SEX DIFFERENCES IN RESPONSE OF THE THYROID GLAND AND ITS SENSITIVITY TO THYROTROPIC HORMONE AFTER ADMINISTRATION OF ESTRADIOL, TESTOSTERONE, AND PROGESTERONE

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Experiments with Sprague-Dawley rats showed that after injection of estradiol benzoate, testosterone propionate, and progesterone the weight of the thyroid gland and the thyroxine-binding capacity (TBC) of the blood plasma proteins were higher in females than in males. The level of total thyroxine (TT_4) and the free thyroxine (FT_4) index were lower in females than in males after injection of testosterone propionate and progesterone. In males estradiol benzoate raised the TT_4 and FT_4 levels and in females it led to an increase in the TT_4 and TBC content. Testosterone propionate lowered the sensitivity of the thyroid gland to thyrotropic hormone. Progesterone had a stimulating action on the thyroid gland and caused a greater increase in the intensity of its function and its more rapid exhaustion in females than in males.

KEY WORDS: thyroid gland; thyrotropic hormone; estradiol; testosterone; progesterone.

Data in the literature on the effect of sex hormones on the thyroid gland are ambiguous and contradictory [1,2]. One reason for the existing contradictions is that the overwhelming majority of workers have studied the action of sex hormones on the thyroid gland in animals of the same sex, but they have extended their conclusions to both sexes. Recent work has shown that the thyroid gland of males and females reacts differently to progesterone [3].

In the light of these observations the comparative study of thyroid function in males and females under the influence of estrogens, progesterone, and testosterone and of the effect of these hormones on the sensitivity of the thyroid gland to thyrotropic hormone are of considerable interest.

EXPERIMENTAL METHOD

Experiments were carried out on 71 and 77 female adult Sprague-Dawley albino rats. The sex hormones were injected separately and in combination with thyrotropic hormone five times in the course of 10 days in the following doses: estradiol benzoate and testosterone propionate 5 μg of each/100 g body weight, progesterone 0.5 mg/100 g body weight, and thyrotropic hormone (TTH) 0.5 i.u./100 g body weight. An intraperitoneal injection of ^{125}I in a dose of 50,000-80,000 counts/100 sec was given to the rats 12 h before the end of the experiment. Under chloroform anesthesia blood was obtained by puncture of the heart, after which the animals were killed. The thyroid gland was weighed and homogenized in 2 N NaOH and the percentage uptake of radioactive iodine was calculated. The total thyroxine (TT_4) was determined by Murphy's competitive binding method [4], using the Thyopac-4 kit (Radiochemical Centre, Amersham, England). The thyroxine-binding capacity (TBC) of the blood plasma proteins was determined with the Thyopac-3 kit made by the same firm and expressed as the ratio between the values of TBC in the unknown serum and in the control serum [5]. The free thyroxine index (FT_4) was calculated as the ratio between the readings of the Thyopac-4 and Thyopac-3 kits, multiplied by 100. The numerical data were analyzed by computer in accordance with the Olivetti 101 program.

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TABLE 1. Weight of Thyroid Gland, Uptake of Iodine by Thyroid Gland, Total Throxine Level, and Blood Serum TBC and Free Thyroxine Index in Male and Female Albino Rats after Injection of Female and Male Sex Hormones and TTH (M±m)

Series of experiments	Hormone injected	Sex	No. of animals	Relative weight of thyroid gland, mg/100 g body weight	^{125}I uptake by thyroid gland, %/ 100 g wet weight of gland tissue	Blood serum TT_4, μg/100 ml	TBC	Blood serum FT_4 index
I	No hormones (control)	♂	10	6,66±0,45	35,2±3,1	5,57±0,42	0,68±0,008	8,23±0,78
		♀	10	7,30±0,36	51,4±3,7	6,18±0,44	0,70±0,02	8,29±0,90
II	TTH	♂	12	7,76±0,43	102,9±8,6 $P_I<0,001$	5,85±0,46	0,64±0,01 $P_I=0,003$	8,85±0,64
		♀	10	7,71±0,45	112,2±8,7 $P_I<0,001$	6,47±0,54	0,67±0,03	9,39±0,90
III	Estradiol benzoate	♂	8	6,16±0,35	86,7±7,4 $P_I<0,001$	7,76±0,43 $P_I<0,002$	0,63±0,007 $P_I<0,001$	11,88±0,78 $P_I=0,01$
		♀	10	7,09±0,28 $P_{III}=0,05$	44,6±2,8 $P_{III}<0,001$	8,08±0,61 $P_I=0,03$	0,75±0,02 $P_{I,III}=0,03$	10,78±1,10
IV	TTH + estradiol benzoate	♂	8	7,63±0,20	96,1±16,4	6,23±0,72	0,64±0,01	9,41±0,99
		♀	11	7,59±0,34	91,8±13,4	5,82±0,61	0,72±0,02	7,73±0,88
V	Testosterone propionate	♂	8	5,76±0,01 $P_I<0,05$	48,1±3,2 $P_I<0,01$	6,27±0,59	0,62±0,008 $P_I<0,001$	9,84±0,91
		♀	9	6,40±0,39	62,9±5,74 $P_{III}=0,04$	3,88±0,22 $P_{I,III}=0,01$	0,69±0,008 $P_{III}<0,001$	5,43±0,41 $P_{I,III}=0,02$
VI	TTH + testosterone propionate	♂	8	6,39±0,23 $P_{II}=0,01$	80,7±5,5 $P_{II}<0,05$	4,22±0,54 $P_{II}<0,05$	0,63±0,01	6,49±0,80 $P_{II}<0,05$
		♀	9	7,26±0,37 $P_{III}=0,06$	84,1±10,5 $P_{II}<0,06$	3,84±0,67 $P_{II}=0,01$	0,65±0,01 $P_{III}=0,1$	5,86±1,12 $P_{II}=0,03$
VII	Progesterone	♂	8	5,99±0,32	71,2±5,8 $P_I<0,001$	9,21±1,04 $P_I=0,01$	0,65±0,006 $P_I=0,01$	13,72±1,57 $P_I<0,01$
		♀	8	7,25±0,33 $P_{III}<0,01$	69,1±5,1 $P_I<0,009$	5,98±0,53 $P_{III}=0,02$	0,71±0,01 $P_{III}<0,001$	8,07±0,67 $P_{III}=0,008$
VIII	TTH and progesterone	♂	8	7,86±0,55	118,0±11,6	7,45±0,59 $P_{II}<0,05$	0,67±0,01 $P_{II}=0,01$	10,76±0,83
		♀	9	7,51±0,48	102,1±4,7	4,40±0,28 $P_{II,III}<0,01$	0,66±0,02	6,43±0,42 $P_{II,III}=0,01$

