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The experimental study of the immunomodulating action of Semax and Selank on the model of „social" stress

Original Paper

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Abstract This study is devoted to the experimental study of the immunocorrecting action of Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) on the model of "social" stress formed as a result of sensory contact and inter-confrontation. Functional activity of the immune system of laboratory animals was assessed on the basis of standard immunopharmacological tests: delayed-type hypersensitivity reaction (DTH), direct agglutination test (DAT), latex test for studying the phagocytic activity of peripheral blood neutrophils, and evaluation of changes in the leukocyte formula. As a result of the experiment, it was found that, under the influence of "social" stress, changes in the immune response are multidirectional, which confirms the theory of "immune disbalance" under the action of stressors. As a result of studying the influence of Semax and Selank on the model of "social" stress, it was found that the drug proved to be an effective corrector, restoring the cellular and humoral immunogenesis reactions, the phagocytic activity of neutrophils, which indicates the presence of immunomodulating properties, and emphasizes the need for further studies in this scientific direction. This study expands the scientific research base in the field of immunoreaction under stress-induced conditions with the aim of further developing a pharmacological strategy for correcting the revealed disorders by means of substances of a neuropeptide structure.

Keywords *social stress – sensory contact – Semax – Selank – delayed-type hypersensitivity (DTH) reactions – direct agglutination test (DAT) – phagocytic index (PhI) – phagocytic number (PhN)*

INTRODUCTION

Despite a significant number of studies and publications devoted to various aspects of the stress problem, there is still no clearly formulated unified concept of stress as a physiological phenomenon, the mechanisms of its occurrence and formation and the mechanisms underlying the body's resistance to stressful effects of various nature and correction paths. Assessing the level of human stress tolerance is becoming increasingly important and requires detailed study. This is due to the growth of the stress load in modern society due to prolonged social-economic instability, the interests of vocational guidance and many other factors.

Compensatory-adaptive reactions that are formed in the body on the action of the stress factor are primarily aimed at preventing the development of functional disorders on the part of the basic systems of the body in particular the immune system. Immunity, being one of the main regulators of homeostasis, plays one of the leading roles in the processes of adaptation of an organism to stressful influences [Akmaev, 2003; Bulgakova, 2011; Titov, 2008].

From the standpoint of biomedical research the problem of studying "social" stress arouses undoubted interest which is manifested in the active development of models of the formation of "social" stress in the experiment, for example, social isolation, sensory contact, resident intruder, etc.. The study of aspects of various functional systems in particular the immune system in these experimental conditions are related to a new but very relevant at the present time direction – social biology studying her consequences of social conflict.

Currently, researchers pay great attention not only to the study of the influence of factors causing stress-induced states in particular from the immune system but also to ways to eliminate them. At the moment the search for immunomodulators from the group of neuropeptides which are endogenous compounds that play an important role

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in the formation of compensatory-adaptive reactions of the body and regulate important homeostatic functions is promising.

The structural feature of neuropeptides is the presence of several ligand groups of receptor binding which explains their inherent polyfunctionality in the regulation of various molecular biochemical processes. Depending on the place of their release neuropeptides, like all regulatory peptides in principle, can perform a mediator function, regulate the release of hormones, modulate the reactivity of certain groups of neurons, or perform the function of effector molecules (vasomotor, Na + -uretic and other regulatory functions) [Hallberg, 2015; Gabbyasova et al., 2017].

One of the most important mechanisms of action of neuropeptides is their inductive role in the process of cascade release of a number of other peptides in response to changes in the internal environment, which is carried out according to the principle of a peptide regulatory continuum. Moreover, if their joint action is unidirectional, the effect will be cumulative and lasting [Ashmarin & Koroleva, 2002].

Neuropeptides also perform neurotransmitter functions by "cooperating" with non-peptide mediators. Certain combinations of a non-peptide neurotransmitter with one, two, and sometimes three neuropeptides are localized in the same nerve ending. Depending on the frequency and duration of impulses, they are released jointly or separately. Sometimes such neuropeptides are called co-neurotransmitters or co-neurotransmitters [Ashmarin & Obukhova, 1994].

