THE EFFECT OF TESTOSTERONE PROPIONATE ON TOTAL CHOLESTEROL CONTENT OF THE ADRENALS OF EXPERIMENTAL HYPOTHYROID RATS

By

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It is well known that the adrenal cortex and the thyroid have a profound influence on each other. This is illustrated by the surgical removal of one or the other gland, or by the administration of cortical or thyroid preparations. In general thyroidectomy causes a reduction in the size of the adrenal and the removal of the latter leads to a congestion and degeneration of the thyroid tissues (see Hartman & Brownell, 1949). The influence of thyroid status on the functioning of the adrenals, however, is studied currently by the use of goitrogenic compounds as different degrees of thyroid insufficiency can be conveniently produced in experimental animals by suitable adjustments of their dosage levels.

Treatment with goiterogens like thiouracil has been reported to evoke severe atrophy of the adrenal cortex with shrinkage of the fascicular or of all the zones and a change in sudanophilic lipids (Glock, 1945; Baumann & Marine, 1945; and Deane & Greep, 1947). A decline in adrenal weight has also been observed (Leblond & Hoff, 1944; Glock, 1945; Baumann & Marine, 1945; Leathem, 1946; and Zarrow & Money, 1949). Comparatively little attention seems to have been paid to the biochemical responses elicited in the adrenal cortex under hypothyroid conditions. Freidman & Gordon (1950) noted a drop in adrenal ascorbic acid concentration after thiouracil treatment. Similar findings have been recorded by Gabrilove & Soffer (1950) and Perry (1952). The latter investigator also demonstrated an increase in cholesterol concentration of the adrenal but did not observe any loss of weight of the gland.

It has been reported previously that testosterone propionate prevents cystic
transformation of the ovaries in hypothyroid rats probably through a beneficial influence on the thyroid itself (Kar & Sur, 1953). This effectiveness of androgen prompted us to explore whether it exerted any influence on the thyroid-adrenal axis of thiourea-treated rats as indicated by the changes in the total cholesterol concentration of the adrenals.

**EXPERIMENTAL PROCEDURE**

Female albino rats, weighing 62.1 ± 8.7 gm., were used in this study. A total of 36 animals were used of which 12 were treated with thiourea, 12 with thiourea plus androgen and the remaining 12 served as the controls. Daily record of body weight of the rats was carefully kept and all the animals were maintained under uniform husbandry conditions throughout the experimental period.

Thiourea was injected at the rate of 4 mg. daily (in 0.5 ml. of sterile distilled water) for a period of 18 days. In addition to the goiterogen, the second group received 2.5 mg. of testosterone propionate (in 0.25 ml. of sterile sesame oil) twice a week for the same period. In all, 5 injections of the androgen were given to each animal of this group. The control animals were injected with the solvents alone in a similar manner. All the injections were given by the subcutaneous route.

Autopsy was carried out 24 hours after the final treatments. The animals were killed by a blow on the head in order to allow least possible ante-mortem trauma to the adrenals. The glands were quickly dissected out and weighed to the nearest mg. on a chemical balance. The total cholesterol content was determined colorimetrically by the well known Liebermann-Burchard reaction after initial extraction with acetone according to the method of Banerjee & Deb (1951). Histopathological examination of the thyroid of goiterogen-treated rats revealed a typical hypothyroid picture.

**RESULTS**

Table 1 indicates the changes in the total cholesterol content of the adrenals of experimental animals. It is evident that the cholesterol concentration of the gland is significantly enhanced after thiourea treatment. Testosterone propionate administration, however, is associated with a significant reduction in cholesterol concentration as compared to the hypothyroid rats which did not receive this drug. The adrenal cholesterol level of the hormone-treated rats is practically similar to that of the normal controls.
Table 1.
Total cholesterol content of the adrenals of experimental rats.

