# PINEAL-THYROID INTERACTION: DISTORTING EFFECT OF EXPERIMENTAL PARTIAL THYROIDECTOMY OF ANTIHYDROID EFFECT OF PINEAL METHOXYINDOLES

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The inhibitory character of the effect of the pineal hormone melatonin on thyroid gland (TG) function was established as long ago as in the 1960s, and since then it has been confirmed on many occasions by experiments with injection of exogenous melatonin [7, 8, 10], with changes in the lighting conditions [5, 7], and by the results of this inhibitory effect (ways of acting on TG, the sensitivity of individual components of the hypothalamo-hypophyseal system to the action of the hormone, etc.), await clarification. They include the role of the functional state of TG itself when its activity is modified by melatonin.

The aim of this investigation was to compare the effects of preparation of pineal methoxyindoles on the main parameters of TG function in intact and partially thyroidectomized (PTE) rats.

## EXPERIMENTAL METHOD

Experiments were carried out on 110 mature male Wistar rats kept under conditions of a short period of natural daylight. In the animals of experimental series I three-quarters of TG was removed under ether anesthesia; control animals underwent a mock operation. Injection of melatonin (obtained from N. N. Suvorov at the S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute) began 12 days after the operation, when TG was in a state of active regeneration. Under these same conditions the effect of another pineal methoxyindole (MI), namely 5-methoxytryptamine (5-MT), was investigated. All procedures were carried out on animals with an intact TG. MI preparations were dissolved in 96% ethanol, then diluted with physiological saline to the required concentration. Both preparations were injected intraperitoneally within an interval of between 17 and 18 h, in the course of 10 days, in doses of: melatonin — 100 µg, and 5-MT — 40 µg/100 g body weight. Uptake of $^{131}I$ by TG was determined 24 h after injection of 3 µCi of $^{131}I$ by the usual radiometric method. Serum levels of thyroid hormones (TRH) and thyroid-stimulating hormone (TSH) and the thyroxine-binding capacity of the serum were determined by means of kits from the firm Byk-Mallincrodt (West Germany). Since these kits are intended for hormone assay in human blood, tests were carried out for "parallelism" and "discovery"; no significant disturbances were found in this case in the determination of serum hormone levels of the rats.

From the TRH-test a preparation obtained from Hoechst (West Germany) was used and was injected 30 min before decapitation in a dose of 100 mg per animal.

## EXPERIMENTAL RESULTS

It will be clear from Table 1 that administration of melatonin for 10 days to animals with an intact TG caused a distinct lowering of the iodine-uptake function of TG, lowering the plasma concentration of $T_4$ from 74.0 ± 3.7 to 55.0 ± 2.1 nmoles/liter and of $T_3$ from 1.5 ± 0.13 to 1.0 ± 0.09 nmole/liter. Under these circumstances the TSH level was only 62% of the control.

After injection of 5-MT similar but less marked changes of the parameters of thyroid activity were found (Table 1). Despite the fact that the $T_4$ level remained within the control limits, the serum $T_3$ concentration in rats receiving 5-MT was significantly lowered, possi-

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TABLE 1. Effect of Daily Injections of Pineal MI for 10 Days on Thyroid Function in Rats

| Parameter | Control (injection of solvent) | Melatonin (100 μg/100 g body weight) | 5-MT (40 μg/100 g body weight) |
|---|---|---|---|
| $^{131}I$ uptake by TG, mg % | 4,1±0,2 $n$=15 | 2,8±0,2* $n$=15 | 3,4±0,2* $n$=15 |
| $T_3$ in plasma, nmoles/liter | 1,5±0,1 $n$=16 | 1,0±0,09* $n$=18 | 1,1±0,07* $n$=18 |
| $T_4$ in plasma, nmoles/liter | 74, ±3,7 $n$=16 | 55,0±2,1* $n$=18 | 78,0±6,0 $n$=18 |
| TSH in plasma, milliunits/liter | 1,6±0,1 $n$=16 | 1,0±0,09* $n$=18 | 1,2±0,08* $n$=18 |

Legend. Asterisk indicates significant difference from control.

bly as a result of disturbance of peripheral deiodination of $T_4$. The circulating TSH level also was definitely lowered through the action of this MI: to 1.2 ± 0.08 milliunits/liter compared with 1.6 ± 0.13 in the control.

