EFFECTS OF CYPROTERONE ACETATE ON THE ADENOHYPOPHYSIAL CELLS OF MALE RATS

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Summary. Cyproterone acetate, a synthetic antiandrogenic steroid, caused a marked reduction in the weights of the accessory sex glands when given to male rats. The compound also affected the anterior lobe of the pituitary causing a decrease in the numbers of growth-hormone-producing cells. Cyproterone acetate did not inhibit spermatogenesis and the Leydig cells were normal.

Proper functioning of the accessory sex glands in males has been shown to be influenced by the adenohypophysial and gonadal hormones (Burrows, 1949; Parkes, 1966; Turner, 1966). Neumann, Van Berswordt-Wallrabe, Elger, Steinbeck, Hahn & Kramer (1970) reported that an antiandrogen, cyproterone acetate (CA), caused a marked atrophy of the accessory sex glands and suppression of spermatogenesis. While interpreting their results, Steinbeck, Mehring & Neumann (1971) related the effects of CA to local antagonism of endogenous androgen. Although Mietkiewski, Malendowicz & Lukaszyk (1969) carried out some experiments on the effects of CA on rat pituitaries, the effects of the compound on different cell types in the adenohypophysial have not, so far, been studied.

Sixty adult male rats were chosen for the experiment and were allocated to three groups. Group-1 rats served as controls and received only the oil vehicle. The rats in Group 2 each received a daily dose of 2.5 mg CA and those in Group 3 received 25 mg CA daily. The compound was dissolved in peanut oil and 0.1 ml was given orally every day over a period of 30 days. The animals were killed 24 hr after administration of the final dose and various organs were removed, weighed and fixed. Pituitaries were fixed in Helly’s fluid, processed, sectioned at 5 μm and stained with Mallory’s triple stain and with modified periodic acid Schiff (PAS)—methyl blue–orange G methods. Differential cell counts were made in the sections stained with PAS—methyl blue–orange G, applying the procedure of Rasmussen (1933). For cell-type classification, the methods of Hildebrand, Rennels & Finerty (1957) and of Lakshman (1965) were followed. The testes were fixed in Bouin’s fluid, sectioned at 7 μm and stained with Mallory’s triple stain and haematoxylin–eosin.

The investigations revealed that administration of CA to adult male rats was associated with a decrease in the weights of the accessory sex glands (Text-fig 1). Similar observations have been reported by Whalen, Luttge & Green (1969), Neumann et al. (1970) and Steinback et al. (1971). Cyproterone acetate

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exerted no significant influence on the testes and did not inhibit spermatogenesis at the dose levels employed. The weight changes of various organs at autopsy are shown in Table 1. The adenohypophyses of CA-treated rats did not differ in weight from those of the control group. Differential cell counts in the adenohypophyses of CA-treated animals revealed a marked decrease in the number of alpha-acidophils in the animals of both the low- and high-dose treatments. No variation was noted, however, between the controls and the treated animals in the number of beta-basophils, the source of thyrotrophin, and in the number of delta-basophils, the source of gonadotrophins (Purves, 1961). The results of the present investigation confirm those of previous observers that CA exerts its effects on the androgen-dependent structures such as the seminal vesicles, prostate and levator ani (Whalen et al., 1969; Neumann et al., 1970; Steinbeck et al., 1971). Neumann et al. (1970) reported that the effects of CA were mediated by way of a feed-back mechanism on the hypothalamic receptors. Steinbeck et al. (1971) described the effects of CA as a local antagonism towards endogenous androgens, thereby resulting in atrophy of the accessory sex glands.

The present investigations have shown that in the CA-treated animals there was a marked decrease in the number of acidophils (Table 2), which have been shown to be the source of growth hormone and of prolactin in the adenohypophysis (Purves, 1961). It has been inferred that the primary action of CA as an antiandrogen is in the blood plasma but not at the actual site of androgen production, the testis. In support of this statement, the Leydig cells were quite normal in all the CA-treated animals in the present study. Our observations lend support to the views of Whalen et al. (1969) that CA reduces the activity of androgen in the blood and androgen-dependent structures. Androgens and
Table 1. Relative weights of various tissues of adult male rats treated with cyproterone acetate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sem. ves.</th>
<th>Prostate</th>
<th>Testes</th>
<th>Epididymis</th>
<th>Adrenals</th>
<th>Levator ani</th>
<th>Pituitary</th>
<th>Thymus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1. Control, oil</td>
<td>129·4</td>
<td>202·4</td>
<td>1090·5</td>
<td>232·4</td>
<td>18·0</td>
<td>221·1</td>
<td>3·8</td>
<td>247·3</td>
</tr>
<tr>
<td></td>
<td>± 17·2</td>
<td>± 19·3</td>
<td>± 93·0</td>
<td>± 20·2</td>
<td>± 1·18</td>
<td>± 21·3</td>
<td>± 0·86</td>
<td>± 36·4</td>
</tr>
<tr>
<td>Group 2. Cyproterone acetate,</td>
<td>125·9</td>
<td>116·8</td>
<td>1226·2</td>
<td>249·6</td>
<td>18·4</td>
<td>71·4</td>
<td>4·1</td>
<td>209·5</td>
</tr>
<tr>
<td>2·5 mg/day</td>
<td>± 14·4</td>
<td>± 9·6</td>
<td>± 23·4</td>
<td>± 19·4</td>
<td>± 2·21</td>
<td>± 9·4</td>
<td>± 0·94</td>
<td>± 28·2</td>
</tr>
<tr>
<td>Group 3. Cyproterone acetate,</td>
<td>115·5</td>
<td>57·1</td>
<td>1239·1</td>
<td>232·3</td>
<td>12·0</td>
<td>57·3</td>
<td>4·2</td>
<td>153·1</td>
</tr>
<tr>
<td>25 mg/day</td>
<td>± 16·0</td>
<td>± 6·2</td>
<td>± 33·0</td>
<td>± 23·4</td>
<td>± 1·73</td>
<td>± 4·4</td>
<td>± 0·10</td>
<td>± 19·8</td>
</tr>
</tbody>
</table>

Twenty animals were used in each group. Values are expressed as mean ± S.E. (mg/100 g body weight).
pituitary growth hormone act synergistically and an adequate amount of both is necessary to maintain normal functioning of the male reproductive system and normal fertility. For this reason, loss of body weight in CA-treated animals has been attributed both to a decrease in the level of pituitary growth hormone and to inadequate levels of androgen which impede anabolism.

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REFERENCES

Whalen, R. E., Luttring, W. G. & Green, R. (1969) Effects of the anti-androgen cyproterone acetate on the uptake of $^{1,2,3}$H-testosterone in neural and peripheral tissues of the castrate male rat. Endocrinology, 84, 217.