Article

Mechanisms of the Antistress Effect of Thymus Peptides

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Abstract: The review presents the results of research conducted from 2008 to 2020 at the Department of Pharmacology of the Pediatric Faculty of the GBOU VPO RNIMU of the Ministry of Health of the Russian Federation, in the Laboratory of the Evolution of Memory Mechanisms of the Department of Higher Nervous Activity of the Faculty of Biology of the Lomonosov Moscow State University and in the Laboratory of Molecular Immunology of the Federal State Budgetary Scientific Institution "Research Institute of Physico-Chemical Medicine" of the FMBA of the Russian Federation. To understand the processes underlying the antistress effect of thymus peptide preparations (thymulin, tactivin, and the 5th fraction of thymosin), radioligand binding to the GABAA receptor, neurochemical studies, and experiments using non-selective opiate and serotonin receptor blockers have been conducted. Based on the data obtained, it is assumed that by triggering the cytokine cascade, thymus peptides increase the level of the inhibitory amino acids taurine and glycine, alter the balance of monoamines serotonin/norepinephrine in favor of the former and activate opioid neurons, which in turn limits the damaging effects of stress reactions.

Keywords: stress, stress-limiting system, functional disorders, thymus, thymalin, tactivin, 5th fraction of thymosin.

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1. Introduction

The problems of stress as the most common nonspecific response of the body to any stimulus and adaptation to it concern not only physiologists, but also doctors. Back in 1936, H. Selye, having put forward the theory of adaptation syndrome, showed that in any stressful state a three-phase process occurs in the body, in which the main shifts are detected by the endocrine organs, mainly the pituitary gland, adrenal glands and thymus. However, in modern schemes of stress and stress-limiting systems, neither the thymus nor the peptides produced by it found a place [1]. It is assigned only the role of a stress-dependent organ.

At the same time, there are close direct and inverse connections between the thymus and the hypothalamic-pituitary system. It is known that shutting down the function of the pituitary gland leads to aplasia of the thymus, a decrease in the secretion of its hormones by epithelial cells and an acceleration of age-related gland involution [2]. Direct regulation of thymus activity by the hypothalamus can be carried out through the sympathetic and parasympathetic parts of the autonomic nervous system [3; 4]. In turn, the neuroendocrine centers of the hypothalamus differentiate during embryogenesis under the influence of the thymus [5]. Various fractions of thymosin and opioid peptides secreted by the thymus stimulate the synthesis of certain releasing factors, followed by increased secretion of gonadotropins and prolactin [6]. At the same time, there is evidence in the literature that various peptide preparations of the thymus affect not only the activity of the immune system, but also affect all types of metabolism [7-13]. At the same time, their action is diametrically opposed to the action of GC, which are one of the leading participants in the implementation of the stress system [1].

In addition, there are known facts of correction of various types of stress. Thus, under infectious stress, the introduction of tactivin (a preparation of thymus polypeptides) into the body of children suffering from acute respiratory diseases led to a rapid recovery of immune status indicators and recovery of sick children [14-17]. Its inclusion in the complex of therapy for visceral leishmaniasis led to a significant reduction in both the duration of treatment for children [18] and leveled the toxic effect of the 5-valent antimony drug pentostama (Great Britain). To correct intoxication stress, tactivin was administered to Wistar rats, which contributed to the effect of systemic

detoxification in total endotoxemia in experimental acute peritonitis caused by gram-negative microflora [19], and in chronic benzene intoxication in male CBA mice, a decrease in the activity of cytochromes P-450, C-reductase, benzpyrenhydroxylase, and epoxide hydrase was noted.

Tactivin monotherapy led to normalization of enzyme activity. At the same time, with subacute intoxication, accompanied by increased activity of enzymes of the second phase of xenobiotic metabolism: glutathione-S-transferase and epoxidihydraz, the drug reduced their activity [20; 21]. An equally pronounced effect of the drug was obtained in rats with a burn injury accompanied by a violation of the function of vital organs. The administration of tactivin eliminated signs of intoxication, reduced the zone of secondary necrosis, and promoted the formation of full-fledged skin regenerates with the formation of hair follicles and sebaceous glands [22]. A synthetic pentapeptide similar to a fragment of thymopoietin (from the 32nd to the 36th amino acid residue), thymopentin has a protective effect in case of stress damage to the stomach [23]. When intoxicated with heavy metals (in particular, lead poisoning), oxidative stress develops, in which pronounced cognitive disorders are observed, which were also eliminated by the administration of tactivin [24].