Along with the mediator function within the synapse neuropeptides are capable of transmitting information over longer distances, even within the whole organism. The objects of the distant action of neuropeptides are the pre- and postsynaptic zones of neurons, as well as other cells. At the same time, neuropeptides can facilitate or inhibit an impulse transmission and have other effects on the state of the neuron, that is function as neuromodulators. In addition, many neuropeptides are capable of exhibiting pronounced neurotrophic growth properties [Ashmarin & Obukhova, 1994; Semmens & Elphick, 2017].

Thus, the area of physiological activity of peptides is diverse which explains a wide range of pharmacological properties of neuropeptide drugs manifested in the effect on the state of the cardiovascular, nervous, endocrine, digestive, reproductive and other systems but especially interesting and little studied is the issue of regulation of the immune system which for all its autonomy is under the control of nervous and endocrine influences [Ashmarin & Koroleva, 2002; Hallberg, 2015].

The confirmation of neuropeptide regulation of immunity is the discovery of neuropeptide receptors on lymphocytes and monocytes of peripheral blood as well as on cells of bone marrow origin [Gromov, 1992]. Neuropeptides control the expression of secondary cellular messengers, cytokines and other signalling molecules, as well as the launch of genetic programmes for apoptosis and antiapoptotic defence, involving immunocompetent cells in the process [Gabbyasova et al., 2017]. An important feature is the ability of neuropeptides to regulate the balance of pro- and anti-inflammatory cytokines, which is accompanied by their effect on the generation of nitric oxide and other oxidative processes [Ashmarin & Obukhova, 1994].

Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) are the perspective drugs as correctors of stress-induced disorders. They are from the group of neuropeptide analogues which play an important role in regulation of homeostasis and adaptation to the stress factors. Semax and Selank are popular neuropeptide drugs registered on the territory of the Russian Federation and characterized by nootropic and neurometabolic influences [Dolotov et al., 2015; Skrebitskiy et al., 2016]. Researches on various aspects of drug`s pharmacological action are perspective in order to expand the possibilities of its practical application. Semax has an antihypoxic effect, improves memory and attention, increases resistance to stress damage and also reduces the severity of the clinical manifestations of ischemic stroke. To date, this peptide is the only neurotropic drug, used in clinical practice, based on ACTH fragments. It should be noted that Semax is also being actively investigated as a representative of domestic preparations of the glyproline structure including proline-containing di- and tripeptides (PG, GP, PGP), the group of which also includes Selank. These drugs were created by attaching the PGP tripeptide to the C-termini of unstable regulatory peptides (corticotropin 4-7 and tuftsin), which made it possible to solve the problem of stabilization in vivo and to supplement them with the effects of PGP itself [Ashmarin et al., 1997; Eremin et al. 2005]

Tuftsin (Thr-Lys-Pro-Arg), described in 1970 at the Tufts Institute, has the ability to stimulate phagocytosis exhibiting an immunomodulatory effect and to reduce the number of metastases in the lungs in an experiment on mice, having established itself as an anticarcinogenic peptide. One of the important features of tuftsin is its "targeted" action due to specific receptors expressed on neutrophils, monocytes / macrophages and NK cells. This tetrapeptide is obtained by "excision" of IgG from the Fc-fragment using tuftsin endocarboxypeptidase and aminopeptidase N zinc metalloprotease associated with the membrane of the macrophage. In this "free" state, tuftsin has a stimulating effect on target cells. After the tetrapeptide is combined with its receptor, the complex is internalized by the macrophage [Perel'muter et al., 2004].

The action of tuftsin is not limited to the activation of phagocytosis. A peptide has the ability to induce various changes in the functional activity of a number of cells endowed with receptors for it. Thus, tuftsin stimulates the migration and differentiation of macrophages, optimizes the cellular cooperation of macrophages, T and B lymphocytes and NK cells, and also enhances hematopoiesis in the bone marrow. It should be noted that macrophages, when absorbing tuftsin, as well as its analogues, are able to release IFN-γ and TNF-α -. Thus, the attachment of tuftsin to the receptor leads to the stimulation of the functional activity of macrophages and neutrophils, which results in complete phagocytosis in the foci of inflammation and lymphoid formations [Perel'muter et al., 2004; Volkova et al., 2016].

