INTERACTION BETWEEN THE HYPOTHALAMIC-HYPOPHYSEAL SYSTEM AND THYROID GLAND AT DIFFERENT AGE PERIODS

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Age differences in interaction between the hypothalamic-hypophyseal system and the thyroid gland were studied with consideration to both direct and feedback control. In old age significant disturbances affect both direct and feedback components of this system; the sensitivity of thyroid tissue to TSH and of the hypothalamus and pituitary to the action of T_4 is increased. The increased sensitivity of the hypothalamic-hypophyseal system to T_4 is largely determined by activation of the deiodination of T_4 by the adenohypophysis. The reactivity of the thyroid gland and hypothalamic-hypophyseal complex to the corresponding factors is reduced. KEY WORDS: hypothalamus; pituitary; deiodinating power; thyroxine; aging.

Interaction between the hypothalamic-hypophyseal system (HHS) and the thyroid gland is largely determined by: 1) the effect of thyroid-stimulating hormone (TSH) on the secretion of thyroid hormones (T_4, T_3); 2) the effect of T_4 and T_3 on the synthesis and secretion of TSH [3, 6, 12, 14]. The object of this investigation was to study age differences in the interaction between HHS and the thyroid gland, with consideration to both direct and feedback control.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats of three age groups: 1.5-2, 8-10, and 28-32 months. The blood TSH concentration in the experimental animals was determined by a radioimmunologic method using kits from the firm CEA-IRE Sorin (France), and in the pituitary by means of a biological method [8] in the modification described in [13]. TSH from Spofa (Czechoslovakia) was used to plot a calibration curve and the results were expressed in international units (i.u.) per milligram of tissue and per total weight of adenohypophysis. The concentration of total thyroxine (T_4) in the blood was determined by Thyopac radioisotope kits (Radiochemical Centre, Amersham, England) and total triiodothyronine (T_3) was determined by a radioimmunologic method with kits from CEA-IRE Sorin (France). The deiodinating power of the pituitary tissue was investigated by incubating slices (100 mg) at 37°C, with 60 agitations per minute, in Krebs–Ringer phosphate buffer (pH 6.4) with $T_4 = {}^{131}I$ ($25 \cdot 10^{-8}$ M), and also by subsequent thin-layer chromatography of extracts of the medium. The control contained the same component but without the slices. The results were expressed in nanomoles of T_4 decomposed in 180 min per 100 mg tissue [7]. The sensitivity of the glands (thyroid, adenohypophysis) was judged from the threshold reactions to addition of minimal amounts of hormone; reactivity was judged from the range of changes in reactions on addition of increasing quantities of hormone.

EXPERIMENTAL RESULTS AND DISCUSSION

The blood TSH level was increased in adult animals compared with those aged 1.5-2 months, and significantly reduced in old animals. TSH synthesis underwent similar changes, as shown by the content of the hormone in the adenohypophysis (Table 1).

The decrease in the TSH concentration in the adenohypophysis of the old animals was not connected with a change in the weight of the organ, which remained unchanged compared with its weight in the adult animals. During aging the sensitivity and reactivity of the thyroid tissue to the action of TSH changes. This was shown by determining the total T_4 concentration in the blood before and 1, 2, and 3 h after injection of TSH in a dose of 0.5, 1, and 3.5 units/100 g body weight. In the old animals the sensitivity of the thyroid parenchyma to the

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TABLE 1. TSH Content in Adenohypophysis and TSH, T_4, and T_3 Levels in Blood of Rats of Different Ages

Age of rats, months	Weight of adenohypophysis, mg	TSH			T_4, μg/100 ml	T_3, ng/100 ml
		adenohypophysis		blood		
		i.u./mg	i.u. per gland	ng/ml		
1½—2 (I)	3,0±0,9 (n=20)	35,0±1,3 (n=20)	105,0±2,4 (n=20)	4,4±0,3 (n=10)	8,1±0,5 (n=30)	250,0±35,0 (n=10)
8—10 (II)	6,5±1,6 (n=20)	57,0±2,7 (n=20)	370,0±3,7 (n=20)	6,1±0,8 (n=12)	5,6±0,8 (n=30)	195,0±21,0 (n=10)
P_{II-I}	>0,05	<0,001	<0,001	<0,05	<0,001	>0,05
28—32 (III)	7,2±0,8 (n=10)	22,0±1,7 (n=10)	158,0±3,0 (n=10)	3,3±0,5 (n=10)	4,2±0,2 (n=25)	93,0±4,3 (n=10)
P_{III-II}	>0,05	<0,001	<0,001	<0,001	<0,001	<0,02

Legend. n) Number of rats.

