The State of the Immune System in Thyroidectomized Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 135, No. 2, pp. 178-181, February, 2003
Original article submitted August 14, 2002

Disorders in the immune system manifesting in decreased weight and cellularity of lymphoid organs, decreased count of large granular lymphocytes, suppression of the immune response and metabolic activity of macrophages were observed in experimental animals 1-6 months after thyroidectomy. The intensity of these disorders depends on the period elapsed after the surgery. These disorders can result from not only changes in the levels of the pituitary-thyroid hormones, but also disturbances in the endocrine function of the thymus in thyroidectomized animals.

Key Words: *thyroid; immune system; hypothyrosis; rats*

Despite morphological and functional autonomy, the neuroendocrine and immune systems closely interact through hormones, cytokines, cell adhesion molecules, and receptors [12]. The endocrine function of the thymus, the central organ of the immune system, is regulated by pituitary hormones. It was shown that pituitary thyrotropic hormone (TSH) does not directly modulate the secretion of thymic hormones, but its effect is mediated through thyroid hormones [15]. Thyroid function largely determines the immune status of the organism [9]. Thyroidectomy leads to suppression of the endocrine function of the thymus, cellular and humoral immunity, which manifest in inhibition of T-suppressors, T-cell proliferation, antibody production, and decreased level of hemagglutinins [1,7]. Thyroidectomy does not change cellular reactions or stimulates them [11]. Presumably, changes in the immune system after thyroidectomy are phase-dependent [6].

Cooperation of T and B lymphocytes, mononuclear phagocyte system, and many other cells, whose effects are realized through mediators, plays the key role in the formation of specific immune reactions. However, the data on the effect of thyroidectomy on the immune system are scanty and contradictory. We investigated the delayed effect of thyroidectomy on immunological parameters in rats.

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MATERIALS AND METHODS

Male Wistar rats (n=46, 80-120 g) were obtained from vivarium of Institute of Oncology. Thyroidectomy was carried out under ether narcosis. Control (sham-operated) animals were subjected to the same manipulations, except removal of the thyroid gland.

The animals were weighed and decapitated under ether narcosis 1, 3.5, and 6 months after surgery. The absolute weights of the thymus, spleen, their indexes (ratio of the organ to body weight, mg/g), and cell composition of lymphoid organs were evaluated.

The endocrine function of the thymus was evaluated as described previously [10]. The pituitary thyrotropic function (TSH), serum levels of the major thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) were measured by enzyme immunoassay (DSL kits). Peritoneal exudate macrophages (PEMP) were isolated as described previously [5]. Metabolic activity of phagocytes was studied in the NBT test [14]. The number of antibody-producing cells (APC) in the serum was evaluated as described previously [13].

The count of T lymphocytes in the peripheral blood was evaluated by spontaneous rosette formation (E-RFC) by detecting receptors to guinea pig erythro-

0007-4888/03/1352-0154$25.00

cytes on T cells [2]. The number of large granular lymphocytes (LGL) was evaluated in smears stained after Romanowskii [4].

The data were statistically processed using Student's *t* test.

RESULTS

One to six months after thyroidectomy the serum level of T_3 decreased 1.5-2.5 times in comparison with the control. The level of T_4 one month after thyroidectomy was 81.07±11.71 and 71.25±1.79 ng/ml, respectively ($p<0.05$), and after 3.5 and 6 months it decreased 2.6 and 4.1 times, respectively. TSH level increased more than 20-fold during this period. Low levels of thyroid hormones and high level of TSH after thyroidectomy indicate the development of hypothyrosis in experimental rats. Enhanced hypothyroxinemic reaction is observed after removal of 50-100% of the gland and is usually proportional to the size of the removed fragment [8].

The endocrine function of the thymus essentially decreased in hypothyrosis: thymulin level decreased 1.7 times in comparison with the control 3.5 months after thyroidectomy.

Removal of the thyroid gland led to changes in the lymphoid organs, manifesting by a decrease in their absolute size and cell number (Table 1). One month postoperation the absolute weight of the thymus markedly decreased, while the weight of the spleen decreased throughout the observation period. The thymus index decreased 1 month after the surgery and then somewhat increased, which can be explained by essential body weight loss (by 1.4 and 2.4 times 3.5 and 6 months after the operation, respectively). In contrast to the thymus index, the splenic index decreased throughout the observation period. Considerable changes in this parameter were observed as early as 1 month after surgery (Table 1). Cell number decreased in both the thymus and spleen 1-6 months after the intervention in all experimental animals. After 6 months the total count of thymocytes decreased 3.3 times and that of splenocytes 4.4 times compared to the control.

Decreased cell count in the spleen after thyroidectomy coincided with suppression of the immune response, which can be a manifestation of changed relationships between cell number and functions in immune organs. Primary humoral immune response to sheep erythrocytes (classical thymus-dependent antigen) decreased 3.5 and 6 months after thyroidectomy (Table 2). The total number of APC gradually decreased throughout follow-up. Other scientists also noted suppression of the humoral immune response after thyroidectomy [9].

