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Thymus Polypeptide Preparation Tactivin Restores Learning and Memory in Thymectomied Rats

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We studied the effects of tactivin and splenic polypeptides on learning and memory of thymectomized animals. In 3-week rats, thymectomy blocked active avoidance conditioning. Injections of tactivin (0.5 mg/kg) during 1 month after surgery restored learning capacity; splenic polypeptides were ineffective.

Key Words: *thymus; thymectomy; learning; memory*

Interactions between the nervous and immune systems are in the focus of attention of specialists of various scientific profiles [3,4]. Cooperation of the two systems in learning and in cognitive disorders remains not studied.

Cognitive disorders in patients with Alzheimer's disease are paralleled by dysfunction of the immune system. Presumably, immune disorders induce imbalance in the neuroendocrine immunomodulation network, this, in turn, modified cognitive processes [2].

The key structures of the nervous system in learning and memory processes are well known, while the immune system components involved in these processes are not yet identified. We think that the most probable structure here is the thymus, the central organ of the immune system [7]. Its involvement in the learning and memory processes is proven by thymectomy [10,15]. However, the possibility of correcting the memory disorders under conditions of unbalanced neuroimmune interactions in thymectomied animals remains unclear. We suggest using the Russian immunotropic drug tactivin from cattle thymus [8], effective in combined therapy for many diseases associated with immunodeficiency [1]. Tactivin accelerates the learning of rats, developing the food-getting and defense conditioned reflexes [5,7]. Use of thymosine, a thymic polypeptide drug, compensates for the cognitive functions after brain injury or completely restores them in rats [12-14].

Despite the fact that tactivin has been used in clinical practice for many years, studies of its physiological effects are still in progress; it is essential to detect the mechanisms of its activities and presumably extend the clinical applications of the drug.

We studied the possibility of correcting mnestic disorders under conditions of unbalanced neuroimmune interactions in thymectomied animals.

MATERIALS AND METHODS

The study was carried out on Wistar rats (n=60) kept under standard vivarium conditions at 12/12 h day/night schedule with free access to water and food.

Active avoidance response was conditioned (CAAR) in a shuttle box (60×30×30 cm) divided with a wall with a hole (10×10 cm) into two compartments of the same size. The compartments had electrified grid floor made of steel rods (0.6 cm in diameter, 1 cm distance between the rods). CAAR was trained according to the standard method. The animals were exposed to conditioned stimulus (700 Hz sound) for 10 sec, after which unconditioned stimulus was added, electric current (0.7 mA). The sound and current were

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switched off during animal's passage through the hole into the other compartment of the box (avoidance reaction). If the animal attempted to move during acoustic signal alone (avoidance reaction), the current was not switched on and the sound was switched off. If the animal did not pass into the other compartment when it was exposed to the stimuli, the signals were automatically switched off 10 sec after exposure to the current. Each experiment consisted of 25 presentations with 30-sec intervals between the signals. Experiments were carried out daily during 7 days until the formation of a stable reflex (more than 80% avoidance reactions in response to signal presentations). The number of avoidance and riddance reactions was recorded.

In experimental series I, group 1 rats (n=10) received intraperitoneal injections of tactivin (0.5 mg/kg) every other day for 1 month. Group 2 animals (n=10) received splenic polypeptides (0.5 mg/kg), identical to tactivin by biochemical method of derivation. Group 3 animals (control; n=10) received 0.9% NaCl. The volume of injections was the same for all drugs – 0.5 ml.

In experimental series II, the animals were sham-operated. Injections of the drugs in the same doses as in series I were started on the next day after the operation.

In experimental series III, thymectomy was carried out in rats aged 3 weeks (160 g). Injections of tactivin (n=10), splenic polypeptides (n=10) in the above doses, or saline (n=10) were started on the next day after the operation and were carried out during 1 month every other day, after which CAAR was trained in all animals.

The results were statistically processed by Statistica 6.0 software using nonparametric Wilcoxon's test.

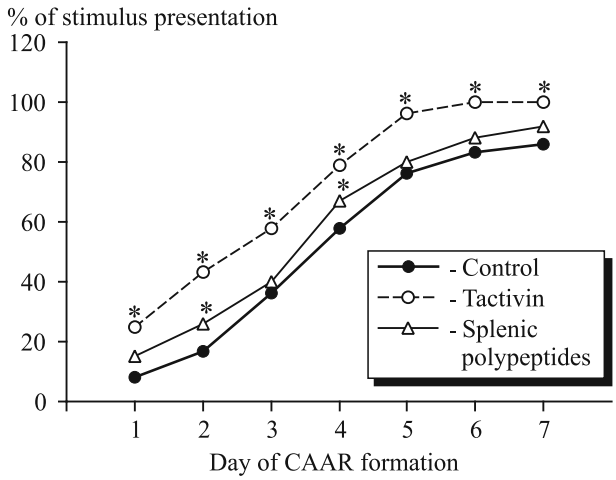

Fig. 1. Dynamics of CAAR formation in animals without thymectomy. Here and in Figs. 2, 3: ordinate: number of AA. *p<0.05 in comparison with the control.

