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INFLUENCE OF PEPTIDE BIOREGULATORS ON THE RESISTANCE OF THE ORGANISM OF RATS UNDER SIMULATION OF COLD-STRESS DISADAPTATION

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Abstract. ***Background.*** Biologically active regulatory peptides (RPs) are the drugs of new type that act selectively on targets, with having no significant side effects. ***The aim*** of the study was to investigate the potential effect of the peptide preparations Cortexin and Semax on the resistance of rats, being exposed to simulated cold-stress maladaptation. ***Materials and methods.*** White outbred male rats were injected intraperitoneally twice daily with placebo (n = 30), Cortexin 5 mg/kg (n = 30) or Semax 0.3 mg/kg (n = 30). Three days after the start of the injection course, the cold-stress effect was simulated in the climate chamber (Feutron, Germany) by cooling the air to 5 °C at a relative humidity of 75–80%. ***Results.*** The use of RP significantly increased the duration of the rectal temperature plateau-period within 35 °C (moderate hypothermia): in animals of the Cortexin group from 10 days to 12 days, and in animals of the Semax group, from 10 to 14 days. Cortexin demonstrated moderate immunomodulatory properties, and Semax had a more pronounced immunomodulatory effect. Both preparations showed a stress-protective effect. The use of RP provided to delay the decrease in the rat general motor activity and exploratory behavior which develops under the influence of a simulated cold-stress factor. A slower rate of decrease in the swimming time of rats under the influence of RP was registrated. ***Conclusion.*** The meteoadaptogenic, stress-protective and nootropic effect of regulatory peptides, primarily Semax, was confirmed in rats on a model of cold-stress exposure.

Key words: experimental model; rats; hypothermia; Cortexin; Semax; regulatory peptides; physical performance; low temperature; open field test.

ВЛИЯНИЕ ПЕПТИДНЫХ БИОРЕГУЛЯТОРОВ НА РЕЗИСТЕНТНОСТЬ ОРГАНИЗМА КРЫС В УСЛОВИЯХ МОДЕЛИРОВАНИЯ ХОЛОДО-СТРЕССОРНОЙ ДЕЗАДАПТАЦИИ

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Резюме. ***Введение.*** Биологически активные регуляторные пептиды (РП) — новый класс препаратов, оказывающих избирательное действие на мишени, при этом не обладающих существенными побочными эффектами.

Целью исследования явилось изучение потенциального влияния пептидных препаратов кортексина и семакса на резистентность организма крыс в условиях моделирования холодо-стрессорной дезадаптации. ***Методы исследования.*** Белым беспородным крысам-самцам вводили внутрибрюшинно дважды в сутки ежедневно плацебо (n = 30), кортексин 5 мг/кг (n = 30) либо семакс 0,3 мг/кг (n = 30). Через трое суток после начала инъекционного курса моделировали холодо-стрессорное воздействие в условиях климатической камеры Feutron (Германия) путем охлаждения воздуха до 5 °C при относительной влажности 75–80%. Стрессорный фактор создавали, используя специфический световой режим (круглосуточный свет), звуковую невротизацию (непрерывная громкая рок-музыка), а также ограниченный рацион питания (15 ккал/сут). Изучали динамику ректальной температуры, показателей физической работоспособности в тесте с плаванием, поведенческих реакций в тесте «Открытое поле», количества лейкоцитов, нейтрофилов и лимфоцитов, сывороточных уровней кортизола и инсулина, белков теплового шока HSP-70 и гипоксия-индуцибельного фактора HIF-1α. ***Результаты.*** Применение РП статистически значимо увеличивало продолжительность периода плато ректальной температуры в пределах 35 °C (умеренная гипотермия): у животных группы кортексина с 10 до 12 суток, а у животных группы семакса — с 10 до 14 суток. Кортексин показал умеренные иммуномодулирующие свойства, а семакс обладал более выраженным иммуномодулирующим эффектом. Оба препарата показывали стресс-протективный эффект. Применение РП позволяло замедлять снижение общей двигательной активности и поисково-исследовательской активности крыс, развивающееся под влиянием моделируемого холодо-стрессорного воздействия. Отмечен более медленный темп снижения времени предельного плавания крыс под действием РП. ***Заключение.*** Подтверждены метеоадаптогенный, стресс-протективный и ноотропный эффекты регуляторных пептидов, в первую очередь семакса, у крыс на модели холодо-стрессорного воздействия.

