INFLUENCE OF TESTOSTERONE PROPIONATE ON
THE PLASMA AND LIVER PROTEINS
OF HYPOTHYROID RATS*

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(Received for publication, July 23, 1948)

Clinically a relationship between thyroid activity and blood protein levels has been indicated by a hyperproteinemia in myxedema (1) and is correlated with an increase in globulin levels (2). This relationship has been observed in dogs (3) and has been seen repeatedly in thyroidectomized rats and in rats fed antithyroid drugs (4–6). Since a decrease in weight of the seminal vesicles followed thyroidectomy (7) and thiourea feeding (8), the implication that androgen production is waning in hypothyroidism invited the study of testosterone propionate action in rats fed antithyroid drugs. These data aid in determining whether hypothyroidism or hypogonadism is of primary importance in causing the rise in plasma globulin associated with both conditions. Furthermore, an effect might be anticipated, since androgen administration induced nitrogen retention in a cretin (9).

Liver size and the ratio of liver protein to body weight increased after thiouracil feeding (10). In view of the known protein anabolic action of androgens (11) studies concerning liver protein in the hypothyroid state with and without concomitant androgen are presented.

EXPERIMENTAL

Male rats of the Long-Evans strain were used when 150 days old and were kept in metabolism cages for measurement of daily food intake. The rats were raised on Purina fox chow (20.1 to 23.9 per cent protein) and it was also fed during the experimental period. Thiourea and thiouracil,1 were added as 0.5 per cent of the diet, and the rats fed ad libitum. Other groups received thiourea or thiouracil and testosterone propionate1 or were normal rats with and without androgen, but all were pair-fed with the group on the goitrogenic substance alone, as thiourea and thiouracil reduce

* Supported by the Protein Metabolism Fund of the Bureau of Biological Research, Rutgers University, initially, and completed under a contract with the Office of Naval Research, Navy Department.

1 Thiouracil (deravet) was supplied by Dr. Mark Welsh, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, and testosterone propionate (perandren, Ciba) was supplied by Dr. E. Oppenheimer, Ciba Pharmaceutical Products, Summit, New Jersey.
food intake. After a 20 to 27 day experimental period the rats were lightly anesthetized with ether and bled from the heart. Hematocrit, non-protein nitrogen, total plasma protein, albumin, and globulin were determined. Albumin and globulin were separated by the Howe method (12), as modified by Robinson, Price, and Hogden (13). Nitrogen values were corrected for non-protein nitrogen and converted to protein by use of the factor 6.25. Liver nitrogen was determined after the organ had been dried to constant weight at 95° and ground to uniform consistency.

Results

Thiourea feeding reduced food intake to an average of 273 gm. per rat for 20 days, as compared to the 335 gm. consumed by rats eating ad libitum. The reduced food intake resulted in a loss in body weight which, however, was greater in the thiourea-fed rats than in pair-fed controls. Testosterone propionate administered subcutaneously at a level of 0.1 mg. daily did not prevent weight loss, although this androgen caused retention of urinary nitrogen in men on a restricted caloric intake (14).

Thiourea-fed rats exhibited a decrease in hematocrit and an increase in non-protein nitrogen, but an increase was not observed in normal rats on reduced food intake. Of the deviations from normal in rats fed thiourea, only non-protein nitrogen remained within the normal range in rats receiving both thiourea and androgen. Total plasma protein was increased by thiourea, owing to an increase in concentration of plasma globulin, while plasma albumin levels were unaltered (Table I). The androgen had a tendency to reduce the elevated plasma protein levels, but the differences were not significant. In the normal rat on restricted food intake, the plasma globulin level had a tendency to be higher than in rats fed ad libitum, being 2.72 gm. per cent compared with 2.51 gm. per cent. Androgen administration reduced the plasma globulin to a normal concentration, but in all cases the data are of border line significance.

Although the daily dosage of 0.1 mg. of testosterone propionate was adequate in maintaining weight of the seminal vesicles in castrated rats, this dosage was essentially ineffective in maintaining normal plasma protein levels in hypothyroid rats. It seemed advisable to repeat the entire experiment with 0.5 mg. of androgen daily, but the results generally duplicated the data obtained with the lower dosage.

The possibility that a toxic action of thiourea may have masked the action of testosterone on the concentration of plasma protein prompted the use of thiouracil. Thiouracil fed at 0.5 per cent reduced food intake to 300 gm. per rat over 20 days, causing a modest loss in body weight, which was duplicated by pair-fed controls. 0.5 mg. of testosterone propionate was used alone and in combination with thiouracil. Loss in body
weight was not prevented by testosterone propionate, but the increase in non-protein nitrogen and the decrease in hematocrit induced by thiouracil could be largely prevented by androgen administration. Thiouracil in-

**TABLE I**

*Plasma Protein Concentrations in Rats Treated with Thiourea (0.5 Per Cent) and Testosterone Propionate (0.1 Mg.)*

