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INFLUENCE OF SELANK, PRO-GLY-PRO AND PRO-GLY-PRO-LEU ON THE INTENSITY OF REDOX REACTIONS IN IMMUNOCOMPETENT ORGANS UNDER CONDITIONS OF "SOCIAL" STRESS

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ABSTRACT — The experiment investigated the effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on the intensity of redox reactions in immunocompetent organs (thymus and spleen) on the model of "social" stress. The intensity of redox processes was assessed by determining the intensity of lipid peroxidation (LPO) in immunocompetent organs (thymus and spleen) and catalase activity. "Social" stress, formed in the experiment, is accompanied by an increase in the peroxidation processes in immunocompetent organs, which contributes to the development of stress-induced functional disorders of the immune system. Under the influence of "social" stress, the activity of the investigated antioxidant enzyme in the thymus and spleen increased in comparison with the corresponding indicators in intact rats. Against the background of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu administration under "social" stress, its pronounced corrective effect on lipid peroxidation rates is observed, as evidenced by a decrease in spleen and thymus tissue homogenates of male rats in the baseline level of TBA-reactive products, speed of spontaneous and ascorbate-dependent lipid peroxidation, and catalase activity.

INTRODUCTION

In the age of scientific and technological progress in modern society, the relevance of stress is caused by the continuous growth of social, economic, technological, environmental and other changes in our lives. In recent years, special attention of scientists has been given to the study of social stress, which is characterized as a mass adaptation syndrome, which reflects the degree of physiological and psychosocial stress, psychophysiological and socio-psychological adaptation and maladaptation in extreme situations [1]. One of the non-specific reactions to stressful effects of various nature is the development of oxidative imbalance, leading to a change in the functional activity of various systems at the cellular, tissue and organ levels [2, 3, 4]. Long stress loads lead to the accumulation of products of lipid peroxidation processes, which serves as a signal for mobilization of the neurohumoral and immune regulation system and as a result activation of the antioxidant defense of the body [5]. Considering the above, the question arises sharply about the search for means of correction of the data of the violated protective functions of the body as a result of stressful exposure. From the standpoint of modern medical science, the most promising in this direction are neuropeptides [6, 7, 8], which include the registered drug Selank, as well as new synthetic compounds Pro-Gly-Pro and Pro-Gly-Pro-Leu.

The aim of research

study the effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on the intensity of redox reactions in the thymus and spleen under the conditions of "social" stress.

MATERIAL AND METHODS

White non-linear rats (males, 6–8 months old) were used as experimental animals. In order to create a "social" stress in the experiment a model of intermale confrontations was chosen. Animals were placed in pairs in experimental cells separated by a septum which prevents physical contact but has openings that provide sensory contact. Every day the partition was removed for 10 minutes which overwhelmingly led to agonistic collisions (confrontations) [9]. Groups of animals with alternative types of behavior were formed: aggressive type — in case of repeated victories experience (winner, aggressor) and submissive type - in case of defeats (victim). Laboratory animals were divided into 5 groups (n = 10): a group of intact males; a group of animals that were exposed to stress for 20 days (sensory contact); a group of individuals treated intraperitoneally with Selank at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days;a group of individuals treated intraperitoneally with Pro-Gly-Pro at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days;a group of

individuals treated intraperitoneally with Pro-Gly-Pro-Leu at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days. The intensity of redox processes was assessed by determining the intensity of lipid peroxidation in immunocompetent organs (thymus and spleen) and catalase activity [10].

The experiment results 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 was used with the Student t-test with the Bonferroni correction. Statistically significant differences were considered at $p<0.05$.

RESULTS AND DISCUSSION

Under conditions of "social" stress, an increase in the initial, spontaneous, as well as ascorbate-dependent levels of lipid peroxidation in the spleen was observed. The initial level of TBA-reactive products increased among aggressors by 57% ($p<0.01$), among victims — by 38% ($p<0.05$). The level of spontaneous lipid peroxidation in rats with an aggressive type of behavior was statistically significantly increased by 35%, in individuals with a submissive - by 31% compared with the control group of animals ($p<0.05$). "Social" stress led to an increase in the rate of ascorbate-dependent lipid peroxidation by almost 60% ($p<0.001$) in aggressors and 49% ($p<0.01$) in victims. In addition, the level of catalase activity in spleen tissue in animals with aggressive behavior increased by 63% ($p<0.01$), and in rats with submissive - by 28% ($p<0.05$) (Table 1).

