Cortisone Hypertension in Potassium-Deficient Rats with a Renal Ligature

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In collaboration with Malcolm K. Smith, B.A.

The pressor effects of cortisone were explored in potassium-deficient and control diet rats. It was found that marked hypertension was induced by cortisone only when there was the combined background of a renal-ligature, potassium depletion, and adrenalectomy.

Previous studies have shown that a specific depressor response occurs in normotensive and hypertensive rats following deprivation of dietary potassium. Cortisone restores the lowered blood pressures of such potassium-deficient rats to their initial normotensive or hypertensive levels. Although a similar depressor response occurs in human subjects, when fed a potassium-deficient diet and in association with clinical states of potassium depletion, a rise of blood pressure occurs in most patients with Cushing's syndrome, despite the presence of potassium deficiency. In the following studies we have explored similar circumstances in which cortisone might induce hypertension in potassium-deficient rats.

I. Effect of Cortisone on Blood Pressures of Adrenalectomized, Potassium-Deficient Rats with a Renal Ligature

In a preliminary experiment a series of male Long-Evans rats, aged five weeks, was subjected to uninephrectomy and application of a figure-of-eight renal ligature to the remaining kidney. Eight weeks later those rats that did not develop hypertension were divided into two groups. During the remaining experimental interval, seven rats (group I) ingested potassium-deficient diet and seven other rats (group II) ingested stock diet. Four weeks later, all rats were tail-bled for determination of plasma potassium and then were subjected to bilateral adrenalectomy. During the following seven days, 2 mg. of cortisone acetate was injected subcutaneously, twice daily, into all rats. Blood pressures were obtained with the microphonic manometer at the onset, prior to and one week after adrenalectomy.

The rats of group I had an average plasma potassium content of 3.2 mEq./L. (range: 3.0 to 3.4) after four weeks of ingesting potassium-deficient diet. Their average blood pressure rose from 117 mm. Hg, prior to adrenalectomy, to 170 mm. Hg (range, 154 to 188) during the seven postoperative days during which cortisone was injected. The average plasma potassium content in the control rats of group II was 6.4 mEq./L. (range, 5.7 to 7.2). In contrast to the rats of group I, their average blood pressure rose slightly from a preadrenalectomy level of 101 mm. Hg to an average of 115 mm. Hg (range, 106 to 150), one week after cortisone injections were initiated.

The hypertensive effect of cortisone in this preliminary experiment was explored further in the following experiment.

Methods: A group of 24 intact rats (B-I) was fed the potassium-deficient diet for eight weeks, following which half of the rats were bilaterally adrenalectomized. Cortisone acetate, 1.5 mg., was injected subcutaneously twice daily for 14 days and blood pressures were obtained after 7 and 14 days. For control purposes, similar studies were made in 12 adrenalectomized and 10 intact rats fed stock ration.

A second group (B-II) of 20 rats was uninephrectomized and fed potassium-deficient diet for eight weeks, after which half of the animals were bi-
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Table 1.—Effect of Cortisone on Blood Pressure of Rats Fed Potassium-Deficient and Control Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of Rat</th>
<th>Potassium-Deficient Diet</th>
<th>Stock Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Rats</td>
<td>Aver. wt.</td>
<td>Average blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gm.</td>
<td>mm. Hg</td>
</tr>
<tr>
<td>B-I</td>
<td>Rats—Intact kidneys</td>
<td>12</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>ADRX*</td>
<td>12</td>
<td>(102-156)†</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>10</td>
<td>106</td>
</tr>
<tr>
<td>B-II</td>
<td>Uninephrectomized rats</td>
<td>10</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>ADRX</td>
<td>10</td>
<td>(88-134)</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>10</td>
<td>123</td>
</tr>
<tr>
<td>B-III</td>
<td>Uninephrectomized rats with a renal ligature</td>
<td>12</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>ADRX</td>
<td>12</td>
<td>(128-220)</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>8</td>
<td>300</td>
</tr>
</tbody>
</table>

* Adrenalectomized.
† Range of values.

Laterally adrenalectomized. Cortisone was administered as above to these rats as well as to a control group of 18 uninephrectomized rats fed stock ration, of which half also were adrenalectomized prior to cortisone administration.

A third group of rats (B-III) was subjected to uninephrectomy and placement of a figure-of-eight renal ligature. Eight weeks later 20 rats which postoperatively remained normotensive were fed the potassium-deficient diet. After eight weeks, 12 rats were adrenalectomized and cortisone was administered as above to all rats as well as to 15 control, renal-ligated rats fed stock ration.

