Effect of Hypophysectomy on Cardiovascular Actions of ACTH and STH

By Ernesto D. Salgado, M.D., Ph.D.

These experiments indicate that the pituitary adrenocorticotropic hormone (ACTH) and somatotrophic hormone (STH) share the ability to produce hypertension, nephrosclerosis, myocarditis and periarteritis nodosa in the intact rat. In the absence of the hypophysis rise in arterial pressure was less and no vascular lesions were observed.

It has been shown by Selye that rats treated with high doses of lyophilized anterior pituitary material (LAP) develop nephrosclerosis, myocarditis, polyuria and hypertension. In an analysis of the pathogenesis of this syndrome somatotrophic hormone (STH) was singled out as the active principle responsible for the toxic actions of LAP.

The present study deals with the effect of high doses of STH and adrenocorticotropic hormone (ACTH) in both intact and hypophysectomized rats. To counteract the infection-promoting activity of ACTH the animals were given antibiotics. From this experiment we hoped to clarify two points: (1) whether ACTH will produce hypertension and cardio-renal lesions in the intact rat, and (2) whether STH and/or ACTH will produce hypertension and lesions in the absence of the pituitary.

Materials and Methods

One hundred male Sprague-Dawley rats weighing 100 to 110 Gm. were divided into 8 groups as outlined in table 1. At the beginning of the experiment, all animals were unilaterally nephrectomized and those of the last 4 groups hypophysectomized in addition. The animals received 1 per cent NaCl (as drinking fluid) and Purina Fox Chow ad libitum.

ACTH (Connaught Laboratories, 1 i.u./mg.) was given subcutaneously at the dose of 4 i.u./rat/day during the first week and 8 i.u. thereafter. After preliminary studies with different retarding agents, it was found that 2 injections per day of ACTH in Mazola oil will increase the weight of the adrenals of the hypophysectomized animals. Consequently, the ACTH was triturated and suspended in Mazola oil and given twice a day (0.2 ml. each time). STH (Armour, Lot R 269-183 equivalent to 75 per cent of Armour's standard) was given dissolved in 0.85 per cent NaCl and in a volume of 0.2 ml. twice a day. The daily dose was raised from 1 to 3 mg. during the first week, to 5 mg. on the eighth day, to 7 mg. on the twentieth day, and to 8 mg. on the thirtieth day. All animals received penicillin G procain, penicillin G sodium and dihydrostreptomycin diluted with 0.85 per cent NaCl so that each 0.2 ml. dose delivered 10,000 units of penicillin and 25 mg. of dihydrostreptomycin. Injection was three times a week subcutaneously. Blood pressure determinations were performed by the method of Friedman and Freed at intervals indicated in figure 1. On the last day of the experiment, an arthritis test was performed: 0.2 ml. of 1:37 Dextran solution was injected into the left hind paw of the rats of several groups and measurements of the diameters of the paws were taken at various intervals.

All animals were killed after 36 days of treatment and several organs fixed in Bouin's fluid for weighing and histologic study; sections were stained with hematoxylin-eosin as well as the PAS procedure of McManus. The statistical significance of differences between means was established by application of Student's t test.

Results

The results of body weight, fluid intake and blood pressure measurements are presented graphically in figure 1. It can be seen there that as regards body weight, STH increased growth above the controls in both intact and hypophysectomized animals, and the combined treatment with ACTH induced intermediate values. On the other hand, ACTH diminished growth in intact animals, whereas in hypophysectomized animals the values of
TABLE 1.—Organ Weights of Unilaterally Nephrectomized Animals Receiving ACTH and/or STH