Ключевые слова: экспериментальная модель; крысы; гипотермия; кортексин; семакс; регуляторные пептиды; физическая работоспособность; низкая температура; тест «Открытое поле».

INTRODUCTION

In the last decade, the Arctic region has been undergoing active economic development due to its rich raw material potential. This requires the involvement of large number of specialists from various fields in order to develop modern infrastructure [1, 2]. At the same time, the work of these specialists is associated with number of objective difficulties associated with geographical features of the region. Workers, especially those whose activities are carried out outdoors, at sea, etc., are affected by number of climatic, professional, sanitary, and epidemiological factors, such as insufficient solar radiation, low temperatures in different seasons, unusual light conditions, frequent strong wind, sharp fluctuations in air humidity depending on weather, unstable characteristics of the geomagnetic field, unfavourable environmental conditions, poorly developed infrastructure, limited ability to move and communicate with people, widespread bad habits, etc. [2, 3]. These factors lead to development of various disorders of adaptation process in a significant proportion of the Arctic region staff, significantly reducing the functional capabilities of their body [4]. Thus, resistance of the specialist's body to the impact of the Arctic region's conditions is one of the determining factors for successful performance of human's functional duties. One of the approaches aimed at increasing the resistance of the human body to impact of extreme factors is pharmacological correction of a functional state [5, 6].

The main directions of increasing resistance of the body include elimination of possible functional state disorders (acute and chronic diseases, symptoms of asthenic syndrome, excessive psychological stress), increasing non-specific resistance (hardening, physical training, psychological preparation) [7]. Recently, pharmacological line, one of the directions of work to increase resistance of the body using regulatory peptides (RP) has been actively studied [5]. To date, more than 1500 RP have been identified, which are synthesised by apudocytes — structural and functional units of the APUD system [5]. The main characteristics of RP include multifunctionality and high affinity for certain receptors. Some RPs act as regulators, modulating the release of other RP. The duration of RP action is up to 90 minutes, which can be explained by the formation of functionally active metabolites [8]. The spectrum of biological effects of individual RP includes antinociceptive, immunomodulatory, anti-anxiety impact, as well as a stimulating effect on memory, training and behavior. Since the conditions of the Arctic region can have a depressing effect on neuroendocrine system with subsequent development of maladaptation phenomena [7, 8], the study was conducted on the effectiveness of using individual RP as biological regulators of the body's resistance to the effects of the stress-cold factor.

AIM

To investigate the potential effect of peptide bioregulators on resistance of rats, being exposed to simulated cold-stress maladaptation.

MATERIALS AND METHODS

The study was conducted on white mongrel male rats weighing 180–220 g, obtained from the Federal State Unitary Enterprise "Rappolovo Laboratory Animal Nursery" and subjected to a 14-day quarantine. The maintenance and animal handling in the experiment complied with the requirements of the Order of the Ministry of Health of the Russian Federation dated 01.04.2016 N 199n "On approval of the rules of good laboratory practice". Animals were kept in ventilated cages with 6 individuals at relative humidity of 40–60 %, air temperature of 20–22 °C, and light regime of 12:12 with the lights on at 8:00 a.m. Complete feed PK-120 (OOO "Laboratorkorm", Moscow) was used with free access to water.

Maladaptation in rats was induced using a previously developed original cold-stress model [9]. The animals were placed in a Feutron climate chamber, where the temperature was maintained at +5 ± 1 °C and humidity was 75–80 %. Additional stress factors included a specific light regime (round-the-clock light, taking into account the predominantly nocturnal nature of the rats' life), sound neurotisation, and a limited diet (PK-120 feed (OOO Laboratorkorm, Moscow) in the amount of 3 g per 100 g of animal weight, which approximately corresponds to an energy value of 15 kcal/animal per day) with free access to water. The duration of the simulated exposure was 14 days, during which maladaptation in animals was developed. This state was regarded as the development of immunodeficiency (in the form of leukopenia, lymphopenia and neutropenia), pronounced imbalance of individual hormones (cortisol and insulin), decrease in the effectiveness of the stress-limiting systems (impaired ability to synthesise HSP-70), as well as a significant decrease in motor activity and physical performance of laboratory animals.

