Influence of sodium restriction upon two models of renal hypertension

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Summary

1. Restriction of dietary salt intake does not affect the development or maintenance of hypertension in rats with unilateral renal ischaemia whether the contralateral kidney is present (Goldblatt 2 model) or not (Goldblatt 1 model).

2. Acute dietary salt depletion induces a similar loss of sodium and fall in body weight with little change in blood pressure in both normal and hypertensive rats.

3. Excision of the ischaemic kidney in rats with short-term (<50 days) Goldblatt 2 hypertension restores the mean blood pressure to normal, whereas Goldblatt 1 hypertensive rats show only a partial response. Previous salt depletion of this model enhances the blood pressure response to nephrectomy.

4. Sodium retention plays no part in the development or maintenance of Goldblatt 2 kidney hypertension. However, although sodium retention is normally involved in the Goldblatt 1 model, hypertension can develop in the absence of dietary sodium.

Key words: angiotensin antagonist, Goldblatt hypertension, nephrectomy, sodium balance.

Introduction

Sodium retention plays a well-established role in the hypertension which occurs in advanced renal disease and after bilateral nephrectomy in man (Brown, Düsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971; Ledingham, 1971). When hypertension is induced in the rat by constriction of a renal artery, the presence or absence of an undisturbed contralateral kidney is of critical importance and the role of sodium retention is more complex. Thus, when the contralateral kidney is removed (Goldblatt 1 kidney hypertension), hypertension is associated with an elevation of exchangeable sodium (Tobian, Coffee & McCrea, 1969) and positive sodium balance (Swales, Thurston, Queiroz & Medina, 1972). When the opposite kidney is left in situ (Goldblatt 2 kidney hypertension), exchangeable sodium is normal in established hypertension (Tobian et al., 1969), and, in the more marked degrees of blood pressure elevation at least, sodium balance is negative (Möhring, Möhring, Naumann, Philipp, Homys, Orth, Dauda, Kazda & Gross, 1975; Swales et al., 1972; Leenen, Scheeren, Omylanowski, Elema, Van der Wal & de Jong, 1975).

However, evidence on the changes in sodium balance during the early phases of blood pressure elevation is more contradictory. Our group could find no evidence of sodium retention in the immediately pre-hypertensive phases (Swales et al., 1972). Leenen et al. (1975) observed a positive sodium balance for the first 10 days after operation and this fell to control values in more severely hypertensive animals, whereas Möhring et al. (1975) demonstrated a positive sodium balance for longer periods. Thus the role of sodium retention in the genesis of the hypertension is an unresolved problem.

This study was designed to resolve these discrepancies by studying the effect of dietary salt depletion in each of these models of renal hypertension, first during the development of hypertension and then after its establishment. In addition, we have
measured the degree of sodium depletion produced by dietary restriction in normal and hypertensive animals.

**Methods**

**Animals**

White Wistar rats of either sex, weighing 150–250 g, were used throughout.

**Dietary study**

Twenty-eight animals were divided into four groups, depending on (i) whether the contralateral kidney was present or not and (ii) whether sodium depletion followed renal artery constriction immediately or after a period of normal salt diet.

*Group 1.* Goldblatt 2 kidney hypertensive rats, normal salt–low salt diet: \( n = 8 \). Hypertension was produced by placing a silver clip (0.2 mm internal diameter) on the left renal artery under ether anaesthesia with the opposite kidney undisturbed. After the operation the rats received normal rat chow containing 0.205 mmol of sodium/g and 0.163 mmol of potassium/g, and had free access to tap water for 21 days. Thereafter they were given a low sodium diet of equal calorie value but containing 0.0138 mmol of sodium/g and 0.190 mmol of potassium/g with distilled water *ad libitum* to drink.

*Group 2.* Goldblatt 1 kidney hypertensive rats, normal salt–low salt diet: \( n = 7 \). These were given the same dietary regime as the animals of group 1 but, 1 week before the left renal artery was clipped, the right kidney was removed.

*Group 3.* Goldblatt 2 kidney hypertensive rats, low salt–normal diet: \( n = 6 \). These were clipped according to the same procedure as for group 1 but immediately after surgery they received the low sodium diet for 21 days, followed by 21 days on normal sodium diet.

*Group 4.* Goldblatt 1 kidney hypertensive rats, low salt–normal salt diet: \( n = 7 \). These were prepared by the same procedure as group 2 but immediately after operation received low salt diet for 21 days, followed by 10 days on the normal salt diet.

The rats were weighed and their blood pressure was measured by an indirect photoelectric tail method (Swales & Tange, 1970), before renal artery clipping and twice weekly afterwards.

