

MNEMOTROPIC EFFECTS OF THYMUS PEPTIDES IN NORMAL AND PATHOLOGICAL CONDITIONS

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The abstract presents the results of research that reported how immune and nervous systems collaborate to regulate learning and memory processes. The research was conducted by the Department of Higher Nervous Activity of Lomonosov Moscow State University from 2009 to 2020. Wistar rats served as experimental subjects. A study was made of the effect of thymic preparations such as tactivin, 5th fraction of thymosin and thymalin on production of conditioned reflexes (conditioned active avoidance reflex (CAAR), conditioned passive avoidance reflex (CPAR), conditioned food-procuring reflex (CFPR) both in normal and pathological conditions (thymectomy, aging, neurotoxic effect of heavy metals and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)). Research indicates that thymus peptides showed a positive effect on cognitive functions. In normal conditions, they enhanced production of CAAR and CFPR with a prolonged retention of the memory trace in the CPAR task. Thymectomy resulted in restoration of conditioned reflexes lost after surgery. Cognitive functions were also improved in 18–24-month-old rats and following neurotoxic exposure. Thus, thymus peptides exert broad regulatory effects beyond immunity. The thymus also communicates with the central nervous system (CNS), potentially influencing cognitive processes like learning and memory.

Keywords: memory, conditioned reflexes, thymus, thymalin, tactivin, 5th fraction of thymosin

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МНЕМОТРОПНЫЕ ЭФФЕКТЫ ПЕПТИДОВ ТИМУСА В НОРМЕ И ПРИ ПАТОЛОГИИ

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В обзоре представлены работы, проведенные на кафедре ВНД МГУ им. М. В. Ломоносова с 2009 по 2020 год и посвященные вопросу взаимодействия работы иммунной и нервной систем в регуляции процессов обучения и памяти. Все эксперименты проводились на крысах Wistar. Исследовали действие пептидных препаратов (тактивина и тимозина фракции 5) и гормона тимуса тималина на выработку условных рефлексов: активного избегания (УРАИ), пассивного избегания (УРПИ) и пищедобывательного рефлекса (ПУР) как в норме, так и при некоторых патологических состояниях (тимэктомии, старении, нейротоксическом воздействии тяжелых металлов и метилфенилтетрагидропиридина (МФТП)). Во всех исследованиях пептиды тимуса продемонстрировали положительные эффекты на когнитивные функции. В норме они ускоряли выработку УРАИ и ПУР, а также на их фоне отмечалось более длительное сохранение памятного следа в модели УРПИ. После тимэктомии наблюдалось восстановление способности к выработке условных рефлексов, утраченной после операции. Также восстанавливались когнитивные функции у крыс в возрасте 18–24 месяцев и при нейротоксических воздействиях. Таким образом, регуляторные эффекты пептидов тимуса выходят далеко за пределы работы иммунной системы, а тимус не только выполняет важную роль в работе иммунной системы, но и принимает участие в процессах обучения и памяти совместно с различными структурами центральной нервной системы.

Ключевые слова: память, условные рефлексы, тимус, тималин, тактивин, 5-я фракция тимозина

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Neuroimmunoendocrinology as a new field of medicine and biology emerged from the active study of the intricate interactions between the nervous, immune, and endocrine systems. Smooth cooperation between the systems makes it possible for the body to adapt to the changing conditions. In 1936, Hans Selye, who defined the theory of stress, highlighted that the stress response involves the hypothalamic-pituitary-adrenal axis and the thymus. However, the thymus had long remained a gland susceptible to stress-induced involution under the influence of hormones of the

adrenal cortex. The thymus is primarily described as the essential organ for T-cell lymphopoiesis in the majority of studies. However, even immunology provides an extremely superficial description of thymus peptides (TP), which is more commonly based on research conducted in 1970–1980s. Thus, the description can be referred to as terra incognita in comparison with that of hormones from other organs. Thymulin, discovered in 1977, still lacks detailed description regarding its receptors and direct intracellular signaling cascades. According to PubMed, the

number of studies on thymulin is vanishingly small, which may be partly explained by the age-related involution of the thymus and the concomitant decrease in the production of its peptides.

