Arterial Wall Potassium in Renal Hypertensive Rats

By S. CHARLES FREED, M.D., SHIRLEY ST. GEORGE, PH.D., AND RAY H. ROSENMAN, M.D.

An elevation of potassium content of the aorta is found in renal hypertensive rats. Reduction of hypertension by potassium deprivation is followed by a proportional decrease in the aorta potassium content. Restoration of hypertension in such rats by cortisone administration is associated with a return of the aorta potassium content to the previous elevated levels. It is suggested that the potassium content of the arteries influences arterial tone and, by altering peripheral vascular resistance, may be a significant factor in blood pressure regulation.

FROM REPEATED observation in this laboratory, it has been suggested that potassium plays an active role in the regulation of blood pressure. Additional support to this concept may be obtained from the results reported by Tobian and associates, who demonstrated an increase in potassium content of the aortas of rats made hypertensive by several methods, renal ligation, DCA administration, and adrenal regeneration. Daniel and Dawkins have partially confirmed this finding in renal and spontaneous hypertensive rats. On the other hand, we have recently shown that hypotensive rats have a substantially decreased aorta potassium content.

In order to demonstrate more conclusively the dynamic role of potassium in the regulation of blood pressure, the following experiments were designed: (a) to confirm the results of Tobian and associates on the elevated potassium content of the aorta in renal hypertension, (b) to determine the changes in the potassium (and sodium) concentration in the aortas of such rats following depression of blood pressure due to potassium deprivation, and (c) to study the cation concentrations after restoration of the blood pressure to the previous hypertensive levels induced by cortisone administration.

METHODS

Effect of Renal Hypertension on the Sodium and Potassium Content of the Aorta. A group of 6 week old male rats (Long-Evans) was subjected to the Grollman procedure for the induction of hypertension, i.e., uninephrectomy and a figure-eight ligature on the remaining kidney. Blood pressure readings were determined weekly by the microphonic manometer, and at the end of 6 weeks, the rats were separated into two groups: hypertensives, demonstrating a systolic blood pressure above 140 mm. Hg, and normotensives, with blood pressures under 130 mm. Hg systolic. The renal ligated hypertensive and normotensive rats, as well as a group of intact control rats, were killed. The aortas were removed, as described by Tobian and Binion, and analyzed for sodium and potassium by the flame photometer method used in this laboratory.

Effect of Potassium Deprivation on Sodium and Potassium Content of the Aortas of Hypertensive Rats. A group of renal ligated rats whose systolic blood pressures averaged 166 mm. Hg systolic was fed a diet prepared synthetically, containing 0.006 per cent potassium which has been repeatedly demonstrated to lower the blood pressure of hypertensive and normal rats. After ingesting this diet for 6 weeks there was a significant depression of blood pressure. A group of normal rats fed this diet for a similar interval developed hypotension. Both groups were killed and the aortas were removed for sodium and potassium analyses.

The Effect of Cortisone on Sodium and Potassium Content of the Aortas of Hypertensive Rats Subjected to Potassium Deprivation. A group of renal ligated hypertensive rats was subjected to the low potassium diet for 6 weeks, at the end of which time the average systolic blood pressure was reduced from an average of 174 mm. Hg to 132 mm. Hg. The rats were then injected subcutaneously with 2 mg. cortisone acetate daily for 5
TABLE 1.—Electrolyte Composition of Aortas of Renal Hypertensive Rats on Normal and Low K Diets

