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Effects of the new ghrelin receptor antagonist agrelax on compulsive overeating induced by acute and chronic stress in rats

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ABSTRACT

BACKGROUND: Intense and prolonged stress can be detrimental to both psychological and physical health. Stress often leads to the development or worsening of compulsive overeating. Compulsive overeating is characterized by recurrent episodes of consuming large amounts of food, accompanied by a sense of loss of control.

AIM: To study the effects of the ghrelin receptor antagonist agrelax on compulsive overeating induced by acute and chronic stress in rats.

MATERIALS AND METHODS: The study involved 150 male and 15 female Wistar rats. To simulate compulsive overeating, the animals received a high-calorie mixture based on chocolate paste three times a week, while maintaining free access to standard food and water. Compulsive behavior was assessed using the marble burying test. Different groups of animals were exposed to various stressors, including maternal deprivation, limb electrical stimulation, partial sensory and complete social isolation, and acute vital stress. Agrelax, a ghrelin receptor antagonist, was administered intranasally at a dose of 1 μg/μL, 10 μL in each nostril, for 7 days.

RESULTS: Compulsive behavior was evaluated using the marble burying test. The experimental group on a high-calorie diet buried significantly more marbles than the control group ($p < 0.01$). After a 7-day course of Agrelax, the number of buried marbles significantly decreased, reaching the control group values ($p < 0.05$). A model of compulsive overeating in rats was successfully developed by providing high-calorie food three times a week. After a 7-day course of Agrelax, the consumption of high-calorie food significantly decreased ($p < 0.05$). Limb electrical stimulation significantly increased the consumption of high-calorie food ($p < 0.05$). After a 7-day course of Agrelax, the consumption of high-calorie food significantly decreased ($p < 0.01$). Maternal deprivation stress significantly increased the consumption of high-calorie food ($p < 0.001$). After a 7-day course of Agrelax, the consumption of high-calorie food decreased, reaching the control group values. In animals raised under partial sensory and complete social isolation, Agrelax did not significantly reduce the consumption of high-calorie food. In animals subjected to acute vital stress, Agrelax did not reduce the consumption of high-calorie food.

CONCLUSIONS: The data obtained suggest new ways for synthesizing peptide pharmacological agents based on ghrelin and its antagonists to treat eating disorders.

Keywords: compulsive overeating; maternal deprivation; limb electrical stimulation; social isolation; vital stress; marble burying test; agrelax; ghrelin.

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Влияние нового антагониста грелиновых рецепторов агрелакса на компульсивное переедание, вызванное острым и хроническим стрессами у крыс

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АННОТАЦИЯ

Актуальность. Сильные и продолжительные стрессы могут быть опасны как для психологического, так и физического здоровья человека. Нередко стресс приводит к развитию или усугублению компульсивного переедания. Компульсивное переедание характеризуется рецидивирующими эпизодами поедания большого объема пищи с чувством утраты контроля над собой.

Цель — изучить действие антагониста рецепторов грелина агрелакса на компульсивное переедание, вызванное острым и хроническим стрессами у крыс.

Материалы и методы. В исследовании было задействовано 150 самцов и 15 самок крыс линии Вистар. Для моделирования компульсивного переедания животные получали высококалорийную смесь на основе шоколадной пасты 3 раза в неделю при сохранении свободного доступа к стандартному корму и воде. Компульсивность в поведении оценивали с помощью теста закапывания шариков. В качестве стрессорных воздействий для разных групп животных использовали материнскую депривацию, электростимуляцию конечностей, частичную сенсорную и полную внутривидовую изоляцию, острый витальный стресс. Антагонист рецепторов грелина агрелакс вводили интраназально 1 мкг/1 мкл, по 10 мкл в каждую ноздрю в течение 7 дней.

Результаты. Проведена оценка компульсивного поведения в тесте закапывания шариков. Опытная группа животных, получающая высококалорийное питание, закапывала достоверно большее количество шариков, чем контрольная ($p < 0,01$). После 7-дневного курса агрелакса количество закопанных шариков значимо снижалось, доходя до значений контрольной группы ($p < 0,05$). Отработана методика компульсивного переедания у крыс при выдаче высококалорийной пищи 3 раза в нед. После 7-дневного курса агрелакса потребление высококалорийной пищи достоверно снижалось ($p < 0,05$). Воздействие электростимуляции конечностей значимо увеличивало количество съедаемой высококалорийной пищи ($p < 0,05$). После 7-дневного курса агрелакса потребление высококалорийной пищи достоверно снижалось ($p < 0,01$). Стресс материнской депривации значимо увеличивал потребление высококалорийной пищи ($p < 0,001$). После 7-дневного курса агрелакса, потребление высококалорийной пищи снижалось до показателей контрольной группы. У животных, выращенных в условиях частичной сенсорной и полной внутривидовой изоляции, применение агрелакса не дало выраженного эффекта снижения количества потребляемой высококалорийной пищи. У животных, перенесших острое витальное воздействие, применение агрелакса не снижало количества потребляемой высококалорийной пищи.

