Effect of Adrenalectomy upon the Pressor Action of Potassium in Hypotensive, Potassium-Deficient Rats

By S. Charles Freed, M.D., Ray H. Rosenman, M.D., and Malcolm K. Smith, A.B.

The administration of potassium to hypotensive, potassium-deficient rats results in a prompt restoration of their lowered blood pressure to normotensive levels. Similar repletion of the potassium deficit in adrenalectomized rats is only partially effective in restoring the blood pressure to normotensive levels. The spontaneous retention of potassium which occurs in potassium-deficient rats following adrenalectomy fails to restore lowered blood pressures to normotensive values.

It has been repeatedly demonstrated in this laboratory that when either normotensive or hypertensive rats are deprived of dietary potassium, blood pressure falls to hypotensive and normotensive levels, respectively. Although this depressor effect is associated with a somewhat diminished peripheral vascular responsiveness to pressor substances, its mechanism has not been fully clarified. It is not known, for example, whether the alterations of circulatory dynamics induced by potassium depletion result directly from a diminished content of potassium of the vascular tissues or whether they are mediated in part through changes in other organs such as the adrenal glands. In this regard, we have found that the administration of cortisone restores the lowered blood pressures of previously normotensive and hypertensive rats to their respective control levels, without correction of their potassium depletion. This evidence suggests that potassium deficiency might in some way induce a suppression of adrenal cortical steroid secretion and through this mechanism induce the depressor effect.

In order to determine whether the adrenal cortex is essential to the restoration of the blood pressure normally observed following such potassium repletion, potassium was administered to hypotensive, potassium-deficient rats in the absence of the adrenals.

I. THE EFFECT OF ADMINISTRATION OF POTASSIUM UPON THE BLOOD PRESSURE OF 24 HOUR-ADRENALECTOMIZED, POTASSIUM-DEFICIENT RATS

Material and Methods. Two groups of male rats, 13 weeks old, (Long-Evans) were subjected to a one-stage bilateral adrenalectomy. One group (I) of 10 rats ingested a potassium-deficient diet during the previous eight-week interval, the second group of six rats (II) being maintained upon stock ration. Twenty-four hours postoperatively each rat was injected subcutaneously with 4 ml of isotonic (1.14 per cent) solution of potassium chloride. Blood pressures were obtained with the microphonic manometer in all rats prior to injection of potassium chloride solution, and again in 1 and 24 hours. For further control purposes similar studies were done in animals not adrenalectomized but which were given diets as above, group III consisting of 10 rats fed the potassium-deficient diet and group IV of six rats fed stock ration.

Results. The results are shown in table 1. The subcutaneous injection of isotonic potassium chloride solution into potassium-depleted rats adrenalectomized 24 hours previously (Group I) induced a rise in blood pressures from an initial average of 76 mm. Hg to 90 mm. Hg after one hour and to 98 mm. Hg after 24 hours. However, the injection of potassium chloride solution into intact, potassium-deficient rats (group III) induced a greater rise in blood pressures, from an initial average of 79 mm. Hg to 94 mm. Hg in one hour and to an average...
TABLE 1.—Effect of Potassium Administration upon Blood Pressure of 24-Hour Adrenalectomized, Potassium-Deficient Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Rats</th>
<th>Avg. Wt. (Gm.)</th>
<th>Diet</th>
<th>Adrenalectomy</th>
<th>Avg. and Ranges of Systolic Blood Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>183</td>
<td>K-Deficient</td>
<td>Yes</td>
<td>Prior to KCl Injection After KCl Injection 1 Hr. 24 Hrs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76 (60-84) 90 (60-104) 98 (60-110)</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>210</td>
<td>Stock</td>
<td>Yes</td>
<td>110 (94-120) 73 (88-90) 96 (70-116)</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>174</td>
<td>K-Deficient</td>
<td>No</td>
<td>70 (66-94) 94 (82-116) 116 (90-142)</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>200</td>
<td>Stock</td>
<td>No</td>
<td>114 (96-120) 93 (64-110) 112 (100-126)</td>
</tr>
</tbody>
</table>

of 116 mm. Hg 24 hours after the injection. On the other hand, the injection of potassium chloride solution induced a transient fall of blood pressure in the adrenalectomized and in intact rats fed stock ration (groups II and IV).

A similar experiment was then attempted in which potassium was injected into potassium-deficient rats which were adrenalectomized three days and 30 days previously.

