STATE OF CERTAIN ENDOCRINE GLANDS UNDER THE INFLUENCE OF DOSES OF METHYLTHIOURACIL, WHICH BLOCK THE THYROID GLAND IN RATS

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It was shown [4] that methylthiouracil (MTU), just like thyroidectomy, causes a cessation of the synthesis of growth hormone in the anterior lobe of the pituitary in rats. In our previous study, we established [2] that during the first days of the influence of MTU on animals, the weight of the thymus gland, which is commonly believed to be related to growth processes (although its role in this process has not been sufficiently clarified), is significantly reduced. Other authors [1] have observed a decrease in the weight of the thymus gland in chickens under the influence of thiouracil and sulfidin, assuming that this decrease is independent of the endocrine system. On the other hand, according to certain data [10], one of the thioureates—propylthiouracil—stimulates ACTH formation in the pituitary. In turn, ACTH, both exogenous and endogenous, gives rise to involution of the thymus gland—a property on the basis of which a test for ACTH preparations on newborn rats has been proposed [6].

Thus, it might have been thought that in the chain of results of athyrosis, together with a cessation of the synthesis of growth hormone in the anterior lobe of the pituitary, there is also an intensification of ACTH secretion. As is known from the literature data [8, 12, 13], any unfavorable influence on the organism (cold, traumatic injuries, intoxication by various drugs, etc.) leads to an intensification of the ACTH secretion from the pituitary, which gives rise to characteristic changes in the organism, e. g., involution of the lymphoid tissue (in particular the thymus gland), increase in the weight of the adrenals, decrease in the ascorbic acid content of the adrenals and increase in the secretion of corticoids, etc. This reaction to stress occurs, as is well known, through the pituitary-adrenal system, and it is not observed in hypophysectomized animals (although the thymus may be reduced in weight to some degree [12, 13]. In this work we attempted to determine whether the action of methylthiouracil on the rat organism is of the nature of stress, and to what it is due—athyrosis or a side effect of methylthiouracil.

EXPERIMENTAL

Female rats weighing 60-80 g were hypophysectomized by a parapharyngeal method, and 10 days after the operation the action of MTU on their thymus glands was tested. MTU (20 mg) was administered in the form of an aqueous suspension, intraperitoneally, for a period of 3 days (parenteral introduction of MTU gives the same effect as administration per os). MTU was also administered to rats in which the pituitary, for one technical reason or another, was not removed during the operation, i. e., animals that might be considered to have been subjected to a sham operation. The absence of the hypophysis was established after the animals were killed. Analogous experiments were conducted on thyroidectomized rats. Thyroidectomy was performed according to the procedure described in the Practicum on Endocrinology [3]; the operation was successful (the percent death of the animals was negligible).

In addition, we conducted a series of experiments with enteral administration (with food) of various doses of MTU and thyroidin to normal and thyroidectomized rats over a period of 5 days. On the sixth day the animals were killed, and the weight of the thymus and thyroid glands and adrenals was determined. The tibias were removed and treated by the method of Greenspan et al. [11].

TABLE 1. Influence of MTU on the Weight of the Thymus and Width of the Cartilage of Normal, Hypophysectomized, and Thyroidectomized Rats (Average data of two experiments)

Animals	No. of animals	Preparation	Weight of thymus (in mg%)	Decrease in weight of thymus (in %)	Width of cartilage (in μ)	Difference in width of cartilage (in μ)
Normal	17	—	253,5	40,9	250	— 59
	17	MTU	149,8		191	
Sham hypophysectomized	8	—	251,4	29,5	240	— 14
	11	MTU	178,2		226	
Hypophysectomized	5	—	260,3	14,9	120	+ 15
	5	MTU	221,7		135	
Thyroidectomized rats	14	—	252,0	10,3	137	— 3
	16	MTU	135,9		134	

RESULTS

Intraperitoneal administration of MTU over a period of 3 days, in a dose of 20 mg daily (Table 1), causes a substantial decrease in the weight of the thymus gland in intact rats (by 40.9%), less in sham hypophysectomized rats (by 29.5%), and an entirely negligible decrease, lying within the limits of the variations, in hypophysectomized and thyroidectomized animals (by 14.9 and 10.3%, respectively). From Table 1 it is also evident that thyroidectomy causes a substantial decrease in the weight of the thymus (by 40%), while in rats that had undergone a no less substantial surgical trauma—the operation of sham hypophysectomy—there was no such decrease.

Table 2 presents the data of experiments on intact and thyroidectomized rats which received various doses of MTU and thyroidin with their food. As can be seen from Table 2, a direct relationship between the dose of MTU and the decrease in the weight of the thymus was observed in the intact rats (at doses of 20 mg/100 g and 30 mg/100 g, the weight was reduced by 27 and 33%, respectively; at 80 mg/100 g it was reduced by 50.1%). Not one of the doses of thyroidin restored the weight of the thymus to any significant degree, although, judging by the weight of the thyroid gland of these rats, doses of 20 and 3 mg were effective; however, they were somewhat greater than the physiological doses, because, as can be seen from Table2, they not only prevented hypertrophy of the thyroid gland, which set in under the influence of MTU, but also reduced its weight below the norm. A dose of 1 mg is the closest to the physiological. Thus, the weight of the thyroid gland in rats which received 30 mg of MTU and 1 mg of thyroidin was 17.3 mg %; that of the normal (control) rats was 16.5 mg %; that of the rats which received 30 mg of MTU alone was 31.6 mg %. Nonetheless, even this dose did not influence the decrease in the weight of the thymus under the influence of MTU. It also did not eliminate the increase in the weight of the adrenals observed under influence of MTU (see Table 2, experiment No. 3).