To study the thermal state of the rats, a TPEM-1 rectal thermometer was used, recording body temperature every hour during the first day of observation, and then every 24 hours during the rest of observation period. The rats were taken out of the climatic chamber daily to study spontaneous behavioural activity in the Open Field test (Open Science Research and Production Complex, Moscow). For this purpose, each mouse was placed in the centre of a square chamber measuring 100 × 100 × 30 cm. A bottom of the chamber was divided into 25 squares with a side length of 20 cm; 16 holes with a diameter of 3 cm (burrows) were symmetrically located at common corners of the squares. Then a stopwatch was started and the number of intersections of sectors, number of stands, peeks into burrows, defecations, urinations, and acts of grooming were recorded for 3 minutes. The search and exploratory activity (SEA), general motor activity (GMA), emotional lability (EL) and aggressiveness were assessed [6]. To assess physical performance of rats, a swimming time-test with maximum weight was used (the weight was 8% of rat's body weight) in water of comfortable temperature (22–24 °C) [7, 12]. After quarantine, all animals were trained to swim (5 daily swimming sessions of maximum duration). Based on the training results, the average group values of maximum swimming time were calculated. If after training the animal's swimming time differed from the average group by more than 30%, the animal was excluded from further study. The criterion to finish the test was the first dive of an animal to the pool bottom for more than 5 s.

To study the immunological parameters, we used data of a blood test with determination of absolute leukocyte counts and leukocyte count using a Sysmex KX 21n automatic haematology analyser (Sysmex Europe GmbH, Germany).

The concentration of cortisol and insulin in blood serum was determined by enzyme-linked immunosorbent assay (ELISA) using the Cortisol-ELISA-BEST and Insulin-ELISA-BEST diagnostic kits (Vector BEST, Russia).

As a marker of stress exposure, the content of heat shock protein (HSP) family in serum with molecular weight of 70 kDa (HSP–70) was determined using the Hsp70 High Sensitivity ELISA Kit (Enzo Life Sciences, Inc., Switzerland).

To assess the expression of transcriptional hypoxia-inducible factor (HIF-1α) in rats as a marker of hypoxia, the Enzyme-linked Immunosorbent Assay Kit for Hypoxia Inducible Factor 1 Alpha (Cloud-Clone Corporation, USA) was used.

All laboratory studies were performed on 1, 2, 3, 5, 7, 10, 12 and 14 days of the experiment. To study the effect of peptide bioregulators on resistance of the rats under conditions of simulated cold-stress exposure, drugs with actoprotective and nootropic activity were selected, including under hypothermia: Cortexin (OOO GEROPHARM, Russia) and Semax (AO Peptogen, Russia) [10]. When choosing the range of studied doses of drugs, interspecies conversion factor was used [11]. The rats were randomised into three groups depending on an administered drug: placebo group (n = 30), Cortexin group (n = 30) and Semax group (n = 30).

A general scheme of the experiment is shown in Figure 1. The studied drugs were administered to rats intraperitoneal 2 times a day. The administration began 3 days before the onset of exposure to the cold-stress factor. Cortexin was administered at a dose of 5 mg/kg once a day, which showed the greatest effect in studies on an air hypothermia model [5]. Semax was used at a dose of 0.3 mg/kg once a day, which showed the maximum antioxidant and neuroprotective activity [10].