In the field of neurobiology, innervation of the thymus by the fibers of the autonomic nervous system and their neurotransmitter supply have been studied in sufficient detail. It allowed to expand understanding of how the central nervous system regulates the immune functions. At the same time, regulation of CNS by TP is studied in scarce and solitary studies though the situation with other hormones is totally different. Pioneering work in this field was carried out by Russian authors in the end of 1980s. It involved several brief messages describing behavioral and neurophysiological effects of thymosin fraction 5 (TF5). In rats, when developing the appetitive instrumental task (AIT), TF5 reduced the latent period of escape to the feeder and “shifted lateralization of motor control towards the left hemisphere,” which manifested itself in an increase in the number of instrumental movements with the right paw and left-sided turns [1]. In rabbits, intracerebroventricular injection of TF5 in low concentrations increased the number of defensive reactions, as well as reduced the latency period and threshold of occurrence of such reactions to a cutaneous nociceptive stimulus. The effect was not eliminated by naloxone. On the contrary, higher concentration of TF5 suppressed defensive reactions [2]. In baboons, TF5 reduced aggression, while myelopeptides had the opposite effect [3]. In rhesus monkeys, TF5 increased the amplitude of evoked potentials in the somatosensory cortex in response to kinesthetic and nociceptive stimulation, but suppressed tactile one [4]. Based on the results, the authors concluded that TP may have an analgesic effect. However, new works of other authors have shown the analgesic effects of thymulin and its synthetic analog when inflammation was developed [5]. Literature analysis has found (and still continues to do so) a significant gap in the understanding of the effect of TP on the electrophysiological properties of neurons, homeostasis of neurons and glia, the functional state of the brain and mental functions. This made our long-term research devoted to this issue pressing as we focused on the methods used to study the processes of education and memory of laboratory rats who were administered immunotropic drugs. The experiments describe the effect of TP on memory of laboratory rodents and allow to develop a hypothesis stating that the thymus is an organ of stress-limiting system [6–10] and that its activity can make the body more resistant to neurotoxic effects [11], producing neurotropic and neuroprotective effects [12–16]. The results are especially pressing due to the ageing of population and growth of age-dependent CNS diseases of various etiology. Principal results of our research were obtained at the Department of Higher Nervous Activity of Lomonosov Moscow State University from 2009 to 2020 [17–28].

MATERIALS AND METHODS

All studies utilized Wistar rats with an initial body weight of 180–200 g. The animals were kept under standard vivarium conditions with free access to rodent chow and water as well as with a 12:12-hour light-dark cycle. During the pre-experimental treatment protocol, experimental animals received 0.5 ml intraperitoneal (IP) injections of test peptides once a day for 5 consecutive days at a consistent time. These included thymulin at a dose of 0.15 mg/kg; thymic polypeptides (tactivin, Patent No. 2112523, 1998, Russia) at a dose of 0.5 mg/kg; 5th fraction of thymosin (Hoffman-La Roche Inc., Nutley) at a dose of 0.25 mg/kg, and 0.5 mg/kg of spleen polypeptides obtained similar to tactivin at the Laboratory of Molecular Immunology and

Biochemistry of the Federal Clinical Research Center of Physical and Chemical Medicine of Federal Medical and Biological Agency of Russia. Piracetam, a nootropic agent, was administered as a reference drug at a dose of 300 mg/kg in the comparison groups, whereas control animals received normal sterile saline.

Experiments were conducted as per the principles of GLP (National standard of the Russian Federation GOST R 53434-2009 and International Convention of European Communities Council Directives, November 24, 1986, 86/609/EEC).

Summary of the methods is provided.