Выводы. Полученные данные предполагают новые пути синтеза фармакологических средств пептидной природы на основе грелина и его антагонистов для коррекции пищевой зависимости.

Ключевые слова: компульсивное переедание; материнская депривация; электростимуляция конечностей; социальная изоляция; витальный стресс; закапывание шариков; агрелакс; грелин.

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BACKGROUND

The World Health Organization defines overweight and obesity as conditions characterized by abnormal or excessive fat accumulation that may impair health [1]. Obesity results from a sustained positive energy balance, where excessive calorie intake exceeds energy expenditure [2]. Obesity is associated with an increased incidence of pathological conditions, including type 2 diabetes, cardiovascular diseases, and cancer, and significantly reduces life expectancy [3–6].

Pharmacological treatment of obesity is an evolving area of pharmacology burdened with severe drug-related side effects and challenges due to the lack of data on the long-term effects of medications on obesity-associated morbidity and mortality. For example, the anti-obesity drug sibutramine poses cardiovascular concerns [7], while rimonabant has been linked to an increased risk of suicide [8]. Orlistat, a specific inhibitor of intestinal lipases [9], is used to manage obesity. However, the high frequency of pronounced clinically significant side effects, mainly gastrointestinal, complicates its widespread use in clinical practice [10, 11].

The drug with the fewest side effects, semaglutide, a glucagon-like peptide-1 receptor (GLP-1R) agonist, can only be used in combination with physical activity and a low-calorie diet [12].

New opportunities in the treatment of obesity have emerged due to the discovery of the role of orexigenic peptides (ghrelin, orexins, and obestatin) in the mechanisms of eating behavior [13, 14].

Ghrelin is a peptide hormone produced in the gastric mucosa and the arcuate nucleus of the hypothalamus, which consists of 28 amino acids and includes three isoforms: acylated ghrelin, nonacylated (desacyl ghrelin), and obestatin [15]. The ghrelin receptor has two molecular forms, GHSR1A and GHSR1B, but only GHSR1A is biologically active. GHSR1A receptors are primarily located in the pancreatic islets, adrenal glands, thyroid gland, myocardium, and brain structures such as the anterior pituitary gland, arcuate nucleus of the hypothalamus, hippocampus, *substantia nigra*, and ventral tegmental area [16]. Ghrelin is involved in the regulation of eating behavior, dependence on psychostimulants and alcohol [17], body weight [18], energy expenditure [19], and also influences glucose homeostasis [20] and insulin secretion [21]. Ghrelin has also been shown to be involved in stress response [22]. In patients with binge eating disorder (compulsive overeating), low peripheral ghrelin levels were observed before meals, which may be associated with the neurochemical mechanisms of this disorder [16].

Food addiction has not been yet recognized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a distinct disorder, however, there are some similarities between certain eating disorders and substance use disorders [23, 24]. These similarities include cravings, decreased control over consumption, increased impulsivity, and altered reward sensitivity. Binge eating disorder and bulimia nervosa have been proposed as phenotypes that may reflect these similarities to a greater extent.

Binge eating disorder is the most common eating disorder, characterized by recurrent episodes of overeating during which a person consumes an excessive amount of food without feeling hungry. Overeating episodes are usually accompanied by a feeling of lack of control with an inability to refrain from eating or to stop eating once it has started [24]. Like psychoactive substances, highly processed foods contain increased amounts of potentially addictive substances (e.g., refined carbohydrates) that are rapidly absorbed and can quickly affect the central nervous system. In an experiment, rats preferred saccharin over cocaine when given a choice [25].

Currently, only one drug (lisdexamfetamine dimesylate) has been approved by the US Food and Drug Administration in 2015 for the treatment of binge eating disorder [26]. However, its use is limited by side effects, including a high risk of misuse and cardiovascular diseases [27].

