Modifying Effect of Pineal Peptide Hormones on the Reactivity of Rat Thyroid Gland to Cooling

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 12, pp. 652-654, December, 1997
Original article submitted November 22, 1996

The study explores the effect of pineal peptide hormones (epitalamin) on the pituitary-thyroid system in cold exposure. It is shown that pineal hormones block hyperreactivity of the thyroid to acute cold stress, while in chronic cooling they modulate the adaptive reaction of the thyroid gland to cold. Thus, pineal peptides can modulate the thyroid reaction to cooling. Epitalamin modulates the intensity of peripheral deiodination of thyroxine.

Key Words: *epitalamin; pineal peptide hormones; thyroid gland; thyroid hormones; thyroid stimulating hormone; cold stress*

Since the thyroid gland (TG) is involved in thermogenesis, the hypothalamus-pituitary-thyroid axis readily responses to cooling. A good illustration is presented in the report of E. Tang *et al.* [5], who observed elevation of the serum triiodothyronine (T_3), thyroxine (T_4), and thyroid stimulating hormone (TSH) in albino rats exposed to 4°C for 1 and 5 hours. Other investigators observed a 2-fold activation of T_4-deiodinase in rat pineal gland after 4-h cooling at 4°C attesting to enhanced utilization of thyroid hormones by pinealocytes in hypothermia [4].

On the other hand, our previous studies on clinical (intraoperation biopsy specimens of human TG) and experimental material demonstrated the involvement not only of pineal indoles but also of pineal peptide hormones into regulation of thyroid function [1-3]. These data were obtained under normal temperature, while the role of pineal hormones in the regulation of adaptation of the hypothalamus-pituitary-thyroid system to cold stress has not been evaluated. In this study we attempted to tackle this problem.

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MATERIALS AND METHODS

Experiments were carried out on 78 adult male Wistar rats. The animals were maintained at normal temperature, exposed to acute cold stress (4°C for 30 and 180 min), or chronic cooling (10 days at 10°C), receiving standard food and water supply.

Epitalamin (EP), a peptide preparation from cattle pineal glands, kindly provided by Dr. V. A. Khavinson (*Tsistomedin*, St. Petersburg) was injected intraperitoneally in a dose of 0.25 mg/kg independently or immediately before cold exposure.

Serum concentrations of total T_3, T_4, and TSH were measured by enzyme-linked immunosorbent assay using commercial kits (*Immunotekh*, Russia); concentrations of free T_3 and T_4 were measured by radioimmunoassay using Amersham kits.

RESULTS

As seen from Table 1, 30-min cooling (4°C) leads to a 2.5-fold rise of serum T_3 against the background of a 40% decrease in the T_4 level. This indicates substantial peripheral conversion of T_4. The same pattern was noted for free hormones. The enhanced production of total and free T_3 in cold stress is apparently a compensatory reaction. Judging from

0007-4888/97/0012-1200$18.00

TABLE 1. Effect of Acute Cold Stress (4°C) and EP on Pituitary-Thyroid System in Albino Rats (*M*±*m*, *n*=9-10)

Exposure	Serum hormone concentration				
	T_3, nmol/liter	T_4, nmol/liter	free T_3, pmol/liter	free T_4, pmol/liter	TSH, mU/liter
Control	0.76±0.11	64.80±7.20	2.00±0.18	16.00±1.72	1.65±0.21
Hypothermia, 30 min	2.30±0.29***	38.70±3.40**	3.10±0.27**	9.80±0.87**	2.34±0.21*
EP	0.96±0.12	46.50±4.42	2.90±0.19*	9.80±1.04*	1.70±0.19
Hypothermia, 30 min+EP	1.00±0.09+°°	31.20±4.50++	1.50±0.19°	9.80±1.04+	2.80±0.18+
Hypothermia, 180 min	1.10±0.09*++	121.60±9.30*++	—	—	2.10±0.17
Hypothermia, 180 min+EP	0.69±0.07x	68.80±4.61xx	—	—	2.02±0.19

Note. Here and in Table 2: *p<0.05, **p<0.01, ***p<0.001 compared with the control; +p<0.05, ++p<0.01 compared with 30-min hypothermia without EP; °p<0.05, °°p<0.01 compared with EP; xp<0.05, xx$p$<0.01 compared with 180-min hypothermia.

the dynamics of serum TSH, the pituitary gland is involved into this reaction.