The Selank molecule can be considered a synthetic analogue of tuftsin, containing a fragment of the immunoglobulin class G chain, extended by the Pro-Gly-Pro tripeptide from the C-terminal part of the molecule. Previous studies and the results of clinical trials have confirmed the presence of psychotropic activity of Selank, which manifests itself as a combination of anxiolytic and stimulating effects . In addition, Selank has antidepressant and antiasthenic effects, has a positive effect on cognitive functions, improves memory and speech, increases attention and activates learning processes, in particular, memorizing, analysing and reproducing information . The uniqueness of the properties of the group of drugs with a glyproline structure lies in their psycho-, neuro- and immunotropic activity [Uchakina et al., 2008].

In his experiments, Kolomin showed that Selank, as well as its fragments, changes the expression of mRNA genes for cytokines, chemokines, their receptors and some other genes involved in inflammation. It was shown that Selank and its fragments have a multidirectional effect on the dynamics of expression of the Bcl6 gene, which is directly involved in the formation and development of the immune system, as well as on the dynamics of expression of target genes and corepressor genes of the Bcl6 protein, which protects the cell from apoptosis, regulating various processes in particular, associated with the maintenance of ionic homeostasis of the cell [Kolomin et al., 2013].

In the study by Sever'yanova et al., when administered systemically at a dose of 150 µg / kg, the predominant effect of Semax is a weakening of the humoral immune response, and at a dose of 5 µg / kg, a decrease in the inflammation index in a delayed-type hypersensitivity reaction is seen; with increasing doses the index of inflammation increases. A dose-dependent effect of Semax on the functional and phagocytic activity of neutrophils has been shown on the model of emotional pain stress [Sever'yanova et al., 2013].

Despite the fact that Semax and Selank have been used in clinical medicine for quite a long time, studies aimed at determining the pharmacological activity of the drugs and their mechanisms of action are actively continuing .

The aim of research**:** the study of the immunomodulating action of Semax and Selank on the model of "social" stress.

METHODS

White nonlinear rats (males, 6-8 months old) were used as experimental animals. The rats were kept in standard conditions throughout the experiment. By the Protocol of the Ethical Committee of Federal State Budget Educational Institution of Higher Education "Astrakhan State Medical University" of the Ministry of Health of Russia No. 8 dated 24 November, 2015 and the Order of the Ministry of Health of the Russian Federation No. 199n dated 4 January,2016 "On Approval of the Laboratory Practice Rules", all the animal manipulations were performed in accordance with the requirements of the Directive of the European Parliament and the Council of the European Union on the protection of the animals used for scientific purposes (2010/63/ EU), and the rules adopted by the International Convention for the Protection of Vertebrate Animals used for experimental and scientific purposes (Strasbourg, 1986).

A model of confrontations between males was chosen to create a "social" stress under the experimental conditions. The animals were in pairs in a cage which were separated by a septum preventing physical contact but having openings that provide sensory contact. Each day, the septum was removed for 10 minutes leading in an overwhelming majority to agonistic collisions (confrontations) [Kudryavtseva, 2015]. Groups of animals with alternative types of behaviour were formed: aggressive type in case of repeated experience of victories (the winner, the aggressor) and submissive in case of defeats (the victim). The manifestation of aggression in experimental animals was expressed in the form of vertical and lateral racks ("threat") or attack. Social passivity manifested itself in various acts of individual behaviour: locomotion, sniffing, grooming, movements on the spot, vertical "protective" stands and stillness.

Animals, according to the results of preliminary inter-male confrontations, are divided into four groups: a group of intact animals that received intraperitoneal water for injection in an equivalent dose (n = 10); a group of animals that were subjected to stress for 20 days (sensory contact) and received intraperitoneal water for injection in an equivalent dose (n = 20, 10 aggressors /10 victims); a group of animals that received intraperitoneally Semax at a dose of 100 mcg / kg /day under conditions of 20-day stress (sensory contact) course of 20 days (n = 20: 10 aggressors /10 victims); and a group of animals that received intraperitoneally Selank at a dose of 100 mcg / kg / day under conditions of 20-day stress (sensory contact) course of 20 days (n = 20:,10 aggressors /10 victims).

Standard immunopharmacological methods were used for studying the functional activity of the immune system of animals: delayed-type of hypersensitivity reaction (DTH) with determination of the reaction index, direct agglutination test (DAT) with determination of antibody titre, latex test for phagocytic activity of peripheral blood neutrophils and evaluation of the leukocyte formula. Corpuscular T-dependent antigen (erythrocytes of ram) was used as an antigenic stimulus in DTH and DAT [Mironov, 2012].

