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 test[7]. 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 effect[1]. When compared with prednisone, cyproterone acetate has approximately $^1/_5$ 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 $^1/_5$ of the corticoid potency of prednisone, expressed by the decrease of the spleen weight.

P. D. Broulik and L. Starka

IIIrd Medical Clinic,
Faculty of General Medicine, Charles University,
U nemonice 1, Praha 2 (Czechoslovakia), 16 June 1975.

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Effect of Cortexolone on the Feedback Action of Dexamethasone

Cortexolone (pregn-4-ene-17α, 21 diol-3, 20 dione) was shown to act as an antiglucocorticoid in the thymus[1]. 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 brain[4]. Specific glucocorticoid receptors have been demonstrated in various areas of the central nervous system[5–8].

In the present study, the role of these cytoplasmic receptors in the glucocorticoid feedback action was investigated by testing the effect of cortexolone 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 ± 1 °C) and controlled relative humidity (50–75%) were used. They were injected s.c. with either 1 mg of cortexolone/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).

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Effect of cortexolone (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	cortexolone	oil	cortexolone
Intraperitoneal injection	saline	saline	dexamethasone	dexamethasone
Resting pre-stress level	12.61 ± 1.74 (9)	9.98 ± 2.08 (10)	3.22 ± 0.72[a] (10)	4.48 ± 1.46[a] (10)
Increment induced by histamine stress	16.03 ± 3.86 (9)	14.90 ± 2.18 (10)	6.55 ± 1.56[a] (10)	14.69 ± 1.90 (10)

Mean ± SEM in μg corticosterone/100 ml plasma. [a]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.

2 h later, the animals received i.p. either 50 µg of dexamethasone/100 g (Oradexon, Organon) (Groups 3 and 4), or 0.2 ml of physiological saline/100 g (Groups 1 and 2). 2 h after the i.p. injection, 1 ml of blood was withdrawn from the saphenous vein, under light ether anaesthesia, within 2 min of removing the animal from its cage. Histamine (1 mg/100 g) was injected i.p., followed by blood withdrawal from the abdominal aorta 30 min later. Pre- and after-stress plasma corticosterone was determined by the competitive protein-binding method[9]. Cortexolone did not interfere with corticosterone determination, since 3 h after administering s.c. the above dose of cortexolone to rats adrenalectomized 24 h earlier plasma corticosterone equalled that in the adrenalectomized controls (0.57 ± 0.08 µg/100 ml v.s. 0.54 ± 0.05 µg/100 ml; number of determinations is 9 in both groups).

Results and discussion. Dexamethasone administration lowered the resting plasma corticosterone level (Table). After histamine, corticosterone level in the dexamethasone-treated rats rose, the increment being significantly smaller than in the controls (Table). Cortexolone exerted no effect on the stress reaction of rats (Group 2 in the Table). This finding seems to be at variance with that of JONES et al.[10], a difference probably due to the fact that we administered cortexolone in 10 times lower doses than they did.

Cortexolone administration prior to dexamethasone did not prevent the decrease in the resting corticosterone level (Group 4 in the Table), but in these animals histamine stress induced an increment in plasma corticosterone similar to that in the vehicle-treated controls (v.s. Group 4 and Group 1 in the Table).

Our interpretation of these data is that cortexolone probably displaces dexamethasone from the hypothalamic and/or extrahypothalamic corticosteroid receptor sites, and thus prevents dexamethasone from inhibiting stress-induced ACTH release. The data favor the assumption that the corticosteroid feedback action depends on the binding of the hormone to specific receptors in the target cells, the mechanism of feedback action being in this respect similar to that of other well-known corticosteroid effects. It was suggested[11,12] that the mechanisms controlling ACTH-release under non-stress and stress conditions are functionally dissociable. Our present data seem to support this assumption by indicating that the site and/or the mechanism of dexamethasone suppression of resting ACTH secretion are distinct from those depressing stress induced ACTH release.

Summary. Cortexolone in a dose of 1 mg/100 g body wt., administered to rats prior to dexamethasone, prevented dexamethasone from suppressing stress-induced ACTH-release without interfering with the effect of dexamethasone on the resting plasma corticosterone level.

ZSUZSANNA ÁCS and E. STARK[13]

Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O. Box 67, H-1450 Budapest (Hungary), 23 June 1975.

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Effect of Progesterone on Human Corticosteroid 21-Hydroxylation

The biochemical basis of the genetically inherited metabolic disorders known as the adrenogenital syndrome[1,2] is as yet not fully understood. While two forms, the 'salt-losing' and the 'non-salt-losing' varieties, are known, both of which appear to result from defective adrenal 21-hydroxylation capability, it is not yet known whether these represent a single or two genetic defects[3,4]. Researches on these possibilities have recently been reviewed elsewhere[5]. The present account reports the results of experiments to investigate whether independent active sites for the 21-hydroxylation[6] of progesterone to 11-deoxycorticosterone (DOC) and of 17α-hydroxyprogesterone to 11-deoxycortisol (Reichstein's compound S) are present in human adrenocortical microsomal protein. This investigation formed part of a communication[7] presented at the meeting of the Southern Society for Pediatric Research in 1974.

Two normal human adrenals were obtained fresh postmortem and the external fat and connective tissue were trimmed off. The weight of the 2 glands was 7.07 g. They were cut into small pieces in about 100 ml cold 0.25 *M* sucrose. The suspension was homogenized using a motor-driven glass-teflon homogenizer and centrifuged at 600 *g* for 10 min to remove nuclear components, unbroken cells and unwanted debris[8]. The supernatant was centrifuged at 8,720 *g* for 10 min to separate the heavy mitochondria and twice at 26,700 *g* for 30 min to remove light mitochondria. The microsomes were isolated from the supernatant by centrifugation at 78,500 *g* for 90 min. They were gently hand-homogenized in 1–2 ml *Tris*-HCl, 50 m*M*, pH 7.45 containing 3 m*M* $MgCl_2$ and the protein concentration determined by the biuret method. Determination of the cytochrome P450 content of the microsomal protein was performed from the optical extinction at 450 nm after treatment with dithionite and carbon monoxide[9].

Incubations were performed for 5 min with agitation in a Dubnoff incubator maintained at 37 °C. The reaction mixtures contained microsomal enzyme (1.7 mg protein); trisodium isocitrate, 11 µmoles (Sigma); pigheart iso-

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