The passive avoidance conditionong (PAC) is analyzed in a traditional two-chamber (PAC) and modified three-chamber (mPAC) setups. The traditional PAC chamber consisted of two compartments with the lighted side and the dark side separated by a door. In the dark compartment a floor provides an electric foot shock (0.8 mA). Before developing the reflex and on the days of subsequent testing, the rat was placed in a light compartment with its back to the opening leading to the dark compartment. The animal was experiencing an electric foot shock when it entered the dark compartment until it returned to the light side [29]. At 24 hours, 3 days, 1 week and 2 weeks after the conditioned passive avoidance reflex was obtained, the rat was again placed in the light compartment and the latency period (LP) of entering the dark compartment was recorded. The test terminated when the rat entered the dark compartment or after 180 seconds if the rat did not leave the light one. In the mPAC [21, 30] setup, the same training protocol was utilized though an additional dark compartment was available. Thus, the light area was located in the middle. The modification allowed to add a space component to the formed memory trace about the location of the footshock exposure as previously it was unclear if the animal avoided the shock due to fear or decreased anxiety and, as a consequence, less avoidance of open light areas. The modification also allowed for an additional registration of the selected compartment. The LP of entering a compartment was recorded for the setup as well. A dangerous compartment was associated with a foot shock, and a safe one was associated with the lack of it [29].

Shuttle box active avoidance (SBAA) was developed in rats in a shuttle box with an electrified floor. After 10 s of isolated exposure of a conditioned stimulus (sound of 700 Hz), an unconditioned stimulus (electric current of 0.7 mA) was applied to the floor for no longer than 10 s. When the rat moved to another half of the compartment in an attempt to avoid the current (avoidance reaction), both stimuli weren't applied any longer. If the rat changed location under the influence of a conditioned stimulus only (avoidance reaction), the unconditioned stimulus was still applied and the sound was off [31]. SBAA was developed on a daily basis (25 trials, 30 seconds each) during 7 days until a stable reflex was formed. Over 80% of successful avoidance, often measured within a set number of trials, was considered as the training criterion [29].

Appetitive instrumental task (AIT) was acquired according to the method developed by T. A. Mering (1988) [32]. After 12 hours of food deprivation, animals were placed into the chamber separated by a wall with a hole cut into it. By standing on the platform located under the hole, the animal could get some food from the hole. A 400 Hz tone that sounded for 15 s served as the conditioned stimulus. If the animal takes the food (positive reaction), the conditioned stimulus acts as a terminal signal. It took 5 days to produce AIT. Every experiment included 11 trials with a 60 s interval between the signals. Over 80% of positive responses is considered as the reflex-producing criterion [29].

Three-week-old animals underwent thymectomy and sham surgery. Each group of animals (with thymectomy and sham

surgery) was divided into subgroups. Starting from the next day, TP preparations (tactivin and thymulin) or saline solution (control animals) were injected intraperitoneally every other day in the rats. Acquisition of SBAA started one month following the surgery [22].

Statistical processing of the results was performed using the Statistica 8.0 (StatSoft Inc., USA). The inter-groups differences were evaluated using the nonparametric Mann–Whitney U test. Changes within the group (between time points and trials) were assessed using the nonparametric Wilcoxon Signed-Rank test. The significance levels were set at $p < 0.05$.

DISCUSSION OF RESULTS

Effects of thymus preparations on the acquisition of a conditioned passive avoidance reflex

Acquisition of memory trace and, as a consequence, avoidance behavior in the SBAA and PAC tests is utilized to assess the effects of substances on the formation and reproduction of a memory trace both in normal conditions, and in amnesia. A series of experiments done in 2011–2014 [18, 20, 21] have shown that prior to PAC formation, LP of entering the dark compartment varied from 2 to 6 s without a statistically significant difference. Exposure to an unconditional stimulus significantly increased the latency period of entering a dark compartment across all experimental groups as compared to LP prior to PAC acquisition ($p < 0.001$). Meanwhile, the animals receiving piracetam (a nootropic reference drug) avoided the dangerous compartment throughout the testing period. Under the influence of TP (tactivin, thymosin fraction 5 and thymulin), a statistically significant increase in LP was observed at 1 and 2 weeks as compared with a control group that was injected with the same amount of normal saline. At the same time, spleen peptides caused a statistically significant increase in LP for mice to enter the dark compartment at 24 hours and 3 days only as compared with the control group [18, 20, 21]. To illustrate these effects, data from a 2014 experiment are given (Table 1). Thus, a prolonged retention of memory trace is seen with thymus polypeptides, and rapid extinction of this effect is observed with spleen polypeptides.