However, in the examples listed above, the immune system exerted too much influence on the course of the process, and therefore it was difficult to separate the direct immunomodulatory and antistress effects of the thymus drug. To confirm the assumption about the involvement of the thymus in the work of the stress-limiting system, it was necessary to use models of stress-related effects in which the involvement of the immune system would be less significant. To do this, in joint work conducted from 2008 to 2020 at the Department of Pharmacology of the Pediatric Faculty of the state budgetary educational institution of higher professional education RNIMU of the Ministry of Health of the Russian Federation, in the Laboratory of the Evolution of memory Mechanisms of the Department of Higher Nervous Activity of the Faculty of Biology of the Moscow State University. Experimental studies have been conducted in the Laboratory of Molecular Immunology of the Federal State Budgetary Institution "Research Institute of Physico-Chemical Medicine" of the FMBA of the Russian Federation, which have proved that thymus peptides have anxiolytic activity [25-27] and antistress activity under emotional stress, both during learning [24; 28-30] and against the background of functional disorders avoidance reactions (failure of the conditioned reflex of active avoidance and a change in the location of the hole) [31-35].

The purpose of this work was to summarize the data obtained on the mechanisms of the effect of thymus peptides (tactivin and thymosin fractions 5 and thymulin) on the functioning of the stress-limiting system.

2. Materials and Methods

The experiments were conducted on Wistar rats weighing 180-200 g. The animals were kept in standard vivarium conditions with free access to water and food and a 12-hour light-dark regime. Before starting the study, the level of motor activity of animals in a mink chamber and an open field was tested in all animals to form groups of identical behavior. For 5 days (at the same time), once a day, experimental animals were intraperitoneally injected with a preparation of thymus polypeptides (tactivin, the 5th fraction of thymosin or thymulin), reference (piracetam, diazepam) and control drugs (saline solution, spleen polypeptides prepared in a similar way to tactivin and/or solvent for timulin) in a volume of 0.5 ml. All experiments were conducted in accordance with the Principles of Good Laboratory Practice (National Standard of the Russian Federation GOST R 53434-2009) and the provisions of the International Convention on "Rules for Working with Experimental Animals" (European Communities Council Directives, November 24, 1986, 86/609/EEC).

Radioligand analysis of GABAA receptors (the experiments were conducted jointly with the Laboratory of Radioisotope Research Methods of the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences, head, Doctor of Medicine, Professor G.I. Kovalev). For the ex vivo experiment, tactivin was administered intraperitoneally for 5 days once a day at a dose of 0.5 mg/ kg (experimental group, n=10), or 0.5 ml of saline solution (control group, n=10). The animals were removed from the experiment after 24 hours after the last injection. After decapitation, the hypothalamus and frontal cortex were isolated from the brain, which were immediately frozen in liquid nitrogen and stored in a low-temperature refrigerator at - 85 °C. The preparation of membrane preparations containing GABAA receptors in these structures was carried out using modified methods [36; 37]. The protein concentration in the samples was determined using the standard Lowry O.N. method [38].

Biochemical determination of the content of monoamines, excitatory and inhibitory amino acids in the rat brain (part of the experiments were conducted jointly with the Laboratory of Neurochemical Pharmacology of the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences, head, Candidate of Medical Sciences, V.S. Kudrin). Prior to the start of the conditioned response of active avoidance production, experimental groups of animals received one of the studied thymus peptide preparations (timulin, tactivin, or the 5th fraction of

thymosin) for 5 days, and control animals were injected with saline/spleen peptides/ thymulin solvent. When the number of avoidance reactions reached 80%, a functional violation of the conditioned response of active avoidance (failure of the avoidance reaction) was performed. The animals were decapitated 1 hour after the last injection of the drugs. The brain was extracted on ice and the frontal cortex, hypothalamus, nucleus accumbens, striatum, and hippocampus were isolated. The structures were frozen and stored in liquid nitrogen. On the day of the study, the structures were homogenized, and a supernatant was prepared in which monoamines and metabolites, or amino acid content were determined by high-performance liquid chromatography with electrochemical detection [39].

