

Data presented in this paper indicates that the pineal gland of the 13-day-old cockerel is affected, either directly or indirectly, by the administration of luteinizing hormone. Since it has been shown that LH has no effect on pineal uptake of ^{32}P in vitro¹⁰ it may be hypothesized that the exogenous LH causes an increase in release of testicular hormones which then decrease pineal activity via a negative feedback mechanism. Furthermore, this decreased pineal activity may be a decrease in release or synthesis of Gn-RH which would decrease pituitary LH production.

The results obtained from 3- and 10-day-old birds indicate that this mechanism may not be developed until about 13 days post-hatching. Differences in pineal and testis uptake of ^{32}P by 3- and 10-day-old birds are probably due to the differences in body weights (Table III).

Future studies will attempt to further define the pineal-gonadal relationship.

Summary. The glandular uptake of radioactive phosphorus (^{32}P), administered carrier-free, was used as an endpoint for the study of the effects of luteinizing hormone (LH) on the testis and pineal gland of 3-, 10- and 13-day-old White Leghorn cockerels. Pineal uptake of ^{32}P of the

13-day-old birds decreased and testis uptake of ^{32}P increased following LH treatment. Maximum effects were observed when 20 μg LH was administered 4.0 h before autopsy. Although testis uptake of ^{32}P increased following LH treatment in 3- and 10-day-old cockerels, pineal uptake of ^{32}P remained unchanged.

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¹⁸ G. W. SNEDECOR, *Statistical Methods*, 5th edn. (Iowa State College Press, Ames, Iowa 1956).

¹⁹ C. A. NAGLE, D. P. CARDINALI, N. P. LABORDE and J. M. ROSNER, *Endocrinology* 94, 294 (1974).

²⁰ W. F. WHITE, M. T. HEDLUND, G. F. WEBER, R. H. RIPPEL, E. S. JOHNSON and J. F. WILBER, *Endocrinology* 94, 1422 (1974).

²¹ N. P. PLOTNIKOFF, A. J. PRANGE, JR., G. R. BREESE, M. S. ANDERSON and I. C. WILSON, *Science* 178, 417 (1972).

²² D. P. CARDINALI, C. A. NAGLE and J. M. ROSNER, *Gen. comp. Endocr.* 26, 50 (1975).

Corticosteroid-Like Effect of Cyproterone and Cyproterone Acetate in Mice

Cyproterone (6 chloro δ^6 -1,2 α -methylene, 17 α -hydroxy progesterone SH 80 881 Schering) and cyproterone acetate (17 α -acetoxy, 6 chloro, 1 α , 2 α -methylene 4,6 pregnandiene 3,20 dione SH 80 174) are two of the most active antiandrogenic steroids blocking the peripheral action of both endogenous and exogenous testosterone¹⁻³. Their blocking effect is manifested in the peripheral target tissues, the seminal vesicles, the prostate and sebaceous glands. The majority of experiments suggest that the mechanism of the antiandrogenic action of cyproterone acetate consists in competitive inhibition of the action of the androgen testosterone or dihydrotestosterone at androgen receptor sites in the target organs. Cyproterone acetate is not only an antiandrogen but also a powerful gestagen. Free alcohol cyproterone is a weaker antiandrogen but has no gestagen activity¹. Cyproterone acetate was reported to decrease the adrenal weight and level of circulating corticosteroids in the rat^{1, 2, 5, 6}.

In order to ascertain the corticosteroid-like activity of cyproterone acetate and cyproterone, the drug was administered to intact male mice of strain H (Velaz, Prague) weighing 40 g. The animals were fed a standard

laboratory diet (Velaz) containing 23% protein with water ad libitum, and were kept in an indirectly illuminated room with a controlled temperature of $24 \pm 2^\circ\text{C}$. The mice were divided into 4 groups of 8 each. Cyproterone acetate Schering SH 80 714 and cyproterone Schering SH 80 881 were administered in a standard laboratory diet in doses of 5 mg/day p. animal for 21 days. Corticoid prednisone Spofa was given in the food in a dose of 1 mg/day p. mouse for 21 days. The animals were weighed before and after the experiment and their food consumption was checked daily. No food was left, so

¹ W. ELGER, R. VON BERSEWORDT-WALLRABE and F. NEUMANN, *Naturwissenschaften* 54, 549 (1967).

