THE EFFECT OF POTASSIUM DEFICIENCY UPON ADRENOCORTICAL SECRETION IN THE RAT 1

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The potassium-deficient rat exhibits several features in common with the untreated adrenalectomized rat, among which are subnormal growth, lowered blood pressure (1-3), diminished blood pressure responsiveness to pressor substances (4), and decreased tolerance to trauma. It therefore was considered important to determine whether the depressor response induced by potassium depletion might in fact be due to an associated state of adrenocortical insufficiency induced by the chronic potassium depletion. Such a mechanism appeared plausible particularly in view of our finding that the administration of cortisone rapidly returns the lowered blood pressures induced by potassium deficiency in rats to their initially normotensive (5) or hypertensive levels (6).

MATERIALS AND METHODS

A series of male rats (Long-Evans strain), initially aged 5 to 6 weeks, was used in this investigation. The rats were divided into three groups. One group of 6 rats (I) was fed a synthetic ration deficient in potassium, as previously described (2); this diet contained 0.004 per cent potassium and 1.4 per cent sodium.2 A second group of 8 control rats (II) was fed the same synthetic ration but with added potassium chloride; it contained 0.52 per cent potassium and 1.4 per cent sodium.2 For further control purposes a third group of 10 rats (III) was fed stock laboratory ration (containing 0.78 per cent potassium, 0.80 per cent sodium). Seven weeks later the blood pressure of each rat was obtained with the microphonc manometer (7). Each rat was tail-bled for determination of plasma potassium 48 hours prior to collection of adrenal venous blood.

The secretion of adrenocortical steroids then was determined in all rats by the following technique. Under light ether anesthesia the rat was injected intramuscularly with 2 mg. sodium heparin, the abdominal cavity of the rat was opened and the right adrenal gland excised. The left kidney was "slipped" out of its capsule and removed after ligation of its vascular pedicle. A polyethylene cannula was introduced into the left renal vein through a small incision just proximal to the pedicle ligature and was ligated in place in such a manner that its bevelled distal tip approximated the left adrenal vein as the latter entered into the renal vein. Any accessory veins which emptied into the adrenal vein were then ligated. Another ligature was placed about the left renal vein at the juncture with the inferior vena cava. The cannula was brought out through a left lateral stab wound, the abdominal incision closed and the animal placed in a restraining cage. The adrenal venous blood was drained by gravity into a cold, heparinized test tube held in a chilled container filled with ice. In general, collection of blood was continued over a period of 60 to 120 minutes, during which 2.5 to 4.0 ml. of blood was obtained.

Each sample of adrenal venous blood was subjected to the following analysis for its steroid content. One to 2 ml. of plasma were extracted with 50 ml. of chloroform. The phenylhydrazine chromogen was extracted with 1 ml. reagent and developed overnight at room temperature according to the procedure of Silber and Porter (8). The curves of the reactive steroids were read between 320 and 450 mu, using 0.5 ml. cuvettes in a Beckman Model DU spectrophotometer. From these data values were computed for steroids absorbing maximally at 350 and 410 mu, by the system of Vickerstaff (9) for two component mixtures on the assumption (10, 11) that corticosterone (compound B) and 17-hydroxycortisone (compound F) are the main products of the adrenal effluent, other C19 and C21 steroids which have been detected by paper chromatography contributing less than 10 per cent of the total absorption at each of the two significant wave lengths, 350 and 410 mu. The fact that for the rat, the extinction of 17,21-dihydroxy, 20-keto-steroids at 410 mu is 5 times that of the predominating corticosterone at 350 mu (8) and also that the absorption peaks are well separated, validates the use of this type of calculation. The amount of Silber-Porter chromogen of aldosterone is too small to be detected by this method, since aldosterone is secreted at a rate of only 0.2 to 0.8 mg per Kg. per hr. (11). Corticosterone (Merck)3 was used as the standard for compounds with absorption maxima at 350 mu and 17-hydroxycorticosterone (Merck) for those at 410 mu. Most of the curves

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1 Aided by Grants from the American Heart Association, Life Insurance Medical Research Fund, San Francisco Heart Association and the National Institute of Health, Grant H-1006, Public Health Service.

2 As determined by flame photometry of ashed diet.

3 Provided by the courtesy of Dr. Frederick K. Heath of Merck & Co., Inc., Rahway, New Jersey.
ADRENOCORTICAL SECRETION IN POTASSIUM DEFICIENT RAT