<table>
<thead>
<tr>
<th>No. of rats</th>
<th>Treatment</th>
<th>Body weight*</th>
<th>Hematocrit</th>
<th>Non-protein nitrogen</th>
<th>Total protein</th>
<th>Albumin</th>
<th>Globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Thiourea</td>
<td>294-256</td>
<td>40.5</td>
<td>±1.0†</td>
<td>68</td>
<td>6.66</td>
<td>4.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±3.4</td>
<td>±0.10</td>
<td>±0.12</td>
<td>±0.09</td>
</tr>
<tr>
<td>12</td>
<td>&quot; + testosterone propionate</td>
<td>294-259</td>
<td>41.3</td>
<td>±1.1</td>
<td>60</td>
<td>6.41</td>
<td>3.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±3.2</td>
<td>±0.11</td>
<td>±0.15</td>
<td>±0.09</td>
</tr>
<tr>
<td>12</td>
<td>Normal, pair-fed</td>
<td>288-271</td>
<td>45.4</td>
<td>±0.8</td>
<td>58</td>
<td>6.10</td>
<td>3.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±3.2</td>
<td>±0.07</td>
<td>±0.06</td>
<td>±0.09</td>
</tr>
<tr>
<td>6</td>
<td>&quot; + testosterone propionate</td>
<td>303-280</td>
<td>46.3</td>
<td>±1.2</td>
<td>57</td>
<td>5.93</td>
<td>3.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±4.0</td>
<td>±0.07</td>
<td>±0.14</td>
<td>±0.14</td>
</tr>
</tbody>
</table>

* Initial and final.  
† $e = \sqrt{\frac{\sum d^2}{n(n - 1)}}$.

**TABLE II**

*Plasma Protein Concentrations in Rats Treated with Thiouracil (0.5 per cent) and Testosterone Propionate (0.5 Mg.)*

Each group consisted of twelve rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body weight*</th>
<th>Hematocrit</th>
<th>Non-protein nitrogen</th>
<th>Total protein</th>
<th>Albumin</th>
<th>Globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiouracil</td>
<td>336-326</td>
<td>44.4</td>
<td>6.81</td>
<td>3.26</td>
<td>3.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>±0.5</td>
<td>±0.09</td>
<td>±0.08</td>
<td>±0.17</td>
</tr>
<tr>
<td>&quot; + testosterone propionate</td>
<td>331-317</td>
<td>46.4</td>
<td>6.85</td>
<td>3.36</td>
<td>3.59</td>
<td></td>
</tr>
<tr>
<td>Normal, pair-fed</td>
<td>336-315</td>
<td>48.7</td>
<td>6.04</td>
<td>3.19</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>&quot; + testosterone propionate</td>
<td>324-312</td>
<td>49.7</td>
<td>6.08</td>
<td>3.23</td>
<td>2.85</td>
<td></td>
</tr>
</tbody>
</table>

* Initial and final.

increased plasma globulin concentrations in the absence of a change in plasma albumin levels (Table II), and the administration of androgen was without effect. The increase in plasma globulin in rats due to thiouracil is associated with an increase in $\alpha$-globulin (6), and $\alpha$-naphthylthiourea
incites a similar reaction in dogs (15). The antithyroid drugs have varied toxicities, and thus their action might be to stimulate the adrenal, the secretions of which increase serum globulin (16). The action of antithyroid drugs on plasma protein levels would seem to be independent of adrenal excitation, however, since these compounds reduce adrenal activity (17, 18). Furthermore, normal globulin levels can be maintained in hypophysectomized rats with thyroxine (4), and adrenocorticotropic hormone does not release globulin in these animals (19).

Table III reveals that thiouracil will increase liver weight significantly without changing the percentage of water or protein. Consequently the total liver protein in the body and the liver protein in gm. per 100 gm. of body weight were significantly above normal. Testosterone propionate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Liver weight</th>
<th>Water</th>
<th>Total protein</th>
<th>Liver protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gm. per 100 gm. body weight</td>
<td>per cent</td>
<td>gm. per cent dry weight</td>
<td>gm. per 100 gm. body weight</td>
</tr>
<tr>
<td>Thiouracil</td>
<td>15.2±0.9</td>
<td>71.0±0.3</td>
<td>2.93±0.13</td>
<td>66.9 ±1.2</td>
</tr>
<tr>
<td>+ testosterone propionate</td>
<td>13.2±0.7</td>
<td>70.3±0.3</td>
<td>2.63±0.11</td>
<td>67.2 ±1.2</td>
</tr>
<tr>
<td>Normal, pair-fed</td>
<td>10.9±0.6</td>
<td>70.1±0.3</td>
<td>2.27±0.10</td>
<td>69.9 ±1.7</td>
</tr>
<tr>
<td>+ testosterone propionate</td>
<td>10.9±0.9</td>
<td>69.9±0.3</td>
<td>2.27±0.13</td>
<td>70.1 ±1.5</td>
</tr>
</tbody>
</table>

was essentially without effect on the liver water or protein in thiouracil-fed or normal pair-fed rats. The increase in liver weight induced by thiouracil was less pronounced when androgen was administered concomitantly. The increase in the ratio of liver protein to body weight is obtained only after thiouracil feedings (10), thyroidectomy favoring liver atrophy (20). The thiouracil action is surprising in the wake of reduced food intake, since the liver can be depleted of protein quickly (21). The increase in liver weight might also be aided by an increase in fat (22) and glycogen (23), but contradictory data have also been reported regarding these components in the liver (23, 18).

**SUMMARY**

Hypothyroidism induced by feeding thiourea or thiouracil resulted in an increased concentration of total plasma protein, plasma globulin, and
non-protein nitrogen. Plasma albumin concentration was not changed, but the hematocrit decreased. An increase in liver size, while water and protein remained at normal percentages, resulted in an increased liver protein in the body after thiouracil feeding. Testosterone propionate in doses of 0.1 and 0.5 mg. daily did not alter the plasma or liver proteins of hypothyroid rats, except to reduce the non-protein nitrogen. The slight rise in plasma globulin sometimes associated with restricted food intake was prevented by testosterone propionate administration, and the increase in liver weight induced by thiouracil was less pronounced when androgen was administered concomitantly.

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