In the modified PAC (mPAC) setup, rats quickly entered the dark compartment before developing a reflex similar to the standard model. Also, a day after the reflex was developed, a multiple statistically significant increase in LP of entry into the “dangerous” compartment was observed in all groups ($p < 0.001$). Table 2 shows the data from a series of experiments in 2014. Administration of TP preparations (tactivin, thymulin, and the 5th thymosin fraction) and piracetam reference standard resulted in a statistically significant increase in LP of entry into the dangerous compartment as compared to LP of the control animals throughout the observation period (Table 2). Spleen polypeptides led to a statistically significant increase in LP of entry into the “dangerous” dark compartment during the first three days only similar to the experiments with a standard PAC model.

The effect of preparations on the choice of a “safe” dark compartment (where the animal is safe from the electric shock) within a modified PAC setup was also analyzed. The animals that were administered TP and piracetam, a widely used nootropic compound, chose a “safe” dark compartment whereas the effect was not seen among the control animals [21].

Based on the results of analysis assessing TP effects, a conclusion can be made about a long-term mnemotropic effect of peptides during PAC production both in standard, and modified setups. Compared to the temporary relation between the experimental environment and current in the standard PAC unit, the modified setup deals with a more complicated task. It memorizes the site of current exposure, spatial differentiation and the choice of a safe compartment. The animals who were administered thymus polypeptides could solve the problem successfully, which proves that TP have a nootropic activity associated with spatial memory [29].

Effect of thymus preparations on the acquisition of a conditioned active avoidance reflex

In experimental animals that were administered TP and piracetam, the release rate of SBAA was faster than in control animals and in those with spleen peptides [8, 17–20, 33, 34]. Figure 1 presents the results of an experiment conducted in 2017 that confirmed the idea.

Table 1. LP of entering a dark compartment following a standard production of PAC

Time points	Latent period of entering the dark compartment, s					
	Tactivin group	Thymulin group	Thymosin fraction 5 group	Spleen peptide group	Control group	Piracetam group
Prior to PAC production	3.1 + 0.5	3.3 + 0.7	3.5 + 0.5	4.2 + 0.8	3.2 + 0.5	2.8 + 0.3
24 hours	138.3 + 4.5 [^]	139.0 + 4.6 [^]	137.8 + 2.8 [^]	150.4 + 1.3 ^{^*}	130.2 + 3.5 [^]	180.0 ^{^*}
3 days	118.3 + 3.4	126.3 + 0.5 [*]	117.4 + 3.1	116.3 + 2.1	111.7 + 1.8	180.0 [*]
1 week	120.3 + 0.5 [*]	120.3 + 0.8 [*]	119.1 + 1.2 [*]	109.0 + 0.7	108.3 + 2.5	180.0 [*]
2 weeks	120.5 + 2.2 [*]	121.2 + 0.3 [*]	120.0 + 1.5 [*]	100.3 + 1.1	100.3 + 1.3	180.0 [*]

Notes: n (in every group) = 20; [^] — $p < 0.001$ s compared with LP prior to PAC production; ^{*} — $p < 0.05$ as compared with the control.

Table 2. LP of entering the “dangerous” compartment following a standard production of mPAC

Time points	Latent period of entering the dark compartment, s					
	Tactivin group	Thymulin group	Thymosin fraction 5 group	Spleen peptide group	Control group	Piracetam group
Prior to PAC production	3.8 + 0.6	3.1 + 0.5	3.3 + 0.6	4.6 + 0.5	5.4 + 0.8	2.8 + 0.3
24 hours	146.5 + 2.7 ^{^*}	158.3 + 3.5 ^{^*}	145.3 + 2.5 ^{^*}	138.3 + 4.5 ^{^*}	60.1 + 9.2 [^]	180.0 ^{^*}
3 days	139.4 + 1.5 [*]	147.8 + 0.8 [*]	139.2 + 3.3 [*]	106.5 + 1.9 [*]	58.7 + 5.5	180.0 [*]
1 week	128.5 + 3.3 [*]	130.7 + 1.3 [*]	127.6 + 2.6 [*]	60.0 + 4.6	46.6 + 6.1	180.0 [*]
2 weeks	125.7 + 2.8 [*]	130.1 + 3.3 [*]	124.4 + 6.1 [*]	56.6 + 3.7	46.3 + 1.2	167.4+3.2 [*]

Notes: n (in every group) = 20; [^] — $p < 0.001$ s compared with LP prior to PAC production; ^{*} — $p < 0.05$ as compared with the control.

