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GLYPROLINES AS MODULATORS OF IMMUNOREACTIVITY WITHIN CONDITIONS OF "SOCIAL" STRESS

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The most important direction in the development of modern medical science is the study of protective, compensatory and pathological reactions of the organism that occur in response to various stress factors. The aim of the study is the subsequent development of methods for pharmacological correction of these reactions. The remedies for the correction of stress-induced immunity disorders are represented by the glyprolin group – the Selank drug and the Pro-Gly-Pro peptide compound – and are of particular interest.

The aim of the experiment was to study the immunomodulating effect of glyprolines on the basis of the "social stress" model.

Materials and methods. The experiment was performed on non-linear male rats aged 6-8 months. A model of a sensor contact was used as a model of the experimental "social stress". The animals were divided into groups (n = 10): a "control" group was represented by individuals with aggressive and submissive types of behavior, formed within the conditions of the experimental "social stress" for 20 days; and 2 experimental groups in which the animals were intraperitoneally administered Selank (100 μg/kg) and Pro-Gly-Pro (100 μg/kg) against the background of the experimental "social" stress once a day for 20 days. A functional activity of the immune system was studied on the basis of standard immunopharmacological tests: a delayed-type hypersensitivity test (DTH test), a direct agglutination test (DAT), a latex test for studying the Neutrophil phagocytic rate of peripheral blood, and the essessment of the leucogram.

Results. It has been established, that within the conditions of the "social" stress, the changes in the immune response are multidirectional. That fact confirms the theory of "the immune disbalance" caused by the action of stressors. As a result of studying the effect of glyprolines within the conditions of "the social stress", Selank and Pro-Gly-Pro proved to be effective immunocorrectors, restoring cellular and humoral immunogenesis reactions as well as the phagocytic activity of neutrophils and leucogram indices.

Conclusion. The carried out study expands understanding of the immunoreaction pathogenesis within the stress-induced conditions in order to further develop a pharmacological strategy for correcting the revealed disorders through the substances of the neuropeptide structure.

Keywords: glyprolines, Selank, Pro-Gly-Pro, social stress; delayed-type hypersensitivity (DTH) test; direct agglutination test (DAT); phagocytic index (PhI); phagocytic number (PhN), leucogram

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ГЛИПРОЛИНЫ КАК МОДУЛЯТОРЫ ИММУНОРЕАКТИВНОСТИ В УСЛОВИЯХ «СОЦИАЛЬНОГО» СТРЕССА

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Важнейшим направлением развития современной медицинской науки является изучение защитных, компенсаторных и патологических реакций организма, возникающих в ответ на действие различных стрессогенных факторов с целью последующей разработки способов фармакологической коррекции. В качестве перспективных средств коррекции стресс-индуцированных нарушений иммунитета интерес представляют представители группы глипролинов: лекарственный препарат Селанк и пептидное соединение Pro-Gly-Pro.

Цель исследования – изучение иммуномодулирующего действия глипролинов на модели «социального» стресса.

Материалы и методы. Эксперимент выполнен на нелинейных крысах-самцах (6–8 мес.). В качестве экспериментального «социального» стресса использовали модель сенсорного контакта. Животные были разделены на группы (n=10): группа «контроль»; группа животных с агрессивным и субмиссивным типами поведения, сформированные в условиях экспериментального «социального» стресса в течение 20 дней и 2 опытные группы – животные, которым на фоне «социального» стресса внутрибрюшинно вводили Селанк (100 мкг/кг) и Pro-Gly-Pro (100 мкг/кг) 1 раз в сутки в условиях стрессорного воздействия в течение 20 дней. Функциональную активность иммунной системы изучали с помощью стандартных иммунофармакологических методов: реакции гиперчувствительности замедленного типа (РГЗТ), реакции прямой гемагглютинации (РПГА), латексного теста по изучению фагоцитарной активности нейтрофилов периферической крови и оценки лейкоцитарной формулы.

Результаты. Установлено, что в условиях «социального» стресса изменения иммунного реагирования имеют разнонаправленный характер, что подтверждает теорию «иммунного дисбаланса» при действии стрессирующих факторов. В результате изучения влияния глипролинов в условиях «социального» стресса было установлено, что Селанк и Pro-Gly-Pro проявили себя как эффективные иммунокорректоры, восстанавливая клеточную и гуморальную реакции иммуногенеза, а также фагоцитарную активность нейтрофилов и показатели лейкоцитарной формулы.

