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The role of kisspeptin-10 in the regulation of the hypothalamic-pituitary-gonadal axis in post-traumatic stress disorder

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ABSTRACT

Background. In post-traumatic stress disorder (PTSD), sexual dysfunctions are observed that do not respond well to psychotherapy. Recently, kisspeptin neuropeptides have been proposed for the treatment of sexual behavior disorders. They influence the hypothalamic-pituitary-gonadal axis, playing a role in the regulation of sexual behavior and affecting the levels of sex hormones. It has been shown that kisspeptins can also influence stress hormones, which may play a key role in maintaining sexual function.

Aim of the study — to investigate the effect of intranasal and intraperitoneal administration of kisspeptin-10 on the levels of sex hormones and stress hormones in animals with post-traumatic stress disorder caused by restriction and vital stress.

Materials and methods. Male Wistar rats were placed in a cage with receptive females for 15 minutes daily over 14 consecutive days, and the presence of sexual behavior was observed. Subsequently, the rats underwent procedures of restraint or vital stress. After the stress and intranasal and intraperitoneal administration of kisspeptin-10, blood was collected, and the concentrations of hormones (GnRH, FSH, LH, testosterone, kisspeptin and corticosterone) were determined using the enzyme-linked immunosorbent assay (ELISA) method.

Results. Restraint and vital stresses reduced the concentration of sex hormones and increased the level of corticosterone. The administration of kisspeptin-10 increased the concentration of luteinizing hormone and gonadotropin-releasing hormone after different types of stress, both with intranasal and intraperitoneal administration, while the concentration of testosterone increased only with restraint stress and systemic administration of the drug, and the concentration of follicle-stimulating hormone did not significantly change after the administration of kisspeptin. When evaluating the level of kisspeptin in the blood, it was found that the administration of kisspeptin-10 increased its concentration with both intraperitoneal and intranasal administration.

Conclusion. Thus, emotional stress reduces the concentration of sex hormones and increases the level of corticosterone. Kisspeptin-10 increases the level of sex hormones and reduces the content of corticosterone.

Keywords: kisspeptin-10, vital stress, restriction stress, sex hormones, corticosterone

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Роль кисспептина-10 в регуляции гипоталамо-гипофизарно-гонадной системы при посттравматическом стрессовом расстройстве

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АННОТАЦИЯ

Актуальность. При посттравматических стрессовых расстройствах (ПТСР) наблюдаются половые дисфункции, которые плохо поддаются психотерапевтическому воздействию. В последнее время для лечения нарушений репродуктивной сферы предложены нейропептиды группы кисспептина. Они оказывают влияние на гипоталамо-гипофизарно-гонадную ось, участвуя в регуляции полового поведения и в контроле уровня половых гормонов. Показано, что кисспептины могут влиять и на гормоны стресса, что может играть ключевую роль в поддержании половой функции при различных стрессовых воздействиях.

Цель исследования — изучить влияние курсового интраназального и внутрибрюшинного способов введения кисспептина-10 на уровни половых гормонов и гормонов стресса у животных с посттравматическим стрессовым расстройством, вызванным рестрикционным и витальным стрессами.

Материалы и методы. Самцов крыс линии Вистар в течение 14 последовательных дней помещали в клетку с рецептивными самками на 15 минут и оценивали характер полового поведения, затем крысы-самцы подвергались процедуре рестрикционного или витального стрессов с последующим курсовым введением кисспептина-10. После стресса и введения кисспептина-10 у животных производили взятие крови и определяли концентрацию гормонов (гонадотропин-рилизинг гормона (ГнРГ), фолликулостимулирующего гормона (ФСГ), лютеинизирующего гормона (ЛГ), тестостерона, кисспептина и кортикостерона) методом иммуноферментного анализа.

