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EFFECTS OF MELANOCORTINSON THE BEHAVIOR OF RATS IN THE TEST OF ELEVATED CRUCIFORM MAZE AND EXPERIMENTALLY INDUCED OF SOCIAL STRESS

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ABSTRACT — In this study we have investigated the effects of melanocortins (group analogs of neuropeptides) on the psychoemotional state of rats under conditions of experimental social stress. The study was carried out on male rats which were injected intraperitoneally for 20 days with the neuropeptide drugs Semax and ACTH(6-9)-Pro-Gly-Pro at a dose of 100 µg/kg/day starting from the 1st day of stress exposure. The psychoemotional state of the animals was evaluated by means of the behavioral test of elevated cruciform maze. It was found that intraperitoneal administration of neuropeptides (Semax, ACTH(6-9)-Pro-Gly-Pro) helps to reduce high anxiety levels in animals both with aggressive and submissive types of behavior under conditions of experimental social stress via their psychomodulatory effects.

KEYWORDS — experimental social stress, neuropeptides, melanocortins, Semax, ACTH(6-9)-Pro-Gly-Pro, psychomodulatory effect.

INTRODUCTION

Recent studies indicate that a variety of stressful influences play an important role in the development of depressive disorders [1, 2, 3]. The modern society with its accelerated pace of life, the lack of physical activity, lack of time facilitate the development of stress-related conditions which act as risk factors for both mental and somatic disorders. [1, 7]. Therefore, the issues of timely prevention and correction of stress and possible solutions how to cope with its clinical outcomes have remained relevant. There is a promising trend to use for correction of pathological conditions of the nervous system drugs from the group of analogs of neuropeptides which are similar to natural endogenous regulators of the body functions. [4, 5, 6, 8]. Melanocortins are synthesized at the Kurchatov

Institute of Molecular Genetics (Moscow, Russia). The registered drug Semax (ACTH(4-7)-Pro-Gly-Pro) and the new compound ACTH(6-9)-Pro-Gly-Pro are of special interest due to their potency of compensating for stress-related damage.

The aim of research

is to study the effect of neuropeptides/melanocortins on the psychoemotional state of white male rats under conditions of experimental social stress.

MATERIAL AND METHODS

The study was carried out on 70 white male rats. All manipulations with rats were conducted in compliance with the DIRECTIVE 2010/63/EU on the protection of animals used for scientific purposes. The animals were divided into groups (n=10): group 1 — intact animals (control); group 2 — rats exposed to social stress for 20 days and 2 groups of experimental animals exposed to social stress and receiving neuropeptides at doses of 100 mg/kg per day intraperitoneally for 20 days: registered drug Semax and new compound ACTH(6-9)-Pro-Gly-Pro. In our experimental model of social stress rats were paired-housed in cages separated by a transparent partition with holes. The rats were able to see, hear and smell each other, but at the same time the partition prevented from physical interaction. The septum was removed for 10 minutes every day, resulting in intermale confrontation. As a result, groups of animals with aggressive and submissive behaviors were formed. The anxiety-related behavior of the rodents was assessed by using the test of elevated cruciform maze.

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 difference were considered at p 0.05.

RESULTS

Modeling of experimental social stress on male rats led to similar changes in behavioral indicators in groups of animals with aggressive and submissive

behaviors indicating the formation of high anxiety which manifested itself as a decrease in the number of stands by more than 45% ($p < 0.05$), the number of exits into the open sleeves of test by 45% ($p < 0.05$) and 35% ($p < 0.05$); reducing the time spent on open sleeves by 32% ($p < 0.05$) and 40% ($p < 0.05$); decrease in the number of exits to the center by 47% ($p < 0.05$) and 30% ($p > 0.05$); a decrease in the time spent in the center by 36% ($p < 0.05$) and 45% ($p < 0.001$) in the groups of aggressors and victims respectively in comparison with intact animals.

There was also a statistically significant increase in the number of visits to the closed sleeves and the number of fecal boluses by almost 100%, the number of *peeking* from the closed sleeves by almost 50% in groups of rats with both aggressive and submissive behaviors compared to control animals.

The results of experiment in the test of elevated cruciform maze showed that the neuropeptides were responsible for similar changes against the background of social stress: the time spent on open arms increased significantly by more than 40% ($p < 0.05$) in comparison with the stressed group of rats (Fig. 1).