<table>
<thead>
<tr>
<th>Group no.</th>
<th>No. of rats</th>
<th>Blood pressure mm./Hg</th>
<th>Serum K mEq./L.</th>
<th>Serum Na mEq./L.</th>
<th>Aorta* K mEq./Kg.</th>
<th>Aorta* Na mEq./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>28</td>
<td>114</td>
<td>5.2</td>
<td>146</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(92-124)</td>
<td>±0.18†</td>
<td>±1.0</td>
<td>±1.8</td>
</tr>
<tr>
<td>2</td>
<td>Figure 8 ligature Normotensive</td>
<td>10</td>
<td>116</td>
<td>5.1</td>
<td>142</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(96-136)</td>
<td>±0.28</td>
<td>±1.1</td>
<td>±2.8</td>
</tr>
<tr>
<td>3</td>
<td>Figure 8 ligature Hypertensive</td>
<td>12</td>
<td>171</td>
<td>4.9</td>
<td>143</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(148-194)</td>
<td>±0.17</td>
<td>±1.3</td>
<td>±3.8</td>
</tr>
<tr>
<td>4</td>
<td>Figure 8 ligature Hypertensive on low K diet</td>
<td>8</td>
<td>129</td>
<td>2.9</td>
<td>176</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(110-152)</td>
<td>±0.20</td>
<td>±7.1</td>
<td>±5.1</td>
</tr>
<tr>
<td>5</td>
<td>Normal on low K diet</td>
<td>12</td>
<td>82</td>
<td>2.8</td>
<td>144</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(66-92)</td>
<td>±0.16</td>
<td>±3.8</td>
<td>±5.1</td>
</tr>
</tbody>
</table>

*Fat-free dry weight.
†Standard deviation.

RESULTS

In table 1 it can be observed that the potassium concentration in the aortas of hypertensive rats (group 3) was approximately 1.5 percent higher than that of the normal animals (group 1). There was no corresponding elevation of potassium concentration in the serum. The sodium content of the aortas of hypertensive rats was slightly higher than that of the renal ligated normotensive rats, but not significantly higher than that of the intact animals. It can also be seen that there was an elevation in potassium concentration of the aortas of normotensive renal ligated rats (group 2). Following the ingestion of a diet practically devoid of potassium, the blood pressure of hypertensive rats became reduced to approximately normal levels (group 4). In such rats the potassium content of the aorta was likewise decreased to normal values. However, the concentration of potassium in the aortas of intact controls on this potassium-free diet declined to values which were considerably below normal, coincident with hypotensive blood pressure levels (group 5).

In table 2, two significant findings may be observed. In the previously hypertensive rats whose blood pressure and aorta potassium content were reduced to normal levels through potassium deprivation, the administration of cortisone induced a restoration of blood pressure to hypertensive levels, (group 8). At the same time, there was an increase in the concentration of potassium in the aortas even though the serum potassium remained below normal. In contrast, the operated normotensive rats who demonstrated an elevation of aorta potassium content responded to cortisone treatment by a reduction of the aorta potassium to the normal concentration (group 7).

DISCUSSION

The increase in potassium content of the aortas of rats with renal hypertension, in the above experiment, confirms the findings of Tobian and associates. However, we were able to detect only a slight increase in sodium content in the aortas of these hypertensive rats, as compared to the more marked elevation in sodium content reported by these investigators.

The mechanism by which an increase in aorta potassium content might induce hyperten-
TABLE 2.—Electrolyte Composition of Aorta of Renal Hypertensive Rats on Low K Diet after Cortisone Treatment

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Initial blood pressure mm./Hg</th>
<th>Subsequent blood pressure mm./Hg</th>
<th>Serum K mEq./L.</th>
<th>Na mEq./L.</th>
<th>Aorta* K mEq./Kg.</th>
<th>Na mEq./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Normal + cortisone</td>
<td>8</td>
<td>116</td>
<td>122</td>
<td>5.0</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(96-122)</td>
<td>(114-132) ±0.20</td>
<td>±2.1</td>
<td>±1.4</td>
</tr>
<tr>
<td>7</td>
<td>Figure eight ligature Normotensive + cortisone</td>
<td>8</td>
<td>126</td>
<td>134</td>
<td>5.4</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(110-132)</td>
<td>(116-156) ±0.16</td>
<td>±3.2</td>
<td>±3.2</td>
</tr>
<tr>
<td>8</td>
<td>Figure eight ligature Hypertensive on low diet K + cortisone</td>
<td>8</td>
<td>132</td>
<td>172</td>
<td>3.2</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(104-142)</td>
<td>(142-220) ±0.14</td>
<td>±1.7</td>
<td>±2.9</td>
</tr>
</tbody>
</table>