Результаты. Рестрикционный и витальный стрессы снижали концентрацию половых гормонов и повышали уровень кортикостерона в крови. Кисспептин-10 увеличивал концентрацию гонадотропин-стимулирующего гормона и лютеинизирующего гормона после разных видов стресса при интраназальном и внутрибрюшинном введении, тогда как концентрация тестостерона повышалась только при системном введении препарата после рестрикционного стресса. Концентрация фолликулостимулирующего гормона значимо не изменялась после введения кисспептина-10. При оценке уровня кисспептина в крови установлено, что введение кисспептина-10 повышало его концентрацию как при внутрибрюшинном, так и при интраназальном введении.

Заключение. Таким образом, при посттравматическом стрессовом расстройстве, индуцированным рестрикционным и витальным стрессами, наблюдается снижение концентрации половых гормонов и повышение уровня кортикостерона в крови. Курсовое интраназальное и внутрибрюшинное введение кисспептина-10 нормализует уровень половых гормонов и кортикостерона в крови.

Ключевые слова: кисспептин-10, витальный стресс, рестрикционный стресс, половые гормоны, кортикостерон

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INTRODUCTION

The impact of extreme stressful situations on humans, followed by the development of post-traumatic stress disorder, leads to significant changes in the human body, and severe and prolonged stress can lead to reproductive dysfunction [1]. At the same time, the levels of a number of hormones can change significantly [2]. Currently, the neurotropic effects of a number of neuropeptides aimed at overcoming the effects of stress and developing appropriate behavioral strategies in response to stress have been studied [3, 4].

Kisspeptins (KP) are a family of peptides encoded by the *Kiss1* gene. The product of this gene is a hydrophobic protein consisting of 145 amino acids, a precursor of metastatin, a 54-amino acid protein that was originally named for its ability to inhibit metastasis [5].

KP belong to a large family of peptides known as RF-amid peptides, which carry a common arginine-phenylalanine-amide at the C-terminus. During the cleavage of the precursor of kisspeptins, kisspeptins 54, 13, 14, and 10 are formed, but the biological activity of kisspeptin is associated specifically with the last ten amino acid residues at the C-terminus [6]. Kisspeptins are involved in the regulation of mood, emotions, and fertility, have vasoconstrictor activity, and have a direct effect on the reproductive system [7]. Kisspeptins are actively synthesized in the anterior ventral-periventricular and arcuate nuclei of the hypothalamus, as well as in extrahypothalamic structures such as the medial amygdala, hippocampus, bed nucleus of the stria terminalis, thalamus, frontal cortex, midbrain, and pons [8]. From a functional point of view, these brain structures are key limbic and paralimbic areas that perform important functions in mood and behavior control [9].

Glucocorticoid receptors that respond to levels of adrenocorticotropic hormone (ACTH) and corticosterone are expressed on kisspeptin neurons. It has been shown that in mice with a knockout of the glucocorticoid receptor gene in the kisspeptin neurons of the hypothalamus, the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in response to stress did not decrease, in contrast to this indicator in wild-type mice [10]. However, another study found no correlation between glucocorticoids and decreased sex hormone levels, suggesting other mechanisms of interaction [11].

Reproductive behavior is a complex sequence of behavioral and hormonal responses aimed at producing offspring. It includes the selection of mating partners, courtship and copulatory behavior, as well as caring for offspring. It has been shown that kisspeptin is involved in various aspects of reproductive behavior [9]. Sex hormones, along with regulating the reproductive sphere, can also modulate the body's response to stress. Testosterone in rats inhibits the hormonal response to stress, while estrogens enhance it. Hormonal balance can determine the degree of the body's response to stressors [12].

Kisspeptins indirectly affect the reproductive system by influencing the levels of gonadotropin-releasing hormone (GnRH), FSH, and LH in the body. GnRH-containing neurons form a common pathway for fertility regulation, as GnRH secreted by axons can stimulate LH and FSH secretion by the anterior pituitary gland. Gonadotropins, in turn, stimulate the reproductive system through the processes of steroidogenesis and gametogenesis [13].