TABLE 2. Effect of Administration of T_4 on TSH Level in Blood and Adenohypophysis of Adult and Old Rats

Dose	Age, months			
	8—10		28—32	
	blood, ng/ml	adenohypophysis, i.u./mg	blood, ng/ml	adenohypophysis, i.u./mg
Intact (n = 20; I)	6,1±0,8	57,0±2,7	3,3±0,5	22,0±1,7
2 μg/100 g (n = 20; II)	5,0±0,4	51,0±3,7	1,5±0,2	18,0±0,5
P_{II-I}	>0,05	>0,05	<0,001	<0,05
4 μg 100/g (n = 20; III)	3,2±0,7	45,0±1,5	1,3±0,1	17,0±0,7
P_{III-I}	<0,001	<0,001	—	—

action of TSH was increased: after administration of the minimal dose of TSH (0.5 unit/100 g) the greatest increase in the blood T_4 concentration was observed in rats aged 28-32 months, and in animals aged 1.5-2 and 8-10 months the thyroid gland did not react to this dose of the hormone. After injection of TSH in doses of 1 and 3.5 units/100 g body weight the reaction of the thyroid gland was stronger in animals aged 1.5-2 and 8-10 months, whereas in the old animals the blood T_4 level after injection of these doses of TSH was the same as after injection of 0.5 unit/100 g. Furthermore, the response of the thyroid parenchyma to administration of any dose of TSH was delayed: the increase in the blood T_4 concentration in these animals did not take place until 3 h after injection of the TSH, whereas in rats aged 1.5-2 and 8-10 months it was observed after 1 h. Consequently, despite the fact that the sensitivity of the thyroid gland to TSH is increased in old age, the range of its response to TSH was narrowed. Hence, during aging significant changes arise in the reaction of the thyroid gland to effects of the HHS mediated through TSH.

Age changes also were found in the stage of feedback control in the HHS and thyroid gland brought about through the effects of T_4 and T_3 on TSH synthesis and secretion. In this series of experiments a solution of T_4 (Reanal, Hungary) in 50% propylene glycol (0.3 ml) was injected intraperitoneally in doses of 2 and 4 μg/100 g body weight in the course of 7 days into animals aged 8-10 and 28-32 months. The TSH concentrations in the blood and adenohypophysis were determined 24 h after the last injection (Table 2).

As Table 2 shows, injection of T_4 in a dose of 2 μg/100 g led to a significant decrease in the synthesis and secretion of TSH in the old rats, whereas in adult rats the changes were not significant. However, increasing the dose of T_4 to 4 μg/100 g in animals aged 28-32 months did not lead to any further inhibition of TSH synthesis. In adult animals receiving this dose of hormone the TSH level in the blood and adenohypophysis was significantly reduced.

Evidence of age changes in interaction between HHS and the thyroid gland is also given by data showing the relations between the basal TSH level in the blood and adenohypophysis and the blood level of thyroid hormones. In rats aged 28-32 months the blood concentration of T_4 and T_3 is low. This low concentration of thyroid hormones is maintained, incidentally, despite a low TSH concentration in the pituitary and blood, yet by the feedback principle, this should stimulate the synthesis of T_4 and T_3.

The decisive role in the mechanism of realization of the hormonal effect of the iodothyronine on the various tissues, including the adenohypophysis, is played by processes of intracellular deiodination [4, 5, 10, 11].

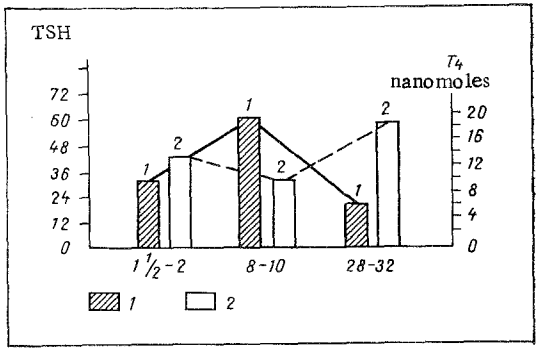

Fig. 1. Correlation between T_4-deiodinating power of pituitary tissue and TSH level in that tissue (in i.u./mg) in rats of different ages. 1) TSH concentration in adenohypophysis; 2) T_4-deiodinating power of adenohypophyseal tissue. Abscissa, age (in months); ordinate, on left, TSH level (in i.u./mg), on right, T_4 deiodinated per 100 mg tissue in 180 min (in nanomoles).

