Changes in Sodium Balance and Hemodynamics during Development of Experimental Renal Hypertension in Dogs

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ABSTRACT

After unilateral nephrectomy and application of a Goldblatt clamp to the remaining renal artery, there was sodium retention of approximately 123 mEq in 15 days. At this time, blood pressure increased from 95 to 142 mm Hg without demonstrable changes in plasma volume or cardiac output. When the accumulation of sodium was prevented and a negative balance induced by a low sodium diet and a single dose of a diuretic agent postoperatively, the blood pressure increased from 102 to 139 mm Hg, but it increased further, to 155 mm Hg, after a normal sodium diet had been restored and there had been a gain of 189 mEq of sodium above control. The accumulation of sodium after application of the Goldblatt clamp does not appear to be necessary for the emergence of hypertension, but it does appear to play some part in determining the magnitude of the rise in pressure.

ADDITIONAL KEY WORDS cardiac output blood pressure plasma volume total peripheral resistance

The sodium ion is clearly essential for elevation in blood pressure only in the types of experimental hypertension resulting from an excessive intake of sodium chloride (1) or from the administration of DCA. In hypertension due to bilateral nephrectomy, an excessive accumulation of sodium has been shown to aggravate the condition, but there is doubt whether it is essential for its emergence (2). In the renal type of experimental hypertension, there is indirect evidence for abnormalities of sodium metabolism or distribution (3), but its role in the development of hypertension is not clear. The present study, therefore, attempted to determine by means of balance studies whether an increase in body sodium plays a role in the development of hypertension and simultaneously to follow the hemodynamic changes that occur with it.

Methods

Studies were conducted in trained unanesthetized dogs in which one catheter had been implanted in the right heart and another in the aorta. Blood pressure and cardiac output were measured at intervals of 3 to 5 days throughout the studies, along with plasma volume determinations by methods previously described (4). The animals were housed in metabolism cages, and except during specified periods, they were maintained on a diet of 56 mEq Na/day and given distilled water ad libitum. Urine was collected daily and analyzed for sodium by flame photometry. On the basis of previous measurements, a sodium loss of 8 mEq/day was assumed to occur from nonurinary sources, but in one animal from each group of experiments the total fecal loss of sodium was also determined for each experimental period. Feces were collected in sulfuric acid (300 ml conc. H₂SO₄ and 100 ml distilled water). Thereafter, an aliquot was taken for leaching of sodium with concentrated nitric acid and analysis by flame photometry.

Experiment 1 (Eight Dogs).—After at least 14 days, during which three control measurements were made, a left nephrectomy was performed under pentobarbital anesthesia, followed by...
Hemodynamic Changes and Sodium Balance during Development of Experimental Renal Hypertension

Table 1

<table>
<thead>
<tr>
<th>Day</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Total sodium intake (mEq/day)</th>
<th>Total sodium balance (mEq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>190</td>
<td>3.5</td>
<td>3.6</td>
<td>4.5</td>
</tr>
<tr>
<td>118</td>
<td>150</td>
<td>3.2</td>
<td>3.9</td>
<td>4.4</td>
</tr>
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<td>90</td>
<td>120</td>
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<td>2.7</td>
<td>3.1</td>
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<tr>
<td>79</td>
<td>119</td>
<td>1.7</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>78</td>
<td>118</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
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<tr>
<td>76</td>
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<td>75</td>
<td>114</td>
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<td>1.4</td>
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<td>74</td>
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<td>1.3</td>
<td>1.3</td>
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<tr>
<td>73</td>
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<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>72</td>
<td>108</td>
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<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>71</td>
<td>106</td>
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</tr>
<tr>
<td>70</td>
<td>104</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Control values. The mean of values obtained on three occasions before operation.

†Cumulative balance for day 1 is the change in balance between day 1 and day 15, and day 15 refers to the change between days 5 and 15. On day 15, therefore, the mean change from control was +123.3 mEq.

Significant differences from the values on the control days obtained by the significance ratio test: $\ddagger P < 0.001$; $\ddagger P < 0.01$.

Results

Experiment 1.—The individual results and mean values for the fourth and fifteenth postoperative days are given in Table 1. It will be seen that application of the Goldblatt clamp led to a mean increase of 46 mm Hg in blood pressure over the 15 days with no evident change in cardiac output or plasma volume, although there was a small fall in hematocrit of 3.5% over this period. Sodium balance was positive, averaging 123 mEq above the preoperative level in 15 days.

The control animals showed a fall in sodium balance after dietary restriction and nephrectomy (mean, -24 mEq), and after the restoration of the dietary sodium, this deficit was repaid in 2 days, with an overshoot of only 45 mEq in 15 days. The mean control blood pressure for this group was $100 \pm 8.7$ (sd) clamping of the right renal artery. The constriction was adjusted to give a reduction to 30% of the mean systemic pressure. This was measured by puncturing the vessel distal to the clamp with a 21-gauge needle connected to a P23D Statham pressure transducer and adjusting the occlusion accordingly. Since difficulties with dietary intake were anticipated over the operative period and it is known that sodium retention occurs after surgical operations, the animal was given no food or sodium on the day of operation, and for 4 days thereafter 10 mEq sodium was given daily with the diet. The intake was then restored to the normal 56 mEq/day and the sodium balance followed for 15 days. Plasma volume and hemodynamic measurements were made at intervals of 3 to 5 days after application of the clamp.

Controls for this experiment were five dogs submitted to the same procedure, except that the Goldblatt clamp once applied was removed.