<table>
<thead>
<tr>
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<th>No. of animals</th>
<th>Adrenal cholesterol (mg./gm. adrenal weight) with S. D.</th>
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<tbody>
<tr>
<td>Controls</td>
<td>12</td>
<td>26.12 ± 9.03</td>
</tr>
<tr>
<td>Thiourea treated</td>
<td>12</td>
<td>41.71 ± 8.84*</td>
</tr>
<tr>
<td>Thiourea plus androgen treated</td>
<td>12</td>
<td>23.24 ± 6.90**</td>
</tr>
</tbody>
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* Significantly different from controls (t = 2.70  P = .02).
** Significantly different from thiourea treated (t = 3.74  P < .01) but the difference is insignificant from controls (t = 0.76  P < .5).

** DISCUSSION **

Perry (1952) noted an increase in cholesterol and a drop in ascorbic acid concentrations of the adrenal after propylthiouracil treatment but failed to evaluate their physiological significance. He, however, considered these alterations to be due to a direct action of the goiterogen on the gland. Besides, he was able to show that the cholesterol and ascorbic acid concentrations of the adrenal of hypothyroid rats declined in a normal manner in response to ACTH or epinephrine which indicated that the functional status of the gland was unaffected. The present observations on a rise in cholesterol content, on the other hand, tend to indicate an alteration in the functional activities of the gland.

Selye (1950) regards thiourea and its derivatives as potent alarming agents because symptoms of stress syndrome like a decline or increase in sudanophilic lipids, were elicited in the adrenal cortex after administration of these compounds (Glock, 1945; Baumann & Marine, 1945). The high lipid content of the cortex reported by the latter investigators is extremely significant as it is in keeping with the present observations on a rise in total cholesterol concentration of the gland. This might be interpreted as an attempt on the part of the gland to resist the alarming action of the goiterogen.

The above interpretation carries the obvious implication that the action of thiourea on the adrenals was mediated through an enhanced output of pituitary ACTH. This would seem to be the converse of Perry's (1952) concept of a direct influence of goiterogen on the gland. As mentioned before, his idea was based on the finding that there was a rise in cholesterol but a decrease in ascorbic concentrations of the adrenal in response to propylthiouracil treatment. He
argued that if an elevation in the cholesterol content was to be reckoned as an indication of the resting state of the gland, then a similar rise in ascorbic acid concentration was to be expected in compliance with the known symptoms of resistance to a stressor agent (see Selye, 1950). This argument, of course, inevitably pointed towards a direct action of the goiterogen and explained such seemingly erratic responses of the two adrenal constituents. But at the same time, it was equally plausible that the decline in ascorbic acid concentration noted by Perry (1952) was an indication of the approaching exhaustion of the gland due to prolonged application of an alarming stimulus like propylthiouracil. Such a view, however, is borne out by the observations that during alarm reaction and the resistance phase of the stress syndrome the initial drop and the subsequent increase in adrenal ascorbic acid definitely precede the analogous changes in the cholesterol concentration of the gland (Sayers & Sayers, 1948). If this is the trend of events during the first two phases of the stress syndrome, it is reasonable to assume that it will not be different in the final stage of exhaustion. Perry’s (1952) findings, in fact, appear to supplement those of Sayers & Sayers (1948) and make a hitherto incomplete picture a more complete one. These facts, therefore, weigh in favour of the view that thiourea acts as a stressor agent and alters the secretory activities of the adrenal cortex as indicated by a rise in its total cholesterol content. On this basis it may further be argued that the lowered cholesterol concentration of the adrenal of androgen-treated animals is an indication that the gland has returned to its normal functioning order. The androgen, in all probability, exerts its influence on the adrenal through an inhibition of pituitary corticotrophic activity.

SUMMARY

Thiourea treatment causes a marked increase in the total cholesterol concentration of the adrenals in rats. Testosterone propionate approximates the cholesterol content of the gland to that of the normal animals. It is suggested that the goiterogen acts as a stressor agent and alters the functional status of the gland through an acceleration of corticotrophic activities of the anterior lobe of the pituitary gland. The lowered cholesterol concentration of the adrenal after androgen administration is probably an indication of its return to a normal functioning order.

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