EFFECT OF PROLONGED ADMINISTRATION OF T-ACTIVIN ON STRUCTURE OF THE THYMUS

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With the development of clinical immunology and the use of immunocorrection in diseases of varied genesis, biologically active substances of the thymus have attracted increasing attention of research workers [1, 2, 4, 5, 8, 9]. T-activin is a complex of immunologically active peptides derived from the thymus; it has immunomodulating properties and exhibits a stimulating effect during depression of, in particular, the T-cell component of immunity, and it is therefore used in the treatment of several diseases [1-3, 5-8]. As a rule correction with T-activin is undertaken in course, but there are no data on its effect on the structure of the organs of immunity under those conditions.

Accordingly the aim of the present investigation was to study the effect of prolonged administration of T-activin on structure of the thymus. Since the thymus is responsible for proliferation, maturation, and migration of thymocytes (TC) with the active participation of the microenvironment and hormones [8, 9], it was decided to use morphometric parameters reflecting the intensity of these processes: the area of the cortex and medulla of the thymus, the density and relative percentage of TC at different stages of development in individual zones of the cortex and medulla.

EXPERIMENTAL METHOD

Experiments were carried out on sexually mature male and female (CBA × C57BL)F_1 mice weighing 24.0 ± 2.0 g. The animals were divided into two groups. The mice of group 1 were given intraperitoneal injections of T-activin in a dose of 1.0 μg/day as follows: injection of T-activin for 5 days followed by an interval of 2 days, for a total of 10, 15, and 20 injections (3 subgroups). Mice of group 2 (control) received physiological saline by the same program. The control consisted of 8 intact mice. After the end of the course of T-activin the animals were weighed and decapitated (3-7 animals in each subgroup), after which the thymus was removed and weighed and fixed in Bouin's fluid. Paraffin sections 4 μ thick were stained with azure-II and eosin and subjected to morphometric analysis. The relative areas of interlobular connective tissue, and of the cortex and medulla (objective 20, ocular 10), the density of TC in the subcapsular, middle, and inner zones of the cortex and medulla, and the relative percentages of transformed TC (TTC), namely blast cells and mitotically dividing cells (MC) in the zones specified above (objective 90, ocular 10) were calculated. The numerical data were subjected to statistical analysis by the Wilcoxon–Mann–Whitney U test.

EXPERIMENTAL RESULTS

Prolonged administration of T-activin had practically no effect on the weight of the thymus or on its weight index (Table 1). However, there was some increase in the relative area of the cortex after 10 and 15 injections of T-activin compared with the control, differences from which became significant ($P \leqslant 0.05$) after 20 injections of T-activin (Fig. 1a). The relative area of the medulla was correspondingly reduced, and that of the interlobular connective tissue was a little lower than in the control, but not until 20 injections of T-activin had been given (Fig. 1b). In the subcapsular zone of the cortex (Fig.

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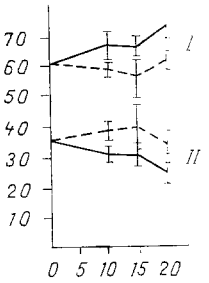

Fig. 1

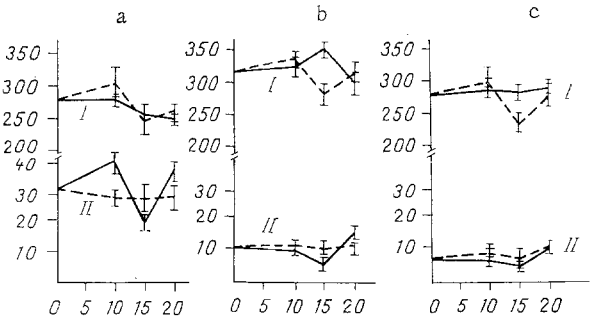

Fig. 2

Fig. 1. Changes in area of cortex and medulla of thymus under the influence of T-activin. Abscissa (here and in Figs. 2 and 3): number of injections of T-activin (experiment — continuous line) and physiological saline (control — broken line); ordinate, area (in percent, M ± m) of cortex (I) and medulla (II).

Fig. 2. Changes in cell density and number of TTC in different zones of thymus cortex after injections of T-activin. Ordinate, cell density (I) and number of TTC (in percent, M ± m) (II) in subcortical (a), middle (b), and inner (c) zones of cortex.

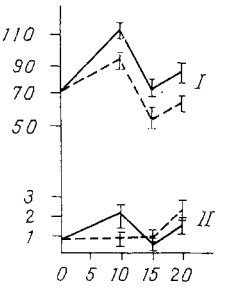

Fig. 3. Changes in cell density and number of TTC in medulla of thymus after injections of T-activin. Ordinate, cell density (I) and number (in percent, M ± m) of TTC (II).

TABLE 1. Changes in Weight and Weight Index of Thymus following Injection of T-Activin (M ± m).

Parameter studied	Normal	Injection of T-activin					
		10 injections		15 injections		20 injections	
		control	experiment	control	experiment	control	experiment
Weight of thymus, mg	35,0±4,0	31,3±1,9	33,3±1,9	37,0±2,0	42,3±5,0	37,8±2,2	37,3±2,3
Weight index of thymus	0,8±0,1	0,9±0,1	0,8±0,03	0,8±0,1	0,8±0,1	0,8±0,03	0,8±0,1

Legend. Weight·index of thymus calculated as ratio of body weight to weight of thymus.

2a), against the background of some decrease in cell density after 15 and 20 injections, fluctuation of the curve representing the number of TTC was observed with a peak after 10 and 20 injections and a trough after 15 injections; the increase in the mean took place on account of a marked increase of individual variability. Curves of mitosis in this zone in the experimental and control animals virtually coincided, with a peak after 15 injections. In the middle and inner zones (Fig. 2c) of the cortex the density of TC did not exceed the control values until 15 injections of T-activin had been given, and this was accompanied by corresponding fall in the number of TTC. After 20 injections the number of TTC rose and actually exceeded its initial level. The number of MC in these zones was the same in the

experimental and control series. In the medulla (Fig. 3) T-activin caused an increase in cell density compared with the corresponding control after 10, 15, and 20 injections; the character of the curves, moreover, was similar. The relative percentages of TTC and MC in the medulla remained virtually unchanged after administration of T-activin.

The following conclusion can be drawn from analysis of the results. Prolonged administration of T-activin caused no pathological changes in the thymus but affected proliferation and migration of TC. Injection of T-activin for 10 days caused an increase in proliferation of TC and their preparation for migration from the thymus, as shown by an increased degree of transformation of TC in the subcortical zone, some increase in area of the cortex, and an increase in the density of TC in the medulla. Injection of T-activin for 15 days ended with a rather different phase in activity of the thymus: Some increase was observed in the density of TC in the middle and inner zones of the cortex, a decrease in the density of TC in the medulla, and a tendency for the number of TTC in the cortex to diminish. Probably these changes may be evidence of the recently finished wave of migration of TC from the thymus. Injection of T-activin for 20 days induced a new wave of proliferation and preparation for or the beginning of migration of TC from the thymus, as shown by an increase in the intensity of transformation in the cortex and in the density of TC in the medulla.

The investigation thus showed that prolonged administration of T-activin to normal young animals causes no pathological changes in the thymus, does not disturb the fluctuating character of thymus function, but intensifies the transformation and migration of thymocytes.

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