With the introduction of Selank, the initial level of TBA-reactive products in the spleen decreased by 26% ($p<0.05$) in individuals with aggressive behavior and in animals with submissive — by 25% ($p> 0.05$) relative to the stress group. This drug statistically significantly adjusted the indicators of both spontaneous lipid peroxidation in aggressors by 27% ($p<0.05$) and in victims by 36% ($p<0.05$), and ascorbate-dependent lipid peroxidation in 48% ($p<0.001$) in aggressors and 34% ($p<0.05$) in victims compared with stressed animals. In addition, the catalase level in the spleen decreased statistically significantly under the influence of Selank in stressed rats with aggressive behavior by 31% ($p<0.05$) and in individuals with submissive - by 29% ($p<0.05$). The effects of the neuropeptides Pro-Gly-Pro and Pro-Gly-Pro-Leu under experimental stress conditions showed the following results. So, with the introduction of Pro-Gly-Pro, the level of TBA-reactive products in the spleen decreased in aggressor rats by 22% ($p> 0.05$) and in animal victims by 36% ($p<0.05$), and spontaneous Sex of aggressors by 36% ($p<0.01$) and 42% ($p<0.01$) in victims and ascorbate-dependent sex on average by 28% ($p<0.05$) in rats with aggressive and submissive behaviors in relation to to stressed animals. The level of catalase in the tissue of the spleen against the background of "social" stress under the influence of Pro-Gly-Pro decreased in the aggressors by 44% ($p<0.01$) and 36% ($p<0.01$) in the victims. The use of Pro-Gly-Pro-Leu under stress conditions showed a decrease in the initial level of TBA-reactive products in the spleen of stressed individuals with aggressive behavior by 27% ($p<0.05$) and in animals with submissive — by 31% ($p<0 , 05$) relative to the stress group. The level of spontaneous LP under the influence of Pro-Gly-Pro-Leu decreased by 40% ($p<0.01$) in aggressors and by 47% ($p<0.001$) in victims; as well as the level of ascorbate-dependent LPO among aggressors — by 37% ($p<0.01$) and among victims — by 19% ($p> 0.05$). Catalase activity in the spleen homogenate under stress Pro-Gly-Pro-Leu decreased in aggressor rats by 35% ($p<0.05$) and in individuals of victims — by 38% ($p<0.01$) compared with the stress group ". In the thymus homogenate against the background of "social" stress, an increase in the level of TBA-reactive products was noted by 37% ($p<0.05$) among aggressors and by 57% ($p<0.01$) in victims relative to the control group. "Social" stress also led to an increase in the thymus rate of spontaneous lipid peroxidation in animals with aggressive by almost 40% ($p<0.01$) and submissive — by 52% ($p<0.01$) types of behavior. The rate of ascorbate-dependent lipid peroxidation under experimental stress was statistically significantly increased by 29% ($p<0.05$) in aggressors and by 45% in victims ($p<0.05$) in relation to control animals. Catalase activity against the background of "social" stress increased in male rats of aggressors by 57% ($p<0.01$), in animal victims — by 32% ($p<0.05$) compared with the "control". The use of Selank under stress was accompanied by a decrease in the initial level of TBA products in the thymus tissue by more than 30% in aggressors ($p<0.01$) and in victims by 26% ($p<0.05$) relative to the stress group. Under conditions of "social" stress, Selank reduced both the rate of spontaneous lipid peroxidation in aggressor rats by 34% ($p<0.01$) and in individuals of victims by almost 20% ($p<0.05$), and ascorbate-dependent LP in an average of 30% in aggressors ($p<0.01$) and victims ($p<0.05$) relative to animals exposed to stress. The catalase level with the introduction of Selank decreased by more than 30% ($p<0.01$) among aggressors and by 28% ($p<0.05$). Under the influence of Pro-Gly-Pro, animals with an aggressive type of behavior showed a decrease in the initial level of TBA products by 16% ($p> 0.05$) and in individuals submissive by 22% ($p<0.05$).

In addition, Pro-Gly-Pro contributed to the suppression of both spontaneous lipid peroxidation

Table 1. *The effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on lipid peroxidation and catalase activity in the spleen of male rats under the conditions of "social" stress*