The similar direction of the changes in the plasma thyroid hormone and TSH concentrations is evidence of an inhibitory action of pineal MI on the hypophyseothyroid system with disturbance of the negative feedback mechanism in the thyroid hormone — TSH system.

To study the role of central components of the hypothalamo-hypophyseo-thyroid system in the realization of the inhibitory effect of pineal MI a TRH test was carried out (Fig. 1). It was shown that the TSH-TRH reaction was not only preserved in the animals receiving both melatonin and 5-MT, but it was much more demonstrative: in animals receiving melatonin the rise of the serum TSH level amounted to 280%, whereas in animals receiving 5-MT it was 233% at the corresponding basal level, and in animals receiving only the solvent, the TSH response was only 181% of its initial value.

The results are evidence that under short daylight conditions administration of melatonin and 5-MT does not induce loss of sensitivity of the adenohypophyseal thyrotrophs to stimulation by TRH, as has been suggested [6] but the fall in the TSH level in circulation during these procedures is most probably due to blocking of TRH release from the hypothalamus.

Investigations [10] have shown that the trend of the effect of melatonin and also, perhaps, of other MI in relation to functions of the various endocrine systems depend on several factors. In the present study we attempted to find out whether the action of pineal MI on TG maintains its inhibitory character under conditions of compensatory growth.

It will be clear from Table 2 that 12 days after the experiment the serum $T_4$ level in PTE rats was somewhat depressed, whereas the TSH level had risen to 2.0 ± 0.07 mU/liter compared with 1.6 ± 0.13 mU/liter in non-PTE rats. The thyroxine-binding capacity of the blood plasma was unchanged. On the 22nd day after the experiment (controls II and III) a progres-

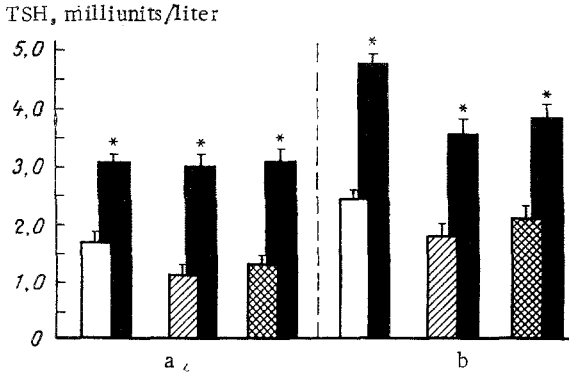


Fig. 1. TRH test in intact rats (a) and PTE rats (b) receiving pineal MI. Unshaded columns — control, oblique shading — injection of melatonin, cross-hatching — injection of 5-MT, black columns — TRH test. Asterisk indicates significant difference between TRH-induced increase in TSH concentrations and corresponding basal level.

TABLE 2. Effect of Pineal MI on Thyroid Function of PTE Rats (M ± m)