We have previously shown that intraperitoneal administration of kisspeptin-10 increased testosterone levels and sexual motivation in rats, whereas intranasal administration of kisspeptin increased only motivation without altering blood testosterone levels [14–16]. However, the concentrations of other sex hormones after stress, as well as a comparison of different types of stress and their effect on hormone levels, have not been studied, which determined the aim of our study.

AIM

The aim is to investigate the effect of intranasal and intraperitoneal administration of kisspeptin-10 on sex hormone and stress hormone levels in animals with post-traumatic stress disorder caused by restrictive and predator stress.

MATERIALS AND METHODS

During the experiments, 42 male Wistar rats of reproductive age (90–100 days) were studied. The animals were preliminarily divided into 7 groups, which were kept in standard cages with free access to water and food. The first group consisted of intact control males. The second group consisted of males subjected to restrictive stress without drug administration. The third group included males receiving intranasal kisspeptin-10, and the fourth group included males receiving intraperitoneal administration of the drug after restrictive stress. A similar division was observed for males that underwent predator stress (groups 5–7). Each animal male was placed in a cage with receptive females for 15 minutes a day for 14 consecutive days, and the presence of sexual behavior was recorded.

Restrictive stress was produced according to the method [17], in which the animal was immobilized in an individual pen for 6 hours a day for 5 days. Ten days after restraint stress, the animals were administered kisspeptin-10 intranasally and intraperitoneally for 5 days. On the last day of kisspeptin-10 administration, blood was collected from males to determine hormone levels using enzyme-linked immunosorbent assay (ELISA).

Predator stress in animals was induced using the method described in [18], according to which they were placed with a tiger python to create a model of psychological

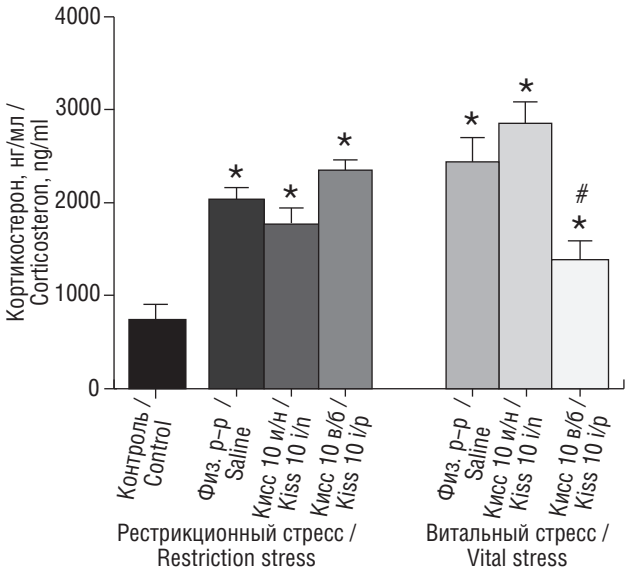

Fig. 1. Effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of corticosterone in the blood of animals with PTSD induced by restriction and vital stress. * — p <0.01 relative to intact control; # — p<0.01 relative to the group of rats with vital stress

Рис. 1. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень кортикостерона в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,01 относительно интактного контроля; # — p <0,01 относительно группы крыс с витальным стрессом