Statistical processing of research materials.

Statistical processing of the obtained data was carried out using the STATISTICA 8.0 program (Statsoft, USA), using the Student's t-test, nonparametric criterion, Mann-Whitney, as well as using Fisher's F-test for radioligand analysis.

3. Results

Activation of the GABAergic system

Using ex vivo radioligand analysis, no statistically significant differences were found in the number of GABA receptors in control and experimental animals not exposed to emotional stress. The results of the ex vivo experiments were evaluated using Cm and B-Max values, reflecting the degree of affinity of the receptor to the ligand (nM) and the number of ligand binding sites (fmol/mg protein), respectively. The results did not reveal significant differences in the number of receptors studied in the hypothalamus (Fig. 1) and in the frontal cortex between the control and experimental groups.

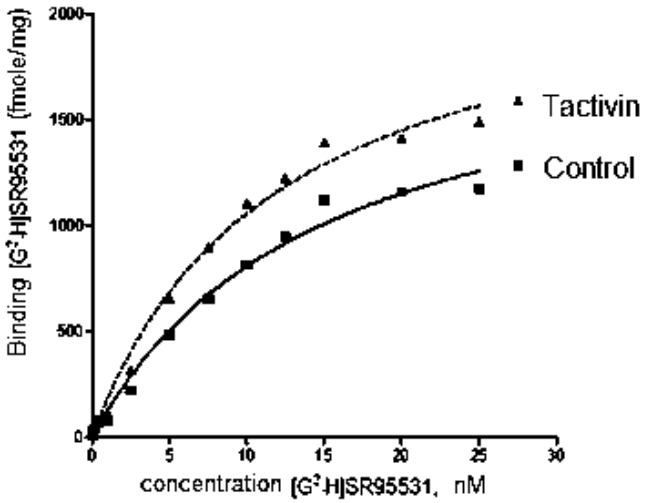

Figure 1. Binding characteristics of the selective ligand of the GABAA receptor [G-3H]SR95531 to the hypothalamic membranes of Wistar rats (intact animals) (n=20). Fischer's F-test, p=0.30

GABA levels in some structures of the rat brain were studied using high-performance liquid chromatography with electrochemical detection against the background of emotional stress caused by a malfunction of the avoidance reaction. As can be seen from the data presented in Table 1, the administration of tactivin to animals exposed to emotional stress caused by a malfunction of the avoidance reaction did not affect the level of the inhibitory amino acid GABA in the studied structures of the rat brain [40].

Table 1. GABA level (mmol/d) in the brain structures of Wistar rats on the background of emotional stress (failure of the conditioned reaction of active avoidance) (n=20)

Composition	EVPGABA content in brain structures in animal groups		The level of significance of the difference in results (p control, - experience)
	control	against the background of tactivin	
The Hypothalamus	0,844 ± 0,057	0,813 ± 0,056	0,7
The Frontal cortex	0,415 ± 0,009	0,406 ± 0,004	0,423

The nucleus accumbens	1,032 ± 0,059	0,988 ± 0,048	0,59
The Striatum	0,549 ± 0,017	0,538 ± 0,026	0,747
The Hippocampus	0,451 ± 0,017	0,442 ± 0,019	0,725

Thus, the stress-protective activity of the thymus polypeptide drug tactivin under emotional stress does not seem to be associated with the activation of the GABAergic system [41].

The level of monoamines in the structures of the brain

High-performance liquid chromatography with electrochemical detection was used to study the level of monoamines in some brain structures against the background of thymus peptides. The administration of tactivin [42], as well as thymulin and thymosin fraction 5 [43], significantly reduced dopamine levels in intact rats in the frontal cortex. The level of dopamine in the striatum increased statistically significantly, which explains the increase in motor activity against the background of the drug in behavioral tests. An increase in norepinephrine levels was also noted in the hippocampus.