**Balance studies**

The effects of acute dietary sodium depletion were studied in a separate series of Goldblatt 2 (\( n = 8 \)) and Goldblatt 1 (\( n = 13 \)) rats, which had previously developed hypertension (9–45 days) on a normal salt diet, and a group of unoperated control animals (\( n = 11 \)). Each animal was placed in a metabolic cage and sodium balance studies were carried out according to the procedure previously described (Swales et al., 1972). After receiving a normal diet (presented as paste) with free access to distilled water for 5 days they were given the low salt diet. Each animal was weighed and the blood pressure measured before and after 3 days on low salt diet.

**Excision of ischaemic kidney**

Further groups of Goldblatt 2 (\( n = 11 \)) and Goldblatt 1 (\( n = 8 \)) rats with sustained hypertension on the normal diet were subjected to left nephrectomy under ether anaesthesia 28–50 days after renal artery constriction. The indirect blood pressure and weight were measured on several occasions before and 24 h after operation. In another group of Goldblatt 1 (\( n = 8 \)) rats nephrectomy was performed after treatment with low salt diet for 7–10 days.

All results are expressed as mean values \( \pm \text{SEM} \). Student's *t*-test was employed in the statistical analysis of the data.

**Results**

**Diet studies**

A significant degree of hypertension developed in both the Goldblatt 1 and 2 kidney rats (group 1 and group 2) receiving normal salt diet within the 21 days after renal artery clipping (Fig. 1). A 7.3% fall in body weight of the Goldblatt 2 and a 4.2% fall of the body weight of the Goldblatt 1 rats was observed when the low salt diet was introduced (Fig. 2), but the blood pressure did not change in either group.

The Goldblatt 1 and 2 kidney rats receiving low salt diet (group 3 and group 4) from day of operation developed hypertension more rapidly, which was unaffected by the change back to normal salt diet (Fig. 3). However, a small rise in body weight did occur at this point (Fig. 4). The initial blood pressure of the Goldblatt 1 kidney rats was slightly higher than that of the Goldblatt 2 animals and this appears to be the result of recent unilateral nephrectomy.
Dietary sodium and renal hypertension

**FIG. 1.** Blood pressure (mean±SEM) of Goldblatt 1 (- - - -) and Goldblatt 2 (——) rats after renal artery constriction (clip left renal artery: at arrow) on normal diet, followed by a period on low salt diet.

**FIG. 2.** Body weight (mean±SEM) of Goldblatt 1 (- - - -) and Goldblatt 2 (——) rats after renal artery constriction on a normal diet.

**FIG. 3.** Blood pressure of Goldblatt 1 (- - - -) and Goldblatt 2 (——) rats after renal artery constriction (clip left renal artery: at arrow) on low salt diet.

**FIG. 4.** Body weight of Goldblatt 1 (- - - -) and Goldblatt 2 (——) rats after renal artery constriction on low salt diet.

**TABLE 1.** Effects of low sodium diet on urine volume, sodium loss, body weight and blood pressure

Results show the total fall in body weight, change in sodium balance, with the body weight and blood pressure before and at the end of 3 days. The urine volume is the mean daily volume in three groups of animals on the day before institution of the low salt diet.

<table>
<thead>
<tr>
<th>Animals</th>
<th>Urine volume (ml/day)</th>
<th>Total sodium loss (mmol)</th>
<th>Initial body wt. (g)</th>
<th>Total body weight fall (g)</th>
<th>Initial blood pressure (mmHg)</th>
<th>Final blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 11)</td>
<td>17:8±3:11</td>
<td>1:15±0:19</td>
<td>175:3±7:59</td>
<td>10:0±1:78</td>
<td>92:5±4:22</td>
<td>92:5±4:72</td>
</tr>
<tr>
<td>Goldblatt 1</td>
<td>21:8±2:80</td>
<td>1:02±0:13</td>
<td>172:1±6:36</td>
<td>11:7±1:93</td>
<td>157:5±5:33</td>
<td>143:1±10:12</td>
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<td>hypertensive</td>
<td>(n = 13)</td>
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<td>(n = 8)</td>
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</table>
Sodium balance

Pilot studies indicated that maximum sodium depletion occurred by the end of the third day after commencement of the low salt diet; after this sodium balance was achieved. The low sodium diet caused a similar fall in body weight and loss of sodium in the Goldblatt hypertensive and normal rats, but a small non-significant fall in blood pressure (14·6 ± 8·19 mmHg; \( P > 0·1 \)) occurred only in the Goldblatt 1 rats (Table 1).

Effects of nephrectomy

Removal of the ischaemic kidney of eleven Goldblatt 2 kidney hypertensive rats restored the blood pressure to normal values with a fall from 176·4 ± 3·87 mmHg to 98·8 ± 2·39 mmHg (\( P > 0·001 \)). However, a smaller but significant change from 173·1 ± 5·34 mmHg to 132·5 ± 9·36 mmHg (\( P < 0·05 \)) was observed in eight Goldblatt 1 kidney hypertensive rats. In another eight Goldblatt 1 kidney animals given low salt before left nephrectomy, a significantly greater fall from 195·6 ± 20·6 mmHg to 113·8 ± 8·8 mm Hg occurred (\( P < 0·05 \)).