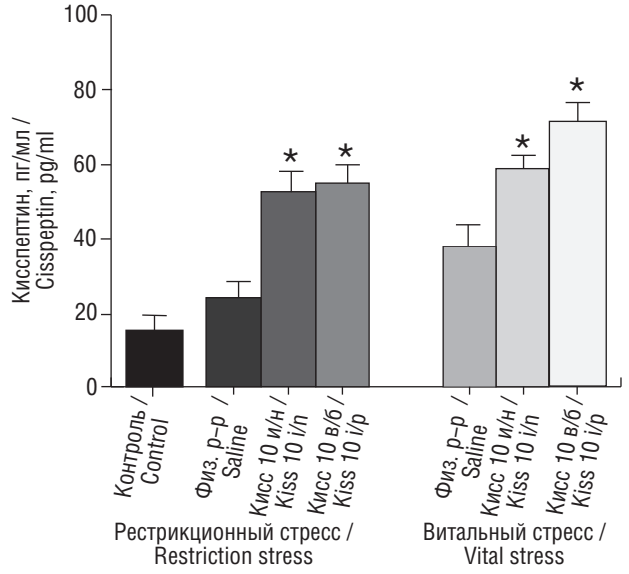

Fig. 2. Effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of kisspeptin in the blood of animals with PTSD induced by restriction and vital stress. * — p <0.01 relative to the intact control group

Рис. 2. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень кисспептина в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,01 относительно группы интактного контроля

trauma. Male rats were subjected to predator stress once. On the 10th day after stress, the animals were administered kisspeptin-10 for 5 days. Thirty minutes after the last administration, the animals were decapitated and total blood sampling was performed.

The drug used was an analogue of mammalian kisspeptin, kisspeptin-10. The drug was administered intranasally at a dose of 20 μg in 20 μl, 10 μl in each nostril, and intraperitoneally at a dose of 1 mg/kg in a volume of 0.5 ml [14]. Saline solution was used as a control.

The concentrations of corticosterone, GnRH, FSH, LH, testosterone, and kisspeptin in the blood of animals were determined by solid-phase competitive enzyme-linked immunosorbent assay using the ELISA Kit for Corticosterone (Cort), ELISA Kit for GnRH, ELISA Kit for Follicle Stimulating Hormone (FSH), ELISA Kit for Luteinizing Hormone (LH), ELISA Kit for Testosterone (Testo), and ELISA Kit for Kisspeptin 1 (KISS1) from Cloud Clone (USA) in full accordance with the manufacturer's instructions.

Statistical significance was assessed using GraphPad Prism 10 software. Normality of distribution was assessed using the Shapiro-Wilk and Kolmogorov–Smirnov test. To compare the groups, we used one-way ANOVA and the Kruskal–Wallis test, followed by Tukey's post-hoc analysis. Differences were considered statistically significant at a significance level of p <0.05. The data are presented as "mean ± standard error of the mean".

RESULTS AND DISCUSSION

Post-traumatic stress disorder (PTSD), caused by restrictive and predator stress, is characterized by changes in the activity of the hypothalamic-pituitary-gonadal and adrenal systems. Repeated administration of kisspeptin-10 partially normalizes hormonal disorders in animals with PTSD.

The concentration of corticosterone in the blood of male rats was significantly higher in stressed animals compared to intact ones: 2.72-fold increase in cases of restrictive stress and 3.28 times higher in cases of predator stress. With intraperitoneal administration of kisspeptin-10, the group with predator stress had significantly lower corticosterone levels compared to stressed animals — 1.8 times lower (Fig. 1).

Intranasal and intraperitoneal administration of kisspeptin-10 statistically significantly increases its content in the blood of animals subjected to restrictive and predator stress. Under restrictive stress and intranasal administration of the drug, the concentration of kisspeptin in the blood increases 2.6 times compared to the control, and with intraperitoneal administration, it increases 2.8 times compared to the control. Under predator stress and intranasal administration, the concentration of kisspeptin increases 1.85 times compared to the control, and with intraperitoneal administration, it increases 2.24 times compared to the control. No statistically significant difference in the concentration of kisspeptin in the blood was found with intranasal and intraperitoneal administration of the drug (Fig. 2).

The concentration of GnRH in the blood of male rats is significantly reduced in stressed animals compared

to intact controls, both under restrictive and predator stress. In animals subjected to restrictive stress, GnRH decreased 2.69 times, and in animals subjected to predator stress, blood GnRH decreased 2.61 times. Intranasal administration of kisspeptin-10 did not show a significant increase in blood GnRH, but there was a tendency toward an increase, and intraperitoneal administration of the drug showed a significant increase in blood GnRH after restrictive stress—by 2.18 times, and after predator stress — by 1.75 times (Fig. 3).