A number of models of compulsive overeating have been developed in rodents. The restricted access model is of greatest interest. It involves intermittent exposure to fats to induce episodes of binge eating [28–30].

Intense and prolonged stress can be detrimental to both psychological and physical health. Stress disorder can be triggered by a traumatic experience, including vital stress or life-threatening situations, characterized by a subjective sense of threat to life, with rapid dynamics, significant loss of the body's functional reserves, and a "trace of reactions" in the delayed period [31]. Most often, vital stress can be observed among participants in armed conflicts [32].

Equally relevant are the stress of social isolation associated with restrictive measures during COVID-19 [33], and the stress of maternal neglect, which is increasingly observed in a society marked by rapid technological development. Unfortunately, it is not uncommon for mothers to show more interest in their smartphones than in their own children, which inevitably leaves an imprint on the developing psyche of children.

The negative impact of stress on the body is comparable to the risks that arise from alcohol and psychoactive substance use. The consequences of the aforementioned stressors include sleep disturbances, lack of physical activity, and eating disorders, which often lead to obesity.

The neurotransmitter dopamine plays a key role in the brain's reward system. Experiments have shown that the metabolic circuits of the hypothalamus interact with the brain's dopamine system to regulate eating behavior [34, 35].

It has been demonstrated that the brain's reward circuit associated with compulsive overeating is similar to that of substance addiction. Enzyme immunoassay revealed that body weight in rats negatively correlated with D2 receptor

levels. In other words, the heavier the rat, the lower the density of D2 receptors in the striatum [36].

An intermittent feeding schedule with palatable food resulted in increased activation of dopamine D1 and μ1-opioid receptors, as well as reduced binding to dopamine D2 receptors in the dorsal striatum [10].

Existing therapeutic approaches to correct excess weight and obesity do not always lead to significant clinical and physiological effects, indicating the need for exploring new treatment strategies for the pharmacological management of obesity. Moreover, the available drugs for obesity treatment are typically administered orally or via injection, as are many experimental medications. Therefore, the development of innovative, effective, and safe pharmacological methods that ensure high-quality weight loss is of critical importance.

AIM: To study the effects of the ghrelin receptor antagonist Agrelax on compulsive overeating induced by acute and chronic stress in rats.

MATERIALS AND METHODS

The study involved 150 male and 15 female Wistar rats weighing 200–250 g, obtained from the Rappolovo laboratory animal breeding facility (the Leningrad Region). The animals were housed in vivarium in standard plastic cages with free access to water and food, under inverted light conditions (8AM to 8PM) at a temperature of 22 ± 2 °C. Throughout the experiment, the principles of humane treatment of laboratory rats were observed in accordance with the rules of laboratory practice (Order of the Ministry of Health of Russia No. 267, dated 19.06.2003).

After being received from the breeding facility, the animals underwent a 2-week quarantine in the designated block of the vivarium.

Female Wistar rats were housed in plastic cages (40×50×20 cm) in groups of five, with *ad libitum* access to food and water. One male was placed into each cage, and the next day, vaginal smears were collected from the females to detect spermatozoa. Using light microscopy, pregnancy was confirmed, and it was considered day zero. Once pregnancy was confirmed, the animals were placed in individual cages. Pregnancy lasted for 20 ± 2 days.

Maternal deprivation model. Rats were placed in individual plastic cups for 180 min for ten consecutive days from Day 2 to Day 12 of the postnatal period. Visual contact with the mother was excluded. After maternal deprivation and milk feeding, the rats were raised in standard cages with 5 animals in each. Males aged 90–100 days and weighing 200–250 g were used in the experiment [37].

Raising animals under conditions of partial sensory and complete social isolation. Social isolation during ontogenesis can alter the psycho-emotional status of animals and cause disturbances in the neurotransmitter systems of the brain during the establishment of neuroendocrine interactions. This subsequently leads to persistent modifications of neuroendocrine, immune and visceral responses in the adult organism [38]. The litters of rats were separated from their mothers on Day 21 of life and housed in individual plastic cages measuring 40×30×25 cm. From Day 93 of life, the rats were included in the main experiment.

The rats included in the experiment were divided into five groups:

1) without stress (*n* = 30);
2) maternal deprivation stress (*n* = 30);
3) partial sensory and complete social isolation (*n* = 30);
4) electrical stimulation of limbs (*n* = 30);
5) acute vital stress (*n* = 30).