Results: The blood pressure responses of the three groups of rats are shown in table 1. The average blood pressure obtained in adult male rats in our laboratory is 109 mm. Hg (range, 92 to 130). As shown in table 1, cortisone induced only a slight rise of blood pressure in the intact rats, comparable levels being observed in the animals fed stock ration and those ingesting potassium-deficient ration. We did not observe any potentiation of the blood pressure response in the adrenalectomized animals.

A somewhat greater pressor response to cortisone occurred in the uninephrectomized animals with intact adrenals, the average blood pressure rising to 130 mm. Hg in those fed potassium-deficient diet and to 140 mm. Hg in those fed stock ration. As observed above, this pressor response was not augmented by adrenalectomy.

Significant and occasionally marked hypertension was induced by cortisone in the adrenalectomized, renal-ligated rats which ingested the potassium-deficient diet, as was observed in the preliminary experiment. A much lesser pressor response occurred in the renal ligated, potassium-deficient rats with intact adrenals and in the control animals fed stock ration.

II. EFFECT OF VARYING SODIUM INTAKE ON BLOOD PRESSURE OF ADRENALECTOMIZED, RENAL-LIGATED RATS FED K-DEFICIENT DIET

In the preceding experiments it was shown that adrenalectomized, potassium-deficient rats with a renal ligature usually responded to cortisone administration with a marked pressor response. The following experiment was performed in order to evaluate any possible role of sodium ion in this hypertensive response.

Methods: A series of 37 uninephrectomized rats with a renal-ligature about the remaining kidney
TABLE 2.—Effect of Cortisone with Varying Sodium Intake on Blood Pressure of Adrenalectomized, Renal-Ligated Rats Fed Potassium-Deficient Diet

<table>
<thead>
<tr>
<th>Group I. Rats Fed Potassium-Deficient Diet-Normal Sodium</th>
<th>Group II. Rats Fed Potassium-Deficient Diet-Excess Sodium</th>
<th>Group III. Rats Fed Potassium-Deficient Diet-Deficient Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Rats</td>
<td>Average Weight</td>
<td>Average Blood Pressure Day 7</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>11</td>
<td>298</td>
<td>145</td>
</tr>
<tr>
<td>(114-220)</td>
<td>(122-200)</td>
<td>(104-176)</td>
</tr>
</tbody>
</table>

and which remained normotensive for 10 weeks postoperatively was utilized. The potassium-deficient diet was fed to 24 rats for eight weeks and subsequently each animal was subjected to bilateral adrenalectomy. The rats then were divided into two groups and cortisone was injected subcutaneously (2 mg. twice daily) into all rats and at the same time tap water was given to 11 rats (group I) while 13 rats (group II) received one per cent sodium chloride solution to drink. The remaining 13 rats (group III) were fed the same synthetic ration except that the diet contained no sodium in the electrolyte mixture. (The latter ration contained 0.006 per cent potassium and 0.01 per cent sodium.) Blood pressures were obtained after 7 and 14 days.

RESULTS

The results are presented in table 2. As in the preceding experiments, a significant and often marked pressor response to cortisone was observed in the adrenalectomized, “renal-ligated” rats which were previously depleted of potassium (group I), their average blood pressure rising to 158 mm. Hg after 14 days. A lesser rise of average blood pressure was observed in the rats which were similarly treated but which concomitantly ingested excess sodium ion (group II), their average blood pressure rising to 147 mm. Hg. The rats which were deprived of dietary sodium as well as potassium (group III) exhibited an even lesser rise of blood pressure, the average rising to 137 mm. Hg after 14 days of cortisone administration.

DISCUSSION

The data indicate that the administration of cortisone induced a slight pressor response in intact rats which reached greater proportions in uni-nephrectomized rats, but which was not augmented in such rats by either adrenalectomy or prior depletion of potassium. Although cortisone exerted a slight to moderate pressor response in all groups of animals that were studied, marked or severe hypertension occurred only when cortisone was administered to rats that concomitantly were (1) renal-ligated, (2) depleted of potassium and (3) adrenalectomized.

It is difficult to assess the precise role of the three experimental substrate factors in this observed hypertensive response. As noted by others2-14 and by us,4 cortisone, in the dosage used, appears to have only slight or occasionally moderate pressor effects in intact rats. Prior potassium (K) depletion appeared to sensitize the adrenalectomized, renal-ligated rat to the pressor effect of cortisone in some unknown manner. In intact rats, cortisone rapidly returns blood pressures markedly lowered by depletion of K1 to normotensive levels.4 Moreover, when the blood pressures of renal or DCA-induced hypertensive rats are lowered by K-deficiency,21 cortisone also rapidly restores their lowered blood pressures to their initial hypertensive levels,6 despite persistence of their K-depleted states. However, this appears to be a restorative process4 and the blood pressure levels of such K-deficient rats following administration of cortisone are only of a magnitude similar to their cortisone-treated controls.5,6 On the other hand, previous data16 suggested that K-depletion may possibly sensitize the vasculature of the cortisone-treated animal to renal pressor substances.