Заключение. Данное исследование расширяет представление об общих закономерностях иммунореагирования в условиях стресс-индуцированных состояний с целью последующей разработки фармакологической стратегии коррекции выявленных нарушений посредством веществ нейропептидной структуры.

Ключевые слова: глипролины, Селанк, Pro-Gly-Pro, «социальный» стресс, реакция гиперчувствительности замедленного типа (РГЗТ), реакция прямой гемагглютинации (РПГА), фагоцитарный индекс (ФИ), фагоцитарное число (ФЧ), лейкоцитарная формула

Список сокращений: РГЗТ – реакция гиперчувствительности замедленного типа, РПГА – реакция прямой гемагглютинации, ФИ – фагоцитарный индекс, ФЧ – фагоцитарное число

INTRODUCTION

The studies devoted to the the mechanisms of the dysfunctional changes in the immune system within the conditions of the “social” stress, as well as the development of methods for their correction, are the main directions of development in modern immunology and pharmacology. The action of stressors, regardless of their nature, leads to the “strain” of homeostasis of the organism on the whole and the immune system, in particular. That was confirmed by a lot of works on the study of Hans Selye’s general adaptation syndrome, which consider the involution processes of the thymic lymphatic apparatus as an obligatory part of the stress triad. Stress-induced immune disorders can develop at any stage of the stress response, being the cause of decline in adaptive skills of the body and the development of, for example, secondary immunodeficiency states, autoimmune and allergic processes [1–3].

The interest in research aimed at finding means for correcting changes in the immune response, morphofunctional disorders in the immunocompetent cells and organs against the background of the influence of vari-

ous stress factors, has recently increased significantly [4, 5]. The greatest achievement of molecular biology and medicine was the possibility of synthesizing bioregulators, in particular the ones of peptide nature, and the creation of new highly effective drugs on their basis. These drugs exhibit, among others, stress protective properties [6–8].

As a result of the research in recent years, a new class of regulatory peptides – glyprolines – has been isolated; most of them are promising as therapeutic agents [9]. It should be noted that at the moment, a representative of this group, Selank, synthesized at the Institute of Molecular Genetics of the Russian Academy of Sciences, is in active use in clinical medicine. This drug was created by attaching Pro-Gly-Pro tripeptide to the C-termini of the unstable regulatory peptide Taftsin which solved the problem of *in vivo* stabilization and supplemented it with the effects of Pro-Gly-Pro itself [10]. As well as the already registered drug Selank, Pro-Gly-Pro tripeptide itself is of considerable interest from the standpoint of long-term benefits of practical implementation in clinical pharmacology. This peptide is a structural fragment of Selank, and, in addition, it has a physiological activity of its own [9, 11]. The analysis of the experimental data confirms the uniqueness of the properties of the preparations with the glyproline structure which consists in the combination of psycho-, neuro- and immunotropic kinds of activity [9, 12, 13], and makes it promising to study various aspects of the pharmacological action of glyprolines in order to expand the possibilities of their practical application.

The aim of the research is to study immunomodulatory effects of glyprolines on the "social" stress model.

MATERIAL AND METHODS

Laboratory experiments

The study was performed on 70 non-linear male white rats, aged 6–8 months, obtained from the vivarium of the laboratory of physiology, morphology, genetics and biomedicine of Astrakhan State Medical University (Russia, Astrakhan). Throughout the experiment, the rats were kept in standard vivarium conditions of Astrakhan State Medical University. By the Order of the Ministry of Health of the Russian Federation No. 199n dated 04 January, 2016 "On Approval of the Laboratory Practice Rules" and 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, 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).

Experimental model

The "social" stress was chosen as an experimental model. The main methodological technique of this experimental model is a permanent residence of partners against the conditions of sensor contacts, which form aggressive and submissive kinds of behavior in animals [14–17]. This model is widely used in studying various aspects of the influence of chronic aggression on brain neurochemistry, physiological functions, behavior and catastasis of animals. Therefore, and it is highly productive in terms of obtaining new and original data and their interpretation. These factors suggest similarity between the animals' state and the one observed in humans.

The males were placed in pairs in experimental cells, separated by a septum preventing them from a physical contact, but it had holes providing their sensor contacts. Every day, the septum was removed for 10 minutes. It overwhelmingly led to agonistic collisions (confrontations) [14].