TABLE 1. Effect of Thyroidectomy on the Weight and Cell Count of the Thymus and Spleen (*M*±*m*)

Parameter			Period after thyroidectomy, months		
			1	3.5	6
Body weight, g		control	100.0±12.6	178.2±9.4	246.6±20.2
		experiment	126.6±11.2	131.2±12.8*	100.8±24.4*
Thymus weight, mg		control	279.8±19.6	235.0±26.7	145.2±28.0
		experiment	206.1±18.8*	193.0±20.7	101.2±24.4
Spleen weight, mg		control	693.0±54.8	809.4±74.3	898.0±112.4
		experiment	506.7±46.6*	513.6±28.3*	271.8±53.7*
Thymic index		control	2.8±0.2	1.3±0.1	0.6±0.1
		experiment	1.7±0.1*	1.4±0.3	1.0±0.2
Splenic index		control	6.9±0.3	4.4±0.3	3.9±0.7
		experiment	4.1±0.9*	3.9±0.3	2.8±0.3
Cellularity of thymus,	$\times 10^6$	control	63.9±17.1	222.9±54.1	121.6±13.7
		experiment	42.3±11.1	173.2±26.5	37.1±4.1*
	$\times 10^6$/mg	control	0.23±0.07	0.92±0.17	0.82±0.07
		experiment	0.20±0.08	0.89±0.15	0.32±0.07*
Cellularity of spleen,	$\times 10^6$	control	959.2±59.5	333.4±55.5	659.6±38.4
		experiment	361.3±17.9*	303.8±61.2	149.0±93.2*
	$\times 10^6$/mg	control	1.38±0.41	0.63±0.09	0.73±0.07
		experiment	0.70±0.05	0.57±0.03	0.46±0.14

Note. Here and in Table 2: *$p<0.05$ compared to the control.

TABLE 2. Effect of Thyroidectomy on Some Parameter of Rat Immune System (*M*±*m*)

Parameter			Period after thyroidectomy, months		
			1	3.5	6
Leukocytes,	$\times10^9$/liter	control	5.6±0.7	11.4±3.4	4.2±0.9
		experiment	7.0±0.9	11.6±1.2	4.7±1.2
Lymphocytes	%	control	79.0±5.8	74.0±8.7	74.0±6.7
		experiment	84.5±9.4	80.4±5.8	70.6±3.0
	$\times10^9$/liter	control	6.23±4.31	8.47±3.68	8.47±3.68
		experiment	7.87±0.98	9.51±1.38	7.29±0.64
E-RFC	%	control	11.5±9.3	16.7±1.7	—
		experiment	14.2±2.1	14.0±2.1	22.3±1.9
	$\times10^9$/liter	control	0.439±0.105	0.877±0.304	—
		experiment	0.448±0.124	1.421±0.402	1.708±0.121
LGL	%	control	0.7±0.1	3.8±1.0	3.7±0.5
		experiment	1.0±0.2	1.4±0.4*	1.2±0.7*
	$\times10^9$/liter	control	0.13±0.03	0.26±0.06	0.26±0.06
		experiment	0.12±0.04	0.18±0.05	0.13±0.08
APC, per 10^6 splenocytes		control	66.0±26.3	287.0±12.3	71.0±5.6
		experiment	72.5±16.3	224.0±24.5*	35.2±11.7*
Total		control	15 055.4±756.2	10 4495.0±4753.3	25 754.9±9821.8
		experiment	5967.0±88.6*	74 051.9±1506.2*	7433.5±394.0
PEMP stimulation index		control	1.52±0.27	1.43±0.15	1.26±0.07
		experiment	1.23±0.19	1.02±0.06*	1.08±0.15
PEMP functional reserve		control	54.3±16.1	43.3±5.6	26.4±7.7
		experiment	43.2±15.6	5.3±1.2*	14.8±10.0

No appreciable changes in leukocyte count, absolute ($\times10^9$/liter) and relative (%) content of lymphocytes and T-lymphocytes were observed 1-6 months after thyroidectomy (Table 2). The relative number of LGL, a morphological substrate of natural killer cells [4], trended to increase 1 month after the operation and notably decreased 3.5-6 months after removal of the thyroid gland. It is known that thyroid dysfunction results in phasic changes in the activity of natural killers, depending on blood level of thyroid hormones. Activity of natural killer cells increased in experimental animals with hypothyrosis at the early terms (up to 14 days) after surgery and then remained unchanged [3].

Abnormal hormonal background after thyroidectomy led to a decrease of metabolic activity of PEMP. Metabolic activity of PEMP decreased 1-6 months after thyroidectomy (the value for 3.5 months postoperation was significant). The stimulation index and the functional reserve of PEMP decreased in comparison with the control at this term.

Hence, disorders in the immune system developing 1-6 months after thyroidectomy consisted in decreased weight and cell count of lymphoid organs, decreased count of LGL, suppression of the humoral immune response and metabolic activity of macrophages. The intensity of these changes largely depended on the period elapsed after removal of the thyroid. Apart from changes in the levels of the pituitary-thyroid hormones, these disorders can result from reduced endocrine function of the thymus after thyroidectomy. These data are important for rehabilitation of patients with thyroid diseases complicated by hypothyrosis.

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