Effect of Sodium Restriction on Renal Hypertension and on Renin Activity in the Rat

By L. W. Miksche, M.D., Ulrike Miksche, and F. Gross, M.D.

ABSTRACT

Control rats and rats with experimental renal hypertension due to unilateral stenosis of one renal artery received a standard diet (0.23% sodium) and a sodium-deficient diet (0.004% sodium), alternately, during which time blood pressure and plasma renin activity were determined. At the end of the experiment, renin content of the kidneys was measured.

In normotensive control rats, the sodium-deficient diet did not affect blood pressure, but plasma renin activity and renin content of the kidneys increased. In rats with renal hypertension, restriction of sodium supply was followed by a fall in blood pressure to normotensive levels, provided that an intact contralateral kidney was present. Similarly, sodium-deficient diet prevented the development of hypertension if given immediately after placing the clip on one renal artery. Restriction of sodium supply provoked a marked increase in plasma renin activity, whereas renin content of the ischemic kidney was only slightly, but significantly, higher than in rats with normal sodium intake. Contrary to this, in unilaterally nephrectomized rats with renal hypertension, neither hypertension nor plasma renin activity or renin content of the kidneys was affected by sodium-deficient diet. In control rats with unilateral nephrectomy, plasma renin activity was only half that of intact rats, and restriction of sodium provoked no more than an increase up to normal values of intact rats. Sodium loss by the contralateral kidney may contribute to both the antihypertensive effect of a sodium-deficient diet and the increase in plasma renin activity.

ADDITIONAL KEY WORDS sodium deficiency sodium excretion plasma renin activity kidney renin content unilateral nephrectomy kidney weight blood-pressure reduction

Sodium has been claimed to play a permissive role in the development of hypertension due to constriction of one or both renal arteries in the rat (1, 2). This conclusion was drawn from observations made in adrenalectomized rats, maintained with low doses of desoxycorticosterone acetate (DCA), which did not develop hypertension after the placing of a clip on one renal artery. On the other hand, a diet low in sodium was reported to have only an insignificant effect or none at all on the development or maintenance of that type of renal hypertension (3-5). Some of these papers, however, did not give details of the sodium content of the diet, and diets of varying sodium content had not been administered successively to the same animals. Furthermore, some studies referred to unilaterally nephrectomized rats, whereas in others, rats with both kidneys had been used. The present investigation has been undertaken to obtain more precise information on the role of sodium and of unilateral nephrectomy in the development and maintenance of hypertension due to renal ischemia. In addition, the effects of renal ischemia and of sodium deficiency, which both stimulate production and release of renin, have been studied with regard to their influence on plasma renin activity (PRA) and on renin content of the kidneys.
Material and Methods

Male Sprague-Dawley rats (SIV-50 strain), weighing 150 to 180 g, were used. Under ether anesthesia, the left kidney was exposed from a midline incision in the skin of the back, and a silver clip, 0.2 mm in width, was placed on the left renal artery. For the studies with unilaterally nephrectomized rats, the right kidney was removed at the time of clamping the left renal artery. In the corresponding controls, the right kidney was removed, using the same approach. During the experiments each rat was kept separately.

Systolic blood pressure was measured plethysmographically, under light ether anesthesia, once a week, according to the method of Wilson and Byrom (6). The mean of three subsequent readings was taken as the actual value.

As a standard diet, rat chow with a sodium content of 0.23% (96 mEq/kg) and tap water were given. The sodium-deficient diet was prepared according to Hartroft and Eisenstein (7) and consisted of casein (20%), saccharose (30%), dextrose (35%), cellulose (25%), corn oil (7%), sodium-free salt mixture (48%), and vitamin mixture (2%). The sodium content of this diet was 0.004% or 1.74 mEq/kg. Control groups were given. The sodium-deficient diet was switched to the standard diet. Three weeks later, all animals were killed. PRA was measured before the operation and 4 weeks after the operation, just before switching to the sodium-deficient diet.

