong>Frusemide-treated</strong> (n = 102)</td>
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<tr>
<td>MAP</td>
<td>113 ± 11.9</td>
<td>140 ± 12.6</td>
<td>144 ± 12.8</td>
<td>149 ± 11.9</td>
<td>143 ± 16.4</td>
<td>134 ± 12.9</td>
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<tr>
<td>PRC</td>
<td>0.93 ± 0.54</td>
<td>2.24 ± 1.43</td>
<td>1.85 ± 0.8</td>
<td>1.71 ± 1.05</td>
<td>0.87 ± 0.46</td>
<td>0.92 ± 0.35</td>
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20 and 30. In the high sodium diet group, plasma renin concentration was significantly higher than in the standard diet group on day 3. On day 5 high sodium intake resulted in plasma renin concentrations lower than in the standard diet group. On days 12, 20 and 30 no difference was detected between the plasma renin concentration of the standard diet and high sodium diet group.

In the frusemide-treated group plasma renin concentration was significantly lower than in the untreated control animals on standard diet, 3, 5, 12 and 20 days after aortic ligation. On day 30 no difference was detectable between the two groups.

Discussion

A sodium-deficient diet failed to alter the development, maintenance and severity of hypertension in this model. In models with constriction of one renal artery with intact contralateral kidney low-salt diet has been reported to have little effect on the blood pressure (Redleaf & Tobian, 1958; Fischer & Klein, 1963). A delayed onset of hypertension was, however, described (Conway, 1969). In rats with hypertension due to compression of one kidney and removal of the contralateral kidney dietary salt restriction reduced blood pressure (Grollman & Harrison, 1945). Thus the role of sodium in the pathophysiology of experimental renal hypertension varies in different models; most of the evidence points to sodium-independence if the contralateral kidney is intact and to sodium dependence if the contralateral kidney is removed (Swales & Tange, 1971). In our model (Fernandes et al., 1976) the vasopressor function of the 'endocrine' kidney is not affected by sodium deprivation. It is noteworthy that the pattern of renin response that follows aortic ligation was not affected by the sodium-deficient diet at days 3, 5 and 12. During the late phases (days 20 and 30) sodium-deficient diet resulted in renin levels which were higher than those of control animals on standard sodium diet. The higher renin levels did not affect the blood pressure.

In the group on high salt diet the elevation of blood pressure after ligation of the aorta was equally severe on days 3 and 5. Thus at early phases sodium does not appear to play an important role in our experimental model.

On days 12, 20, 25 and 30 the blood pressure of the group on high sodium diet decreased and remained consistently lower than in the groups on standard diet and on sodium-deficient diet. These results are similar to the observations of Dauda et al. (1973) and of Möhring, Möhring, Petri, Haack & Hackenthal (1975). In their studies, high salt intake minimized malignant hypertension due to constriction of one renal artery with intact contralateral kidney. This effect was considered the result of renin suppression by sodium. In our model, the phases at which the blood pressure was decreased by high sodium intake were associated with renin levels not different from the control group on standard diet. Thus the decrease in blood pressure produced by high sodium intake does not appear to be mediated by renin suppression in our model.

The effect of high sodium intake on renin at day 3 and 5 after aortic ligation needs separate comment. Three days after aortic ligation plasma renin concentration of the high sodium-intake group was actually higher than in the control animals on standard diet at the same phase. Activation of the adrenergic nervous system is considered to take place in renal hypertension and sodium appears to be essential for activation of noradrenaline turnover (de Champlain, Krakoff & Axelrod, 1968). Ikeda, Fujii & Seki (1972) also noted an increased renin level in hypertensive rabbits on a high salt regimen compared with a similar group on a low salt diet. It is therefore possible that high sodium intake is responsible for an increase in adrenergic activity and consequently renin stimulation at the onset of hypertension in the group subjected to high sodium intake. Five days after aortic ligation, renin levels were lower in the group on the high sodium diet, compared with controls on standard diet. Hypertension was equally severe. Thus, the influence of high sodium intake on the blood pressure of our model does not appear to be mediated by renin.

Frusemide (36 mg day⁻¹ kg⁻¹) effectively reduced blood pressure at all phases. During the early phases, the increase in renin levels which follows aortic ligation was significantly blunted by frusemide treatment. This is in contrast with the well-known renin stimulation produced by acute administration of frusemide (Brown, Davis & Johnston, 1966), and suggests that the long-term anti-hypertensive action of frusemide may alter renin secretion by a secondary mechanism. At present, both the anti-hypertensive action of frusemide, and the reason for the changes in renin
levels that we have described, await final explana-
tion.

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