Each group was further divided into two subgroups:

1) intact animals (*n* = 10);
2) experimental group that included animals with access to high-calorie sweet mixture three times a week (*n* = 20).

To simulate compulsive overeating, the experimental group was provided with additional high-calorie food three times a week, with access for one hour. Throughout the entire experiment, animals had free access to water and standard pelleted food. The high-calorie food consisted of a paste prepared by mixing chocolate paste, crushed rat pelleted food, and water in the following weight ratio: 52% of chocolate paste, 33% of pelleted food, and 15% of water. The calorie content was 3.63 kcal/g. Before the overeating session, the standard rodent food present in each cage was weighed to assess food consumption over 24 h the following day. The recorded parameters included: the amount of standard food consumed; the amount of chocolate paste consumed during the 1-hour access period; and the animals' weight (measured once a week on a strictly scheduled day) [39].

Marble burying test. This test was proposed as a model for obsessive-compulsive disorder, related to obsessive thoughts and behavior [40]. A cage measuring 20×25×17 cm was filled with a 5 cm layer of sawdust, and 20 glass marbles of 1 cm in diameter were placed evenly spaced on top. A rat was placed in the cage for 30 min. After this time, the number of marbles covered by sawdust by more than two-thirds was counted [41, 42]. In this experiment, each animal was tested three times.

Electrical stimulation of limbs (or foot shock; FS). FS has been widely used as a method for inducing measurable discomfort in animals for over 100 years. To induce stress, the animal was placed in a special chamber with an electrified floor, where electrical stimulation of the limbs was applied with a current of 0.6 mA for 30–60 s [43]. The FS chamber used in the experiment was designed by the staff of the Institute of Experimental Medicine (IEM).

Experiments were conducted in 5-day cycles. The effect of stress and the drug on the rats' behavior was assessed on Day 5. On Day 1, rats were given the chocolate-food mixture without additional stimuli, as described above. On Day 3, one hour before feeding the treat, rats underwent electrical

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stimulation of the limbs for 30 s, and on Day 5, for one minute. The drugs were administered intranasally on Day 5, 30 min after FS and 30 min before feeding the mixture.

Method for modeling psychological trauma. Psychological trauma is defined as a strong, brief exposure to external negative circumstances, leading to the development of negative emotional reactions such as fear, anxiety, terror, despair, etc., as well as the formation of somatic disorders (ICD-10, 1993). Psychological trauma was modeled by a stressful situation in which the animal experienced its partner's death caused by a predator's actions [44]. Each animal was subjected to an acute psychotraumatic situation once. A group of 20–22 rats was placed in a terrarium (dimensions 1.2×0.7×1 m) with a tiger python. The python strangled and swallowed one of the animals in the presence of the others, who experienced the death of their conspecific. During the experiment, the following behavioral acts were recorded: locomotion, sniffing, movement in place, upright posture, grooming, freezing, and resting (sitting quietly without motion). After this, the rats were removed from the terrarium and their behavior was tested over the next few days.

At the S.V. Anichkov Department of Neuropharmacology of the IEM, a peptide analog of the ghrelin antagonist Agrelax (1 μg/1 μl was) was synthesized using genetic engineering methods. During Week 6 of the experiment, it was intranasally administered to half of the experimental group, with 1 μL per nostril, for 7 consecutive days.

Statistical analysis. The normality of the data distribution in the samples was tested using the Kolmogorov—Smirnov test. For normally distributed data, one-way ANOVA analysis was used to detect statistical differences between multiple groups, while the Student's *t*-test for independent samples was performed to compare two groups. In the absence of normal distribution, a non-parametric analog for analysis of variance was used. For pairwise comparisons, the Mann—Whitney test was used. Differences were considered significant at a significance level of 95% ($p < 0.05$). Statistical data processing was performed using GraphPad Prizm v.6.

RESULTS

In this study of compulsive behavior using the marble burying test, the experimental group of animals that received additional high-calorie food buried a significantly greater number of marbles ($p < 0.01$) compared to the control group. This indicates increased compulsive behavior and confirms the development of compulsive overeating. After a 7-day course of Agrelax administration, the number of buried marbles significantly decreased, reaching the control group values ($p < 0.05$), which indicates an improvement in the compulsive behavior manifestations (Fig. 1).