Thyroidin did not restore the weight of the thymus in two variations of the experiment in thyroidectomized animals (see Table 2): 1) thyroidin for five days in a dose of 20 mg, 10 days after the operation (experiment No. 3); 2) thyroidin for seven days in a dose of 3 mg daily, beginning with the day of the operation (experiment No. 4).

In experiment No. 1, as can be seen from Table 2, in the thyroidectomized and normal rats, the reaction of the thymus to 20 mg of MTU was the same; however, judging by external characteristics, the thyroidectomized rats tolerated MTU poorly during the experiment. This effect was confirmed in experiment No. 4; MTU in a dose of 40 mg per 100 g of body weight induced a lowering of the weight of thymus by 34.8% in the normal animals, while in a dose of 60 mg/100 g in the thyroidectomized animals the lowering of the weight of the thymus was 18.5%; at the same time, the increase in the weight of the adrenals under rhe influence of MTU was only 1.6 mg % in the normal animals, and 10.3 mg % in the thyroidectomized animals.

The low sensitivity of the thymus of thyroidectomized rats to MTU, also noted in the case of parenteral administration, gives rise to the question of whether the thyroid hormone is necessary for this reaction. However, as can be seen from experiment No. 1 (see Table 2), the addition of thyroidin to the feed of thyroidectomized rats does not intensity the effect of MTU. On the basis of this, we may believe that the above-mentioned insensitivity is explained by the fact that the reaction of the thymus to thyroidectomy is a maximum.

TABLE 2. Influence of Various Doses of MTU and Thyroidin on the Weight of the Thymus and Thyroid Glands, Adrenals, and Width of the Cartilage of the Tibia in Normal and Thyroidectomized Rats

Experiment No.	Animals	No. of animals	Preparations	Weight of thymus (in mg %)	Decrease in weight of thymus (in %)	Weight of thyroid gland (in mg %)	Weight of adrenals (in mg %)	Width of cartilage (in μ)
1	Normal	9	–	259.2		14.5	–	264
		9	MTU (20 mg/100 g)	188.5	−27.2	28.6	–	230
		9	MTU + thyroidin (20 mg + 3 mg)	222.1	−14.3	11.6	–	228
	Thyroidectomized	9	–	132.2		–	–	143
		8	MTU (20 mg)	99.1	−25.1	–	–	116
		9	MTU + thyroidin (20 mg + 3 mg)	132.2	0	–	–	155
		9	Thyroidin (20 mg)	150.9	0	–	–	163
2	Normal	10	–	328.8		22.3		–
		10	MTU (80 mg/100 mg)	164.1	−50.1	46.9	–	–
		10	MTU + thyroidin (80 mg + 3 mg)	173.2	−47.3	17.1	–	–
		10	MTU + thyroidin (80 mg + 20 mg)	180.3	−45.1	19.3	–	–
3	Normal	8	–	237.7		16.5	31.4	213
		8	MTU (30 mg/100 g)	158.8	−33.2	31.6	35.1	181
		10	MTU + thyroidin (30 mg + 1 mg)	142.3	−40.2	17.3	36.8	168
	Thyroidectomized	12	Thyroidin (3 mg)	155.5		–	–	138
		11	daily for seven days, beginning with the day of the operation	142.9	−0.81	–	–	122
4	Normal	7	–	239.5		12.9	31.5	186
		10	MTU (45 mg/100 g)	156.2	−34.8	28.8	33.1	155
	Thyroidectomized	8	–	100.1		–	39.2	114
		7	MTU (60 mg/100 g)	81.6	−18.5	–	49.5	116

In the experiments, as a rule, a constriction of the cartilage was observed, paralleling the decrease in the weight of the thymus, which also, according to the literature data [9], may most likely be ascribed to the action of endogenous ACTH. Thus, during the first days of the influence of large doses of MTU on the rat organism, there were such characteristic signs of stress as a decrease in the weight of the thymus, which practically was not noted in the hypophysectomized animals, and an increase in the weight of the adrenals. However, the indicated phenomena, as our data show, do not arise as a result of the absence of thyroid hormone in the organism, although this evidently plays some role. It seems to us that light my be cast on this question by new data on the fact that MTU induces degeneration of the intraorgan nerve fibers of the thyroid gland [7], and thus stress here is a result of nerve trauma. Desiring to confirm this, we performed bilateral cutting of n. recurrens in normal rats, without removing the thyroid gland, and after 15 days detected a 25% decrease in the weight of the thymus, while cutting of n. saphenus gave no such effect.

Let us mention that in the experiments of Selye [13], no involution of the thymus is noted after thyroidectomy, in contrast to our observations, as well as certain literature data, which may be explained by the different age of the animals used in the experiment (adult rats in Selye's experiments, and infantile rats in our experiments).

K. Z. Kan [5] observed an intensification of the ACTH secretion under the influence of MTU, explaining this as a result of intensification of the secretion of thyrotropic hormone, induced by MTU. However, as can be seen from our experiments, hypersecretion of ACTH under the influence of MTU also appears when the administration of thyroidin prevents the intensification of secretion of thyrotropic hormone.

Thus, although the action of MTU on the thymus is not specific, it evidently occurs through the pituitary-adrenal system (like any stress), i. e., through the endocrine system.

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