EFFECT OF EXPERIMENTAL THYROTOXICOSIS ON DEVELOPMENT OF COMPENSATORY ADRENAL HYPERTROPHY

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Thyrotoxicosis accelerates the development of compensatory adrenal hypertrophy in rats, and modifies the dynamics of the corticotropin-releasing activity of hypothalamic extracts and the content of ACTH in the pituitary.

Numerous investigations have revealed the stimulation and subsequent exhaustion of adrenocortical function in experimental thyrotoxicosis [3, 4, 13, 14] and in clinical forms of thyroid hyperfunction [2, 5, 7]. On the basis of these results, a definite connection can be postulated between the level of secretion of thyroid hormones and the function of the hypothalamo-hypophyseo-adrenal system.

During the subsequent study of this problem the writer investigated the effect of an excess of thyroid hormones on the development of compensatory adrenal hypertrophy (CAH) in rats after unilateral adrenalectomy, an experimental model of prolonged stress on the hypothalamo-hypophyseo-adrenal system. After destruction of the basal part of the hypothalamus, the increase in ACTH secretion produced under the influence of stress is stopped, but administration of an extract of the hypothalamus containing corticotropin-releasing factor (CRF) normalizes the disturbed process [12]. It was therefore decided to study the effect of experimental thyrotoxicosis on: 1) corticotropin-releasing activity of extracts of the hypothalamus, 2) the content of ACTH in the pituitary, and 3) the state of the residual adrenal (time and intensity of CAH development, adrenal functional activity).

The above-mentioned indices were investigated during the period of CAH development for 14 days after unilateral adrenalectomy.

EXPERIMENTAL METHOD

Two series of experiments were carried out on 240 adult albino rats. In series I (control) the rats underwent unilateral left-sided adrenalectomy, while in series II (main experiments) unilateral adrenalectomy was performed on the animals and thyroid was given in the postoperative period in a dose of 100 mg/100 g body weight daily. An indication of hyperthyroidism was given by an increase in the oxygen consumption per square meter of body surface of rat per day, determined by Kalabukhov's method.

The rats were decapitated 24 h and 5 and 14 days after the operation, and the right adrenal, pituitary, and hypothalamus were removed. The degree of CAH was judged from the relative weight of the adrenals (in mg/100 g body weight), and adrenal function was judged from the content of ascorbic acid (AA) in the gland determined by the method of Gol'dshtein and co-workers [1], and the cholesterol content determined by the method of Knobil and co-workers [11]. The content of ACTH in the pituitary was determined in recipient rats weighing 180-240 g by the method of Birmingham and co-workers [10], as modified by Skebel'skaya [6]. To determine corticotropin-releasing activity of the hypothalamus (CRAH), the method of Arimura and co-workers [9] was used. This consists essentially of the preparation of extracts of the hypothalamus and their subsequent testing on recipient rats whose hypothalamo-hypophyseo-adrenal system

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TABLE 1. Relative Weight of Adrenals, and Content of AA and Cholesterol in Adrenals (in percent of initial values) at Various Times after Unilateral Adrenalectomy in Control Rats and against the Background of Thyrotoxicosis

Time after operation	Statistical index	Unilateral adrenalectomy			Thyrotoxicosis and unilateral adrenalectomy		
		relative weight of adrenals	content of ascorbic acid	content of cholesterol	relative weight of adrenals	content of ascorbic acid	content of cholesterol
24 h	*M*	129	90	90	107	72	81
	±*m*	5	2,7	4,7	2	1	3,3
	n	21	11	10	10	10	10
	P				<0,001	<0,001	>0,1
5 days	*M*	157	96	78	153	61	76
	±*m*	7	3	7,4	3	1,8	5,6
	n	23	15	9	11	11	10
	P				>0,5	<0,001	>0,5
14 days	*M*	161	64	172	133	83	118
	±*m*	8	4	11	3	3	7,4
	n	21	11	10	10	10	10
	P	—	—	—	<0,001	<0,001	<0,001

Note. Data obtained by study of removed adrenal were used as initial values.