Under the influence of neuropeptides, the time spent in the center increased by 30% ($p < 0.05$) in the group of aggressors, by 50% ($p < 0.01$) in the group of animals with submissive behavior (Fig. 2).

Statistically significant changes were observed in the aggressors and victims when counting the number of *peeking* from the closed sleeves: Semax contributed to a decrease in the indicator by 2 ($p < 0.001$) and 1.3 ($p < 0.05$) times respectively; ACTH(6-9)-Pro-Gly-Pro — 2.4 ($p < 0.001$) and 1.3 ($p < 0.05$) times respectively (Fig. 3).

The number of stands in comparison with the stress group under the administration of the studied compounds increased in the groups of animals with aggressive and submissive types of behavior: under the influence of Semax by 1.9 ($p < 0.01$) times; ACTH(6-9)-Pro-Gly-Pro — 1.9 ($p < 0.01$) and 1.8 ($p < 0.001$) times respectively (Fig. 4).

Due to the use of neuropeptides a statistically significant decrease in the number of fecal boluses was noted in comparison with the stress group of both aggressive rats and the group with submissive behavior: Semax caused a decrease in 4.5 ($p < 0.001$) and

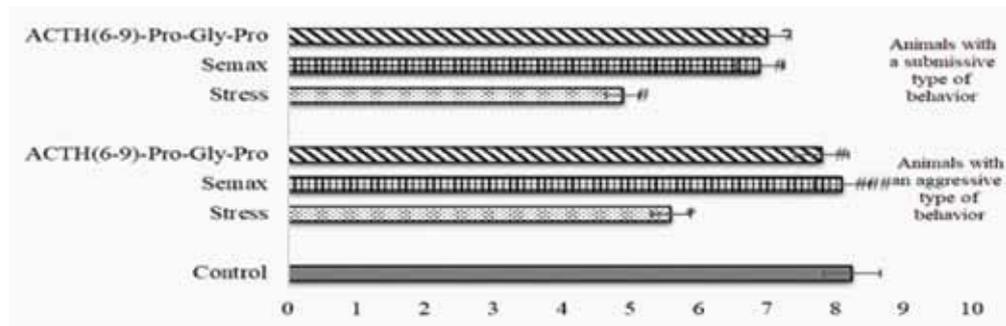


Fig. 1. Time spent by animals on open sleeves in the test of elevated cruciform maze

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — relative to the control; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — relative to stressed animals (Student's t-test)

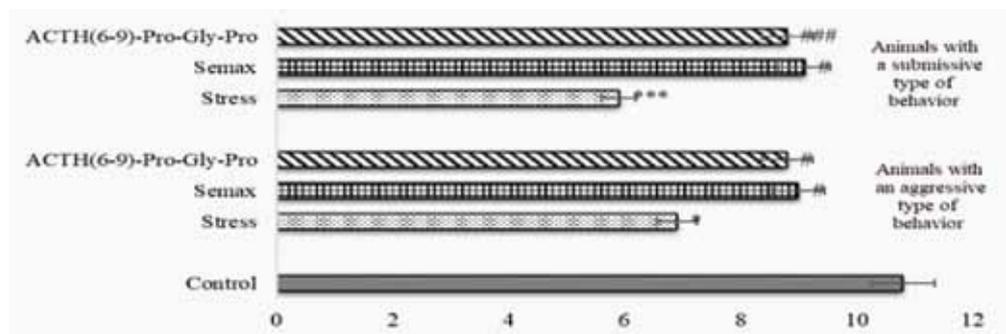


Fig. 2. Time spent by animals in the center area of the elevated cruciform maze.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — relative to the control; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — relative to stressed animals (Student's t-test)