Experiment 2.—Animals with a clip placed on the left renal artery and an untouched contralateral kidney were divided into two groups (C and D) of 16 and 25, respectively. After the operation, both groups received the standard diet for 4 weeks. For further study, only rats with a systolic blood pressure of 160 mm Hg or more were used. Group C was then put on the sodium-deficient diet with addition of 0.6% NaCl for 2 weeks, while group D received the sodium-deficient diet. At the end of this period (6 weeks after operation), eight rats of group C and 15 rats of group D were killed and PRA and renin content of the kidneys measured. The remaining animals were fed the standard diet for 4 more weeks. Subsequently, they were killed and PRA and renal renin determined. PRA was also determined before the operation and 4 weeks after the operation, just before switching to the sodium-deficient diet.

Experiment 3.—Two groups of 10 animals each (E and F) were operated as under experiment 2. Immediately after the operation, the rats of group E received the sodium-deficient diet with the addition of 0.6% NaCl, whereas the rats of group F had the same diet without additional salt. After 3 weeks, both groups were switched to the standard diet. Three weeks later, all animals were killed. PRA was measured before the operation and 3 and 6 weeks afterwards. Renal renin content was determined at the end of the experiment. Two rats of group F had complete necrosis of the left kidney and were excluded.

Experiment 4.—In two groups of 12 rats each (G and H), the left renal artery was clamped, and at the same time the right kidney was removed. During 3 weeks after the operation, both groups were fed the standard diet. Subsequently, group G received the sodium-deficient diet with the addition of 0.6% NaCl for 2 weeks, whereas group H had the same diet without additional salt. After this period, both groups had the standard diet again for 3 weeks, followed by another period of 2 weeks of sodium-deficient diet for group H and of the same diet with added 0.6% NaCl for group G. During the experiment, four rats of group G died and were eliminated. PRA was determined before the operation and 3, 4, 5, 8, and 10 weeks afterwards. Renal renin content was measured at the end of the experiment. Experiment 5.—In 23 rats the right kidney was removed, the left kidney remaining untouched. Subsequently, all animals received the standard diet for 4 weeks. Afterwards, the rats...
were divided into two groups of 13 and 10 animals each (J and K). The rats of group J were fed the sodium-deficient diet with the addition of 0.6\% NaCl for 2 weeks, whereas the rats of group K received the sodium-deficient diet. PRA was determined 6 weeks after nephrectomy.

**Results**

Experiment 1.—The effects of the sodium-deficient diet on the variables studied in intact rats are summarized in Table 1. Whereas sodium restriction had no influence on blood pressure, PRA was approximately three times higher than with the standard diet, and renin content of the kidneys was about doubled. These results correspond well with former observations (9, 10).

Experiment 2.—The data obtained in groups C and D are summarized in Table 2. During the 2-week period of sodium deficiency, body weight remained stable, but blood pressure fell from hypertensive to normotensive levels (Fig. 1). After these 2 weeks of sodium restriction, PRA had reached extremely high values, that were more than ten times normal and more than five times those measured in renal hypertensive animals on the standard diet. Renin content of the ischemic kidney was only slightly, but significantly, affected by sodium restriction, the values being about 20\% higher (P<0.01) than with the standard diet. In the contralateral, un-

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard diet (g)</th>
<th>Na-deficient diet (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>256.5 ± 8.2</td>
<td>253.2 ± 10.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>108 ± 4.6</td>
<td>112 ± 4.8</td>
</tr>
<tr>
<td>PRA*</td>
<td>148 ± 9.6</td>
<td>452 ± 40.8</td>
</tr>
<tr>
<td>Renin content of kidneys†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>45.0 ± 1.8</td>
<td>80.4 ± 3.4</td>
</tr>
<tr>
<td>right</td>
<td>41.3 ± 1.1</td>
<td>78.1 ± 1.8</td>
</tr>
<tr>
<td>Kidney weight (mg)</td>
<td>992 ± 30.8</td>
<td>990 ± 26.2</td>
</tr>
<tr>
<td>left</td>
<td>992 ± 30.8</td>
<td>990 ± 26.2</td>
</tr>
<tr>
<td>right</td>
<td>992 ± 25.3</td>
<td>974 ± 42.6</td>
</tr>
</tbody>
</table>

*Plasma renin activity, ng angiotensin-1\-2 hr\-1; 1\% angiotensin/g cortical tissue; 1\% group of animals.