LH concentration was significantly lower after exposure to both restrictive and predator stress —2.55 and 1.96 times lower, respectively. Intranasal and intraperitoneal administration of kisspeptin-10 increases blood LH levels in animals with PTSD induced by restrictive and predator stress. LH levels after intranasal and intraperitoneal administration increased by 1.42 and 1.62 times, respectively, compared to the group of rats with restrictive stress. In the group of rats with predator stress, LH levels increased by 1.40 and 1.56 times, respectively, with intranasal and intraperitoneal administration of kisspeptin-10 (Fig. 4).

During the study of FSH levels in the blood of male rats, it was found that the concentration of the hormone statistically significantly decreased by 1.8 times under restriction stress and by 1.3 times under predator stress compared to the intact control, however, no statistically significant differences were found between the restriction and predator stress groups and the groups with the administration of kisspeptin-10 (Fig. 5).

Blood testosterone levels decrease statistically significantly under restrictive stress (p=0.0012). There are no statistically significant differences during predator stress, but there is a tendency toward a decrease in testosterone levels. Intraperitoneal administration of kisspeptin-10 increases testosterone concentration in male rats under restrictive stress (p=0.0126). In predator stress, both intranasal and intraperitoneal administration of kisspeptin-10 had no statistically significant effect on testosterone levels (Fig. 6).

In PTSD induced by restraint and predator stress, a decrease in sex hormone concentration and an increase in blood corticosterone levels were observed. A course of intranasal and intraperitoneal administration of kisspeptin-10 normalizes sex hormone and corticosterone levels in the blood.

PTSD in humans can cause sexual dysfunction that is difficult to treat with psychotherapy [19]. Recently, the use of neuropeptide drugs of the kisspeptin group has been proposed for the drug therapy of reproductive disorders [20]. They affect the hypothalamic-pituitary-gonadal axis, participating in the regulation of sexual behavior and control of sex hormone levels [21]. It has been found that kisspeptins can also affect stress hormones, i.e., they can play a key role in maintaining sexual function under various stressful conditions [15, 22].

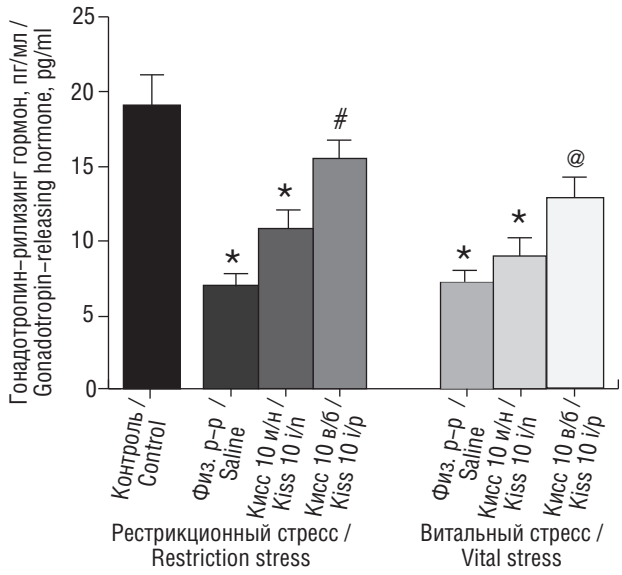

Fig. 3. Effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of gonadotropin-releasing hormone in the blood of animals with PTSD induced by restriction and vital stress. * — p <0.01 relative to the intact control group; # — p <0.05 relative to the group of animals with restriction stress, @ — p <0.05 relative to the group of animals with vital stress

Рис. 3. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень гонадотропин-рилизинг-гормона в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,01 относительно группы интактного контроля; # — p <0,05 относительно группы животных с рестрикционным стрессом; @ — p <0,05 относительно группы животных с витальным стрессом