A latex test with using heparinized animal blood was used to determine the phagocytic activity of peripheral blood neutrophils. Formaldehyde latexes were used as a test object. The neutrophil activity was determined according to the following indices: phagocytic index or % phagocytosis

Table 1. The influence of Semax and Selank on the formation of DTH and DAT in conditions of "social" stress.

Experimental groups (n = 10) / Indicators (M ± m)	Index DTH, %	Titre of antibodies in DAT, log2
Animals with an aggressive type of behavior		
Control	30.83 ± 3.52	224.77 ± 23.27
„Social" stress	16.57 ± 1.75**	40.46 ± 5.81***
„Social" stress + Semax (100 mcg /kg/day)	25.20 ± 2.46*	152.60 ± 18.62###
„Social" stress + Selank(100 mcg /kg/day)	30.38 ± 3.48##	210.56 ± 22.54###
Animals with a submissive type of behavior		
Control	30.83 ± 3.52	224.77 ± 23.27
„Social" stress	20.78 ± 2.54*	103.55 ± 11.64***
„Social" stress + Semax (100 mcg /kg/day)	27.40 ± 2.76	148.21 ± 18.81#
„Social" stress + Selank (100 mcg /kg/day)	28.26 ± 2.66#	231.19 ± 34.91##

*Note: * – p < 0.05, ** – p < 0.01, *** – p < 0.001 – comparing with control; # – p < 0.05, ## – p < 0.01, ### – p < 0.001 – comparing with stress (Student's t-test with Bonferroni amendment for multiple comparisons).*

(number of neutrophils with latex of 100) and phagocytic number (number of latex particles /100).

Blood for determination of the content of the white blood cell was taken while removing the animals from the experiment from the large vessels of the cervical region. Counting was carried out in Goryaev's camera. The percentage ratio of individual forms of leukocytes was estimated in blood smears stained according to Romanowsky-Giemsa.

The results of the experiment were statistically processed using programs: Microsoft Office Excel 2007 (Microsoft, USA), BIOSTAT 2008 Professional 5.1.3.1. To process the results obtained, we used the parametric method (determination of Student's t-test). The significance of differences in the experimental groups was assessed at a significance level of $p \leq 0.05$.

RESULTS

The obtained results confirm the formation under stressful conditions of the immune imbalance, which is manifested by the activation of some and the inhibition of other links of immunity.

In the experiments, it was found that prolonged confrontations between males suppressed DTH and DAT in animals with aggressive and submissive behaviours in comparison with control animals. The index of delayed-type of hypersensitivity reaction in aggressors decreased by more than 45% ($p < 0.01$) and in victims by more than 80% ($p < 0.001$). In the humoral link of immunity, the aggressor animals showed significant changes in the indicator: a decrease in the antibody titre by more than 30 % ($p < 0.05$) and victims showed more than 50% ($p < 0.001$) compared with the control indicators (Table 1).

As it can be seen from the results presented in Table 1, Semax and Selank contributed to the restoration of the studied indicators: the index DTH of aggressors was increased by more than 50% ($p < 0.05$) and 80% ($p < 0.01$) , respectively, and for victims, it increased by 30% ($p > 0.05$) and 35% ($p < 0.05$), respectively. As for the formation of anti-erythrocyte antibodies in the DAT, the titre of hemagglutinins was increased in animals with an aggressive type of behaviour by Semax almost four times ($p < 0.001$) and by Selank almost four times ($p < 0.001$), and it increased in animals with submissive behaviour by Semax more than 40% ($p <0.05$) and by Selank more than two times ($p < 0.01$) (Table 1).

It was established that the influence of "social" stress was accompanied by the activation of phagocytic index (PhI) and phagocytic number (PhN) on rats with aggressive and submissive behaviours when studying the indicators of phagocytic activity. The phagocytic index increased by 20% among the aggressors ($p > 0.05$) and 30% in the victims ($p < 0.05$). A phagocytic number by 40% among the aggressors ($p < 0.05$) and 20% in the victims ($p > 0.05$), indicates the hyperactivity of the nonspecific link of the immune system (Table.2).