**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of rats</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>115 ± 3.8</td>
<td>116 ± 3.1</td>
<td>105 ± 3.8</td>
<td>102 ± 3.6</td>
</tr>
<tr>
<td>PRA*</td>
<td>15 ± 1.4</td>
<td>16 ± 2.2</td>
<td>18 ± 1.8</td>
<td>16 ± 2.1</td>
</tr>
<tr>
<td>Renin content of kidneys†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>100 ± 7.8</td>
<td>110 ± 6.2</td>
<td>95 ± 8.6</td>
<td>97 ± 6.1</td>
</tr>
<tr>
<td>right</td>
<td>99 ± 7.3</td>
<td>95 ± 6.8</td>
<td>97 ± 8.5</td>
<td>96 ± 6.6</td>
</tr>
<tr>
<td>Kidney weight (mg)</td>
<td>989 ± 76</td>
<td>971 ± 69</td>
<td>1016 ± 86</td>
<td>1000 ± 87</td>
</tr>
<tr>
<td>left</td>
<td>989 ± 76</td>
<td>971 ± 69</td>
<td>1016 ± 86</td>
<td>1000 ± 87</td>
</tr>
<tr>
<td>right</td>
<td>989 ± 76</td>
<td>971 ± 69</td>
<td>1016 ± 86</td>
<td>1000 ± 87</td>
</tr>
</tbody>
</table>

All data are means ± SE. There were ten rats in each group.
Body weight (BW) and blood pressure (BP) of rats with unilateral stenosis of the renal artery, on a standard diet and on a sodium-deficient diet. In group C, 0.6% NaCl was added to the sodium-deficient diet. Ordinate: top curve; g; bottom curve; mm Hg. Abscissa; time in weeks after operation. OP: clamping of the left renal artery.

Experiment 3.—Sodium restriction also prevented the development of hypertension due to clamping one renal artery, and under these conditions, too, a marked increase in PRA occurred. The mean value, however, was only about half that determined under comparable conditions in experiment 2. Rats on the sodium-deficient diet had a delayed gain in body weight (Table 3). Blood pressure did not increase before the standard diet was given, but it reached hypertensive values in the animals that had salt added to the diet (Fig. 2). At the end of the experiment, the renin contents of the two kidneys were similar to those in experiment 2.

Experiment 4.—The results obtained in
unilaterally nephrectomized rats differ fundamentally from those of rats with an intact contralateral kidney. Neither hypertension nor PRA was affected by restriction of sodium, and increase in body weight was only slightly delayed (Table 4). Blood pressure did not drop significantly, remaining similar to values in rats with normal sodium supply (Fig. 3).

Experiment 5—Sodium restriction had no effect on the blood pressure of unilaterally nephrectomized rats, but after 6 weeks, PRA of rats with normal sodium intake (group J) was only half the normal value (Table 5). After 2 weeks of sodium-deficient diet, PRA in group K had reached the level of normal rats on standard sodium intake (group A).
Individual variations of PRA (Fig. 4) were more marked during periods of sodium restriction than during normal sodium intake, being most pronounced in rats with renal artery stenosis and preserved contralateral kidney (group D). On the other hand, only little variation was observed in unilaterally nephrectomized rats whose remaining kidneys were clamped (groups G and H).

The renin content of the kidneys (Fig. 5) increased in a similar way subsequent to sodium restriction (group B) and to clamping the renal artery (group C). Administration of the sodium-deficient diet was an additional stimulus to renin production of ischemic kidneys (group D). After unilateral nephrectomy, the renin content of the remaining ischemic kidney was unaffected by variations in sodium supply and was in the range of that of intact kidneys of rats receiving the standard diet (groups G and H).