² F. NEUMANN and W. ELGER in *Androgens in Normal and Pathological Conditions* (Ed. A. VERMEULEN, Excerpta Med. Int. Congr. Ser. Amsterdam 1965), No. 101, p. 168.

³ F. NEUMANN, W. ELGER and H. STEINEBOCK, *Phil. Trans. Soc. London B* 259, 179 (1970).

⁴ C. DENEFF, M. VANDEPUTTE and P. DE MOOR, *Endocrinology* 83, 945 (1968).

⁵ J. LERNER, *Recent Progr. Horm. Res.* 20, 435 (1964).

⁶ L. STÁRKA, K. MOTLÍK and V. SCHREIBER, *Physiologia bohemoslov.* 21, 233 (1972).

| Group | Body weight final (g) | Seminal vesicle (mg/100 g) | Adrenal (mg/100 g) | Spleen (mg) | Spleen (mg/100 g) | Dry spleen (mg/100 g) |
|------------------------|---------------------------|-------------------------------|--------------------------|-------------------------------|-------------------------------|------------------------------|
| Controls | 37.5 \pm 2.88 (4) | 474.9 \pm 72.4 (2-4) | 15.6 \pm 1.8 (2, 4) | 211.4 \pm 52.4 (2-4) | 562.8 \pm 145.9 (2-4) | 142.0 \pm 36.0 (2-4) |
| Cyproterone acetate | 34.0 \pm 2.68 (3) | 210.6 \pm 37.5 (1, 3, 4) | 8.6 \pm 1.5 (1, 3) | 53.2 \pm 7.8 (1, 3) | 157.7 \pm 26.7 (1, 3) | 38.8 \pm 6.3 (1, 3) |
| Cyproterone | 38.1 \pm 2.10 (2, 4) | 285.8 \pm 32.8 (1, 2, 4) | 13.7 \pm 3.6 (2, 4) | 125.0 \pm 25.3 (1, 2, 4) | 327.2 \pm 60.5 (1, 2, 4) | 82.8 \pm 15.4 (1, 2, 4) |
| Prednisone | 33.3 \pm 1.4 (1, 3) | 630.2 \pm 120.9 (1-3) | 7.5 \pm 0.8 (1, 3) | 52.8 \pm 5.3 (1, 3) | 158.7 \pm 18.2 (1, 3) | 39.7 \pm 4.1 (1, 3) |

Means \pm 95% confidence limits. The numbers of groups with statistically different means are given in brackets.

that the amounts of food eaten corresponded to the dose of given drug. After 21 days the animals were killed, the adrenals seminal vesicles and spleen were removed, cleaned and weighed on a torsion balance. Organ weights were expressed in both absolute and relative values (mg/loog b. wt.) The results were evaluated statistically by means of the Duncan's test⁷. The results are given in the Table. Significant changes were observed in the seminal vesicles, which are a highly androgen-dependent tissues. The administration of cyproterone and cyproterone acetate to intact mice caused a significant decrease compared with controls. Prednisone, on the contrary, stimulated the growth of the accessory sexual glands. The statistically significant decrease in adrenal weight after all 3 steroids was in agreement with observations in rats, cyproterone acetate being approximately equivalent to prednisone^{4,6}. Cyproterone exerts a similar action but to a smaller extent. A dramatic decrease of the weight of spleen was caused by cyproterone acetate and prednisone, and less pronounced but still significantly by cyproterone. The dry weight of spleen corresponds to the extent of the decrease in wet weight of spleen in the experimental animals.

There is a well-known decrease in thymus weight after corticoids^{8,9}, in the spleen; the loss of weight following cortisone treatment is not as pronounced as in the thymus but follows the same pattern^{8,9}. The corticosteroid-like effect has been described in some gestagens^{10,11}. Though cyproterone acetate corticoid-like effect could be connected with its gestagenic properties, this is not valid for

the cyproterone effect: cyproterone has no gestagenic effect¹. When compared with prednisone, cyproterone acetate has approximately $\frac{1}{5}$ of the corticoid potency of prednisone, expressed by the decrease of the spleen weight; and so it corresponds in its efficiency to cortisol. If cyproterone acetate were to exert the corticoid-like effect also in other parameters, the combination of antiandrogenic properties and corticoid action would make this drug suitable for the treatment of virilizing adrenal hyperplasia.