In this study of compulsive overeating in rats, the average consumption of the high-calorie mixture was shown to be 9.1 ± 0.6 g. After a 7-day course of Agrelax, the consumption of high-calorie food significantly decreased ($p < 0.05$) to 5.6 ± 0.6 g. Despite the additional high-calorie mixture, daily consumption of standard food in the experimental group did not differ from that in the control group. After the 7-day course of Agrelax, the consumption of standard food decreased ($p < 0.05$) but did not significantly differ from the consumption of standard food by intact animals (Fig. 2).

Exposure to FS significantly increased the average consumption of the high-calorie mixture ($p < 0.05$). Intranasal administration of Agrelax significantly reduced ($p < 0.01$) the average amount of the treat consumed (Fig. 3).

Evaluation of the effect of maternal deprivation on the consumption of standard food showed that the average daily consumption of the high-calorie mixture did not change relative to the control group, while the overall consumption increased ($p < 0.001$) compared to the control group. Following Agrelax administration, the consumption of the

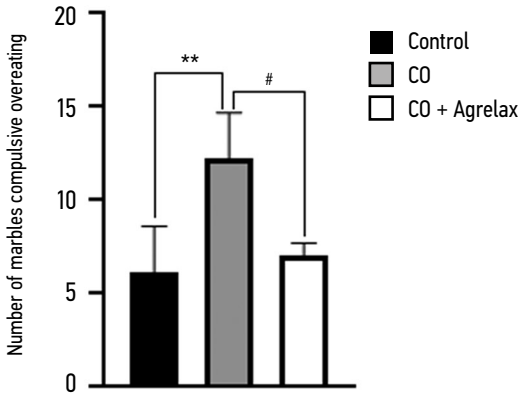

Fig. 1. Compulsive behavior assessment in the marble burying test. CO — compulsive overeating. $^{**}p < 0.01$; $^{\#}p < 0.05$

Рис. 1. Оценка компульсивного поведения в тесте закапывания шариков. CO — компульсивное переедание. $^{**}p < 0,01$; $^{\#}p < 0,05$

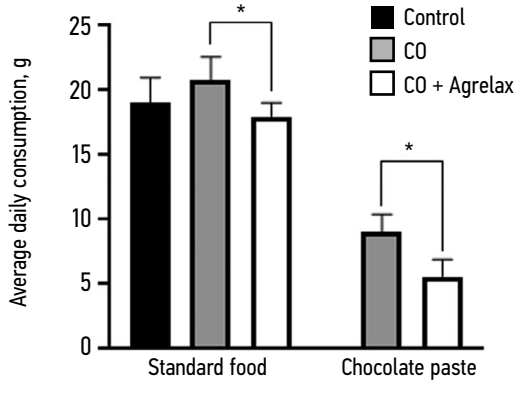

Fig. 2. Effects of agrelax on the consumption of standard pelleted and high-calorie food in the compulsive overeating rat model (CO). $^{*}p < 0,05$

Рис. 2. Влияние агрелакса на потребление стандартного брекетированного корма и высококалорийной пищи у крыс в модели компульсивного переедания (CO). $^{*}p < 0,05$

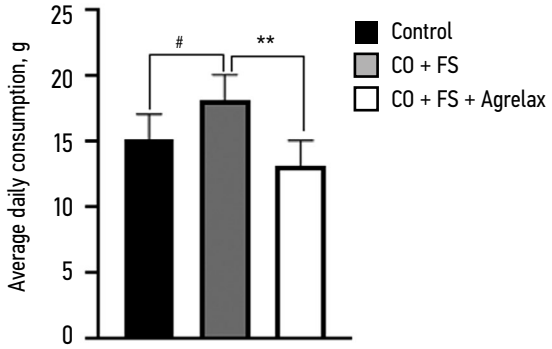

Fig. 3. Effects of limb electrical stimulation and agrelax on the consumption of chocolate-feed mix in the compulsive overeating (CO) rat model. $^{\#}p < 0,05$; $^{**}p < 0,01$

Рис. 3. Оценка действия электростимуляции конечностей и агрелакса на потребление шоколадно-кормовой смеси в модели компульсивного переедания (CO) у крыс. FS — электростимуляция конечностей. $^{\#}p < 0,05$; $^{**}p < 0,01$