In addition to accelerated acquisition of the instrumental response, thymus polypeptides reduced the LP of passage through the opening against the background of the effect of a conditioned stimulus on all days of the experiment. It is also worth noting that in the intersignal period, the rats treated with TP or piracetam showed elements of research activity and preferred to be near the hole in the partition or in the center of the chamber, while the control animals were motionless far from the hole, preferring camera angles [22].

Effect of thymus peptides on the acquisition of a conditioned food procuring reflex

The results of AIT acquisition were similar to ones with negative reinforcement and in case of intraperitoneal [19, 25] and intranasal [36] administrations.

Fig. 2 shows the results obtained during the assessment of changes in AIT production among the animals of different age who were administered thymulin.

Thus, the investigational TP (tactivin, the 5th fraction of thymosin and thymulin) are similar to piracetam in relation to their effects in various methods of developing conditioned reactions, both with negative and positive reinforcement, which may show that they possess mnemotropic properties.

Effect of thymus peptides on the restoration of the ability to produce conditioned reflexes reactions in thymectomized rats

Consequences of thymectomy show that the thymus participates in learning processes. Thymectomy was performed in three-week-old rat pups. To correct their condition, the pups were subsequently injected with TP for a month [22, 26, 37,

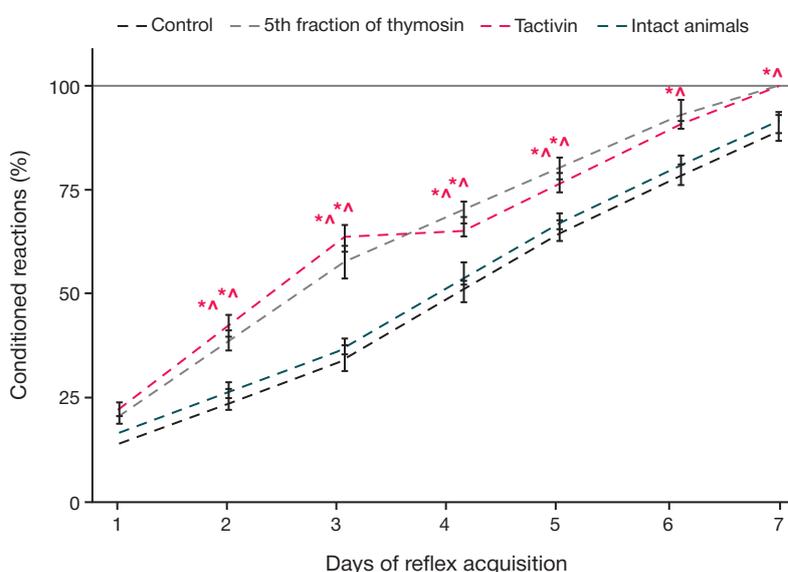


Fig. 1. Acquisition of SBA: *n* (in every group) = 10; ^ — *p* < 0.05 s compared with control * — *p* < 0.05 as compared with intact animals.