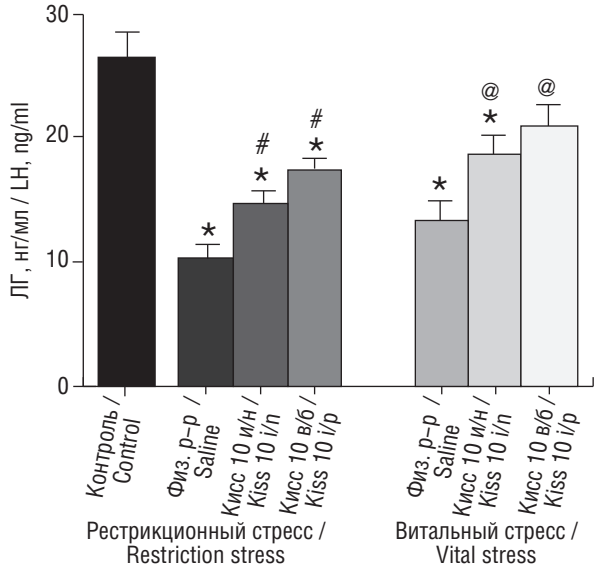

Fig. 4. The effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of luteinizing hormone (LH) in the blood of animals with PTSD induced by restriction and vital stress; * — p <0.01 relative to the intact control group; # — p <0.05 relative to the group of animals with restriction stress; @ — p <0.05 relative to the group of animals with vital stress

Рис. 4. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень лютеинизирующего гормона (ЛГ) в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,01 относительно группы интактного контроля; # — p <0,05 относительно группы животных с рестрикционным стрессом; @ — p <0,05 относительно группы животных с витальным стрессом

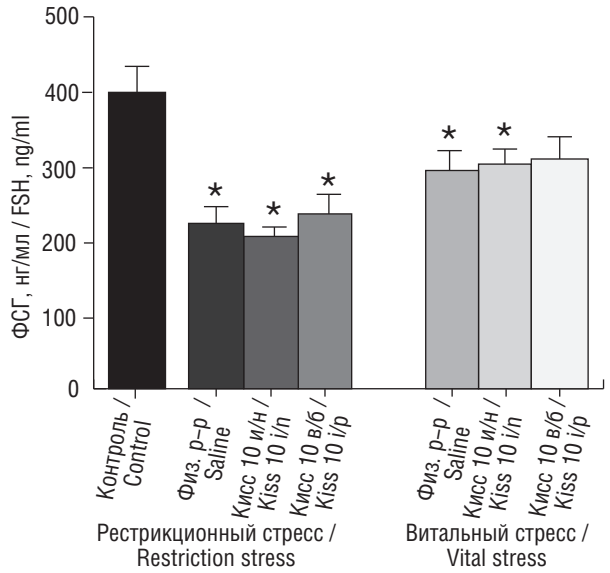

Fig. 5. The effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of follicle-stimulating hormone (FSH) in the blood of animals with PTSD induced by restriction and vital stress. * — p <0.05 relative to the intact control group

Рис. 5. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень фолликулостимулирующего гормона (ФСГ) в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,05 относительно группы интактного контроля