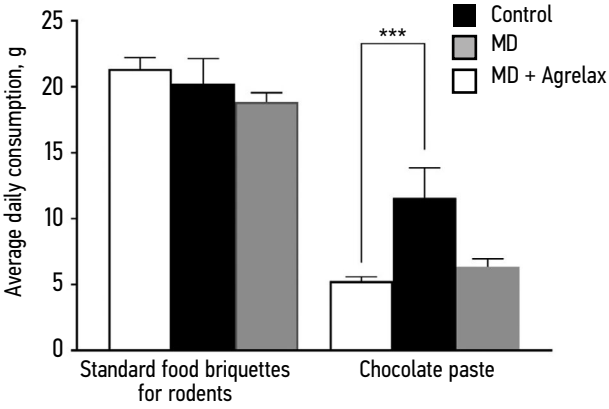

Fig. 4. Effects of the new ghrelin receptor antagonist Agrelax on the consumption of standard food and compulsive overeating in rats raised under maternal deprivation (MD) conditions. Average daily intake is shown $^{***}p < 0.001$ compared to the control (intact) group of animals

Рис. 4. Оценка действия нового антагониста грелиновых рецепторов агрелакса на потребление стандартного корма и компульсивное переедание у крыс, выращенных в условиях материнской депривации (MD). Показано среднее суточное потребление. $^{***}p < 0,001$ относительно контрольной (интактной) группы животных

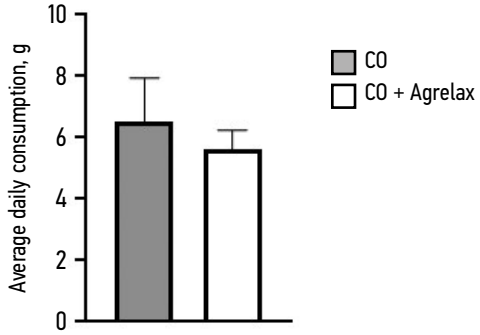

Fig. 5. Effects of agrelax on compulsive overeating (CO) in rats kept under partial sensory and complete social isolation

Рис. 5. Оценка действия агрелакса на компульсивное переедание (CO) у крыс, выращенных в условиях частичной сенсорной и полной внутривидовой изоляции

chocolate-food mixture decreased, reaching the control group values (Fig. 4).

In animals raised under conditions of partial sensory and complete social isolation, the administration of Agrelax did not produce a pronounced effect on reducing the consumption of the chocolate-food mixture (Fig. 5).

In animals subjected to acute vital stress, the administration of Agrelax did not reduce the consumed amount of chocolate-food mixture (Fig. 6).

DISCUSSION

In the present study, compulsive overeating was induced using the high-calorie food overconsumption method. Episodes of overeating were triggered through intermittent exposure to sources of carbohydrates and fats in a restricted-access model of compulsive overeating [28, 30]. The advantage of using intermittent food exposure in the development of compulsive overeating is supported by our earlier data, which demonstrated reduced consumption of high-calorie food in rats following maternal deprivation and a daily feeding regimen [37]. Additional assessments of compulsive behavior during the experiment helped confirm the development of compulsive overeating and evaluate its dynamics during the administration of Agrelax. Recent studies have shown the involvement of the ghrelin system in stress response mechanisms. In a study, the ghrelin receptor antagonist D-Lys GHRP-6 reduced pronounced compulsive behavior induced by the psychological trauma of partner loss [45]. Obsessive-compulsive disorder (OCD) is interpreted as a condition associated with intrusive and disturbing thoughts (obsessions) accompanied by compulsive behaviors (compulsions) aimed at reducing anxiety [46]. The pharmacotherapy of OCD is primarily based on antidepressants, benzodiazepine anxiolytics, and low doses of neuroleptics [46–48]. These drugs differ in their spectrum of action and effects and are associated with numerous side effects, indicating the need to develop new effective treatments for OCD, including those with demonstrated anti-compulsive activity in experimental models. Agrelax developed at the IEM

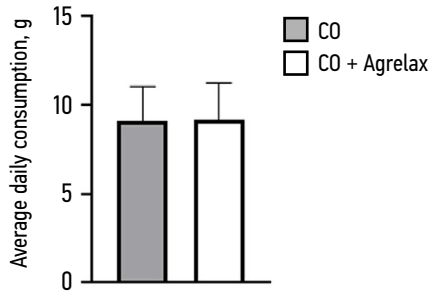

Fig. 6. Effects of Agrelax on compulsive overeating (CO) in rats subjected to acute vital stress

Рис. 6. Оценка действия агрелакса на компульсивное переедание (CO) у крыс, перенесших острое витальное воздействие

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offers several advantages. Due to its peptide nature, the drug is suitable for intranasal administration, enabling not only a reduction in the used dose and rapid central action but also a significant decrease in potential toxic effects.