Summary. Cyproterone and cyproterone acetate exert the corticoid-like effect on the adrenal and spleen weight in the mice. When compared with prednisone, cyproterone acetate has approximately $\frac{1}{5}$ of the corticoid potency of prednisone, expressed by the decrease of the spleen weight.

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⁷ D. DUNCAN, *Biometrics* 11, 1 (1955).

⁸ D. MAOR, E. EYLAN and P. ALEXANDER, *Acta endocr., Copenh.* 74, 201 (1975).

⁹ J. WEYMOUTH, *Radiother. Res.* 8, 307 (1958).

¹⁰ F. CAMANNI, F. MASSARA and G. MOLINATTI, *Acta endocr. Copenh.* 43, 447 (1963).

¹¹ G. FAKETE and S. SZEBERENYI, *Steroids* 6, 159 (1965).

Effect of Cortisolone on the Feedback Action of Dexamethasone

Cortisolone (pregn-4-ene-17 α ,21 diol-3,20 dione) was shown to act as an antiglucocorticoid in the thymus¹. It was found to bind to and to displace the biologically active glucocorticoid from cytoplasmic corticosteroid receptors of the thymus^{2,3} and in some regions of the rat brain⁴. Specific glucocorticoid receptors have been demonstrated in various areas of the central nervous system⁵⁻⁸.

In the present study, the role of these cytoplasmic receptors in the glucocorticoid feedback action was investigated by testing the effect of cortisolone on the feedback action of dexamethasone.

Materials and methods. Male albino rats of the CFE strain, maintained on a standard diet with free access to water, acclimatized to animal room conditions of uniform temperature ($24 \pm 1^\circ\text{C}$) and controlled relative humidity (50–75%) were used. They were injected s.c. with either

1 mg of cortisolone/100 g (Koch-Light Laboratories) dissolved in 0.5 ml of sunflower oil (Groups 2 and 4 in the Table), or 0.5 ml oil/100 g (Groups 1 and 3 in the Table).

¹ K. M. MOSHER, D. A. YOUNG and A. MUNCK, *J. biol. Chem.* 246, 654 (1971).

² A. MUNCK and T. BRINCK-JOHNSON, *J. biol. Chem.* 243, 5556 (1968).

³ N. KAISER, R. J. MILHOLLAND, R. W. TURNER and F. ROSEN, *Biochem. biophys. Res. Commun.* 49, 516 (1972).

⁴ Zs. Ács, unpublished data.

⁵ B. S. McEWEN, J. M. WEISS and L. S. SCHWARTZ, *Brain Res.* 16, 227 (1969).

⁶ B. I. GROSSER, W. STEVENS, F. W. BRUENGER and D. J. REED, *J. Neurochem.* 78, 1725 (1971).

⁷ H. KNITZLEY, *J. Neurochem.* 19, 2737 (1972).

⁸ E. STARK, Zs. Ács, M. PALKOVITS and G. FOLLY, *Acta Physiol. Acad. Sci. hung.* in press (1974).

Effect of cortisolone (1 mg/100 g) on the stress-reaction of rats treated with 50 μg /100 g dexamethasone

| | Group 1 | Group 2 | Group 3 | Group 4 |
|---------------------------------------|-------------------------|--------------------------|---------------------------|---------------------------|
| Subcutaneous injection | oil | cortisolone | oil | cortisolone |
| Intraperitoneal injection | saline | saline | dexamethasone | dexamethasone |
| Resting pre-stress level | 12.61 ± 1.74 (9) | 9.98 ± 2.08 (10) | $3.22 \pm 0.72^*$ (10) | $4.48 \pm 1.46^*$ (10) |
| Increment induced by histamine stress | 16.03 ± 3.86 (9) | 14.90 ± 2.18 (10) | $6.55 \pm 1.56^*$ (10) | 14.69 ± 1.90 (10) |

Mean \pm SEM in μg corticosterone/100 ml plasma. *significantly different ($p < 0.01$) from its respective control group evaluated by the method of analysis of variance for two-way layout. Numbers in parentheses denote number of determinations.