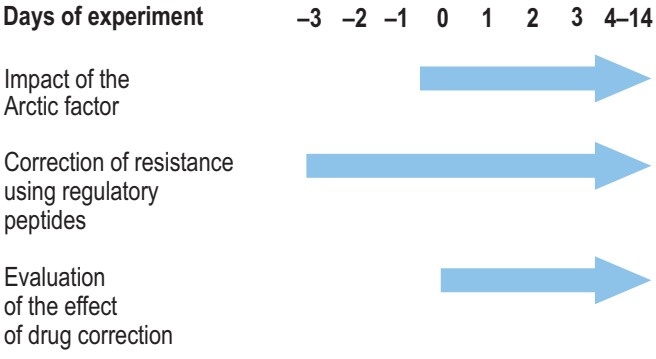

Fig. 1. General scheme of the experiment

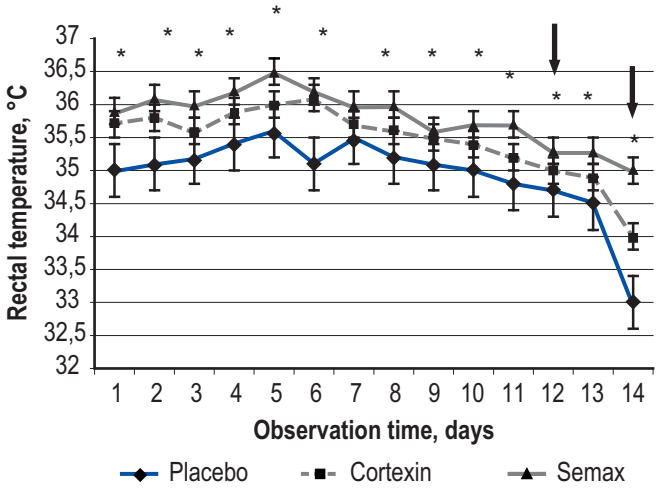

Fig. 2. Minimal values of rectal temperature during the experiment. Sign * is statistically significant difference in rats' indicator in Semax group relative to those in rats from placebo group ($p < 0.05$). Arrows (↓) indicate the end of the temperature plateau within 35 °C in the Cortexin and Semax groups

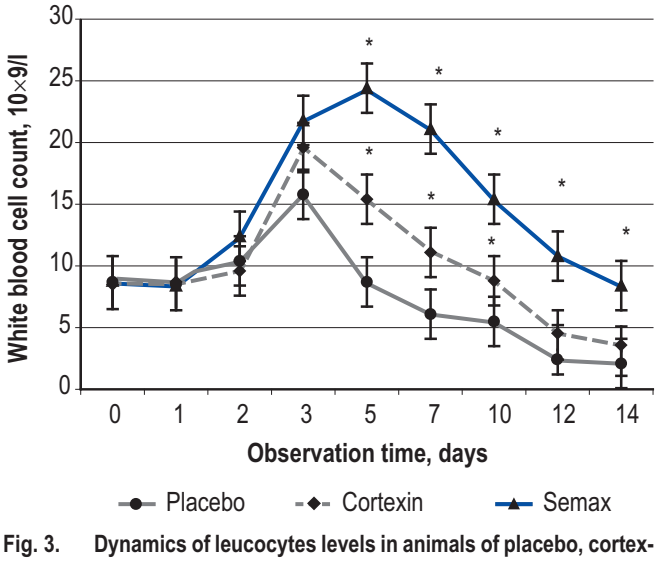

Fig. 3. Dynamics of leucocytes levels in animals of placebo, cortexin and semax groups. The * symbol indicates a statistically significant difference in the indices relative to those in the placebo group ($p < 0.05$)

Statistical processing of the results was carried out using methods of descriptive statistics, dispersion, factor and cluster analysis using the Statistica v.10 software package.

RESULTS AND DISCUSSION

We analysed the dynamics of the rats' rectal temperature (Fig. 2). During the first 5 days, rats of all groups showed a slight increase in rectal temperature, indicating mobilisation of the thermoregulation mechanism, but the most pronounced effect was noted in the Semax group. In addition, the use of RP significantly increased the duration of plateau period of rectal temperature within 35 °C (moderate hypothermia): in animals of the Cortexin group from 10 to 12 days, and in animals of the Semax group from 10 to 14 days.

Thus, the use of Semax allowed maintaining the body's thermoregulatory reserve during 14 days of exposure to the cold-stress factor and did not lead to a breakdown in the adaptive reactions.

To assess the state of immune system in laboratory animals, a haematological study was conducted to determine the absolute number of leukocytes in the placebo, Cortexin and Semax groups. The dynamics of these indicators is shown in Figure 3.

