9. S. L. Kaplan, M. M. Grumbach, and M. L. Aubert, Rec. Prog. Hormone Res., 27, 161 (1971).
10. S. L. Kaplan, M. M. Grumbach, Neuroendocrinology, 4, 255 (1976).
11. G. Y. Rappay, A. Gyevai, L. Kondics, et al., *In vitro*, 8, 301 (1973).
12. L. H. Ress, D. M. Cook, J. W. Kendall, et al., Endocrinology, 89, 254 (1971).
13. T. M. Siler-Khodr, L. L. Morgenstern, and F. C. Greenwood, J. Clin. Endocriniol., 39, 891 (1974).
14. E. Stark, A. Gyevai, and K. Szalay, Can. J. Physiol. Pharmacol., 43, 1 (1965).

EFFECT OF TESTOSTERONE AND ITS 5α-REDUCED METABOLITES ON THYROID FUNCTION AND PROTEIN SYNTHESIS

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The results of many clinical and experimental investigations have demonstrated connections between the thyroid and sex glands [1, 6, 8]. The well-known fact that mainly women are prone to thyroid diseases [2] is evidence of the preventive role of male sex hormone in the pathogenesis of thyroid diseases. However, there is no general agreement in the literature either on the character of the effect of testosterone on function and proliferation of the throid gland or on the mechanisms of this effect.

This paper describes a comparative study of the action of testosterone and its active 5α-reduced metabolites on function and growth of the thyroid gland and on its protein synthesizing activity. The 5α-dihydrotestosterone and 5α-androstane-3β,17β-diol used in the experiments were synthesized at Khar'kov Research Institute of Endocrinology and Hormone Chemistry.

EXPERIMENTAL METHOD

Experiments were carried out on 120 male albino rats. There were three parallel series of experiments. The animals of each series were divided into four groups: one control and three experimental (10 rats in each group). The animals of the three experimental groups received testosterone propionate, dihydrotestosterone, or androstanediol, respectively, in the optimal dose established in preliminary experiments [4, 5], namely 0.5 mg/100 g body weight. All substances were injected subcutaneously in 0.2 ml persic oil daily for 14 days. Since the molecular weights of the compounds were similar, their administration in identical doses enabled their effects to be compared. The control group consisted of rats receiving the oil only. In the experiments of series I the percentage uptake of ^{131}I by the thyroid gland and the ratio between the content of iodinated amino acids in the gland were studied by ascending paper radiochromatography [10], and the plasma protein-bound iodine (PBI) level was studied by the method in [11]. In series II the structural reaction of the thyroid gland was studied in celloidin-paraffin sections stained with azan by Mallory's method. By using these methods it was possible to judge the state of thyroid function. In the experiments of series III activity of protein synthesis in the thyrocytes was determined by measuring β-radiation in total protein precipitated from rat thyroid gland homogenate 30 min after injection of ^{14}C-protein hydrolysate into the animals, on an SBS-2 scintillation counter. The results were subjected to statistical analysis by the Student—Fisher method.

EXPERIMENTAL RESULTS

Uptake of ^{131}I by the thyroid gland of the rats receiving testosterone propionate, expressed as a percentage, was higher than in the control (Table 1); intrathyroid hormone pro-

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TABLE 1. Data on Thyroid Function and Protein Biosynthesis in Rats Receiving Testosterone and Its 5β-Reduced Metabolites (M ± m; n = 10)