The groups of the animals with alternative types of behavior were formed: an aggressive type (in case of repeated victories experience – a winner / an aggressor) and a submissive type (in case of defeats – a victim). In the experimental animals, the manifestation of aggression was expressed in the forms of upright and sideways offensive postures – "threat" or attack. The social passivity was manifested by various acts of individual behavior: locomotion, sniffing, autogrumming, movements in place, upright defensive postures and immobility.

Experimental groups

The laboratory animals with aggressive and submissive kinds of behavior were divided into groups of 10 individuals:

- group of intact males;
- group of the animals that were exposed to stress for 20 days (sensor contacts);
- group of the individuals which were treated with Selank intraperitoneally at the dose of 100 mcg/kg a day from the 1st day of exposure to stress (sensor contacts) for 20 days;
- group of the rats which were treated with Pro-Gly-Pro intraperitoneally at the dose of 100 mcg/kg a day from the 1st day of exposure to stress (sensor contacts) for 20 days.

Methods

The study of the functional activity of the immune system of the animals was carried out according to the "Guidelines for preclinical studies of drugs" on the basis of standard immunopharmacological methods [18]: a delayed-type hypersensitivity test (DTH), a direct agglutination test (DAT), a latex test for studying the phagocytic activity of peripheral blood neutrophils. In addition, the total number of leukocytes in the blood and leucogram were determined. It is important to note that in the formation of a specific immune response in the laboratory animals within the conditions of the experiment, a corpuscular T-depen-

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dent antigen (sheep erythrocytes) was used as an antigenic stimulus in the formulation of DTH and DAT.

To determine the phagocytic activity of peripheral blood neutrophils, a latex test on the basis of heparinized blood of the animals was used. Melanomaldehyde latexes were used as a test object. The activity of neutrophils was determined by the following indices: a phagocytic index or percentage of phagocytosis (the number of neutrophils with latex/100); a phagocytic number (the number of latex particles / 100).

To determine the content of the blood leukocyte count of the test animals, the blood was taken during the removal of the animals from the experiment from large vessels of the cervical area. The calculation was carried out in Gorjaev's chamber. The percentage of individual forms of leukocytes was evaluated in blood smears stained by Romanovsky-Giemsa staining.

Statistical processing of results

The results of the experiment were statistically processed using the following programs: Microsoft Office Excel 2007 (Microsoft, USA), BIOSTAT 2008 Professional 5.1.3.1. To process the obtained results, a parametric method with the Student t-test (with Bonferroni correction) was used. Statistically significant differences were considered at $p<0.05$.

RESULTS

In the course of the experiments, it was established that long-term inter-male confrontations caused the suppression of DTH and DAT in the animals with both aggressive and submissive types of behavior compared to the control animals. The index of the delayed-type hypersensitivity test in the aggressors decreased by more than 45% ($p<0.01$), in the victims – by more than 30% ($p<0.05$). In relation to the humoral immunity in the animal aggressors, more pronounced changes in the indices were observed: a decrease in antibody titer in the aggressors – by more than 80% ($p<0.001$), in the victims – by more than 50% ($p<0.001$) compared with the control indices (Table 1).

Table 1 – Effect of glyprolines on the formation of DTH and DAT within the conditions of the "social" stress

Experimental groups (n = 10) / Indices (M ± m)	Index DTH, %	Titer of antibodies in DAT, log
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" + Selank (100 mcg/kg a day)	30.38 ± 3.48##	210.56 ± 22.54###
"Social stress"+ Pro-Gly-Pro (100 mcg/kg a day)	29.40 ± 3.63##	253.21 ± 23.27###
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+ Selank (100 mcg /kg a day)	28.26 ± 2.66#	231.19 ± 34.91##
"Social" stress+ Pro-Gly-Pro (100 mcg/kg a day)	28.57 ± 2.55#	138.71 ± 12.84#

*Note: * – p<0.05; ** – p<0.01;*** – p<0.001 – relative to the control group; # – p<0.05; ## – p<0.01; ### – p<0.001 – relative to the "stress" group (Student's t-test with Bonferroni correction for multiple comparisons)*

As the results presented in Table 1 show, glyprolines contributed to the restoration of the indices of both immunity units. The index of DTH in aggressors increased in terms of the administration of Selank and Pro-Gly-Pro by an average of 80% ($p<0.01$), in victims – by an average of 30% ($p<0.05$). As for the formation of anti-erythrocyte antibodies in DAT, the indices of the hemagglutinin titer also remained higher than those of the animals of the "stress" group with an aggressive type of behavior by an average of more than 5 times ($p<0.001$). In the animals with a submissive type of behavior, when Selank was administered, the index was 2.2 times higher than that in the "stress" group and 1.3 times higher in the group after the administration of Pro-Gly-Pro ($p<0.05$, $p<0.01$) (Table 1).