It was shown that the studied medicines had a statistically significant effect on the leukocyte content. In rats of all groups, an increase in absolute leukocyte content was noted during the first three days after the onset of cold-stress exposure. In rats receiving Cortexin, this increase was significantly more pronounced in comparison to an increase in leukocyte content in rats of the placebo group. During the period from the 3rd to 10th day of cold-stress exposure, dynamics of the leukocyte count was similar to that in animals from the placebo group, but absolute indicators of the leukocyte count were maintained at the statistically and significantly higher level. The animals in the Semax group showed a more pronounced and prolonged increase in the number of leukocytes: the peak value was observed on the 5th day and was $24.4 \pm 1.2 \times 10^9$/l (statistically significant difference compared to the values in the rats in the placebo and Cortexin groups). Subsequently, a decrease in the leukocyte content was observed, which did not reach the level of leukopenia by the end of the experiment (the lower limit of the norm for rats is 8.0×10^9/l). Thus, under the experimental conditions, Cortexin showed moderate immunomodulatory properties, and Semax had more pronounced immunomodulatory effect.

To study the characteristics of animals' hormonal spectrum, the dynamics of cortisol (as a marker of stress and one of the key factors of the hypothalamic-pituitary-adrenal axis) and insulin (as an indicator of anabolism) in blood serum were assessed (Fig. 4, 5).

Analysis of the dynamics of cortisol content during the period of exposure to a simulated cold stress factor in rats showed that in placebo group, by the 7th day of exposure, there was an increase in the serum level of hormone compared to initial values by more than 10 times. From the 10th day a progressive decrease in its content was observed, reaching values slightly lower than the initial ones by the 14th day ($p > 0.05$).

In rats treated with Cortexin and Semax, an increase in the cortisol level was noted on the 7th day of exposure by 5 and 4 times, respectively. Thus, the increase in cortisol level under the influence of RP was significantly lower than in rats treated with placebo. By the end of the exposure period, a level of cortisol in rats of the RP groups remained within the range of moderate increase (350–500 nmol/l).

The nature of cortisol dynamics in rats of the placebo group may indicate a sharp activation followed by rapid depletion of regulatory reserves of the hypothalamic-pituitary-adrenal axis in the process of modelling cold-stress factors. At the same time, in animals receiving RP, stress-protective effect of drugs was noted.

Under conditions of modelling cold-stress factors, rats of all groups had a significant (approximately threefold) decrease in the level of serum insulin on the 5th day of observation and hypoinsulinemia remaining until the end of the exposure. There were no statistically significant differences between the groups.

As an early marker of adaptive stabilisation of the body's cellular structures, the content of heat shock proteins (HSP-70) was studied in animals of the groups (Fig. 6).

Analysis of the dynamics of the HSP-70 content in blood serum of rats exposed to cold-stress showed that the most pronounced increase in this indicator was observed in animals of the Semax group. Already from the 5th day, a statistically significant difference was observed between the values of this indicator and those in rats of the placebo and Cortexin groups. This trend persisted until the end of the exposure. The result may indicate the ability of Semax to provide a significant and early cross-increase in cell resistance to complex adverse effects (so-called cross-tolerance).

To study the degree of compliance of body's oxygen demand and its delivery, we assessed hypoxia-inducible factor HIF-1α (Fig. 7).

During the period of cold-stress exposure, the placebo group rats showed, in general, statistically insignificant tendency to increase in HIF-1α content, reaching its maximum

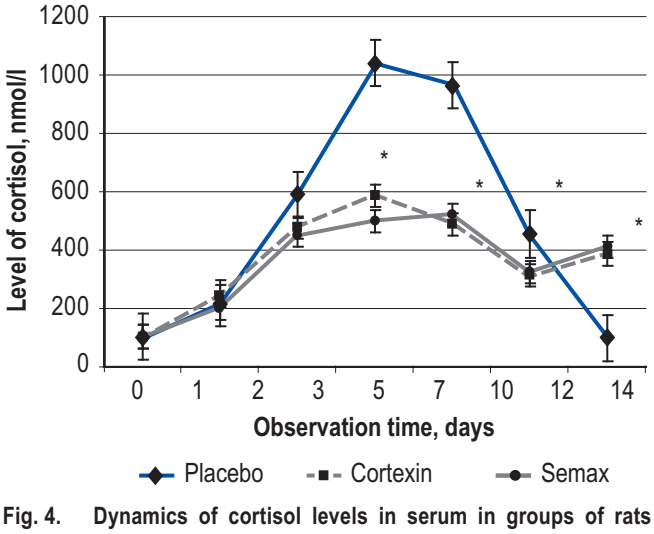

Fig. 4. Dynamics of cortisol levels in serum in groups of rats treated with the studied drugs. The * symbol indicates a statistically significant difference in the indices relative to those in the placebo group ($p < 0.05$)