It was found that the administration of Semax and Selank in conditions of "social" stress restored indicators of PhI and PhN. The phagocytic number was decreased by an average of 20% ($p > 0.05$) in aggressors and more than 50% and 20% in victims ($p < 0.05$ and $p < 0.01$ respectively, Semax and Selank), The phagocytic index decreased almost by an average of 20% in aggressors ($p < 0.05$ and $p > 0.05$ respectively Semax and Selank) and in victims by 30% and 20% ($p < 0.05$ and $p > 0.05$, respectively, Semax and Selank) (Tabl.e 2).

The studying of the influence of "social" stress on the total number of leukocytes and the indicators of leukocyte formula was one of the stages of our work. In the group of stressed rats, the total number of leukocytes decreased by

Table 2. Influence of Semax and Selank on the phagocytic activity of neutrophils in conditions of "social" stress.

Experimental groups (n = 10) / Indicators (M ± m)	Phagocytic index	Phagocytic number, %
Animals with an aggressive type of behaviour		
Control	17.7 ± 1.68	53.3 ± 3.66
„Social" stress	21.0 ± 1.85	74.3 ± 7.37*
„Social" stress + Semax (100 mcg /kg/day)	16.8 ± 1.23	53.2 ± 4.63#
„Social" stress + Selank (100 mcg /kg/day)	16.3 ± 1.87	57.6 ± 4.23
Animals with a submissive type of behaviour		
Control	17.7 ± 1.68	53.3 ± 3.66
„Social" stress	22.9 ± 1.61*	63.7 ± 4.73
„Social" stress + Semax (100 mcg /kg/day)	10.8 ± 1.30###	44.6 ± 4.53#
„Social" stress + Selank (100 mcg /kg/day)	18.4 ± 1.58	50.5 ± 4.65

*Note: * – p < 0.05, ** – p < 0.01,*** – p < 0.001 – comparing with control; # – p < 0.05, ## – p < 0.01, ### – p < 0.001 – comparing with stress (Student's t-test with Bonferroni amendment for multiple comparisons).*

the average of 30% (p < 0.05) in animals with aggressive and submissive types of behaviour in comparison with the control group. There was a decrease in the percentage of eosinophils in stressed animals by 30% (p < 0.05) in the aggressors and more than 40% (p < 0.01) in the victims,. Also, there was a statistically significant increase in segmented neutrophils more than two times (p<0.001) both among the aggressors and the victims and band neutrophils more than 50% (p < 0.01) and almost 90% (p<0.001) in animals with aggressive and submissive types of behavior, respectively (Tabl.e 3).

It was found that in conditions of stress Semax and Selank contributed to the recovery of the total number of leukocytes by 50% (p<0.01) and 90% (p<0.001), respectively, for the aggressors; and by more than 30% (p < 0.05) and 50% (p < 0.001) ,respectively, for the victims, as well as an increase in eosinophils by almost 40% (p < 0.05), both for the aggressors and for the victims under conditions of administration of Semax. In the group of animals which received Selank an increase in eosinophils was by 20% (p > 0.05) in aggressors and 30% (p < 0.05) in victims.

In addition, the administration of Semax decreased band neutrophils by more than 30% (p<0.05) in animals with an aggressive type of behaviour and by 50% (p < 0.001) in animals with a submissive type of behaviour. The administration of Selank decreased band neutrophils by almost 40% (p < 0.05) in the group of aggressors and more than 50% (p<0.01) in the group of victims. The number of segmented neutrophils significantly decreased by almost 50% (p < 0.001) in the aggressors and by 40% (p < 0.01) in the victims under conditions of administration of Semax and ann average of 40% (p < 0.01) in the aggressors and victims under conditions of administration of Selank (Tabl.e 3).

DISCUSSION

A lot of researches have shown that the type and duration of stress-related effects determine the directional nature of changes in immunity, from deep immunosuppression to pronounced immunostimulation, exerting immunoprotective, immunoregulatory or immunopathological effects on the body. Immune imbalance, manifested by the activation of some components of immunity and inhibition of others, can develop at any stage of the stress response (Fedorova et al., 2010), contributing to a decrease in the adaptive capacity of the organism and the development of, for example, secondary immunodeficiency states, autoimmune and allergic processes (Khnychenko & Sapronov, 2003).