Substance injected	Per cent uptake of ^{131}I by thyroid gland	Relative content of iodinated amino acids in thyroid gland, %			PBI	Mean increase in body weight, g	Mean relative weight of thyroid gland, mg	Activity of incorporation of ^{14}C-protein hydrolysate, cpm/mg weight of thyroid gland
		DIT + MIT	I	$T_4 + T_3$				
	24 h after injection of isotope							
Oil	24,49±0,87	58,70±0,46	11,90±0,92	28,70±0,68	38,73±1,07	27,67±1,60	11,06±0,63	1404,01±12,2
Testosterone propionate	33,68±1,07 <0,001	56,24±0,59 <0,002	7,48±0,87 <0,001	36,28±1,09 <0,001	35,16±1,2 >0,1	38,67±1,37 <0,001	8,33±0,29 <0,001	943,36±1,95 <0,001
Dihydrotestosterone	16,54±0,75 <0,001	67,66±0,83 <0,001	8,78±0,69 >0,01	23,64±1,00 <0,001	20,40±0,98 <0,001	28,17±1,54 >0,01	7,63±0,23 <0,001	336,43±1,09 <0,001
Androstanediol	19,91±0,87 <0,001	54,15±0,87 <0,001	10,60±0,57 >0,1	38,58±1,06 <0,001	32,75±1,15 >0,1	34,21±1,18 <0,001	6,76±0,23 <0,001	289,23±1,60 <0,001

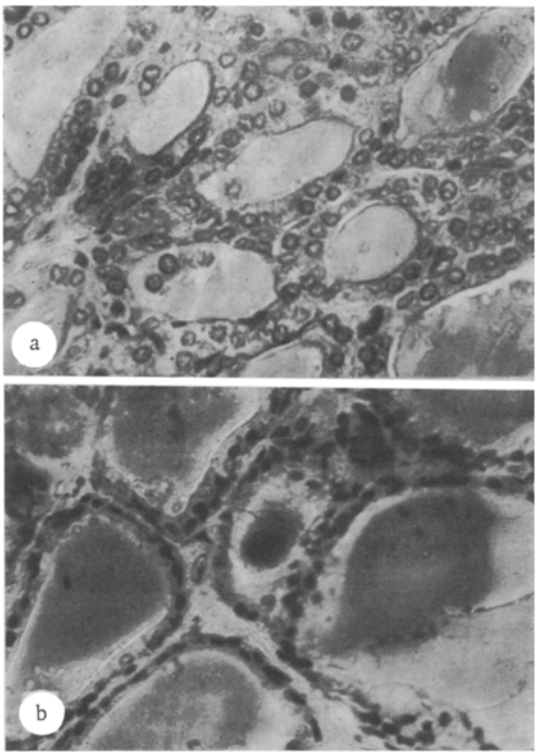

Fig. 1. Thyroid gland of rats on 15th day after injection of persic oil (a) and dihydrotestosterone (b). Fixation: Zenker–formol; staining: Mallory's azan. 250 ×.

duction was shifted toward the formation of active fractions of thyroid hormone ($T_4 + T_3$). The plasma PBI level was unchaged compared with the control. This may perhaps be due to the ability of androgens to depress the thyroxine-binding capacity of the plasma [9].

Percentage uptake of ^{131}I by the throid gland of rats receiving androstanediol was reduced a little. Androstanediol increased the relative content of iodothyronines ($T_4 + T_3$) and reduced the relative content of iodotyrosines (DIT + MIT), evidence of intensification of hormone formation in the throid gland. The PBI level was unchanged under these circumstances (Table 1).

Dihydrotestosterone condiderably reduced the degree of uptake of ^{131}I by the thyroid gland. Intrathyroid hormone formation was significantly weakened in the rats receiving dihydrotestosterone, as shown in the relative content of iodothyronines in the thyroid gland and an increase in inactive fractions of thyroid hormone (iodotyrosines). The plasma PBI concentration was significantly reduced (Table 1).

The structural reaction of the thyroid gland to testosterone and its metabolites varied. Testosterone induced a state of mild functional excitation of the thyroid gland, as shown by a decrease in size of the cycles, a prismatic shape of the thyrocytes, and liquifaction and vacuolation of the colloid. Compared with the control (Fig. 1a), dihydrotestosterone weakened secretory activity of the thyroid gland, as shown by an increase in size of the follicles, a decrease in height of the thyroid epithelium even to the extent of flattening, and the presence of thick, vacuole-free colloid (Fig. 1b). Androstanediol caused no significant changes in thyroid microstructure. An increase in the *de novo* formation of interfollicular islets was observed in the thyroid gland of all experimental animals, indicating inhibition of proliferation in the thyroid parenchyma.