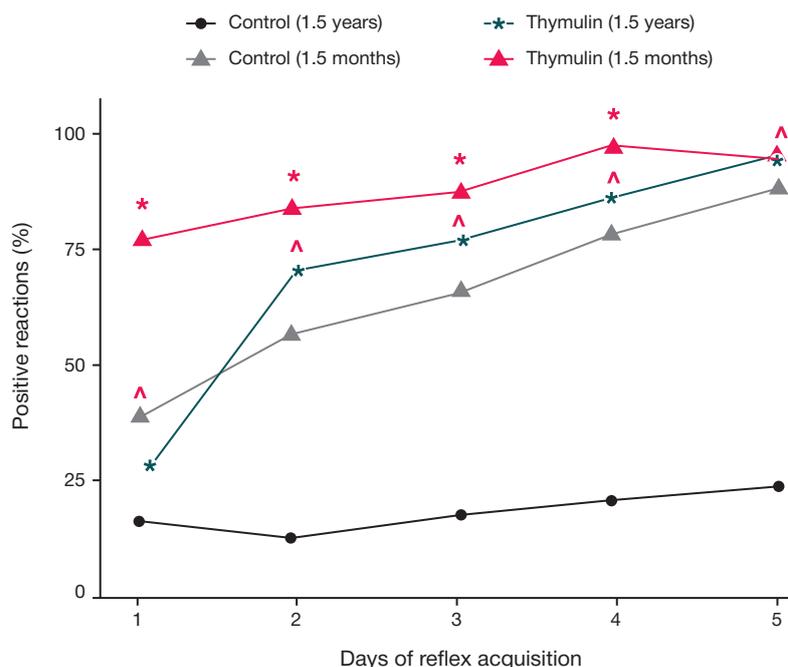


Fig. 2. Acquisition of AIT in rats of various age: *n* (in every group) = 25; * — *p* < 0.05 as compared with control (1.5 months), ^ — *p* < 0.05 as compared with control (1.5 years)

38]. After the time point, they began to develop instrumental reactions. No changes in the acquisition were detected in sham-operated animals. The animals that underwent thymectomy failed to acquire avoidance or appetitive reactions in any series of experiments. However, when thymus or thymulin preparations were used to correct the condition following thymectomy, the learning ability was completely restored just like in the acquisition of SBAA and AIT. The changes in conditioned reflexes after thymectomy were evaluated in experiments conducted in 2018–2019. The animals of the first control group that underwent thymectomy were injected with saline solution, whereas the animals of the second control group that underwent thymectomy were also intraperitoneally injected with 0.05% ZnCl₂ solution in PBS (used as a thymulin solvent). As shown in Figures 3 and 4, it was not possible to develop instrumental reactions (%) in animals of the control

groups, while thymulin resulted in a complete restoration of learning processes with both positive (Fig. 3) and negative (Fig. 4) reinforcement.

A decrease in learning ability after thymectomy has already been shown earlier in mice [39–41]. However, these studies did not use TP to improve this condition. Our studies [22, 26, 37, 38] have shown that thymus peptide preparations and thymulin eliminate cognitive impairments caused by thymectomy.

Effect of thymus peptides on the restoration of the ability to produce conditioned reflexes during aging and neurotoxic effects

TP-induced learning in rats was restored not only after thymectomy, but also during aging and under the influence of various neurotoxic effects. Experiments with old animals

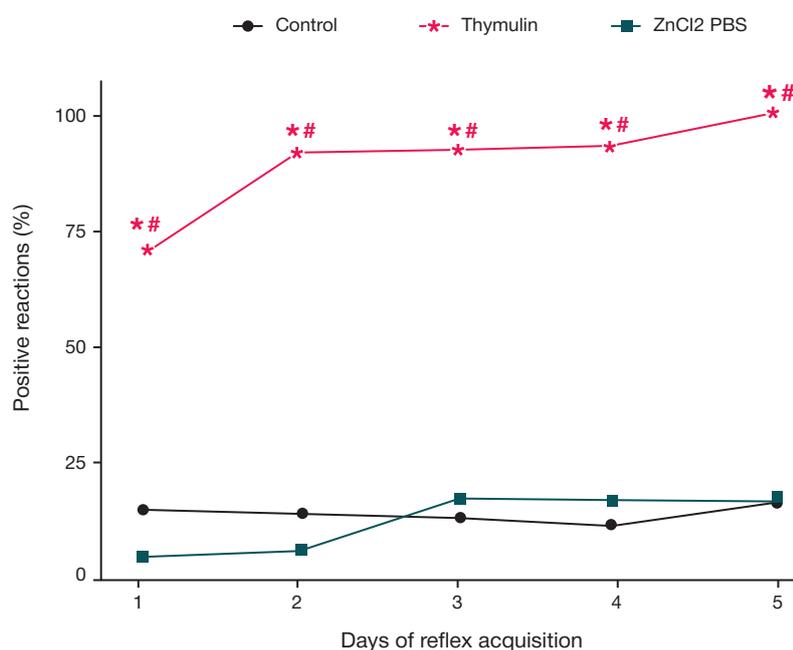


Fig. 3 Acquisition of AIT to a tone in thymectomized rats: *n* (in every group) = 15; * — $p < 0.05$ as compared with control (1.5 months), # — $p < 0.05$ as compared with ZnCl₂ в PBS