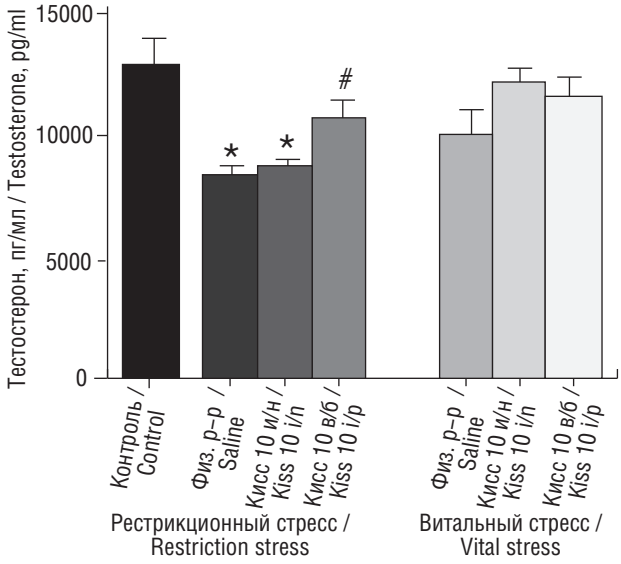

Fig. 6. Effect of intranasal and intraperitoneal administration of kisspeptin-10 on the level of testosterone in the blood of animals with PTSD induced by restriction and vital stress. * — p <0.01 relative to the intact control group; # — p <0.05 relative to the group of animals with restriction stress

Рис. 6. Влияние интраназального и внутрибрюшинного введения кисспептина-10 на уровень тестостерона в крови животных с ПТСР, индуцированным рестрикционным и витальным стрессами. * — p <0,01 относительно группы интактного контроля; # — p <0,05 относительно группы животных с рестрикционным стрессом

It is known that various stressors cause an increase in glucocorticoid levels, which suppresses reproductive function and reduces the level of hormones in the hypothalamic-pituitary-gonadal axis [23]. In the hypothalamus, glucocorticoids suppress GnRH release [24]. After exposure to predator stress — the presence of a predator (python) — male rats exhibited sexual dysfunction in the form of impaired appetitive phase of sexual behavior [15]. In the present study, male rats were subjected to predator stress and restrictive stress, after which their concentrations of sex hormones and stress hormones were determined. Against the background of PTSD induced by restrictive or predator stress, the concentrations of sex hormones (GnRH, FSH, LH, and testosterone) decreased, and the level of corticosterone in the blood increased. A more pronounced decrease in sex hormone levels was demonstrated with restrictive stress compared to predator stress.

When assessing the level of kisspeptin in the blood, it was found that the administration of kisspeptin-10 increased the concentration of the peptide both with intraperitoneal and intranasal administration. It is known that one of the causes of hypogonadotropic sexual dysfunction is a mutation in the *Kiss1* gene. Kisspeptin may therefore be key to initiating and maintaining the function of the hypothalamic-pituitary-gonadal axis [25]. At the same time, glucocorticoid receptors are also expressed in kisspeptin-containing neurons of the hypothalamus [26], suggesting that glucocorticoids may influence the reproductive function of the body through these neurons.

In the present study, the administration of kisspeptin-10 increased the concentration of GnRH and LH after various types of stress and with both intranasal and intraperitoneal administration, whereas the concentration of testosterone increased only with restrictive stress and systemic administration of the drug, and FSH concentrations did not change significantly after administration of kisspeptin. It is likely that kisspeptin-10 stimulated GnRH-containing neurons in the hypothalamus, leading to activation of the hypothalamic-pituitary-gonadal system and normalization of reproductive function in PTSD. Experimental models have demonstrated that kisspeptin plays a key role in modulating reproductive behavior, including sexual motivation and erection in male rats [27, 28]. Kisspeptin also has a positive effect on sexual behavior in humans. The administration of kisspeptin in men caused a decrease in sexual aversion and activation of the limbic system in response to sexual stimuli [20]. Along with the influence of kisspeptin-10 on sex hormone levels, its effect on glucocorticoid content in the development of PTSD has been proven. Intraperitoneal administration of kisspeptin-10 reduced elevated corticosterone levels in animals after predator stress, suggesting possible stress-limiting effects of kisspeptins in rats.

CONCLUSION

1. During the development of PTSD, the hypothalamic-pituitary-gonadal system is suppressed, characterized by a decrease in sex hormone levels and an increase in corticosterone content in the blood.

2. Intranasal and intraperitoneal administration of kisspeptin-10 can normalize the levels of sex hormones and corticosterone in the blood, which indicates the possibility of using kisspeptin group peptide-based agents to correct reproductive function disorders in PTSD.

ADDITIONAL INFORMATION

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