Discussion

The effects of a sodium-restricted diet are of interest with respect to their influence on experimental renal hypertension and on release and production of renin. Marked reduction of sodium intake for 1 week is an effective means of reducing hypertension to approximately normal values, and by the same diet a postoperative increase in blood pressure can be prevented. However, the antihypertensive effect of sodium restriction depends on the presence of an intact contralateral kidney. In the unilaterally nephrectomized animal, the same sodium-deficient diet does not significantly influence an already established hypertension. This different response may at least in part explain the divergent results reported by former investigators who saw either no lowering at all or only a slight reduction in blood pressure during sodium restriction (11). Others, however, observed no difference in response to sodium restriction between renal hypertensive rats that were either unilaterally nephrectomized or had an untouched contralateral kidney (3).

Recently, an initial retention of sodium has been described in unilaterally nephrectomized rats with ischemia of the remaining kidney (12). In unilaterally nephrectomized dogs with hypertension due to renal artery stenosis, a negative sodium balance, induced by dietary sodium restriction and mercuhydrin, did not affect mean arterial blood pressure (13). In another study in dogs with renal artery stenosis and contralateral nephrectomy, sodium retention occurred during normal sodium intake, but sodium balance was negative, when a sodium-deficient diet was given (14).

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TABLE 5

<table>
<thead>
<tr>
<th>No. of rats</th>
<th>Body weight (g)</th>
<th>Systolic BP (mm Hg)</th>
<th>PRA*</th>
<th>Renin content of kidneys</th>
<th>Kidney weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group G</td>
<td>8</td>
<td>155</td>
<td>100</td>
<td>10.0</td>
<td>1.64</td>
</tr>
<tr>
<td>Group H</td>
<td>12</td>
<td>157</td>
<td>100</td>
<td>10.0</td>
<td>1.64</td>
</tr>
<tr>
<td>Group G</td>
<td>8</td>
<td>269</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Group H</td>
<td>12</td>
<td>300</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Group G</td>
<td>8</td>
<td>254</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Group H</td>
<td>12</td>
<td>319</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Group G</td>
<td>8</td>
<td>304</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Group H</td>
<td>12</td>
<td>333</td>
<td>103</td>
<td>6.7</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*ng angiotensin - ml⁻¹ - 12 hr⁻¹; fgroup of animals;

In both cases, blood pressure increased, but to a lesser degree during sodium deficiency. In the absence of the contralateral kidney, but the renal loss of sodium did not prevent the development of hypertension (15). However, when measuring blood pressure, the contralateral kidney eliminated more sodium than a normal kidney (16, 17). In micropuncture studies it has been demonstrated that the contralateral kidney in renal hypertensive rats excretes more sodium than a normal kidney (18). However, when measuring total exchangeable sodium, no difference was found between normotensive rats and rats with hypertension due to unilateral stenosis of the renal arteries (12). In sodium balance studies, an initial sodium retention has been observed in rats with hypertension. When blood pressure rose above 180 mm Hg, sodium loss could occur. This is explained by the contralateral kidney, which is then able to excrete sodium at a rate equal to the renal load. However, when the contralateral kidney is not available, the renal sodium load is not followed by sodium loss, and balance is maintained. The underlying mechanism of increased sodium excretion by the contralateral kidney is not clear, but exposure to elevated blood pressure may be at least one responsible factor (15, 19).

PRA and renin content of the kidneys rose subsequent to sodium restriction, confirming the decrease in sodium intake by the contralateral kidney. In both cases, blood pressure increased, but to a lesser degree during sodium deficiency. In the absence of the contralateral kidney, but the renal loss of sodium did not prevent the development of hypertension (15). However, when measuring blood pressure, the contralateral kidney eliminated more sodium than a normal kidney (16, 17). In micropuncture studies it has been demonstrated that the contralateral kidney in renal hypertensive rats excretes more sodium than a normal kidney (18). However, when measuring total exchangeable sodium, no difference was found between normotensive rats and rats with hypertension due to unilateral stenosis of the renal arteries (12). In sodium balance studies, an initial sodium retention has been observed in rats with hypertension. When blood pressure rose above 180 mm Hg, sodium loss could occur. This is explained by the contralateral kidney, which is then able to excrete sodium at a rate equal to the renal load. However, when the contralateral kidney is not available, the renal sodium load is not followed by sodium loss, and balance is maintained. The underlying mechanism of increased sodium excretion by the contralateral kidney is not clear, but exposure to elevated blood pressure may be at least one responsible factor (15, 19).