Injection of EP without subsequent cooling slightly increased the concentration of T_3 and decreased the level of T_4, i.e., EP slightly stimulated peripheral deiodination of T_4 and had no effect on secretory activity of TG and TSH release into circulation (*in vitro* experiments with fragments of human TG revealed other relationships [2,3]).

In EP-injected rats, 30-min hypothermia induced the same increase in serum T_3 concentration as EP alone and a more pronounced decrease in the T_4 content (52%), indicating a direct antithyroid effect of EP, the level of TSH being increased.

Exposure to 4°C for 180 min also increased the content of T_3 (1.10±0.09 *vs.* 0.76±0.11 nmol/liter in the control) and markedly increased the level of T_4 (about 2-fold). This indicates activation of both T_4 release and, to a lesser extent, its peripheral deiodination. It should be emphasized that serum concentration of T_3 during 180-min cooling rose to a lesser extent, while changes in the content of T_4 were opposite to those observed during 30-min cold exposure. The level of TSH changed insignificantly, which attests to a parapituitary mechanism of the reaction of TG to prolonged cold exposure.

Epitalamin considerably weakened the effect of 180-min hypothermia to TG, especially, to secretion of T_4: the content of thyroid hormones practically did not differ from the control (T_3: 0.69±0.007, T_4: 68.80±4.61 nmol/liter).

It should be noted that pineal peptides produce stronger inhibitory effect on thyroid function and peripheral metabolism of thyroid hormones in acute cold stress, therefore it was interesting to study their effect on pituitary-thyroid function in rats under conditions of long-term (10 day) adaptation to moderate cooling.

As seen from Tables 1 and 2, long-term moderate hypothermia induced a more pronounced elevation of serum T_3 in comparison with 3-h exposure to 4°C (1.70±0.21 *vs.* 1.10±0.09 nmol/liter) and was not associated with activation of T_4 secretion (the level of T_4 was reduced 2-fold in comparison with the controls and animals exposed to 3-h cooling). These data may attest to exhaustion of the secretory potential of TG in long-term cooling, or, more likely, its functional adaptation, when organism's requirement is covered through enhanced peripheral conversion of T_4, all the more that serum level of free T_3 under these conditions rises considerably. Thyroid-stimulatory function of the pituitary remains unchanged.

Injection of EP under these conditions produced an unexpected result: the preparation considerably potentiated suppression of the secretory activity of

TABLE 2. Effect of Chronic Cooling (10°C, 10 days) and Epitalamin on Pituitary-Thyroid System in Albino Rats (*M*±*m*, *n*=9-10)

Exposure	Serum hormone concentration				
	T_3, nmol/liter	T_4, nmol/liter	free T_3, pmol/liter	free T_4, pmol/liter	TSH, mU/liter
Control	0.83±0.11	77.30±5.03	2.06±0.16	13.64±1.32	1.58±0.19
Hypothermia	1.70±0.21*	38.00±4.20*	3.12±0.31*	10.07±1.24	1.92±0.24
Hypothermia+EP	4.25±0.26****+	21.30±1.94**+	2.80±1.69	4.20±2.45*****+	1.42±2.45

TG (T_4 decreased to 21.30±1.94 nmol/liter, i.e., was 3-fold lower then in the control). This was accompanied by a sharp decrease in the content of its free form, while the content of total T_3 increased about 5-fold. Thus, despite the antithyroid effect of EP (judging from T_4 level) overall production of active form of T_3 markedly increased.

Thus, peptide pineal hormones exert unequal effect on the state of the hypothalamus-pituitary-thyroid system in cold stress of various duration and intensity: the effect of EP in 3-h severe cold stress can be considered as a blockage of TG hyperreactivity to stress, whereas in long-term moderate hypothermia the preparation potentiates adaptive thyroid reaction through stimulation of T_3 production. Our findings suggest that peptide pineal hormones can be considered as modulators of thyroid reaction to cold stress.

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