Legend. P_I and P_{II}) number attached to P indicates under of series used for comparison; P_{III}) comparison of males and females of the same series.

EXPERIMENTAL RESULTS

After injection of estradiol, testosterone, and progesterone the weight of the thyroid gland and TBC were higher in the females than the males (Table 1). Sex differences also were found in the TT_4 level and FT_4 index after injection of testosterone and progesterone.

The higher FT_4 level in the males was probably the result of stimulation of the thyroid gland by estradiol, on the one hand, and the low plasma TBC, due to endogenous androgens, on the other hand. In the females estradiol caused the TBC to rise. This evidently led to a brief fall in the blood FT_4 level and, consequently, it activated the hypothalamic-pituitary-thyroid system, as a result of which the plasma FT_4 concentration was equalized. Injection of physiological doses of estradiol into females is known to lead to elevation of the TTH level in the adenohypophysis and blood [6]. In females, after injection of estradiol, the euthyroid state was thus maintained despite the high blood TT_4 level. The thyroid gland of the females under these circumstances was in a state of higher functional stress than in the males.

In males testosterone reduced TBC and the weight of the thyroid gland and also reduced the sensitivity of the thyroid gland to TTH. After simultaneous injection of testosterone and TTH the weight of the thyroid gland, its uptake of iodine, and the TT_4 and FT_4 levels were all lower than after injection of TTH alone. In females testosterone caused a decrease in the FT_4 index. Lowering the blood FT_4 level stimulated the pituitary to produce and secrete TTH. However, instead of the expected rise, a fall was observed in the thyroid hormone level. It was postulated that testosterone reduced the sensitivity of the female thyroid gland to endogenous TTH. This hypothesis was confirmed by the results of experiments in which testosterone propionate and TTH were injected simultaneously.

Progesterone had a stronger effect on males, in which the highest FT_4 index in these experiments was found. In females an increase in thyroid function was observed, with a high level of iodine uptake, but the FT_4 index was unchanged. This can be explained by the higher blood plasma TBC, due to the endogenous estrogens of the female. In the writer's view, after injection of progesterone the female thyroid gland functioned with

greater intensity than the male thyroid. This can be deduced from the greater weight of the female than of male thyroid gland and, in particular, by the lower TT_4 and FT_4 levels after simultaneous injection of progesterone and TTH into females. These results indicate that stimulation of the female thyroid gland additionally to progesterone by exogenous TTH leads to its exhaustion.

The considerable functional stress on the thyroid gland caused by estrogens and intensified by progesterone may be one cause of the hyperplasia of the thyroid gland more often observed in women than in men.

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EFFECT OF NEONATAL ANDROGENIZATION ON HYPOTHALAMIC BIOGENIC MONOAMINES AND PITUITARY FUNCTION IN RATS

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Injection of testosterone propionate into female Wistar rats on the 2nd-4th day after birth did not change the serotonin concentration but sharply reduced the noradrenalin and dopamine concentrations in the hypothalamus of the animals at the age of 3.5 months. This was accompanied by an increase in the prolactin content in the adenohypophysis despite preservation of normal somatotropic activity. The results of this investigation point to a role of catecholamines in the pathogenesis of anovulatory sterility and give greater precision to modern views on the regulation of pituitary gonadotropic function.

KEY WORDS: neonatal androgenization; anovulatory sterility; hypothalamus; pituitary; biogenic monoamines.

Administration of androgens to newborn female rats disturbs the normal process of sexual differentiation of the brain and induces anovulatory sterility. The development of the anovulatory syndrome is linked with depression of the hypothalamic centers regulating secretion of gonadotropins [1,3,5].

This paper gives experimental proof of the participation of biogenic monoamines in the pathogenesis of anovulatory sterility.

EXPERIMENTAL METHOD

Female Wistar rats on the 2nd-4th day after birth received a subcutaneous injection of 150 μg testosterone propionate (TP). The animals were killed at the age of 3.5 months. Intact sexually mature females

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