Testosterone, dihydrotestosterone, and androstanediol thus had different effects on thyroid function, in agreement with modern views on the ability of active testosterone metabolites to induce effects in various organs that differ from (and sometimes may be opposite to) those caused by the native hormone [3, 7].

Both testosterone and its 5α-reduced metabolites, which in the doses used had an anabolic action on the increase in body weight of the animals, reduced the weight of the thyroid gland, but by a different degree (Table 1). The results confirm data in the literature on a decrease in weight of the thyroid gland, accompanied by its hyperplasia, in rats receiving male sex hormone [1].

The study of protein synthesis in the thyroid gland showed that activity of incorporation of ^{14}C-protein hydrolysate into thyroid proteins was considerably reduced by the action of testosterone. An even more marked decrease in protein synthesis was observed by the action of dihydrotestosterone and androstanediol (Table 1).

Analysis of the results suggests that the decrease in weight of the thyroid gland and inhibition of proliferation in it are due to the inhibitory action of testosterone and of its 5α-reduced metabolites on protein synthesis in the thyrocytes. Meanwhile comparison of the results shows a definite difference in the effect of these compounds on intrathyroid hormone formation. All the androgens used had an inhibitory action on total protein synthesis in the gland, whereas testosterone and androstanediol intensify intrathyroid hormone formation compared with the control, but dihydrotestosterone significantly reduced the conversion of iodotyrosines into iodothyronines. Consequently, it can be postulated that whereas testosterone and androstanediol inhibited the synthesis of structural proteins (as shown by decrease in weight of the thyroid gland) but did not prevent thyroglobulin formation, dihydrotestosterone inhibited synthesis not only of structural proteins, as shown by a decrease in weight of the gland, but also of thyroglobulin, which was confirmed by the reduction in hormone formation in the thyroid gland. The property of dihydrotestosterone of weakening hormone formation in the thyroid gland, not only without thereby inducing a goitrogenic effect, as in the case of the thyrostatics belonging to derivatives of thiouracil and mercaptoimidazole, but indeed by inhibiting proliferative processes in the thyroid parenchyma, may prove useful in the search for new biostatic agents.

LITERATURE CITED

1. B. V. Aleshin and N. G. Tsarikovskaya, Usp. Sovrem. Biol., 59, No. 2, 284 (1965).
2. Z. Kh. Zaripova, Probl. Endokrinol., No. 3, 26 (1964).
3. L. A. Loseva, V. G. Degtyar', and V. A. Isachenkov, Probl. Endokrinol., No. 6, 46 (1980).
4. S. L. Matveea, in: Abstracts of Proceedings of the 2nd Republican Conference of Junior Medical Scientists of the Ukrainian SSR [in Russian], L'vov (1979), p. 189.
5. S. L. Matveeva, in: Child and Adolescent Health Care. Neuroendocrine Regulation of Physiological Processes under Normal and Pathological Conditions [in Russian], No. 11, Kiev (1980), pp. 112-115.
6. V. M. Samsonova and V. N. Babichev, Probl. Endokrinol., No. 2, 113 (1977).
7. I. N. Sharkevich, in: Mechanism of Action of Hormones: Pathogenesis, Treatment, Prevention, and Epidemiology of Endocrine Diseases [in Russian], Kiev (1977), pp. 91-92.
8. S. N. Hasan, Pharmacol. Ther., 1, 231 (1976).
9. H. G. Keitel and M. C. Sherer, J. Clin. Endocrinol., 17, 854 (1957).
10. R. Pitt-Rivers, Biochem. J., 82, 108 (1962).
11. G. E. Sheline, M. C. Moor, and D. E. Clarke, J. Clin. Endocrinol., 11, 91 (1951).