Studies of the rat mesoappendix preparation14 indicate that an augmented peripheral vascular response to epinephrine is induced by cortisone in K-deficient rats, which is not observed in control animals. It does not appear that K deficiency acts by inducing a relative or absolute excess of body sodium, inasmuch as the pressor response, induced by cortisone in the renal-ligated rats, was of lesser magnitude.
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when excess sodium intake was provided. Moreover, the rise of blood pressure, induced by cortisone in adrenalectomized rats\textsuperscript{17} or in subtotally nephrectomized rats\textsuperscript{18} occurs on a low sodium intake and may even be diminished by liberal sodium intakes.\textsuperscript{15, 17} The restoration by cortisone of lowered blood pressures of adrenalectomized rats also occurs on a low sodium diet.\textsuperscript{19} The effect of K-deficiency upon protein metabolism also does not appear to be of importance since the pressor effect of cortisone does not depend upon protein intake\textsuperscript{18} and occurs in the presence of a catabolic state.\textsuperscript{19}

The role of adrenalectomy in the observed hypertensive response may be due to the elimination of antagonistic effects of opposing adrenal steroids.\textsuperscript{20} Thus the pressor effect of cortisone in rats fed a low sodium diet and in rats with nephritis is augmented by adrenalectomy.\textsuperscript{13} On the other hand, administration of DCA fails to diminish cortisone-induced hypertension\textsuperscript{11, 17} and adrenalectomy does not augment pressor effects of cortisone in rats fed a liberal intake of sodium.\textsuperscript{12} With the one exception cited above, we have consistently failed to observe any augmentation of the slight or moderate pressor effect of cortisone by adrenalectomy.

The marked pressor response which occurred in the adrenalectomized rats initially depleted of K was observed only when a renal-ligature also was present. Renal damage or compression induced by the renal ligature would appear to be of critical importance in the observed hypertensive response to cortisone, in accord with the observation that cortisone has marked pressor effects in partially nephrectomized rats\textsuperscript{18} and in rats with nephritis.\textsuperscript{19} One possible role of K-deficiency may be the induction of renal enlargement and damage\textsuperscript{21} which, in the presence of a renal ligature, may consequently increase the output of renal pressor substances. Moreover, although it has negligible effects on blood pressures of normotensive or hypertensive human subjects with normal kidney function, cortisone frequently induces severe hypertension in patients with renal damage, regardless of the antecedent blood pressure.\textsuperscript{22}

Our data indicate that cortisone induces only a slight or moderate pressor effect in intact or uninephrectomized rats and in rats with a renal ligature which was not altered significantly by the individual effects of potassium depletion, adrenalectomy or ingestion of excess sodium. However, when the combined background of a renal-ligature, depletion of potassium and adrenalectomy was present concomitantly, cortisone induced a much more marked pressor response, with severe hypertension frequently occurring. It is, therefore, apparent that hypertension can occur experimentally under certain circumstances, despite the presence of a state of potassium deficiency, the experimental substrate being reminiscent of Cushing's syndrome as it occurs clinically.

**Summary**

Cortisone acetate was administered to potassium-depleted and control rats with (1) intact kidneys, (2) uninephrectomy and (3) renal ligatures. Bilateral adrenalectomy was performed in half of each group of animals.

Although cortisone exerted slight to moderate pressor effects in all groups of rats, marked and occasionally severe hypertension occurred only in rats with the combined substrate of renal-ligature, depletion of potassium and adrenalectomy. This pressor response was not augmented by ingestion of excess sodium chloride.

It was concluded that hypertension can be induced under certain circumstances despite the presence of potassium depletion.

**Acknowledgment**

We wish to express our appreciation to Hoffman-LaRoche, Inc. for generous supplies of Litiron used to provide the vitamin supplements of the synthetic diets.

**Summary in Interlingua**

Acetato de cortisona esseva administrate a rattos deplete de kalium e a rattos de controlo, (1) con renes intacte, (2) post uninephrectomia, e (3) con ligatura renal. Adrenalectomia bilatere esseva executate in 50 pro cento de omne gruppo de animales.

Ben que cortisone excerceva leve a moderate efectos pressoral in omne le gruppos de rattos,
marcate e a vices sever hypertension occurreva solmente in ratos con le substrato combinate de ligatura renal, depletion de kalium, e adrenalectomia. Iste responsa pressoral non esseva augmentate per le ingestion de excessos de chlorido de natrium.

Nos concluiveva que hypertension pote esser inducite sub certe conditiones in despecto del presentia de depletion de kalium.

REFERENCES
Cortisone Hypertension in Potassium-Deficient Rats with a Renal Ligature
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