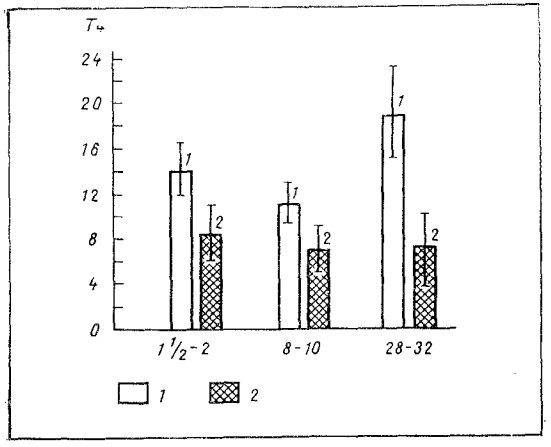

Fig. 2. Effect of 6-MTU on T_4-deiodinating power of adenohypophysis in rats of different ages. Abscissa, age (in months); ordinate, T_4 deiodinated per 100 mg tissue in 180 min (in nanomoles). 1) Control, 2) experiment.

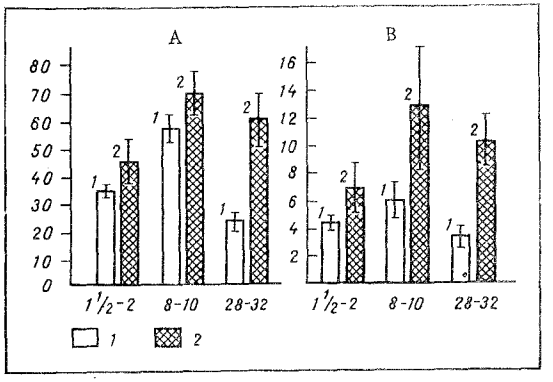

Fig. 3. TSH concentration in adenohypophysis (A) and blood (B) of intact rats of different ages and after administration of 6-MTU. Abscissa, age (in months); ordinate: on left, TSH concentration (in i.u./mg), on right, TSH concentration in blood (in ng/mg). 1) Control, 2) experiment.

That is why to analyze the causes of the changes in interaction between HHS and the thyroid gland during aging it would be a significant step to determine the T_4-deiodinating power of the pituitary at different age periods. During aging of animals there is a marked increase in the deiodinating power of the adenohypophseal tissue (Fig. 1). It can tentatively be suggested that increased deiodination of T_4 in old animals largely explains the increased sensitivity of their HHS to the action of thyroid hormones and the maintenance of a low TSH level despite a fall in the blood T_3 and T_4 concentrations.

Evidence of the importance of deiodination processes in the age changes in the response of the pituitary tissue to T_4 was given by experiments in which 6-methylthiouracil (6-MTU) was given to block peripheral deiodination [1, 2, 9, 11]. A single dose of 6-MTU (10 mg/100 g body weight) was found to lead after 2 h to a marked decrease in the quantity of T_4 deiodinated in the pituitary of animals of all age groups (Fig. 2), and also to a sharp increase in the intensity of synthesis and secretion of TSH, as reflected in the concentrations of the hormone in the pituitary and blood (Fig. 3). Data showing the effect of 6-MTU on old animals were particularly interesting. A low pH level in the blood and adenohypophysis and intensive deiodination of T_4 in the adenohypophysis were found in intact rats aged 28-32 months. After administration of 6-MTU the TSH level in the old animals became higher, and the same as in adult rats after injection of 6-MTU. Depression of the intensity of deiodination by injection of 6-MTU thus to some extent canceled out the age differences in the initial TSH level in the pituitary and blood. Under these circumstances the level of thyroid hormones in the experimental (6-MTU) animals remained the same as in intact animals of the same age.

Hence, relations between the HHS and thyroid gland change with age. In old age substantial disturbances arise at the stages of direct and feedback control of this system: the sensitivity of the thyroid gland to TSH and of the HHS to the action of T_4 increases. This increase in the sensitivity of the HHS to T_4 is largely determined by activation of deiodination of the hormone by the pituitary. Meanwhile the reactivity of the thyroid gland and of the HHS with respect to the corresponding factors is considerably reduced. Changes taking place during aging in interaction between the HHS and thyroid gland thus, on the one hand, limit the range of response of the whole of this complex and unitary system, but on the other hand they adapt this system of control to existence under conditions of low levels of T_4, T_3, and TSH.

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