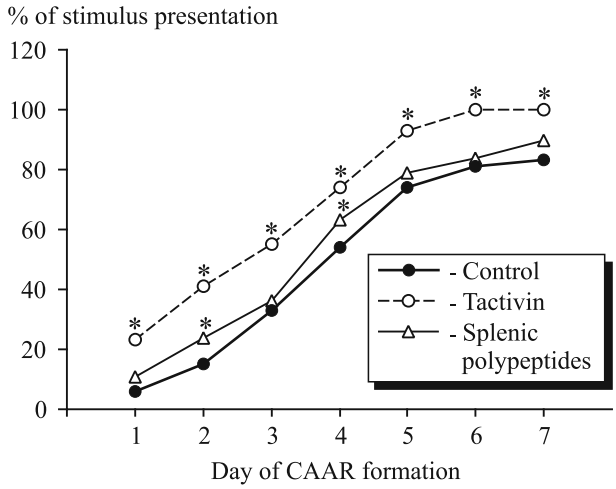

Fig. 2. Dynamics of CAAR formation in animals 1 month after sham-operation.

RESULTS

In series I, animals treated with tactivin demonstrated more rapid learning than controls during the entire experiment (Fig. 1), while animals treated with splenic polypeptides were trained more rapidly only during days 2 and 4. Importantly, tactivin accelerated the formation of avoidance reaction starting from day 1.

Observation of animals during CAAR formation showed that tactivin-treated rats preferred to be by the hole or in the center of the box between the signals and exhibited elements of exploratory activity (rearing, sniffing of the hole edges). Animals receiving saline or splenic polypeptides remained almost motionless in the corners of the box far from the hole.

Sham operation did not affect CAAR learning (Fig. 2). It is noteworthy that the results of experimental series II were similar to those in series I (Fig. 1), *e.g.* significant increase of avoidance reactions after sham-operation was observed on the same days as in intact animals.

In experimental series III, all animals survived after thymectomy. Thymectomy disturbed learning process in controls and rats treated with splenic polypeptides. Conditioned response could not be formed in these rats, which was in line with the data obtained on other models [10,15]. Tactivin-treated animals were trained and showed 80% avoidance reactions (Fig. 3). Hence, tactivin stimulated learning and memory processes disturbed by thymectomy.

This positive effect of tactivin could be explained as follows. Attenuation of the immune response as a result of thymectomy deteriorates learning capacity and memory [9,10] and leads to reduction of norepinephrin concentration in the amygdaline cortex, hypothalamus, striatum, and olfactory bulbs. After thymectomy the concentration of dopamine decreased

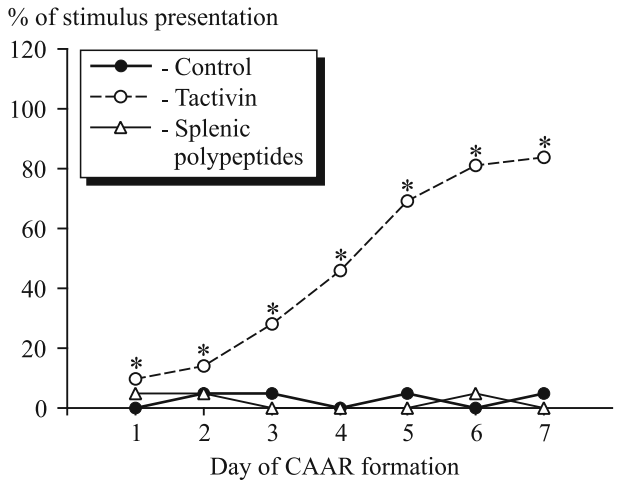

Fig. 3. Time course of CAAR formation in animals one month after thymectomy.

in the olfactory bulbs and the content of 5-hydroxytryptamine decreased in the frontal cortex [11]. These data indicate that learning and memory disorders in thymectomied animals are related with shifts in monoamine content in the brain. Presumably, restoration of these neurochemical parameters could repair the disorders in the learning and memory of thymectomied animals. We showed previously that more rapid CAAR learning in intact animals treated with tactivin was paralleled by a significant increase of norepinephrin level in the frontal cortex, hypothalamus, and striatum, of dopamine in the hypothalamus, and of serotonin in the frontal cortex, amygdala, and striatum [6]. Hence, the direction of these neurochemical shifts was opposite to that of changes developing in thymectomied animals [11]. These data suggested that tactivin could correct the disorders in monoamine levels induced by thymectomy.

These data indicate an important role of the thymus in the regulation of immune processes and its involvement, together with the CNS structures, in the learning and memory processes.

Disorders in the cognitive functions, induced by thymectomy, can be corrected by some immunoactive peptides, specifically, by tactivin.

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