II. EFFECT OF ADMINISTRATION OF POTASSIUM UPON THE BLOOD PRESSURE OF CHRONIC, ADRENALECTOMIZED, POTASSIUM-DEFICIENT RATS

Material and Methods. Three groups of male rats, 5 weeks old, (Long-Evans) were fed the potassium-deficient diet during a preliminary eight-week interval. Group I consisted of five rats which remained intact. Group II consisted of 10 animals which were bilaterally adrenalectomized three days prior to study, and group III comprised 11 rats which were adrenalectomized 30 days prior to study. In each instance blood pressures were obtained prior to, and 1 and 24 hours after a subcutaneous injection of 4 ml. of isotonic solution of potassium chloride. As controls, similar studies also were performed in 10 rats fed stock ration, of which five remained intact and the remainder were adrenalectomized three days previously. As a further control it was established that sham-operated rats reacted as intact rats to administration of potassium.

Results. The blood pressure responses are shown in table 2. It can be noted that, as in the previous experiment, the intact potassium-deficient rats (group I) responded to the administration of potassium chloride solution with a rapid restoration of their blood pressures from an average of 83 mm. Hg to 102 mm. Hg after one hour and to 107 mm. Hg after 24 hours. In contrast, the potassium-deficient rats which were adrenalectomized three days previously (group II) showed only a slight elevation of blood pressure one hour after potassium chloride administration, from an average of 84 mm. Hg to 88 mm. Hg, and a moderate further elevation to 97 mm. Hg by 24 hours. In adrenalectomized, potassium-deficient rats operated upon 30 days* previously (group III),

from an average of 83 mm. Hg to 102 mm. Hg after one hour and to 107 mm. Hg after 24 hours. In contrast, the potassium-deficient rats which were adrenalectomized three days previously (group II) showed only a slight elevation of blood pressure one hour after potassium chloride administration, from an average of 84 mm. Hg to 88 mm. Hg, and a moderate further elevation to 97 mm. Hg by 24 hours. In adrenalectomized, potassium-deficient rats operated upon 30 days* previously (group III),

* After adrenalectomy, retention of potassium contributes to the morbidity and mortality of rats. Restriction of potassium intake permits about 30 per cent of the adrenalectomized rats to survive 30 days or longer (unpublished experiments).
the administration of potassium chloride also induced only a slight rise, from an average of 84 mm. Hg to 87 mm. Hg after one hour. By 24 hours, five animals had died, and in the remaining animals there was no change in blood pressure in two, a slight rise in one, and a fall of blood pressure in three. Injection of potassium chloride solution into the rats fed stock diet failed to affect significantly the blood pressures of the intact animals (group IV), but induced a transient fall of blood pressure in the adrenalectomized animals (group V).

III. The Effect of Adrenalectomy upon the Blood Pressure and Tissue Potassium Content of Potassium-Deficient Rats

It is well known that following adrenalectomy, the serum and tissue content of potassium increases. We have repeatedly observed a significant accumulation of potassium in adrenalectomized rats even though they were previously depleted of body potassium and maintained on a potassium-deficient diet postoperatively. Experiments in progress devised to account for the retention of potassium in similar rats indicate that this retained cation is probably derived from the breakdown of protein combined with the inability to excrete the potassium normally. The spontaneous changes of blood pressure were therefore studied in hypotensive, potassium-deficient rats following adrenalectomy in order to determine whether the postoperative retention of potassium would elevate the blood pressures of such rats.

Material and Methods. A series of male rats, 5 weeks old, was fed the potassium-deficient diet for eight weeks, following which six of the animals (group I) were sacrificed for analyses of potassium concentration of skeletal muscle (thigh), myocardium, and serum, as previously described. The remaining potassium-deficient rats were subjected to bilateral adrenalectomy. Potassium content of the various tissues was determined in 10 of the adrenalectomized rats (group II) on the third postoperative day, in seven (group III) on the fourteenth day, and in 11 rats (group IV) 30 days postoperatively. In all instances the blood pressures were obtained prior to sacrifice. For further control purposes, similar studies also were performed in a series of 11 rats fed stock ration, of which five were sacrificed 14 days following adrenalectomy (group V) and the other six rats remained intact (group VI).