*Fat-free dry weight.
†Standard deviation

Discussion was discussed by Tobian and associates, who considered the possibility that this increase in potassium induces a stronger contraction of the actomyosin of the arterial smooth muscle and thus presumably heightens peripheral resistance. Tobian more recently has been inclined to the concept that the increase in peripheral resistance might stem from a narrowing of the lumen of the peripheral vascular system, due to "water logging," as indicated by the elevation in sodium (and potassium) content of the aortas in their hypertensive rats. However, it would appear from our data that the increased potassium content in the aorta (and the arterial system by extrapolation) may have more physiologic significance than the increase in sodium content. This is supported by the work of Bohr and associates, who demonstrated that potassium increased while sodium depressed contractions of aorta strips in vitro.

In both hypertensive and normal rats, depression of blood pressure through potassium deprivation parallels the decrease in aorta potassium content. It might be argued that these findings have little physiologic relationship and may simply indicate a state of potassium deficiency which would be reflected in any tissue. It has been amply demonstrated, however, that various tissues respond differently to potassium depletion. Thus, myocardium is notoriously more resistant than is skeletal muscle in losing potassium, and the gastrointestinal tract is also relatively resistant to reductions in potassium content. Furthermore, rats with DCA hypertension show a loss of potassium from blood and skeletal muscle, but a gain in aorta potassium content. Thus it is hazardous to generalize on the direction and amount of change in potassium content of one tissue from results obtained in another tissue.

Additional evidence that the potassium content of the arterial vasculature has a dynamic and specific role in regulation of blood pressure may be observed in table 2, group 8. Cortisone administration, to previously hypertensive rats who were deprived of potassium until their blood pressure and aorta potassium content were lowered to normal values, induced a return of blood pressure to hypertensive levels. At the same time there was an elevation of the potassium content in the aortas to the formerly high concentration. It is noteworthy that blood, skeletal muscle, and myocardium did not show any appreciable increase in potassium content under these conditions. It seems reasonable to deduce, in view of the present experimental results, that cortisone restores hypertension in these rats.
perhaps, by increasing the arterial tone through elevation of the arterial content of potassium.

Mention should be made of the potassium content of the aortas of renal ligated normotensive rats. Tobian and Binion obtained similar results in their "operated normotensive" animals. The significance of such findings is obscure. It is tentatively suggested, however, that the added increment of potassium in the aortas of the "operated normotensive" differs physiologically from that of the hypertensive ones. This suggestion is based on the results following cortisone administration. The aorta potassium content of the "operated normotensive" rats was decreased to normal values after such treatment (group 7). On the other hand, cortisone administration increased the potassium content of the aortas of renal-ligated potentially hypertensive animals that were made normotensive by potassium deficiency (group 8).

The mechanism by which renal ligation induces an increase in aorta potassium content is not clear. It is obviously not due to a potassium "flooding" from failure of the kidney to excrete this cation, since no other tissue including blood shows such an increase. It is more likely due to the effect of some as yet unknown disturbance in renal function. In this regard, it may be significant that the hypertension induced by DCA and adrenal regeneration, both of which cause an increase in aorta potassium content, may involve a renal factor, since it is essential to remove one kidney in order to "sensitize" the rats for the induction of hypertension by those procedures.

**Summary**

In renal hypertensive rats, the aorta potassium content is significantly higher than normal. The sodium content is only slightly elevated. Reduction of blood pressure through potassium deprivation is associated with a lowered aorta potassium content. Cortisone administration to potassium-deficient hypertensive rats restores blood pressure and aorta potassium content to the previous elevated levels.

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