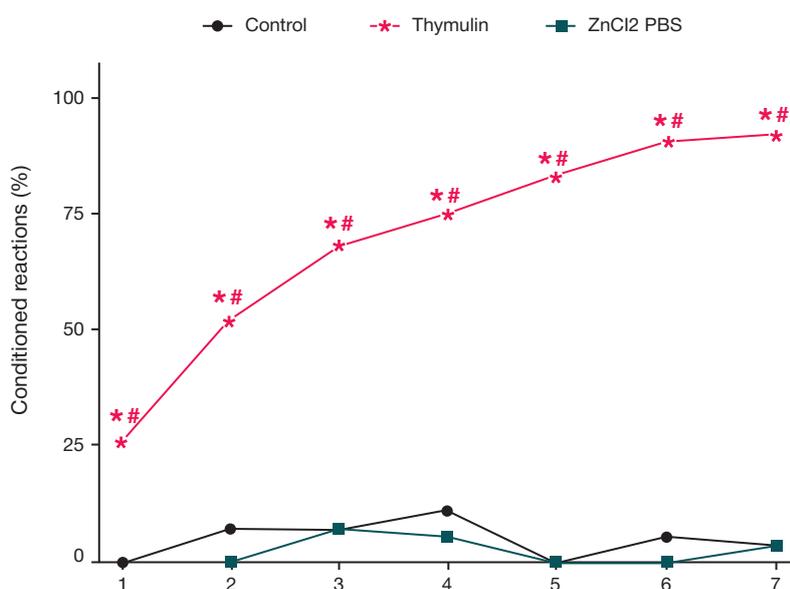


Fig. 4 Acquisition of SBAA in thymectomized rats: *n* (in every group) = 15; * — $p < 0.05$ as compared with control (1.5 months), # — $p < 0.05$ as compared with ZnCl₂ в PBS

(18–24-months-old rats) showed that aging decrease acquisition of instrumental response, both with positive and negative reinforcement. TP allowed to restore the learning ability in animals of this age group [23–25]. It has also been shown that TP reduces cognitive deficits after heavy metal and MPTP intoxication [11, 24, 28].

Possible mechanisms of thymus peptide effect on the CNS

1. There is reason to consider the thymus as part of the body's opioid system, which regulates the physiological and mental response to stress. TP, in particular thymosin and thymulin, exhibit an analgesic activity which is blocked by naloxone, an antagonist of opiate receptor [42]. It has been shown that the components of thymosin fraction 5 contain ligands similar to beta-endorphin and met-enkephalin, and can also bind to the corresponding receptors of nerve cells in the brain [43], whereas thymectomy decreases the level of beta-endorphin in blood [44]. Currently, it is well known that opioid peptides have pronounced mnemotropic effects, affecting short-term and long-term memory systems, as well as being involved in the work of reinforcement and motivation systems, are able to alter the activity of acetylcholinergic and dopamine neurons in the brain, and influence the development of pathological addictions.
2. TP have anti-inflammatory effects, inhibiting pro-inflammatory cascades and reducing the production of pro-inflammatory cytokines, which has been shown, using animal LPS-models of multiple sclerosis and systemic inflammation [45, 46]. In neuroimmunology, inflammation in the central nervous system is considered as one of the central links in the pathogenesis of anxiety and depression, memory disorders and neurodegenerative diseases. The administration of LPS is a pro-inflammatory model of a depressive-like syndrome in rodents, which can be corrected, including by endogenous peptides. Several studies have also shown that TP can influence the activity of macrophages [47]. It is possible that microglia activated by the proinflammatory phenotype could also be a target of TP. The considered analgesic effects of TF5, thymulin, and its synthetic analog can be mediated by both mechanisms simultaneously. Nociception is also associated with acetylcholinergic transmission, and with activation of the nicotinic receptor- $\alpha 7$ subtype in particular, which can be potentiated by the peptide analogue of thymulin [48]. This subtype of receptors is also critically important for memory and cognitive functions. Thus, their exposure in the central nervous system could explain the mnemotropic effects of TP [49–51].
3. The mnemotropic effect of TP is similar to that of nootropic preparations [52]. Removal of the thymus has a negative mnemotropic effect, reducing the ability to learn and remember [40, 41, 53]. Meanwhile, changes in the balance of brain catecholamines are detected. Thymectomy induced a reduction in norepinephrine in the cortex, olfactory bulbs, striatum, amygdala and hypothalamus. There was also a decrease in dopamine in the olfactory bulbs, and 5-hydroxytryptamine in the frontal cortex [53, 54]. In the works of Zhang Y, Saito H, Nishiyama N. (1994), it was shown that thymectomy induced deterioration of learning and memory [40]. Subsequently, they confirmed the data [39, 41].