After emotional stress caused by a malfunction of the avoidance reaction, on the background of tactivin [42], there was a statistically significant increase in serotonin and norepinephrine in the frontal cortex, hypothalamus and striatum (Fig. 2). Similar changes were observed with the use of thymulin and thymosin fraction 5 [43].

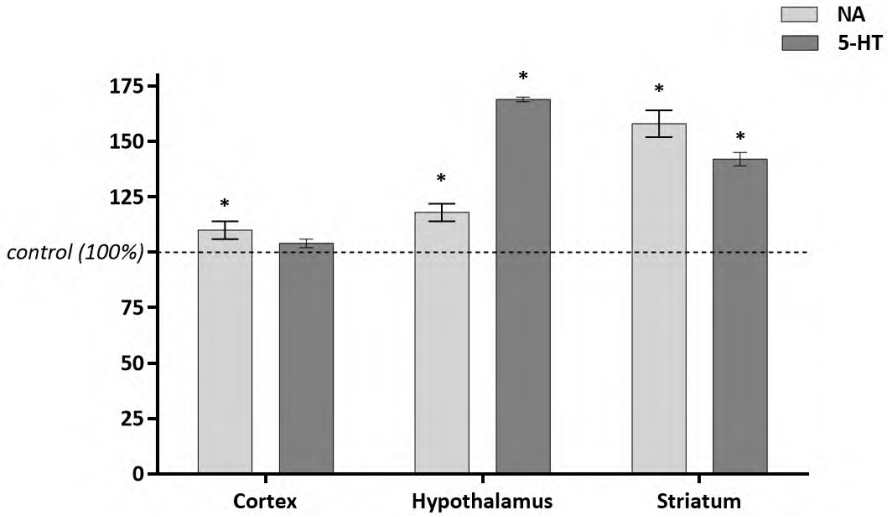

Figure 2. Changes in the level of monoamines in the rat brain on the background of tactivin (failure of the avoidance reaction)
Note: the indicators of the control group are taken as 100%. NA – norepinephrine; 5-HT – 5-hydroxytryptophan (serotonin)

Since these changes were not observed in intact rats, these changes in the monoamine content can be explained by the development of emotional stress in animals caused by a functional violation of the avoidance reaction. Apparently, thymus peptide preparations alter the serotonin/norepinephrine ratio in favor of the former. Considering that an increase in serotonin content is a compensatory response to stress, and a decrease in norepinephrine concentration is associated with manifestations of fear [44; 45], it can be assumed that such a change underlies the positive effect of thymus peptides upon failure of the conditioned active avoidance reaction.

4. Discussion

The level of excitatory and inhibitory amino acids in rat brain structures

When studying the levels of excitatory and inhibitory amino acids in rats without emotional stress, it was found that tactivin (0.5 mg/kg) causes a statistically significant increase in the content of taurine in the hypothalamus and glycine in the frontal cortex [40].

An increase in glycine content in the frontal cortex is observed in selank, which explains its anxiolytic effect associated with the aminoacidergic system of the brain [46]. The prefrontal cortex is responsible for the implementation and coordination of higher cognitive processes in the planning of complex behavioral acts [47]. The frontal cortex is involved in decision-making based on emotional reactions and thus provides the motor component of the emotional response. An increase in glycine levels may reflect the neuroprotective properties of tactivin, which are manifested in the prevention or reduction of manifestations of emotional stress in rats [25; 31-35].

The hypothalamus belongs to the mesolimbic dopaminergic system, which is largely responsible for the development of anxiety states [48]. The administration of tactivin at a dose of 0.5 mg / kg significantly increased the taurine content in the hypothalamus by 1.3 times. Taurine is involved in the regulation of hormone secretion, acetylcholine and GABA [49]. The mechanism of action of taurine includes binding to GABAA receptors, as well as to certain types of glycine-binding receptors, which in turn stimulates the release of vasopressin and oxytocin [50].

Based on these data, it is possible to suggest a possible mechanism of action of thymus peptides on the central nervous system through cytokine cascades. It is well known that thymus peptides activate the T-cell link of immunity, while increasing the production of various cytokines: IL-1, IL-2, IL-6, IL-8, TNFa, and IFu [1; 51; 52]. IL-1 increases the level of taurine in the hypothalamus [53], which is consistent with the neurochemical data presented by us. By increasing the production of IL-1, thymus peptides increase the level of norepinephrine in the hippocampus [32]. Thus, on the one hand, they normalize immunological parameters in case of deviation from the norm in one direction or another, without causing critical disorders [14; 54], and on the other hand, they increase the level of inhibitory amino acids in structures associated with emotional response [40].