Experiment 2 (Five Dogs).—This experiment was designed to follow the development of hypertension in the presence of sodium deficiency. The procedures were the same as in the previous experiment, except that the period on the low sodium diet was extended to 18 days. To insure that the dogs were in negative balance, the dietary sodium restriction (10 mEq/day) started 3 to 4 days before the operation to produce hypertension. In addition, a single dose of hydrochlorothiazide (2 mg/kg) was administered on the fifth or sixth postoperative day. The usual sodium intake of 56 mEq/day was restored to these animals 14 days after the operation and the sodium balance was measured for a further 10 days.
Hemodynamic changes and sodium balance in dog 97 show the development of hypertension during 18 days of sodium depletion and then for 10 days after the restoration of normal sodium intake. D indicates the day on which a single dose of a diuretic (hydrochlorothiazide) was administered orally.

mm Hg and on the fourth postoperative day it was 103 ± 11.4 mm Hg. For comparison with the next group of experiments, four of the animals were followed for 24 days after nephrectomy; the blood pressure had remained at the same level, 102 ± 10.6 mm Hg. There were no consistent changes in the other parameters.

The increase in sodium balance in the experimental group, however, could not be assumed to be necessary for the development of hypertension. The blood pressure had already climbed to 130 mm Hg on the fourth postoperative day in the presence of a small negative sodium balance, a mean of −17 mEq (Table 1).

Experiment 2.—The detailed results of this experiment in one animal (no. 97) are illustrated in Figure 1. The individual and mean data are given in Table 2 for the fourteenth and twenty-fourth postoperative days. After clamping the renal artery, an elevation of 37 mm Hg in blood pressure occurred in the presence of a substantial negative sodium balance (average, −120 mEq). After the normal sodium diet had been restored there was a pronounced rise in blood pressure to 155 mm Hg at the end of the next 10 days. Over
### TABLE 2

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean blood pressure</th>
<th>Cardiac output</th>
<th>Total peripheral resistance</th>
<th>Blood volume</th>
<th>Hematocrit</th>
<th>Cumulative sodium balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>107</td>
<td>130</td>
<td>181</td>
<td>2.6</td>
<td>2.3</td>
<td>3.1</td>
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<tr>
<td>4</td>
<td>110</td>
<td>130</td>
<td>146</td>
<td>3.4</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>175</td>
<td>150</td>
<td>2.8</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>104</td>
<td>122</td>
<td>141</td>
<td>3.1</td>
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<td>2.5</td>
</tr>
<tr>
<td>23</td>
<td>92</td>
<td>142</td>
<td>155</td>
<td>3.1</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td>MEAN</td>
<td>102</td>
<td>139</td>
<td>155</td>
<td>3.0</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>SD</td>
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<td>19.8</td>
<td>14.0</td>
<td>0.26</td>
<td>0.58</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*C = Control values. Mean of values obtained on three occasions before operation. Days 14 and 24 refer to the periods after operation.

†Cumulative balance. Day 14 refers to the change in balance between the third or fourth preoperative day and the fourteenth day after operation; day 24 refers to the change between days 14 and 24 after the operation; on day 24, therefore, the mean change from control was +189 mEq.

Significant differences from the values on the control days obtained by the significance ratio test: tP < 0.001; $P < 0.01; \#P < 0.05.

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**Discussion**

Application of the Goldblatt clamp leads to sodium retention, and after a few days, as a new level of body sodium is reached, the kidney appears to escape from this influence much as it does after the administration of DCA (5). Sodium retention after constriction of the renal artery of the order reported here has also been observed as an incidental finding in the study of the renal effects of DCA. A clip placed on the renal arteries of one member of a parabiotic pair of rats has been shown to reduce sodium output of that member and transfer of fluid to its partner (6). This accumulation of sodium probably explains the rise in extracellular fluid volume observed in the early stages of renal hypertension (7). It has not been possible to determine whether some or all of the retained sodium is held indefinitely within the body. Some retention probably does occur, since elevation of exchangeable sodium has been reported in rats with chronic hypertension (8).

Two mechanisms may account for this sodium retention: first, the clamp itself, by reducing renal artery pressure, can induce sodium retention (9); second, an increase in the renal secretions of aldosterone could lead to an increase in sodium retention (10). Although this was not demonstrate, the results of the Goldblatt clamp (11), and it is likely that the subsequent restoration of the renal circulation has been observed after application of the clamp (12). Increased renal artery pressure, as a result of constriction of the Goldblatt clamp, could raise sodium retention (9); second, a rise in the renal secretion of aldosterone is more likely to be observed in rats with chronic hypertension (10).

In the present study, the clamp itself, by reducing renal artery pressure, can induce sodium retention (9); second, an increase in the renal secretions of aldosterone could lead to an increase in sodium retention (10). Although this was not demonstrated, the results of the Goldblatt clamp (11), and it is likely that the subsequent restoration of the renal circulation has been observed after application of the clamp (12). Increased renal artery pressure, as a result of constriction of the Goldblatt clamp, could raise sodium retention (9); second, a rise in the renal secretions of aldosterone is more likely to be observed in rats with chronic hypertension (10).
be considered to be abnormal in the face of sodium retention.

Since sodium retention increases the pressor response to angiotensin (11), it is also possible that a normal renin secretion, and by inference, angiotensin level, maintained after application of the clamp, could act as a vasocostrictor agent in the presence of sodium retention.

In conclusion, therefore, these experiments show that sodium retention is not essential for the initial elevation in blood pressure in renal hypertension in dogs, but the sodium ion does play a role in determining the level of blood pressure. Since intervals of days passed between hemodynamic measurements, it is impossible to say whether a period of elevated cardiac output occurred with the sodium retention. The elevation in blood pressure, however, appears to be due entirely to an increase in peripheral resistance. It remains, therefore, to be ascertained how the sodium retention results in an additional increase in peripheral resistance.

References
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