<table>
<thead>
<tr>
<th>Group</th>
<th>I ACTH</th>
<th>II STH</th>
<th>III ACTH + STH</th>
<th>IV Hyp-x</th>
<th>V Hyp-x + ACTH</th>
<th>VI Hyp-x + STH</th>
<th>VII Hyp-x + ACTH</th>
<th>VIII Hyp-x + STH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>(Initial)</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Kidney (in mg.)</td>
<td>1470±38</td>
<td>1244±38</td>
<td>2083±100</td>
<td>1746±125</td>
<td>1497±125</td>
<td>512±10.7</td>
<td>1212±38</td>
<td>1372±27</td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>470±25</td>
<td>634±21</td>
<td>750±58</td>
<td>620±46</td>
<td>444±16</td>
<td>531±13</td>
<td>426±10</td>
<td>635±32</td>
</tr>
<tr>
<td>Heart (in mg.)</td>
<td>809±45</td>
<td>710±25</td>
<td>985±48</td>
<td>922±26</td>
<td>319±13</td>
<td>313±13</td>
<td>676±27</td>
<td>616±23</td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>313±16</td>
<td>367±16</td>
<td>359±17</td>
<td>326±12.5</td>
<td>28±8.5</td>
<td>324±9</td>
<td>236±6</td>
<td>282±9.5</td>
</tr>
<tr>
<td>Adrenals (in mg.)</td>
<td>33±2.8</td>
<td>56±2.8</td>
<td>56±3.8</td>
<td>76±7</td>
<td>8±0.36</td>
<td>34±2.8</td>
<td>14±0.45</td>
<td>68±5</td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>13±0.50</td>
<td>29±2.4</td>
<td>21±2.02</td>
<td>28±3.3</td>
<td>7±0.02</td>
<td>35±2.6</td>
<td>5±0.29</td>
<td>31±2.5</td>
</tr>
<tr>
<td>Thymus (in mg.)</td>
<td>52±22.4</td>
<td>152±15</td>
<td>148±24</td>
<td>100±11.7</td>
<td>†</td>
<td>418±20</td>
<td>52±18</td>
<td></td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>86±8</td>
<td>49±13.2</td>
<td>51±8.1</td>
<td>95±11</td>
<td></td>
<td>146±6</td>
<td>35±5.8</td>
<td></td>
</tr>
<tr>
<td>Testes (in mg.)</td>
<td>2724±75</td>
<td>2621±130</td>
<td>2712±203</td>
<td>2592±24</td>
<td>268±11.6</td>
<td>240±21.7</td>
<td>1296±62</td>
<td>1508±71</td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>1088±35</td>
<td>1332±26</td>
<td>955±58</td>
<td>945±31</td>
<td>230±6.4</td>
<td>257±17</td>
<td>452±21</td>
<td>730±33</td>
</tr>
<tr>
<td>Brain (in mg.)</td>
<td>885±12</td>
<td>880±16</td>
<td>890±37</td>
<td>844±22</td>
<td>827±13</td>
<td>769±12.3</td>
<td>1004±19.6</td>
<td>844±16</td>
</tr>
<tr>
<td>*(in mg. %)</td>
<td>344±27.8</td>
<td>453±22</td>
<td>312±22</td>
<td>259±4.7</td>
<td>730±18</td>
<td>823±28</td>
<td>353±8</td>
<td>392±21</td>
</tr>
</tbody>
</table>

All weights are accompanied by the standard error of the mean
* In mg./100 Gm. body weight. † Atrophic

Fig. 1. Changes in body weight, 1 per cent NaCl intake and blood pressure in rats receiving ACTH and/or STH. Treatment started at zero days.
body weight were close to, but always below, those of the controls.

As regards fluid intake (which parallels the diuresis), ACTH, STH and the combined treatment raised the fluid intake above the controls in the intact animals. In the hypophysectomized animals, both ACTH and ACTH plus STH induced a remarkable rise in the fluid intake. STH, in the absence of the hypophysis, did not significantly influence the fluid intake in comparison with the hypophysectomized controls.

As regards the blood pressure, a comparison of the means of the groups (fig. 1) reveals that in the intact rats both ACTH and/or STH produce significant increases in the blood pressure in relation with their controls (p values; .02, .001 and .001 respectively). The same is true in the hypophysectomized rats (p values; .01, .001 and .02 respectively), but the increases were significantly smaller than in the intact rats similarly treated. The mean pressure of the group of untreated hypophysectomized animals was lower, however, than the control group of intact animals. When the means of groups VIII and Y are compared, the difference is significant (p < .001); on the other hand the difference between the means of groups VIII and I is not significant (p = .1). In two subsequent experiments these findings were confirmed.