In animals without thymectomy, TP causes a statistically significant increase in the levels of norepinephrine in the

frontal cortex, hypothalamus, and striatum; dopamine in the hypothalamus, and serotonin in the frontal cortex, amygdala, and striatum [55, 56]. These neurochemical changes were opposite to the changes observed in thymectomized animals [53, 54]. At the same time, in animals without training, intraventricular administration of thymulin decreased the levels of HA and DA in the hypothalamus and increased the level of serotonin (5-HT) in the midbrain [57].

The monoamine profile of thymectomized animals is similar to the balance of neurotransmitters in rodent models of depression, including after administration of LPS [58, 59]. These disorders may also be associated with disruption of the opioid system and activation of pro-inflammatory cascades. Learning and memory processes are associated with thymus-controlled cytokines and cascades [47, 60].

4. The available data show that the hypothalamus is the most likely target for TP in the brain [61], various parts of which are involved in the formation of defensive and nutritional instrumental reflexes [62] and control various cognitive functions [63, 64]. In the work mentioned above, TF5 reduced the intraspecific aggression of baboons, which may be due to the effect of TP on the hypothalamic aggression centers. Intraspecific aggression is regulated by the activity of both the medioventral and lateral hypothalamus [65], and the activity of the latter increases against the background of glucocorticoid deficiency. The connection between TP and the hypothalamus is also seen in early studies with thymectomy in rhesus monkeys, in which surgery reduced the secretion of ACTH and cortisol [44], and administration of TF5 stimulated production of ACTH and corticosterone/cortisol levels [66].

QUESTIONS AND BLANK SPOT

It should be borne in mind that evidence regarding how TP can affect the central nervous system is expanding slowly, making firm conclusions about these mechanisms challenging. It is yet to be determined whether TP produce a direct effect on nerve tissue or are mediated by other mechanisms such as synthesis of cytokines by nerve cells, vascular endothelium, or glia. Do TP receptors exist in the CNS? If they do, where exactly are they localized? What role does the extra-thymic production of TP play in maintaining the adaptive response of the body to stressful factors of various nature (heavy metals, injuries, psycho-emotional stress, etc.)? Is the thymus excluded from the stress-limiting system with age? Does thymus involution affect the functions of the central nervous system? Is it associated with any age-related neurodegenerative diseases?

CONCLUSION

Summarizing the above, it can be assumed that the mnemotropic effect of thymus peptides can be based on the changed activity of various hypothalamic nuclei. Their activity can be regulated both through direct effect of thymus peptides on central receptors with a subsequent development of opioid-like effects, and through mediated cytokine cascades. Thus, by producing polypeptides and thymulin in particular, the thymus is not only responsible for regulating the immune system, but also plays an active role in cognitive development and maintenance of CNS homeostasis, especially in the early stages of development when synaptic connections and mechanisms of stress regulation are actively developed. Reference

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