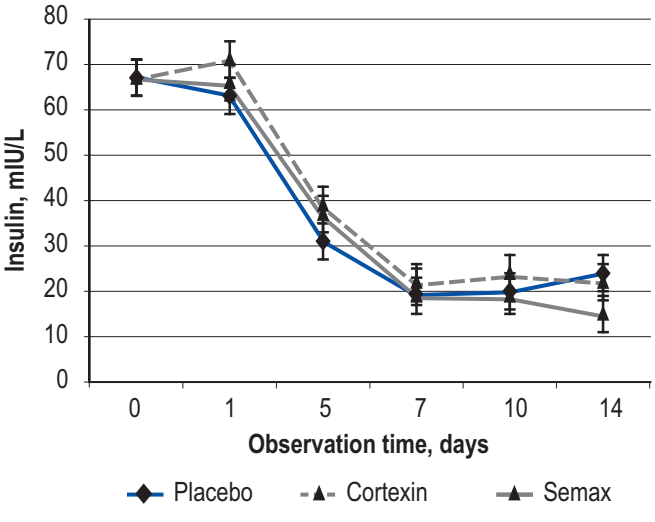

Fig. 5. Dynamics of insulin level in serum of rats treated with the studied drugs. The * symbol indicates a statistically significant difference in the indices relative to those in the placebo group ($p < 0.05$)

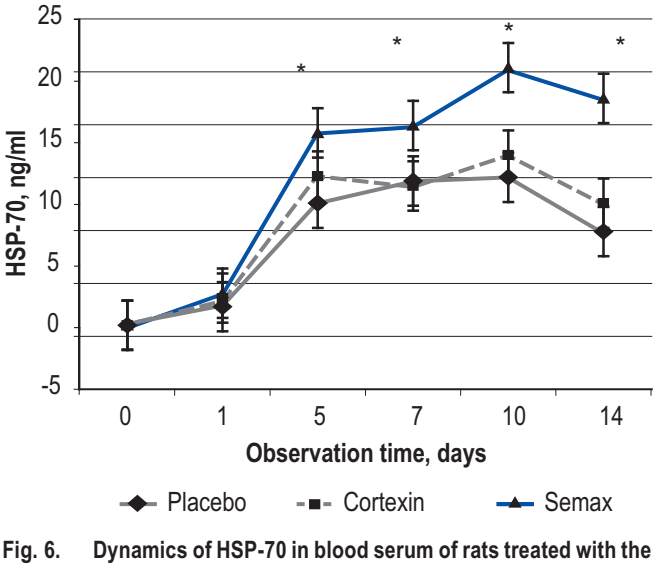

Fig. 6. Dynamics of HSP-70 in blood serum of rats treated with the studied drugs. The * symbol indicates a statistically significant difference in the indices relative to those in placebo group ($p < 0.05$)

level by the 14th day (1.8 times compared to the values in the Semax group rats, $p < 0.05$). It may indicate a tendency to development of tissue hypoxia. In animals of the Cortexin and Semax groups, the HIF-1α content values remained virtually unchanged. Thus, the question of the possible antihypoxic effect of these RPs requires in-depth study.

We have studied the change in the behavioural characteristics of rats under cold-stress conditions. For this purpose, the animals were removed from the climate chamber for a short time (5 min) to perform the "Open Field" test. The test was performed initially, on days 5, 7, 10, 12, and 14 (Tables 1–4).

Analysis of changes in the total motor activity (TMA) of rats during the period of cold-stress exposure showed that animals of all groups had a stable statistically significant tendency for this indicator to decrease by the end of the period. In the rats of the Semax group, the decrease in TMA was significantly less pronounced on days 7–14 of cold-stress exposure, and on the 14th day it decreased by 58% of the initial value. At the same time, in the rats of the placebo group it decreased by 90 %, respectively ($p < 0.05$). Thus, the use of Semax made it possible to slow down the decrease in the total motor activity of rats until the end of the cold stress exposure. In rats treated with Cortexin, the effect of slowing down the TMA was less prolonged: on the 12th day, the TMA values were 61 % lower than the initial values compared to those in the placebo group (83 %, $p < 0.05$), and on the 14th day, the TMA values were approximately similar in animals of both groups.