Discussion

The renal handling of sodium in Goldblatt 1 and 2 hypertension involves important differences. Thus in the one-kidney model the sodium-conserving action of renal ischaemia will be countered by the natriuretic effect of the increased tubular osmotic load (Wesson & Anslow, 1948), whereas in the two-kidney model raised perfusion pressure in the contralateral kidney will exert a natriuretic action (Lowitz, Stumpe & Ochwadt, 1968). Theoretically therefore dietary salt restriction might produce different degrees of sodium depletion in the two models with differing effects upon blood pressure. In the present work such differences in sodium excretion and associated loss of body weight were not statistically significant although urine volume was significantly greater in two-kidney hypertensive animals compared with either the one-kidney model or normal rats (Table 1). This finding is consistent with our previously published observations upon rats receiving a normal salt intake (Swales et al., 1972). In another earlier study with acute sodium depletion by peritoneal dialysis we were able to reduce the blood pressure of Goldblatt 1 kidney hypertensive animals, although not to normal levels (Swales & Tange, 1971). Later studies suggested that most rats with this form of hypertension were in positive sodium balance; on the other hand, sodium retention clearly was not an essential prerequisite since a minority of animals showed no such positive balance and yet were severely hypertensive (Swales et al., 1972).

Our results are consistent with those reported by Mikeshe, Mikeshe & Gross (1970) in that dietary sodium restriction of Goldblatt 1 hypertensive rats neither prevented the initial rise in blood pressure nor did it significantly ameliorate established hypertension. It is possible that renin secretion and sodium retention play a reciprocal role in this model. Thus Gavras, Brunner, Vaughan & Laragh (1973) found that neither infusion of angiotensin antagonist nor dietary salt depletion would reduce the blood pressure of Goldblatt 1 kidney hypertension when these manoeuvres were applied singly. Together, however, they produced a substantial reduction in blood pressure. Liard (1973) observed a similar synergism in lowering blood pressure between frusemide-induced sodium depletion and nephrectomy. In the present studies dietary sodium depletion also enhanced the blood pressure-lowering action of nephrectomy although two animals remained hypertensive after both procedures. These observations are therefore consistent with a balance of renal-humoral and volume-expansion mechanisms in Goldblatt 1 hypertension although extrarenal mechanisms may also perpetuate it. The more severe and acute sodium depletion produced by peritoneal dialysis may account for its hypotensive effect compared with that of dietary sodium depletion.

In the present study dietary salt restriction failed either to prevent the development of hypertension or ameliorate established hypertension in the Goldblatt 2 model. This observation has an important bearing upon pathogenesis of hypertension. On the basis of metabolic balance studies both Möhring et al. (1975) and Leenen et al. (1975) have suggested that an initial phase of sodium retention plays a role in the development of blood pressure elevation. Mikshe et al. (1970), using a similar experimental protocol to our own, did indeed find that dietary salt restriction prevented or reversed hypertension in this model. The sodium content of our diet was slightly lower than that used by Mikshe et al. and it produced a greater acute loss in weight, so that the discrepancy cannot be explained in terms of lesser degrees of sodium depletion in our animals. The explanation of this discrepancy...
must remain uncertain. The sodium retention observed by Leenen et al. (1975) and Möhring et al. (1975) was expressed as a proportion of rapidly increasing body weight and not in absolute terms, so that it is difficult to compare our balance data with their studies. However, the degree of sodium retention observed by these workers was clearly substantially less than the sodium loss produced by our low salt diet, which amounts to 10% of the rats' exchangeable sodium (Tobian et al., 1969). It seems therefore that sodium retention is not an essential factor in the development of Goldblatt 2 hypertension. It is noteworthy that sodium retention of a similar order to that observed by Leenen et al. can be produced in rats by unilateral nephrectomy (Swales et al., 1972) and sodium retention was maximal in the first few post-operative days and in the animals with a tighter clip (Leenen et al., 1975). Thus it is possible that the acute reduction in nephron mass was responsible for the sodium retention at this stage. Studies with an angiotensin antagonist have indicated that the renin-angiotensin system plays a vital role in the early phase of hypertension in the Goldblatt 2 model (Pals, Masucci, Denning, Sipos & Fessler, 1971; Brunner, Kirshman, Sealey & Laragh, 1971; Thurston & Swales, 1974). In longer standing Goldblatt 2 hypertension the antagonist induces a smaller fall in blood pressure (Thurston & Swales, 1974), and although sodium depletion enhanced its action the blood pressure remains well above normal levels (Gavras, Brunner, Thurston & Laragh, 1975). Since this agent does not therefore produce a fall in blood pressure to normal, another factor has to be invoked. In the absence of evidence that sodium retention fulfills this role, it seems likely that peripheral vascular changes induced by hypertension may be responsible.

Acknowledgments
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References