| Parameter | Control I (PTE rats, 12th day) | Control II (PTE rats, 22nd day) | Control III (PTE rats, 22nd day, solvent) | Control IV (rats undergoing mock operation, 22nd day, solvent) | Melatonin (100 μg/100 g, PTE rats) | 5-MT (40 μg/100 g, PTE rats) |
|---|---|---|---|---|---|---|
| $^{131}I$ uptake by TG, mg % | — | $5,7\pm0,9^{IV}$ $n=10$ | $5,9\pm0,5^{IV}$ $n=10$ | $4,5\pm0,5^{II, III}$ $n=10$ | $4,3\pm0,55^{II, III}$ $n=10$ | $5,6\pm0,5^{IV}$ $n=10$ |
| $T_3$ in plasma, nmoles/liter | $1,3\pm0,11$ $n=12$ | $1,0\pm0,07^{IV}$ $n=12$ | $1,0\pm0,06^{IV}$ $n=12$ | $1,5\pm0,1$ $n=14$ | $1,4\pm0,1^{II, III}$ $n=15$ | $1,1\pm0,1^{IV}$ $n=15$ |
| $T_4$ in plasma, nmoles/liter | $50\pm1,8$ $n=12$ | $31\pm1,7^{I, IV}$ $n=12$ | $26,0\pm1,6^{I, II, IV}$ $n=12$ | $78,0\pm3,1^{I, II, III}$ $n=14$ | $58,0\pm1,8^{II, III, IV}$ $n=15$ | $30,0\pm1,7^{I, IV}$ $n=15$ |
| $T_3$-Binding, relative units | $0,89\pm0,07$ $n=10$ | $0,76\pm0,04^{I, IV}$ $n=10$ | $0,72\pm0,07^{I, IV}$ $n=10$ | $0,86\pm0,09^{II, III}$ $n=10$ | $0,83\pm0,07^{II, III}$ $n=15$ | $0,75\pm0,1^{I, IV}$ $n=15$ |
| TSH in plasma, milliunits/liter | $2,0\pm0,07$ $n=12$ | $2,0\pm0,1^{IV}$ $n=12$ | $2,2\pm0,2^{IV}$ $n=12$ | $1,7\pm0,1^{II, III}$ $n=14$ | $1,6\pm0,1^{I, II, III}$ $n=15$ | $1,8\pm0,1^{III}$ $n=15$ |

Legend. I, II, III, IV) Difference from corresponding control is significant.

sive fall of the plasma $T_3$ and $T_4$ levels was observed, against the background of a steadily increased TSH concentration, and also an increase in the degree of $^{131}I$ uptake by tissue of the regenerating TG. However, the results of the $T_3$-binding test (Table 2) do not allow the state of the PTE rats to be regarded as hypothyroid. The data show that the tyroxine-binding capacity of the blood plasma of PTE rats is reduced; the possibility of increased conversion of the free form of $T_4$ into the more active $T_3$ hormone cannot be ruled out. This conclusion is confirmed by the results of investigations [3] showing activation of the hypothalamo-hypophyseal complex in rats subjected to unilateral thyroidectomy, which leads to intensification both of compensatory growth and of hormone production in TG, and to rapid restoration of the normal thyroid status [1].

Under the conditions of the experimental model used, the effect of 10 daily injections of melatonin can be interpreted as normalizing. For instance, values of the parameters of $^{131}I$ uptake by regenerating TG tissue in response to melatonin did not differ from those in animals undergoing the mock operation (control IV); the thyroxine-binding capacity of the blood plasma and the $T_3$ and TSH levels also coincided with the basal levels. Only the $T_4$ concentration was significantly reduced (58.0 ± 1.8 nmoles/liter compared with 78.0 ± 3.1 nmoles/liter in control IV). Administration of 5-MT did not cause any significant changes in the parameters studied compared with their values in controls II and III (Table 2). The results of the TRH test, conducted on PTE animals receiving pineal MI (Fig. 1) are evidence that the thyrotrophs of the adenohypophysis remain sensitive to the influence of TRH even when production of the latter, induced by partial thyroidectomy, is stimulated. Injection of MI did not enhance the TSH-TRH reaction, unlike in experiments on animals with an intact TG: under the influence of melatonin the increase in the TSH concentration under the influence of an injection of TRH amounted to 175%, whereas under the influence of 5-MT it was 200%, compared with 215% in the control series.

It was thus shown on the example of TG that the trend of reactions of the endocrine system to pineal MI largely depends on the initial state of the target organ and of the hormonal background. This phenomenon is manifested particularly clearly during the action of the pineal hormone melatonin and, to a lesser degree, of 5-MT. Even though it is most widely held that melatonin is an inhibitor of thyroid function, on the whole it is evidence that the effects of melatonin are rather mainly modulating in character.

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