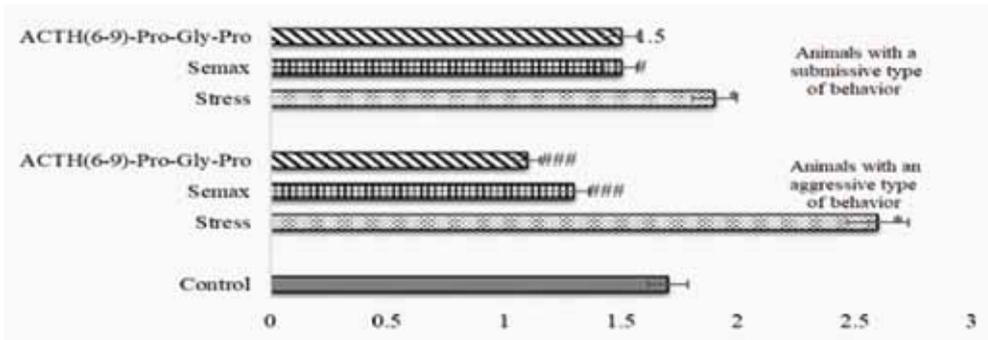


Fig. 3. Number of "peeking" from closed sleeves of the Elevated cruciform maze

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — relative to the control; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — relative to stressed animals (Student's t-test)

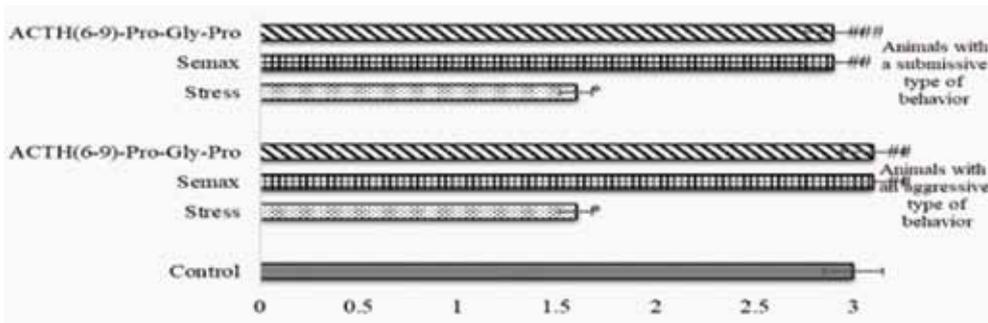


Fig. 4. Number of stands of animals in the test «Elevated cruciform maze»

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — relative to the control; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — relative to stressed animals (Student's t-test)

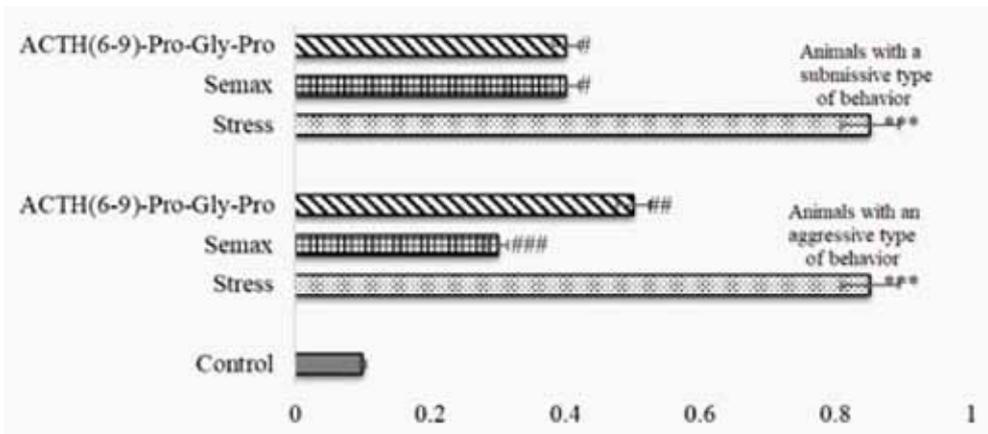


Fig. 5. Number of fecal boluses in the test «Elevated cruciform maze»

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — relative to the control; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — relative to stressed animals (Student's t-test)

2.6 ($p < 0.05$) times; ACTH(6-9)-Pro-Gly-Pro — 2.3 ($p < 0.01$) and 2.7 ($p < 0.05$) times respectively (Fig. 5).

However, less pronounced changes were observed when evaluating the indicators: *visiting open sleeves*, *visiting closed sleeves* and *exits to the center* and were not statistically significant in all cases.

CONCLUSION

The outcomes of the study of the behavior of white male rats in the tests of elevated cruciform maze allow us to conclude that the use of of neuropeptides (Semax, ACTH(6-9)-Pro-Gly-Pro) due to their psychomodulatory effects help to reduce anxiety in animals both with aggressive and submissive types of behavior in a model of social stress.

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