When studying the phagocytic activity indices of peripheral blood neutrophils in the animals exposed to the "social" stress, an increase in the phagocytic index (PhI) and a phagocytic number (PhN) was found in the rats with both aggressive and submissive types of behavior. There was an increase in the phagocytic index by 18% in aggressors ($p>0.05$) and by almost 30% in victims ($p<0.05$), a phagocytic number was increased by 40% in aggressors and by 20% in victims ($p>0.05$). These factors indicate a hyperreactivity of a nonspecific element of the immune system (Table 2).

Table 2 – Effect of glyprolines on the phagocytic activity of neutrophils within the conditions of the "social" stress

Experimental groups (n = 10) / Indices (M ± m)	Phagocytic index	Phagocytic number, %
Animals with an aggressive type of behavior		
Control	17.7 ± 1.68	53.3 ± 3.66
"Social" stress,	21.0 ± 1.85	74.3 ± 7.37*
"Social" stress + Selank (100 mcg /kg a day)	16.3 ± 1.87	57.6 ± 4.23
"Social" stress + Pro-Gly-Pro (100 mcg/kg/a day)	15.9 ± 1.74#	58.7 ± 3.23
Animals with a submissive type of behavior		
Control	17.7 ± 1.68	53.3 ± 3.66
"Social" stress	22.9 ± 1.61*	63.7 ± 4.73
"Social" stress + Selank (100 mcg/kg a day)	18.4 ± 1.58	50.5 ± 4.65
"Social" stress+ Pro-Gly-Pro (100 mcg/kg a day)	20.2 ± 1.83	54.0 ± 3.72

*Note: * – p<0.05; ** – p<0.01;*** – p<0.001 – relative to the control group; # – p<0.05; ## – p<0.01; ### – p<0.001 – relative to the "stress" group (Student's t-test with Bonferroni correction for multiple comparisons)*

When assessing the phagocytosis indices in the group of the animals treated with glyprolines (Selank, Pro-Gly-Pro) against the background of the impact of the "social" stress, it has been found out that the administration of these compounds leads to the restoration of the parameters of nonspecific immunoreactivity. A decrease of phagocytic number was noted among the aggressors and victims by an average of 20% (p>0.05) compared with the stressed animals. The assessment of the phagocytic index in the aggressors showed its slight decrease; and in the victims, it remained at the level of the intact animals. At the same time, it should be mentioned that the most pronounced changes in the studied parameters were notified within the conditions of the administration of Pro-Gly-Pro tripeptide to the aggressors, and less pronounced ones were notified in the victims (Table 2).

An important stage of the work was to determine the total number of leukocytes, as well as to study the indices of the leucogram. Within the conditions of the "social" stress, a decrease in the total number of leukocytes (p<0.05) was observed in both, the aggressors (–29.1%) and the victims (–28.2%) relative to the control group indices. The stressed animals' leucogram showed a decrease in the percentage of eosinophils by 28.6% (p<0.05) in the aggressors and by more than 40% (p<0.01) in the victims. A statistically significant increase in segmented neutrophils by an average of 2 times (p<0.001), in band staple ones – by more than 50% (p<0.01) in the aggressors and by almost 2 times in the victims (p<0.01) should be also notified (Table 3).

It was established that in the "stress" group animals treated with glyprolins, the total number of leukocytes was higher relative to the control values. The administration of these drugs to the stressed animals contributed to an increase in the total number of leukocytes relative to the "stress" group: after the administration of Selank and Pro-Gly-Pro, in the aggressors' group the number of leukocytes was almost twice as high (p<0.001 and p<0.01 respectively); in the group treated with Selank it was more than 1.5 times as high as in the victims (p<0.01); and after the administration of Pro-Gly-Pro, only slight changes were noted (p>0.05).