In table 1, the mean organ weights, (with their standard errors) are listed (both in absolute terms and in mg./100 Gm. body weight).

As regards the kidney weight, it can be seen that treatment with STH in intact animals (group III) resulted in the highest kidney weight, both in absolute and in per cent terms. In hypophysectomized animals, the combined treatment (group VIII) resulted in an increase in both absolute and per cent weight of the kidney in comparison with the hypophysectomized controls.

STH and STH plus ACTH induced a rise in the absolute weight of the heart in intact animals, in comparison with the intact controls. ACTH raised the weight of the heart above that of the hypophysectomized controls only in relative, and ACTH plus STH only in absolute terms.

In the hypophysectomized groups, treatment with ACTH produced adrenals heavier than those of the hypophysectomized untreated controls.

The testis showed different degrees of atrophy in the hypophysectomized animals: the combined treatment with the two hormones diminished the atrophy induced by hypophysectomy.

The brain had, in general, a very constant weight in spite of the different treatment (when expressed in absolute terms), but the STH treated hypophysectomized rats showed a very significant rise in the weight of the brain. This fact too was confirmed in two repetitions of the experiment.

The results of reactivity to injected Dextran are shown graphically in figure 2. In hypophysectomized animals, STH enhanced and ACTH diminished the reaction in a significant (p < 0.01) degree, when compared with hypophysectomized controls. But in comparison with the intact controls, the only significant value is the diminution shown by ACTH treated animals.

At autopsy, macroscopically visible signs of nephrosclerosis and myocarditis were observed in animals of group III and IV, and in 3 animals of group II. An attempt was made to grade these lesions on a semiquantitative basis, using a scale from 0 to +++. The
following is the result of our evaluation:

<table>
<thead>
<tr>
<th></th>
<th>Nephrosclerosis</th>
<th>Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Severity</td>
</tr>
<tr>
<td>Group III STH</td>
<td>88</td>
<td>63</td>
</tr>
<tr>
<td>Group IV ACTH + STH</td>
<td>39</td>
<td>15</td>
</tr>
</tbody>
</table>

On histologic examination, the same differences were seen between groups III and IV, as far as nephrosclerosis and myocarditis were concerned. In addition, histologic examination gave us further information which can be summarized as follows: In group I (intact controls), the impression gained at autopsy was confirmed in general, except that 1 animal showed slight tubular dilatation in the kidney and the presence of some hyalin cast (lesions graded as "+"). In group II (ACTH treated animals), the 3 animals that were hypertensive presented severe lesions in the kidneys graded as "+++", severe lesions in the heart graded as " +++ " and 2 of them severe lesions of periarteritis nodosa in the pancreatic vessels graded as " +++ ". (In the two subsequent experiments these findings were confirmed.) In group III, in addition to what we have already described, 4 animals presented severe lesions of periarteritis nodosa in the pancreatic vessels (graded as "++") , 2 of which had similar lesions in the testis. In group IV, only 1 animal presented slight lesions of periarteritis nodosa in the pancreatic vessels (graded as "+ ") and none of them showed this lesion in the testis.

Regarding hypophysectomized animals, the total absence of lesions in kidneys, heart or vessels was remarkable. Only 1 animal in the combined treatment group showed a fine dust-like deposition of PAS-positive material in the glomerulus, and a very slight tubular dilatation. As far as we could judge by autopsy and by histologic examination of the testes, this animal was completely operated.

**DISCUSSION**

The fact that STH can induce hypertension accompanied by nephrosclerosis and cardiac lesions is not new, it is only a confirmation of the work of Selye. In addition to his finding, we wish to mention that although periarteritis nodosa was not macroscopically seen at autopsy, we nevertheless found it constantly in the pancreatic and less frequently in the testicular vessels upon histologic examination.