Experimental groups (n = 10)	Lipid peroxidation indicators			Catalase activity, %
	The initial level of MDA, M ± m, nmol/g tissue	The rate of spontaneous lipid peroxidation, M ± m, nmol/g · h	The rate of ascorbate-dependent lipid peroxidation, M ± m, nmol/g · h	
Animals with an aggressive type of behavior				
Control	1,75 ± 0,19	2,12 ± 0,23	3,07 ± 0,23	40,56 ± 3,66
"Social" stress	2,76 ± 0,26**	2,88 ± 0,27*	4,90 ± 0,39***	66,33 ± 6,24**
"Social" stress + Selank (100 mcg /kg/day)	2,03 ± 0,15#	2,10 ± 0,24#	2,57 ± 0,33###	45,27 ± 5,15#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	2,15 ± 0,20	1,83 ± 0,21##	3,48 ± 0,37#	36,89 ± 4,31##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,00 ± 0,18#	1,70 ± 0,24##	3,09 ± 0,30##	42,83 ± 4,94#
Animals with a submissive type of behavior				
Control	1,75 ± 0,19	2,12 ± 0,23	3,07 ± 0,23	40,56 ± 3,66
"Social" stress	2,43 ± 0,27*	2,79 ± 0,24*	4,57 ± 0,32**	51,78 ± 4,19*
"Social" stress + Selank (100 mcg /kg/day)	1,81 ± 0,32	1,78 ± 0,28#	3,01 ± 0,48#	36,67 ± 3,72#
"Social" stress + Pro-Gly-Pro (100 mcg/kg/day)	1,54 ± 0,23#	1,61 ± 0,26##	3,30 ± 0,44#	33,11 ± 3,23##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	1,67 ± 0,21#	1,47 ± 0,20###	3,68 ± 0,45	31,84 ± 3,03##

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)*

in animals with aggressive behavior by 39% (p <0.01) and in rats with submissive — by 41% (p <0.01), and ascorbate-dependent lipid peroxidation an average of 21% (p <0.05) among aggressors and victims relative to the stress group. The activity of the catalase enzyme against stress during the use of Pro-Gly-Pro decreased by 36% (p <0.01) in aggressors and by 33% in victims. Under the influence of Pro-Gly-Pro-Leu, stressful animals with aggressive behavior showed a decrease in the initial level of TBA products by 20% (p <0.05) and in male rats with submissive — by almost 30% (p <0, 05). It should also be noted that under the influence of Pro-Gly-Pro-Leu under conditions of "social" stress, spontaneous lipid peroxidation was suppressed by aggressors by 29% (p <0.01) and by 43% in victims (p <0.001), and as well as ascorbate-dependent lipid peroxidation by 24% (p <0.05) in rats with aggressive behavior and in individuals with submissive — by 9% (p> 0.05) relative to animals subjected to stress. In addition, this neuropeptide reduced the level of catalase in the thymus in aggressors by 27% (p <0.05) and in victims by 38% (p <0.01) compared with the stress group.

CONCLUSION

Thus, experimental "social" stress, modeled by 20-day inter-male confrontations, is accompanied by an increase in free radical processes in immunocompetent organs (spleen and thymus), which indicates the immunosuppressive effect of this type of stress exposure. Under the influence of the Selank preparation and new representatives of neuropeptides Pro-Gly-Pro and Pro-Gly-Pro-Leu, its pronounced corrective effect on lipid peroxidation is noted, which is confirmed by a decrease in the tissues of the spleen and thymus of laboratory animals of the initial, spontaneous and ascorbate-dependent levels of lipid peroxidation, as well as a decrease in the activity of the antioxidant enzyme — catalase in conditions of "social" stress.

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Table 2. *The effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on lipid peroxidation and catalase activity in the thymus of male rats under the conditions of "social" stress*

Experimental groups (n = 10)	Lipid peroxidation indicators			Catalase activity, %
	The initial level of MDA, M ± m, nmol / g tissue	The rate of spontaneous lipid peroxidation, M ± m, nmol / g · h	The rate of ascorbate-dependent lipid peroxidation, M ± m, nmol / g · h	
Animals with an aggressive type of behavior				
Control	2,70 ± 0,30	3,01 ± 0,20	2,41 ± 0,20	36,48 ± 2,54
"Social" stress	3,72 ± 0,30*	4,21 ± 0,30**	3,11 ± 0,20*	57,42 ± 5,67**
"Social" stress + Selank (100 mcg /kg/day)	2,56 ± 0,20##	2,77 ± 0,31##	2,18 ± 0,20##	40,09 ± 3,10#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	3,11 ± 0,20	2,55 ± 0,29##	2,48 ± 0,22#	36,50 ± 3,06##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,97 ± 0,21#	2,98 ± 0,27##	2,36 ± 0,20#	41,77 ± 3,19#
Animals with a submissive type of behavior				
Control	2,70 ± 0,30	3,01± 0,20	2,41 ± 0,20	36,48 ± 2,54
"Social" stress	4,24 ± 0,40**	4,60 ± 0,30**	3,50 ± 0,32*	48,40± 3,23*
"Social" stress + Selank (100 mcg /kg/day)	3,13 ± 0,32#	3,71 ± 0,28#	2,43 ± 0,22#	34,67 ± 3,68#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	3,31 ± 0,23#	2,70 ± 0,32##	2,72 ± 0,17#	32,40 ± 3,25##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,98 ± 0,28#	2,63 ±0,25###	3,19 ± 0,25	29,78 ± 3,15##

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)*

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