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 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. 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 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 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.

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>
<thead>
<tr>
<th>Dog</th>
<th>Mean blood pressure Day 15 (mm Hg)</th>
<th>Cardiac output Day 15 (L/min)</th>
<th>Total peripheral resistance Day 15 (units)</th>
<th>Blood volume Day 15 (ml)</th>
<th>Hematocrit Day 15 (%)</th>
<th>Cumulative sodium balance Day 15 (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>104</td>
<td>160</td>
<td>30</td>
<td>48</td>
<td>42</td>
<td>+19</td>
</tr>
<tr>
<td>72</td>
<td>90</td>
<td>120</td>
<td>28</td>
<td>38</td>
<td>60</td>
<td>+7</td>
</tr>
<tr>
<td>74</td>
<td>118</td>
<td>150</td>
<td>54</td>
<td>71</td>
<td>58</td>
<td>-22</td>
</tr>
<tr>
<td>79</td>
<td>93</td>
<td>130</td>
<td>44</td>
<td>80</td>
<td>60</td>
<td>-60</td>
</tr>
<tr>
<td>83</td>
<td>90</td>
<td>140</td>
<td>45</td>
<td>60</td>
<td>50</td>
<td>-6</td>
</tr>
<tr>
<td>85</td>
<td>78</td>
<td>140</td>
<td>32</td>
<td>80</td>
<td>66</td>
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<tr>
<td>87</td>
<td>98</td>
<td>140</td>
<td>30</td>
<td>28</td>
<td>73</td>
<td>38</td>
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<td>140</td>
<td>35</td>
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<td>38</td>
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<tr>
<td>MEAN</td>
<td>96</td>
<td>130</td>
<td>54</td>
<td>54</td>
<td>62</td>
<td>19</td>
</tr>
<tr>
<td>SD</td>
<td>11.3</td>
<td>142</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>13</td>
</tr>
</tbody>
</table>

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

+Cumulative balance for day 4 is the change in balance between day 1 and 4, 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: *P < 0.001; †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. 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 45 mEq in 15 days. The mean control blood pressure for this group was 100 ± 8.7 mm Hg.

The renal artery clamp was removed after 15 days, and the mean sodium balance was measured for a further 10 days.

The sodium content of the blood was determined by the photometric method of Rill and the sodium concentration of the plasma by the method of Fiske and Subbarow. The data obtained were then plotted on a graph to show the relationship between the sodium content of the blood and the sodium content of the plasma.
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

Hemodynamic Changes Occurring with the Development of Hypertension when the Normal Increase in Sodium Balance Is Delayed by a Period of Fourteen Days on a Low Sodium Diet

<table>
<thead>
<tr>
<th></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>Dog 97</td>
<td>107</td>
<td>120</td>
<td>181</td>
<td>2.6</td>
<td>2.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Dog 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>Dog 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>Dog 7</td>
<td>104</td>
<td>122</td>
<td>141</td>
<td>3.1</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Dog 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><strong>Mean</strong></td>
<td>102</td>
<td>139</td>
<td>159</td>
<td>3.0</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>6.6</td>
<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: †P < 0.001; ‡P < 0.01; ††P < 0.05.

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 accumulation 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, however, to continue the balance study long enough to determine whether some or all of the retained sodium is held indefinitely within the body. Some retention probably does occur, since the sodium level of rats with chronic hypertension has been reported to be elevated (8).

Two mechanisms may account for this retention. First, the clamp itself, by reducing renal artery pressure, can induce sodium retention (9); second, a rise in the renin level occurs after constriction of the renal artery (10), and it is likely that the subsequent restoration of the sodium retention by the clamp to normal levels results from this rise in renin secretion. Application of the Goldblatt clamp leads to an increased secretion of renin by the kidney, and thus, it has at least two mechanisms to account for this sodium retention. The renin level of renin might rise to an extra level during constriction of the renal artery and remain at this level during constriction of the renal artery.
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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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