It has already been reported that ACTH sometimes induces hypertension in humans. The 3 ACTH treated animals with high blood pressure showed severe cardiorenal lesions, and 2 of them vascular lesions in the mesenteric vessels. In this connection, it should be recalled that Dougherty reported the presence of lesions similar to those induced with DCA in the kidneys of ACTH treated mice. Ingle, Prestrud and Li reported renal lesions in rats receiving ACTH by continuous infusion.

We have previously reported that administration of thyrotrophic hormone (TSH) to rats is able to produce hypertension, nephrosclerosis and polypnea. Therefore, it seems that 3 different pituitary hormones, ACTH, STH and TSH, are able to produce the same syndrome that was specifically attributed to STH alone. Negative results with ACTH previously reported may have been due to the premature deaths since the animals were not protected with antibiotics. It remains to be seen if results similar to the present can be obtained with other anterior pituitary hormones.

If STH produces hypertension and cardiorenal lesions and ACTH does the same (though less uniformly), combined treatment with the two hormones might be expected to elicit even more severe lesions and hypertension. In the present experiment this was not the case.

It is interesting to note the total absence of lesions in the hypophysectomized animals, in spite of the treatment with ACTH and STH and the fact that they received (and drank) generous amounts of 1 per cent NaCl. It appears that both ACTH and STH, like DCA, need the presence of the hypophysis to produce cardiovascular lesions and hypertension. This dependence on the hypophysis is striking in the case of STH because this hormone, even in the presence of a stimulated adrenal (as in group VIII), fails to produce hypertension and cardiorenal lesions. In the absence of the hypophysis STH displays other actions however, namely, its growth promoting activity and the ability to restore to normal the reactivity of hypophysectomized rats to...
Dextran. We have no explanation for the increase in the weight of the brain in STH treated hypophysectomized rats.

**Summary and Conclusions**

We have studied the effect of treatment with somatotrophic hormone (STH) and adrenocorticotropic hormone (ACTH), separately and in combination, in intact and hypophysectomized rats unilaterally nephrectomized, drinking 1 per cent NaCl and receiving antibiotics.

In intact animals, both STH and ACTH induced hypertension, nephrosclerosis, myocarditis and microscopically visible signs of periarteritis nodosa. STH produced these changes in a much more constant manner than ACTH. The combined treatment with the two hormones resulted in slightly less severe lesions in kidney and heart than seen in the STH treated animals, and the virtual absence of periarteritis nodosa.

In hypophysectomized animals, with lower mean control pressure, both hormones, as well as the combination, produced a rise in blood pressure but the levels reached were significantly below those in the STH treated animals, and the virtual absence of periarteritis nodosa.

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**Summario in Interlingua**

Nos ha studiate le effecto del tractamento con hormon somatotrophic (STH) e hormon adrenocorticotrophic (ACTH) individualmente e in combination—in rattos intacte e in rattos hypophysectomisate que habeva essite nephrectomisate unilateralmente, que biveva un solution de 1 pro cento de NaCl, e que recipieva antibioticos.

In le animales intacte, tanto STH como etiam ACTH induciva hypertension, nephrosclerosis, myocarditis, e microscopicamente visible signos de periarteritis nodose. STH produciva iste alterationes de maniera multo plus constante que ACTH. Le tractamento con STH e ACTH in combination resultava in levemente minus sever lesiones de ren e corde que le tractamento con STH sol. Periarteritis nodose esseva practicamente abente post le tractamento combinato.

In le animales hypophysectomisate (con plus basse pressiones medie de controlo), ambe hormones—individualmente e in combination—produceva un augmento del pression sanguinee, sed le nivels maximal esseva significativemente infra le nivels producte per le tractamento in animales inteacte. In plus, ben que le ingestion de fluido esseva plus alte in animales hypophysectomisate que in animales inteacte recipiente le mesme tractamento, le animales hypophysectomisate non monstравa ulle signo pathologic in ren, corde, o vasos.

**References**

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