The indices of search and exploratory activity (SEA) of rats of all groups during cold stress exposure significantly decreased, in animals of the placebo group SEA ceased by the 14th day. In rats receiving Semax, the indices by the 14th day decreased by 68%, in animals of the Cortexin group — by 81 % ($p < 0.05$ compared with the indices in rats of the placebo group). Thus, the studied RPs slowed down the effects of suppression of the central nervous system function of rats exposed to the simulated cold-stress factor.

The effect of Cortexin and Semax on the indices of aggressiveness and emotional lability of animals was studied (Tables 3, 4).

The dynamics of aggressiveness and emotional lability in rats of all groups during the period of cold-stress exposure retained a two-phase character: maximum indices (with an approximately fourfold increase compared to the initial level) were achieved on the 10th day. Then, a decrease in the results below the initial values was observed. At the same time, the studied drugs did not have a statistically significant effect on these parameters.

The effect of RP on the physical performance of rats exposed to cold stress stimulation was assessed in the maximum swimming time test with weightning. The test was performed initially, on days 5, 7, 10, 12 and 14 (Table 5).

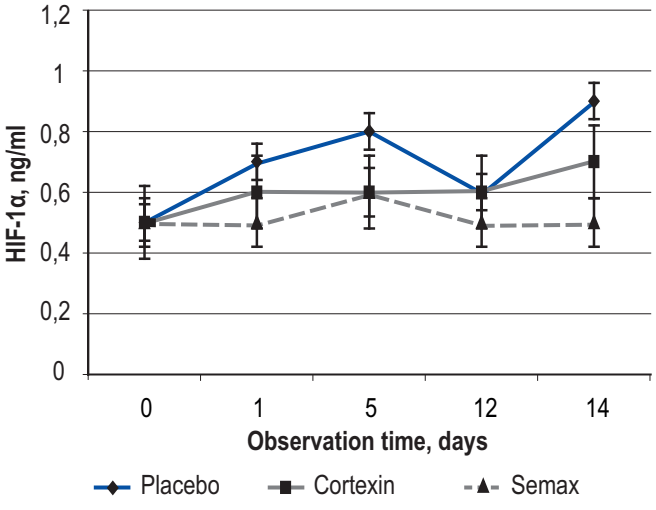

Fig. 7. Dynamics of HIF-1α content in blood serum of rats treated with the studied drugs. The * symbol indicates a statistically significant difference in the indicators relative to those in the placebo group ($p < 0.05$)

Table 1

Dynamics of general motor activity of rats in the Open field test, s (M ± m)

Days of observation	Placebo	Cortexin	Semax
0	115,3 ± 5,7	115,3 ± 5,7	115,3 ± 5,7
5	99,2 ± 4,3	100,2 ± 4,3*	112,2 ± 3,2
7	88,0 ± 3,1*	101,1 ± 3,8*	101,0 ± 4,0*#
10	74,3 ± 4,3*	103 ± 6,3*#	100,2 ± 3,2*#
12	19,5 ± 3,0*	44,5 ± 5,8*#	50,4 ± 4,1*#
14	12,1 ± 2,2*	18,1 ± 2,2*	48,5 ± 3,2*#

Notes.
1. The * symbol indicates a statistically significant difference in the parameters relative to the values of the 0-time point day ($p < 0.05$).
2. The # symbol indicates a statistically significant difference in the parameters relative to those in the placebo group ($p < 0.05$)

Table 2

Dynamics of search and exploratory activity of rats in the Open field test, s (M ± m)

Days of observation	Placebo	Cortexin	Semax
0	17,1 ± 2,2	17,1 ± 2,2	17,1 ± 2,2
5	6,2 ± 1,3*	8,8 ± 1,8*	11,9 ± 2,0*#
7	3,3 ± 1,1*	4,1 ± 0,2*	10,8 ± 1,8*#
10	3,5 ± 0,9*	5,5 ± 0,6*#	5,4 ± 1,2*#
12	1,5 ± 0,2*	3,1 ± 0,7*#	6,2 ± 1,1*#
14	0	3,3 ± 0,5*#	5,5 ± 1,2*#

Notes.
1. The * symbol indicates a statistically significant difference in the parameters relative to the values of the 0-time point day ($p < 0.05$).
2. The # symbol indicates a statistically significant difference in the parameters relative to those in the placebo group ($p < 0.05$).