<p>| Table 3.—Effect of Adrenalectomy upon Blood Pressure and Potassium Concentrations of Potassium-Deficient Rats |
|----------------------------------------------------------|----------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Rats</th>
<th>Avg. Wt. (Gm.)</th>
<th>Adrenalectomy</th>
<th>Avg. and Range of Systolic Blood Pressure (mm. Hg)</th>
<th>Avg. and Ranges of K Concentration in mEq./L. of Wet tissue weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum (mEq./L.)</td>
<td>Muscle (mEq./Kg.)</td>
</tr>
<tr>
<td>I.</td>
<td>6</td>
<td>160</td>
<td>None</td>
<td>81 (86-92)</td>
<td>2.9 ± 0.31 (2.0-3.1)</td>
</tr>
<tr>
<td>II.</td>
<td>10</td>
<td>190</td>
<td>3 days</td>
<td>84 (80-87)</td>
<td>4.1 ± 0.20 (3.0-4.6)</td>
</tr>
<tr>
<td>III.</td>
<td>7</td>
<td>182</td>
<td>14 days</td>
<td>75 (54-98)</td>
<td>4.4 ± 0.11 (3.8-4.8)</td>
</tr>
<tr>
<td>IV.</td>
<td>11</td>
<td>250</td>
<td>30 days</td>
<td>84 (70-110)</td>
<td>6.8 ± 0.91 (5.2-8.4)</td>
</tr>
<tr>
<td>V.</td>
<td>5</td>
<td>157</td>
<td>14 days</td>
<td>79 (56-106)</td>
<td>8.4 ± 0.20 (7.9-8.9)</td>
</tr>
<tr>
<td>VI.</td>
<td>6</td>
<td>200</td>
<td>None</td>
<td>116 (90-124)</td>
<td>4.9 ± 0.11 (4.6-5.2)</td>
</tr>
</tbody>
</table>

* Data from related experiments in which the tissue potassium was determined on the basis of both wet weight and fat-free dry weight in similar rats demonstrated that there was not sufficient difference in values to alter the significance of the above results.
Results. Table 3 contains the data from this experiment. It can be seen that a progressive rise of potassium concentration occurred in the serum and skeletal muscle of the adrenalectomized, potassium-deficient rats (groups II, III, IV), despite maintenance upon the deficient diet. However, there was no significant rise of potassium concentration in the myocardiums of the latter animals.

Despite the rise to normal values of serum potassium which occurred in the adrenalectomized, potassium-deficient rats (groups II, III, IV), their blood pressures remained at hypotensive levels, similar to the values observed in the intact potassium-deficient rats (group I). As expected, a considerable rise of serum potassium concentration and a fall of blood pressure occurred in the rats fed stock ration which were sacrificed 14 days after adrenalectomy (group V), when compared to the values of intact control rats fed stock diet (group VI).

Discussion

As we have previously demonstrated, prolonged deprivation of dietary potassium caused a marked lowering of the rat's blood pressure. This depressor effect is apparently a specific response to potassium deficiency, since the administration of potassium alone promptly restored the blood pressure to control levels. We have suggested that this depressor effect may be in part the result of a suppression of adrenal cortical function induced by chronic potassium deprivation, a postulate supported by our finding that administration of cortisone to potassium-deficient rats restored their lowered blood pressures to control levels, without alleviating their potassium-depleted state.

The present experiments confirmed previous observations that injection of potassium rapidly restores the lowered blood pressures of potassium-deficient rats to normotensive levels. On the other hand, injection of potassium into similar potassium-deficient rats only partially restored blood pressures following removal of the adrenals. Furthermore, the spontaneous retention of potassium occurring after adrenalectomy in other potassium-deficient rats did not result in a rise of the lowered blood pressures. This suggests, of course, that the full restorative effect of acute and chronic potassium repletion upon the blood pressure of potassium-deficient, hypotensive rats requires the presence of the adrenal glands.

The possibility was considered that the failure of potassium administration to restore the lowered blood pressures of adrenalectomized, potassium-deficient rats to control levels might have been due to the loss of peripheral vascular responsiveness consequent to adrenal ablation itself. Thus, Zweifach and associates observed that the peripheral vasculature of rats undergoes a loss of vasomotion and a decreased arteriolar tone within three days of the removal of the adrenals. Nevertheless, unpublished data from this laboratory have demonstrated that potassium-deficient rats, adrenalectomized three days previously, respond to the intravenous injection of noradrenaline with a rise in blood pressure essentially similar to that of intact potassium-deficient rats. It seems possible, therefore, that adrenal insufficiency, per se, was not the major factor in the subnormal blood pressure response to potassium administration observed in the hypotensive, potassium-deficient rats one and three days after adrenalectomy. However, this probably underlies the failure of the adrenalectomized, potassium-deficient rats to show a rise in blood pressure coincident with the gradual spontaneous retention of potassium following adrenalectomy. The fall of blood pressure induced by potassium administration in both intact and adrenalectomized rats which were not depleated of potassium can be ascribed to the toxic effect of an excess amount of potassium in the plasma.

Summary

The parenteral administration of potassium promptly restores the lowered blood pressures of intact potassium-deficient rats to normotensive levels. The administration of potassium to such rats is only partially effective in restoring their lowered blood pressure one and three days after adrenalectomy. The spontaneous retention of potassium which occurred in potassium-deficient rats
during a 30-day interval following adrenalectomy failed to induce an elevation of their lowered blood pressures.

The full restorative effect of induced or spontaneous potassium repletion upon the blood pressure of the hypotensive, potassium-deficient rat requires the presence of the adrenal glands.

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REFERENCES


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