TABLE I

effect of potassium depletion on adrenocortical secretion of the rat

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of rat</th>
<th>Rat no.</th>
<th>Weight (gm.)</th>
<th>Concentration (µg/ml plasma)</th>
<th>Secretory rate (µg/Kg./hour)</th>
<th>Concentration (µg/ml plasma)</th>
<th>Secretory rate (µg/Kg./hour)</th>
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<tr>
<td>I</td>
<td>Rats fed potassium-deficient diet</td>
<td>12A 180</td>
<td>16.2</td>
<td>96.9</td>
<td>2.2</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13A 220</td>
<td>15.6</td>
<td>180.0</td>
<td>2.0</td>
<td>22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14A 250</td>
<td>30.0</td>
<td>305.0</td>
<td>2.7</td>
<td>28.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15A 240</td>
<td>25.0</td>
<td>229.0</td>
<td>1.2</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16A 196</td>
<td>16.2</td>
<td>186.2</td>
<td>1.5</td>
<td>17.3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>17A 230</td>
<td>33.7</td>
<td>84.7</td>
<td>4.3</td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average: 6</td>
<td>219</td>
<td>22.7</td>
<td>180.3</td>
<td>2.3</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range:</td>
<td></td>
<td>(15.6-33.7)</td>
<td>(84.7-305.0)</td>
<td></td>
<td>(1.2-4.3)</td>
<td>(10.8-28.0)</td>
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<tr>
<td>II</td>
<td>Rats fed potassium-deficient diet with added KCl</td>
<td>36A 250</td>
<td>12.5</td>
<td>217</td>
<td>0.7</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37A 250</td>
<td>13.7</td>
<td>303</td>
<td>1.8</td>
<td>39.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38A 242</td>
<td>16.2</td>
<td>92</td>
<td>1.0</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39A 242</td>
<td>23.6</td>
<td>369</td>
<td>2.0</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40A 236</td>
<td>23.7</td>
<td>182</td>
<td>1.8</td>
<td>14.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41A 200</td>
<td>23.6</td>
<td>184</td>
<td>2.2</td>
<td>9.3</td>
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<tr>
<td></td>
<td>42A 218</td>
<td>13.7</td>
<td>217</td>
<td>0.7</td>
<td>10.0</td>
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<tr>
<td></td>
<td>46 240</td>
<td>17.5</td>
<td>178</td>
<td>2.0</td>
<td>21.0</td>
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<tr>
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<td>18.0</td>
<td>215</td>
<td>1.4</td>
<td>14.3</td>
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<td>(92-369)</td>
<td></td>
<td>(0.7-2.0)</td>
<td>(3.1-39.4)</td>
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<tr>
<td>III</td>
<td>Rats fed stock diet</td>
<td>3A 200</td>
<td>57.5</td>
<td>290</td>
<td>5.0</td>
<td>25.0</td>
<td></td>
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<tr>
<td></td>
<td>6A 218</td>
<td>15.3</td>
<td>135</td>
<td>1.3</td>
<td>11.6</td>
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</tr>
<tr>
<td></td>
<td>7A 298</td>
<td>15.0</td>
<td>164</td>
<td>1.6</td>
<td>13.2</td>
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</tr>
<tr>
<td></td>
<td>8A 230</td>
<td>11.2</td>
<td>64</td>
<td>0.8</td>
<td>4.7</td>
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<tr>
<td></td>
<td>47 212</td>
<td>13.0</td>
<td>129.3</td>
<td>3.1</td>
<td>13.2</td>
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<tr>
<td></td>
<td>48 252</td>
<td>14.8</td>
<td>114.8</td>
<td>0.8</td>
<td>6.4</td>
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<td></td>
<td>49 308</td>
<td>6.2</td>
<td>56.9</td>
<td>0.6</td>
<td>5.6</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>50 252</td>
<td>26.2</td>
<td>216.4</td>
<td>1.5</td>
<td>13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 238</td>
<td>26.2</td>
<td>168</td>
<td>1.8</td>
<td>11.3</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2A 220</td>
<td>30.0</td>
<td>266</td>
<td>4.2</td>
<td>37.4</td>
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<td></td>
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<tr>
<td></td>
<td>Average: 10</td>
<td>238</td>
<td>23.3</td>
<td>160.4</td>
<td>2.0</td>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range:</td>
<td></td>
<td>(6.2-57.5)</td>
<td>(56.9-290)</td>
<td></td>
<td>(0.6-5.0)</td>
<td>(4.7-37.4)</td>
</tr>
</tbody>
</table>

of the derived values reported showed absorption maxima at 350 mμ, rarely a shift to 380 and 390 mμ was noted.

RESULTS

The individual and average values for the steroids obtained from the three groups of rats are shown in Table I. At that time the average blood pressure of the potassium-deficient rats was 84 mm. Hg (Range: 78 to 88) in contrast with the average blood pressure of 108 mm. Hg (Range: 94 to 120) in the control rats fed stock diet. The average plasma K of the deficient rats was 3.5 mEq per L. (Range: 2.7 to 3.7) and that of the control rats fed stock diet was 5.6 mEq per L. (Range: 5.1 to 6.6). Elsewhere (3, 5, 12) we have shown that muscle potassium depletion also is present in such rats. The results are presented in terms of the concentrations (µg per ml plasma) and rates of secretion (µg per Kg. weight per hour) of 3 keto, Δ4, adrenal corticosteroids calculated as corticosterone (compound B) and of 17,21,20-dihydroxy, 20-keto-corticosteroids calculated as 17-hydroxycorticosterone (compound F).

