Psychotropic Effects of Thymogen

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Effects of thymogen on the behavior of mice were studied, and the results obtained suggest that this immunomodulator possesses psychostimulatory, antidepressive, and stress-protecting properties which open up new prospects for the use of thymic peptides in psychiatry.

Key Words: *behavior; immunity; thymogen*

Thymus-derived drugs, including thymogen, have been successfully utilized in psychiatry for the treatment of schizophrenia and psychogenic depression. There are reasons to believe that the clinical efficacy of these drugs is associated not only with their immunomodulating properties, but also with their psychotropic activity [1,2,7]. Our previous studies demonstrated that thymogen improves conditioned-reflex activity of August rats and attenuates the standstill reaction in rats of a genetically catatonic strain (bred by V. G. Kolpakov) prone to catalepsy [8].

In the present study we tested thymogen for its influence on behavioral and immunological characteristics of experimental animals, including those under stress.

MATERIALS AND METHODS

A total of 240 random-bred white male mice and male CBA mice weighing 18-22 g were used, divided into groups of 12 animals in each. The test groups received thymogen (Tsitomed) in single intraperitoneal doses of 100 or 15 μg/kg once daily for five days, while the control groups were given intraperitoneal injections of physiological saline also once daily over the same period. The thymogen-treated and control animals were tested for orienting/exploratory behavior in an open field (horizontal and vertical activities, the number of holes explored, and the number of grooming acts and of defecations were recorded) [3]; emotional responsiveness [10] and antidepressive and psychostimulatory effects (as assessed by the duration of "behavioral despair" [11]); behavior in a cruciform maze [9]; reactions to the stress caused by immobilization during 22 h (with measurement of relative organ weights) [6]; and behavior in a conflict situation produced by punishment (with electric shock) of the conditioned drinking reflex [4]. In addition, blood levels of leukocytes and antibodies (hemagglutinins) were determined, as were, after homogenization of the thymus, the number and cytotoxic (natural killing) activity of thymocytes by the release of hemoglobin from lysed target cells (sheep red blood cells) using a spectrophotometer [5].

RESULTS

Thymogen treatment was found to increase the number of mice capable of orderly movement in the cruciform maze and to shorten the duration of behavioral despair (immobility) in the course of swimming for 1-6 or 7-16 min. These findings suggest that thymogen may have antidepressive and psychostimulatory effects (Table 1).

In the group of thymogen-treated mice, the severity of immobilization stress was assigned a

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TABLE 1. Effects of Thymogen on the Behavior of Mice in the Cruciform Maze and in the "Behavioral Despair" Test ($M \pm m$)

Parameter	Control group	Thymogen dose, μg/kg	
		100	15
Number of runs to dead ends of maze	26.50±3.4	33.42±2.2	29.08±2.3
Number of "cycles"	4.67±0.8	7.17±0.4*	6.25±0.6
Mean number of runs per "cycle"	6.35±0.6	4.71±0.2*	5.31±0.3
Percentage of mice with high probability of orderly exploratory behavior	25.00	83.30*	75.00*
Antidepressive effect, sec	147.33±21.4	129.58±14.5	106.25±10.2*
Psychostimulatory effect, sec	432.25±33.6	277.08±31.8*	411.67±36.1

Note. *$p<0.05$ in comparison with the control group.

lower score than in the untreated stressed control group (2-4 *vs.* 6 points). The stress-protecting effect of thymogen was best reflected in the relative weight of the thymus, which remained virtually unchanged (39-41 mg) in the thymogen-treated stressed groups while decreasing significantly to 28.06±5.5 mg in the stressed control group as compared to the intact (unstressed) control group (44.60±3.9 mg; $p<0.05$). Thymogen did not markedly affect the orienting/exploratory activity of the animals in the open field, but mitigated the stress-induced alterations in behavioral patterns, and it also stimulated motor activity (in particular, it increased the number of approaches to the drinking bowl) of mice faced with the conflict situation.

In the group given thymogen in the dose of 100 μg/kg, immunological parameters measured 48 h after the conflict situation were similar to those in the intact control group, whereas leukocytosis (mainly lymphocytosis) was recorded in the untreated group that had been subjected to this situation. In the rats treated with thymogen at 100 μg/kg, cell numbers in the thymus were decreased (probably as a result of redistribution of immunocompetent cells) and the thymocyte cytotoxicity index was lower than in the two control groups, although this index, which reflects the natural killing activity of thymocytes, did not differ significantly from that of thymocytes from intact controls (Table 2). A tendency toward an interrelationship between behavioral and immunological parameters was observed. Thus, the mice that were seen to make more approaches to the drinking bowl tended to have a lowered leukocyte count and

TABLE 2. Behavioral and Immunological Characteristics of Mice in a Conflict Situation ($M \pm m$)

Parameter	Control mice	Control mice in the conflict situation	Thymogen-treated mice (100 μg/kg)
Number of approaches to drinking bowl	–	5.50±0.5	6.27±0.9
Number of electric shocks	–	1.67±0.3	3.10±0.6*
Total motor activity	–	73.33±8.2	103.04±9.3*
Horizontal activity	–	44.33±4.9	62.50±5.4*
Vertical activity	–	9.50±3.6	12.16±2.5
Number of holes explored	–	15.67±4.0	26.03±3.5
Number of grooming acts	–	3.00±0.7	1.82±0.3
Number of defecations	–	0.83±0.5	0.50±0.2
Ratio of horizontal activity to number of explored holes	–	3.25±0.5	3.49±1.2
Leukocytes, 10^6/ml	4.52±0.5	9.71±2.1**	5.77±1.6
Lymphocytes, 10^6/ml	2.42±0.3	6.00±1.9	3.73±1.0
Neutrophils, 10^6/ml	2.12±0.2	3.71±0.8	2.08±0.6
Number of cells per thymus, 10^6	68.70±18.6	77.00±10.9	41.89±5.6*
Thymocyte cytotoxicity index, %	5.33±2.8	18.77±6.5	3.40±1.2*

Note. *$p<0.05$ in comparison with the control group exposed to the conflict situation; **$p<0.05$ in comparison with the intact control group.

an elevated thymocyte count, while most of those reluctant to approach the bowl had, on the contrary, an elevated leukocyte count and a lowered thymocyte count.

The results of this study indicate that the beneficial effect of thymogen on integrative processes in the brain deserves special attention. This drug appears to possess antidepressive and psychostimulatory properties. In stressed animals as well as in animals that had been exposed to a conflict situation, it improved behavioral, somatic, and hemic immunological parameters.

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