Table 3

Dynamics of aggressiveness indicators in the Open field test, points (M ± m)

Days of observation	Placebo	Cortexin	Semax
0	0,7 ± 0,1	0,6 ± 0,1	0,8 ± 0,1
5	2,2 ± 0,3*	2,0 ± 0,2*	2,2 ± 0,2*
7	2,1 ± 0,2*	2,0 ± 0,1*	2,3 ± 0,4*
10	3,5 ± 0,4*	3,4 ± 0,6*	3,2 ± 0,5*
12	1,3 ± 0,8	1,5 ± 0,7	1,6 ± 0,7
14	0,8 ± 0,2	1,0 ± 0,3	0,9 ± 0,3

Notes.
1. The * symbol indicates a statistically significant difference in the parameters relative to the values of the 0-time point day ($p < 0.05$).
2. The # symbol indicates a statistically significant difference in the parameters relative to those in the placebo group ($p < 0.05$).

Table 4

Dynamics of emotional lability of animals in the Open field test, points (M ± m)

Days of observation	Placebo	Cortexin	Semax
0	2,1 ± 0,3	2,0 ± 0,3	1,9 ± 0,2
5	2,0 ± 0,2	1,9 ± 0,2	2,1 ± 0,4
7	2,7 ± 0,5*	2,0 ± 0,7	2,4 ± 0,8
10	3,7 ± 0,3*	3,4 ± 0,4*	3,5 ± 0,3*
12	0,9 ± 0,3*	0,8 ± 0,2*	0,8 ± 0,2*
14	0,9 ± 0,1*	0,8 ± 0,1*	0,9 ± 0,2*

Notes.
1. The * symbol indicates a statistically significant difference in the parameters relative to the values of the 0-time point day ($p < 0.05$).
2. The # symbol indicates a statistically significant difference in the parameters relative to those in the placebo group ($p < 0.05$).

It is assumed, that the effect of Semax is manifested by a slower rate of decrease in the maximum swimming time of rats compared to the rate of placebo group. The effect of Cortexin on the dynamics of the maximum swimming time indicator was insignificant.

Thus, as the result of experiment, it was shown that a course of administration of the neuropeptide preparations Cortexin (5 m/kg daily) and Semax (0.3 mg/kg daily) can increase the resistance of rats to the simulated effect of the cold-stress factor.

CONCLUSION

The obtained experimental data with subsequent analysis of the results showed that proposed cold-stress model simulating conditions of the Arctic region can be used to study the effect of peptide bioregulators on body's resistance in extreme conditions. The results indicating an increase in the resistance of rats to the effects of cold-stress factor with a course

Table 5

Dynamics of maximum swimming time of rats under the conditions of modelling the cold-stress factor, min

Days of observation	Placebo	Cortexin	Semax
0	9,5 ± 0,8	9,8 ± 0,7	9,4 ± 0,6
5	8,4 ± 1,2	8,5 ± 0,9	9,5 ± 1,2
7	5,2 ± 0,6*	7,0 ± 0,5#	7,9 ± 0,8#
10	3,2 ± 0,3*	4,9 ± 0,3#	5,2 ± 0,4#
12	3,1 ± 0,5*	3,6 ± 0,7	5,4 ± 0,6#
14	1,3 ± 0,1*	1,3 ± 0,1	3,2 ± 0,1#

Notes.
1. The * symbol indicates a statistically significant difference in the parameters relative to the values of the 0-time point day ($p < 0.05$).
2. The # symbol indicates a statistically significant difference in the parameters relative to those in the placebo group ($p < 0.05$).

of administration of the neuropeptides Cortexin at a dose of 5 mg/kg and Semax at a dose of 0.3 mg/kg once a day confirm the previously identified frigoprotective effect of these drugs [5]. The results confirm the feasibility of continuing a preclinical study of regulatory neuropeptides, as well as conducting studies of their frigoprotective properties on humans.

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