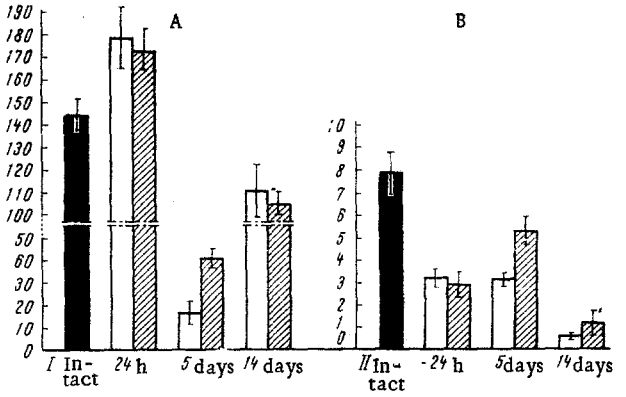

Fig. 1. Corticotropin-releasing activity of hypothalamus (A) and ACTH content (B) in pituitary of rats of series I and II at different times after operation. Ordinate: I) decrease in ascorbic acid content (in mg%) in adrenals of recipient rats after injection of hypothalamic extracts; II) content of ACTH in pituitary of rats (in milliunits/100 μg acetone powder). Black columns indicate intact animals; unshaded columns unilateral adrenalectomy; obliquely shaded columns unilateral adrenalectomy + thyroid feeding.

is preliminarily blocked with chlorpromazine, morphine, and nembutal. The magnitude of the CRAH was judged from the distance between the AA concentration in the left (before injection) and right (1 h after intravenous injection of the extract) adrenals of the recipient rats.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that in the rats of series I stimulation of CRAH was observed after 24 h: the AA level in the adrenals of the recipient rats was reduced by 178±13 mg%, whereas injection of hypothalamic extracts of intact rats reduced the AA by only 144±7 mg% ($P < 0.05$). Meanwhile a considerable increase in weight of the pituitary (124±5.4% compared with intact rats; $P < 0.05$) and a decrease in its

ACTH content were observed, indicating increased secretion of ACTH. These changes are evidently a response not only to a decrease in the corticosteroid content, but also to stress of the operation, for 5 days after adrenalectomy the CRAH was lowered, and a slight increase in its value again occurred only on the 14th day, and was accompanied by a further decrease in the ACTH content in the pituitary.

In full agreement with these changes the relative weight of the hypertrophied adrenal progressively increased (Table 1), to reach a maximum by the 14th day after operation. A parallel increase took place in adrenal function, as shown by the decrease in content of ascorbic acid to 64% of the initial level and the increase in cholesterol content to 172% of the initial level.

In the rats of series II, thyroid feeding led to the development of thyrotoxicosis: the oxygen consumption per square meter of body surface per day was 130±3 and 141±4% compared with the initial value on the 5th and 14th days of thyroid seeding, respectively; the animals' hair fell out; and their aggressiveness was sharply increased.

It will be clear from Fig. 1 that the most significant difference between the dynamics of CRAH in the unilaterally adrenalectomized rats receiving thyroid was its higher level compared with the control experiments 5 days after removal of the adrenals. Consequently, in the presence of thyrotoxicosis at this time, the hypothalamus produced more corticotropin-releasing factor than in the control, unilaterally adrenalectomized rats. Judging from the fact that the ACTH content in the pituitary of the rats of series II was much higher at this time than in the controls, it can be considered that corticotropin-releasing factor accumulated in the hypothalamus, and exerted its ACTH-activating effect only at a later stage (14 days after the operation).

Definite differences were observed in the rats of series II as regards the times of development of CAH. As Table 1 shows, the duration of CAH in the presence of thyrotoxicosis was restricted to a shorter period: by the 14th day after the operation the weight of the hypertrophied adrenal had begun to fall, whereas in the rats of series I it continued to increase. The previously increased level of adrenal function was lowered correspondingly: the AA content rose to 83% of its initial value, but the increase in the cholesterol content was smaller than in the control.

It can be concluded from the data described above that the accumulation of thyroid hormones in the body shortens the times of development of CAH. In the presence of thyrotoxicosis the dynamics of the principal pathogenetic mechanism of CAH (production of corticotropin-releasing factor and secretion of ACTH) is modified. Thyroid hormones perhaps have a definite effect on hypothalamic regulation of the hypophyseo-adrenal system. At the same time, the possibility of a direct effect of thyroid hormones on corticosteroid biosynthesis [8] cannot be ruled out. This would explain the absence of a direct parallel between the CAH indices, on the one hand, and changes in CRAH and in the ACTH content in the pituitary, on the other hand.

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