The opioid system

Since electrical pain irritation is the main stressful factor in the formation of functional disorders of URPI, it is logical to assume that thymus polypeptides have analgesic activity. It is known that two antagonistic systems are involved in pain regulation: nociceptive and antinociceptive. The main mediators of the antinociceptive system are opioid peptides and serotonin. Thus, the most likely mechanisms of substances with analgesic activity are associated with the activation of the serotonergic and/or opiate systems. Studies have been conducted to study the analgesic activity of thymus peptides using a non-selective opioid system blocker (naloxone (5-alpha)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-ONE (in the form of hydrochloride, 0.4 mg/1 ml, manufactured in Poland, administered intraperitoneally at a dose of 1 mg / kg) and a non-selective serotonin receptor blocker (cyproheptadine, manufactured by Sigma, administered intraperitoneally at a dose of 1 mg / kg, 10 minutes before naloxone injection). The "tail twitching" test was used to assess the pain sensitivity of the animals. In all animals, the background value of the latent period (LP) of tail twitching was measured, in relation to which further interpretation of the results was performed. Administration of thymus peptides for 5 days increased the LP of tail twitching, while administration of naloxone 20 minutes before testing reduced it to background values [55-61], thus, administration of thymus peptides leads to an increase in the pain threshold due to activation of the opioid system

Stress-induced analgesia caused by various stressful effects (PCL, Porsolt test, emotional stress caused by a malfunction of the avoidance reaction, acute and chronic immobilization stress) led to an increase in the threshold of pain sensitivity, that is, led to the development of stress-induced analgesia [62; 55; 56; 61]. The administration of naloxone against the background of stress-induced analgesia led to a decrease in tail twitching to baseline values. Thus, the nature of stress-induced analgesia in control animals is determined by the activation of the opioid system alone [56]. An increase in the threshold of pain sensitivity after stress was also observed against the background of thymus peptides, but to a lesser extent than in the control. Thus, the opiate receptor blocker in these animals only partially eliminated the effect of analgesia. The sequential administration of ciproheptadine and naloxone led to a sharp decrease in the pain threshold, which turned out to be lower than the background value, but exceeded the control value [56], that is, this type of stress analgesia, which developed against the background of thymus peptides, has a mixed form of stress-induced analgesia containing opioid and non-opioid (seratonergic) components.

5. Conclusion

It is known that any stressor activates stress and stress-limiting systems, primarily by increasing the activity of the GABA and opioid systems, which leads to a limited stress response. At the same time, an increase in serotonin levels in brain structures is considered as an adaptation option under stress. Shifts in the balance towards serotonin against the background of thymus peptides under stress and activation of the opiate system underlie their stress-protective effect.

Apparently, activation of the stress system simultaneously activates the thymus and increases the level of its polypeptides, which are functional antagonists of the stress system. They increase the body's resistance to stress. The thymus is not only the central organ of the immune system, but also the organ of the stress-limiting system.

Taking these facts into account, the work of the stress-limiting system can be represented as follows. Activation of the stress system leads to stimulation of the thymus through the sympathetic and parasympathetic parts of the autonomic nervous system. This leads to an

increase in the level of thymic peptides, which trigger a cytokine cascade with an increase in the production of various cytokines (IL-1, IL-2, IL-6, IL-8, TNFa, and IFc). In turn, cytokines increase the level of the inhibitory amino acids taurine and glycine, alter the balance of monoamines serotonin/norepinephrine in favor of the former, and activate opioid neurons, which limits the damaging effects of stress reactions.

Thus, under stress, not only the hypothalamic-pituitary-adrenal axis is activated, but also the hypothalamic-pituitary-thymus system, which limits the stress-damaging effect of excessive activity of the hypothalamic-pituitary-adrenal axis.

Application of artificial intelligence: The review is written without the use of artificial intelligence technologies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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