Under the influence of Selank, the number of eosinophils in the aggressors decreased less than in the animals without any pharmacological support. The administration of Pro-Gly-Pro to the stressed animals contributed to the conservation and was higher relative to the stressed group by 30% (p<0.05). In the leucogram of the rats with a submissive type of behavior, the percentage of eosinophils increased by an average of 31% (p<0.05). In addition, in the individuals with an aggressive type of behavior, the administration of Selank against the background of stress led to the maintenance of the content of band neutrophils relative to the intact animals, and that was by 12% lower (p<0.05) relative to the stressed animals. Within the conditions of Selank and Pro-Gly-Pro administration, in the animals with a submissive type of behavior the number of band neutrophils was lower than the values of the stressed group by an average of 50% (p<0.01 and p<0.01, respectively). The percentage of the segmented forms of neutrophils decreased in all the groups by more than 40% relative to the stressed animals (Table 3).

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Table 3 – The effect of glyprolines on the leucogram of the animals under the "social" stress

Experimental groups (n = 10) / Indices (M ± m)	Total number of leukocytes, x10^9/l	Eosinophils, %	Band neutrophils, %	Segmented neutrophils, %	Lymphocytes, %	Monocytes, %
Animals with an aggressive type of behavior						
Control	11.7 ± 0.93	2.8 ± 0.33	2.2 ± 0.23	12.7 ± 1.59	81.5 ± 5.95	0.83 ± 0.15
"Social" stress	8.3 ± 0.82*	2.0 ± 0.21*	3.4 ± 0.25**	26.7 ± 1.81***	67.1 ± 4.27	0.71 ± 0.10
"Social" stress+ Selank (100 mcg/kg a day)	15.7 ± 1.24###	2.4 ± 0.20	2.1 ± 0.36#	16.0 ± 2.10##	78.7 ± 4.87	0.86 ± 0.11
"Social" stress+ Pro-Gly-Pro (100 mcg/kg a day)	15.9 ± 1.54##	2.6 ± 0.21#	3.0 ± 0.60	16.1 ± 1.52##	77.0 ± 3.81	0.86 ± 0.11
Animals with a submissive type of behavior						
Control	11.7 ± 0.93	2.8 ± 0.33	2.2 ± 0.23	12.7 ± 1.59	81.5 ± 5.95	0.83 ± 0.15
"Social" stress	8.4 ± 0.77*	1.6 ± 0.11**	4.1 ± 0.40**	27.1 ± 2.11***	66.4 ± 4.77	0.71 ± 0.10
"Social" stress+ Selank (100 mcg/kg a day)	13.1 ± 0.58###	2.1 ± 0.22#	2.1 ± 0.37##	16.1 ± 2.57##	78.9 ± 4.87	0.86 ± 0.11
"Social" stress+ Pro-Gly-Pro (100 mcg /kg a day)	9.7 ± 0.69	2.1 ± 0.22#	2.0 ± 0.30##	15.0 ± 1.51###	79.9 ± 5.01	1.0 ± 0.10#

*Note: * – p<0.05; ** – p<0.01;*** – p<0.001 – relative to the control group; # – p<0.05; ## – p<0.01; ### – p<0.001 – relative to the "stress" group (Student's t-test with Bonferroni correction for multiple comparisons)*

DISCUSSION

The experiment has resulted in the following. It has been proved that under the influence of "the social stress", the changes in immunoreactivity are multidirectional, which indicates the formation of an immune imbalance, manifested by activation of some and suppression of other elements of the immune system. Thus, against the background of an increase in the phagocytic index and phagocytic number, stressing of animals with aggressive and submissive types of behavior was accompanied by the suppression of cellular and humoral immunity indices. In addition, some characteristic manifestations of stress-reactions on behalf of blood have been revealed: a decrease in the total number of leukocytes and eosinophils, as well as an increase in neutrophils.

As a result of studying the activity of glyprolines against the conditions of the "social" stress, it has been found out that the compounds used in the experimental groups proved to be effective immunocorrector, preserving immunogenesis (cellular and humoral) reactions and indices of phagocytic activity, as well as providing a protective effect on leukocyte blood lineage. The data obtained, indicate the presence of immunomodulatory properties in the studied compounds. It is important to note that the effect of glyprolins on the immune system used to be observed before [19–21], but in this aspect the effect of peptides is studied for the first time.

CONCLUSION

Thus, this study actualizes the search for new immunocorrectors among the representatives of a new class of regulatory peptides – glyprolins, most of which are promising as therapeutic agents.

The fundamental approach used in this work, emphasizes the importance of scientific research in the field of immunoreactivity against stress-induced conditions, in particular, the "social" stress. The aim of further studies is developing a pharmacological correction strategy using Selank and its fragments as representatives of glyprolines, characterized by a wide spectrum of action, as well as a high degree of safety.

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AUTHOR CONTRIBUTIONS

All authors had equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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