Recently,, there has been a significant increase in interest in research aimed at finding remedies for the development of immune responses, morphofunctional changes in immunocompetent cells and organs against the background of various stress factors (Deak et al., 2015). An important achievement of molecular biology and medicine has become the possibility of synthesis of bioregulators, which makes it quite possible to create new highly effective drugs, in particular peptide nature (Ashmarin & Koroleva, 2002; Khavinson et al., 2002). Drugs of the peptide structure (Cerebrolysin, Cortexin and Imunofan) are already widely used in clinical practice (Belokrylov & Malchanova, 1992; Garmanchuk et al., 2009; Formichi et al., 2012; Yugan et al., 2015).

As a result of our experiment, it was found that under the influence of "social" stress changes in immunoreactivity have a multidirectional character, which indicates the formation of an immune imbalance, manifested by the activation of some and the suppression of other immunity units. Thus, the stressing of animals with aggressive and submissive

Table 3. Influence of Semax and Selank on the leukocyte counts of animals in conditions of "social" stress.

Indicators (M ± m) \ Experimental group (n = 10)	Control	„Social" stress	„Social" stress + Semax (100 mcg/kg/day)	„Social" stress + Selank (100 mcg/kg/day)
Animals with an aggressive type of behaviour				
Total number of leukocytes, ×10⁹/l	11.7 ± 0.93	8.3 ± 0.82*	12.5 ± 1.04##	15.7 ± 1.24###
Eosinophils, %	2.8 ± 0.33	2.0 ± 0.21*	2.8 ± 0.24#	2.4 ± 0.20
Band neutrophils, %	2.2 ± 0.23	3.4 ± 0.25**	2.3 ± 0.30#	2.1 ± 0.36#
Segmented neutrophils, %	12.7 ± 1.59	26.7 ± 1.81***	13.3 ± 2.0###	16.0 ± 2.10##
Lymphocytes,%	81.5 ± 5.95	67.1 ± 4.27	80.8 ± 4.9	78.7 ± 4.87
Monocytes, %	0.83 ± 0.15	0.71 ± 0.10	0.81 ± 0.10	0.86 ± 0.11
Animals with a submissive type of behaviour				
Total number of leukocytes, ×10⁹/l	11.7 ± 0.93	8.4 ± 0.77*	11.6 ± 1.01#	13.1 ± 0.58###
Eosinophils, %	2.8 ± 0.33	1.6 ± 0.11##	2.3 ± 0.31#	2.1 ± 0.22#
Band neutrophils, %	2.2 ± 0.23	4.1 ± 0.40**	2.0 ± 0.24###	2.1 ± 0.37##
Segmented neutrophils, %	12.7 ± 1.59	27.1 ± 2.11***	16.4 ± 2.1##	16.1 ± 2.57##
Lymphocytes,%	81.5 ± 5.95	66.4 ± 4.77	78.5 ± 4.4	78.9 ± 4.87
Monocytes, %	0.83 ± 0.15	0.71 ± 0.10	0.82 ± 0.14	0.86 ± 0.11

*Note: * – p < 0.05, ** – p < 0.01,*** – p < 0.001 – comparing with control; # – p < 0.05, ## – p < 0.01, ### – p < 0.001 – comparing with stress (Student's t-test with Bonferroni amendment for multiple comparisons).*

behaviours was accompanied by suppression of the cellular and humoral immunity units, an increase in phagocytic index and a phagocytic number relative to the parameters of intact animals. There was a decrease in the indicators of total number of leukocytes under conditions of "social" stress, and it indicates immunosuppression.

CONCLUSIONS

As a result of studying the influence of Semax and Selank under the conditions of "social" stress, it was established that the applied drugs in experimental groups proved to be the effective immunocorrectors, restoring cellular and humoral immunogenesis reactions, indicators of phagocytic activity, which indicates the presence of immunomodulating properties and emphasizes the need for further in-depth studies in this scientific direction and also shows the practical importance of research on the search for pharmacological correction tools in the development of which an essential role is played by the stress reaction.

This study actualizes the search for new immunomodulators among neuropeptide substances of nature. The fundamental approach of this work emphasizes the importance of scientific research in the field of immunoreaction under stress-induced conditions in particular "social" stress with the aim of further developing a pharmacological strategy of correction by means of neuropeptide substances characterized by a wide spectrum of action, as well as a high degree of safety due to their complete proteolytic degradation.

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