As can be noted in Table I, the potassium-deficient rat as well as the normal animal is capable of putting out considerable amounts of steroids, the deficient animal averaging 180.3 µg per Kg. per hr. and the control rat, 160.4 µg per Kg. per hr. Since the concentrations of corticosterone in the plasma of the two groups are quite similar (22.7 and 23.3 µg per ml plasma), this slight difference in secretory rates may be accounted for on the basis of size, the deficient animals being slightly smaller. In general, corticosterone was
found to be secreted in a tenfold greater concentration than was 17-hydroxycortico- 
sterone. The concentrations and rates of secretion of 17-hy-
droxy corticosterone in the potassium-deficient rats 
were of the same magnitude as in the control rats. 

It can be noted that considerable variation oc-
curred in the plasma concentrations and rates of 
secretion of both steroids. This seems to be char-
acteristic of the adrenal secretion of various ani-
mals tested by present day methods (10, 13-15). 
However, with only an occasional exception, the 
range of values was generally similar in all three 
groups of animals. Considering the relatively 
small sampling, the average values observed in the 
three groups also appeared to be of similar mag-
nitudes.

DISCUSSION

Previous studies from this laboratory have 
shown that dietary potassium deprivation induces 
a fall of blood pressure in normotensive (1) and 
hypertensive (2, 3) rats which is a specific effect 
of potassium depletion (16) and which occurs in 
association with a somewhat diminished blood 
pressure responsiveness to pressor substances (4). 
Administration of potassium to such rats rapidly 
restores their blood pressure responsiveness and 
their blood pressures (16), if the adrenals are in-
tact (12). We have considered (17) the possible 
role of insufficiency of adrenocortical secretion in 
this depressor response to potassium deficiency be-
cause of these and other common features of the 
potassium-deficient and the untreated, adrenalect-
omized rat. That potassium depletion might in-
duce a hypotensive response by suppressing 
adrenocortical function also was suggested by the 
fact that potassium deficiency evokes a chronic 
alarm reaction (18) as well as by our earlier ob-
ervation (5, 6) that cortisone promptly restores 
the lowered blood pressures of potassium-deficient 
rats to their respective normotensive or hyper-
tensive levels without altering their potassium-
defeated state.

On the other hand, some of the responses to 
potassium deficiency are inconsistent with a pat-
tern of adrenocortical insufficiency. Thus, there 
is considerable indirect evidence that potassium 
deficiency stimulates production of adrenocorti-
coids (18-20) by evoking a chronic "alarm reac-
tion" (18). Enlargement of the adrenals occurs 
despite inactivation of the glomerulosa zones, and 
the adrenals of such rats are depleted of ascorbic 
acid (18, 19, 21). Furthermore, such rats also 
exhibit increased liver glycogen and diminished 
glucose tolerance (18, 20), involution of the thy-
us (19, 20) and decreased circulating blood 
eosinophils and lymphocytes (18, 19). Although 
potassium deficiency appears to suppress the secre-
tion of aldosterone (11), on the basis of present 
evidence it seems unlikely that the depressor re-
response might be ascribed to this, since administra-
tion of the analogous hormone, DCA, is without 
pressor effect in potassium-deficient rats and in-
deed has a depressor and toxic effect in such 
animals (22).

We have attempted to clarify the relationship of 
potassium deficiency and adrenocortical function 
by direct determination of adrenal secretion in 
potassium-deficient rats. The values recorded for 
our control rats are in good agreement with those 
recorded by Bush (10) and by Singer and Stack-
Dunne (11), despite the use of a completely dif-
ferent method of analysis. The data in this study 
indicate essentially similar averages and ranges of 
concentration and rates of secretion of corticos-
terone and 17-hydroxycorticosterone by the potas-
sium-deficient rats, when compared to the control 
animals. It is important to point out that the 
technique employed for collection of adrenal ve-
nous blood in this study probably constitutes a 
maximal stimulus for adrenocortical secretion. 
Under these circumstances, however, the potas-
sium-deficient hypotensive rat appeared to re-
pond in a fashion similar to that of the control 
animals. It is of interest that Singer and Stack-
Dunne (11) also recently found that potassium 
deficiency fails to affect corticosterone secretion 
in rats. Therefore, it must tentatively be sug-
gested that the hypotensive response induced by 
potassium deficiency is not mediated by suppres-
sion of adrenocortical secretion. This conclusion 
appears justified in view of the present data and the 
fact that trauma comparable to the operative pro-
cedure used here fails to raise the lowered blood 
pressure of the potassium-deficient rat.

SUMMARY

The effect of chronic potassium deficiency upon 
adrenocortical steroid secretion was studied in
rats. The data indicate that, under the stress of the experimental method, the rates of secretion of corticosterone and 17-hydroxycorticosterone by potassium-deficient rats are essentially similar to those of control animals. It is concluded that the hypotensive response induced by potassium depletion is not mediated by a suppression of adrenocortical secretion of these steroids.

ACKNOWLEDGMENT

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REFERENCES