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Effect of a sodium-deficient diet on body weight (BW) and blood pressure (BP) in unilaterally nephrectomized rats with stenosis of the remaining renal artery. In group G, 0.6% NaCl was added to the sodium-deficient diet. Ordinate and abscissa as in Figure 1.

The degree of increase in PRA during sodium restriction was similar to the one following experimental stenosis of one renal artery, but when the two stimuli acted together, values of PRA up to ten times normal have been measured. This increase was more pronounced in rats on which sodium restriction was imposed when renal hypertension was already established than in rats which received the sodium-deficient diet immediately after the clamping of the renal artery. In contrast to the very marked increase in PRA was the only small additional elevation in renal renin content that sodium restriction elicited in the ischemic kidney. It may be concluded that renal artery...
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PLASMA RENIN ACTIVITY

As shown in FIGURE 4, plasma renin activity in rats on either a normal or a sodium-deficient diet. Column 1: intact rats; columns 2 and 3: rats with experimental hypertension due to stenosis of one renal artery; column 4: unilaterally nephrectomized rats with hypertension due to stenosis of the remaining renal artery; column 5: unilaterally nephrectomized rats. In each column, left: animals receiving standard diet; right: animals on sodium-deficient diet. n: number of rats per group. Ordinate: renin activity expressed in nanogram angiotensin per milliliter plasma per 12 hours of incubation.

Stenosis is already an almost maximal stimulus for the production of renin. Obviously, the capacity of the kidney to release renin is high enough to provide the largely increased PRA that occurred under the combined stimuli of renal ischemia and sodium-deficient diet. The pattern of distribution of renin between the ischemic and the contralateral kidneys was not affected by dietary restriction of sodium. In the contralateral kidney, renin content was...
Renin content of kidneys from normotensive and hypertensive rats on standard and sodium-deficient diets. Left: intact rats; middle: rats with unilateral stenosis of the renal artery; right: unilaterally nephrectomized rats with stenosis of the remaining renal artery. R = right kidney; L = left kidney. In the middle column, R refers to the contralateral, untouched kidney, L to the ischemic kidney. n: number of rats per group. Ordinate: renin content expressed as microgram angiotensin per gram fresh cortical tissue.

Renin content was similarly reduced, independent of sodium supply. Hence, sodium depletion is unable to induce an increase in renin content of the contralateral kidney. This observation suggests that the stimulus that provokes renin depletion in the contralateral kidney is stronger than sodium restriction.

In the absence of the contralateral kidney, renin content in the kidney with the arterial clamp was in the normal range, confirming results of various authors (22-24). It has been suggested that a normal renin content of the clamped kidney in the absence of the contralateral partner might be the consequence of sodium retention and a subsequent increase in total exchangeable sodium (12). By retaining sodium the clamped kidney in the unilaterally nephrectomized rat might maintain renin release within normal range (12). On the other hand, in sheep, after clamping one renal artery, a negative sodium balance was measured if the contralateral kidney was present, whereas after unilateral nephrectomy, sodium balance was maintained. PRA and renin content of the clamped kidneys were elevated in the presence of an untouched kidney, but were in the normal range after contralateral nephrectomy. Simultaneously with the elevated PRA, an increase...
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in plasma aldosterone concentration was measured (15).

In the rat, increased sodium excretion by the contralateral kidney does not prevent the development or maintenance of hypertension, provided the diet contains enough sodium. If, however, sodium supply is reduced, sodium loss may attain a degree that affects elevated blood pressure. In the absence of a contralateral kidney, the ischemic kidney maintains sodium balance. A consequence may be the development of a more stable and in most cases more pronounced hypertension in the unilaterally nephrectomized animal compared with the hypertension in animals with an intact contralateral kidney. Species differences are also of significance: it is more difficult in dogs than in rats to obtain a stable hypertension in the presence of a contralateral kidney, possibly because the dog is more sensitive to negative sodium balance.

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References


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