In this study, the marble burying test was used to evaluate compulsive behavior in rats. This test has traditionally been used to assess the severity of compulsive behavior in rodents and to screen anti-compulsive drugs [42, 49, 50]. Animals are believed to use the available bedding material to bury undesirable sources of discomfort in their home environment. The number of marbles buried reflects the intensity of stereotypical behavior in animals [42]. The effects of ghrelin and its analogs on behavior in the marble burying test in rats are poorly understood. Similar effects have been observed in mice and rats following the administration of anxiolytics, antidepressants, and low-dose neuroleptics [47]. Compulsive behavior serves as a functional component of addictive behavior and is considered a neurobiological factor in alcohol, drug, gambling, and other addictions [51], as well as food-related dependencies [52].

The hypothalamus is the main brain region involved in feeding behavior. Ghrelin acts primarily in the hypothalamus, stimulating food intake behavior aimed at regulating energy homeostasis [53]. The significance of ghrelin signaling in brain regions outside the hypothalamus lies in its influence on learning and memory, reward and motivation, anxiety and depression. Possible targets of ghrelin action include corticotropin- producing neurons in the paraventricular nucleus of the hypothalamus. It has been shown that ghrelin administration activates these neurons [54]. Another possible target of ghrelin is the extended amygdala system, which includes the bed nucleus of the terminal striatum, the central nucleus of the amygdala, the *substantia innominata*, and the shell of the *nucleus accumbens* [54]. The extended amygdala structures receive inputs from dopaminergic neurons of the ventral tegmental area and constitute a main functional system for mediating the emotional and motivational effects of various addictive agents [55].

Evidence from various studies indicates that stress increases vulnerability to addiction, likely by enhancing the reward value associated with addictive substances through a sensitization-like mechanism [56]. This study showed that FS-induced stress increases signs of compulsive overeating of high-calorie foods. Intranasal administration of Agrelax reduces the manifestations of food addiction following electrical stimulation of limbs, suggesting novel avenues for the synthesis and application of peptide pharmacological agents based on ghrelin and its antagonists to address food addiction.

Chronic maternal deprivation stress in animals can serve as a model of maternal neglect in humans. Analysis of experimental data on maternal separation in early ontogenesis shows a significant impact of stress on the development of compulsive overeating [39]. Early psychological stress exerts long-term effects on development and socialization in children and adolescents, increasing the risk of eating disorders and compulsive overeating. During adolescence, hormonal changes and imbalances in excitation and inhibition processes occur, making the role of neurochemical intracerebral processes critical in the development of compulsive overeating [39]. Intranasal administration of Agrelax reduces the manifestations of food addiction, suggesting novel avenues for the synthesis and application of peptide pharmacological agents based on ghrelin and its antagonists to address food addiction.

CONCLUSION

Administration of the novel ghrelin receptor antagonist Agrelax reduces the manifestations of compulsive overeating in rats under conditions of intermittent consumption of high-calorie foods. This approach opens new possibilities for the synthesis and application of peptide pharmacological agents based on ghrelin and its antagonists to address food addiction. Moreover, the studied drug was administered intranasally, enabling not only a reduction in the used dose and rapid central action but also a significant decrease in potential toxic effects.

ADDITIONAL INFORMATION

Authors' contributions. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: N.D. Nadbitova, S.S. Pyurveev, M.A. Netesa, A.A. Lebedev — receiving and data analysis, article writing; P.D. Shabanov — development of the general concept.

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Ethics approval. The present study protocol was approved by the Ethics Committee of the Institute of Experimental Medicine, Protocol No. 2/23 of 06.05.2023.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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REFERENCES

1. www.who.int [Internet]. Obesity and overweight, 2021 [cited: 21.04.2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Westbury S, Oyebode O, van Rens T, Barber TM. Obesity stigma: causes, consequences, and potential solutions. *Curr Obes Rep*. 2023;12(1):10–23. doi: 10.1007/s13679-023-00495-3

3. Al-Sulaiti H, Diboun I, Agha MV, et al. Metabolic signature of obesity-associated insulin resistance and type 2 diabetes. *J Transl Med*. 2019;17(1):348. doi: 10.1186/s12967-019-2096-8

4. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121–135. doi: 10.1016/j.metabol.2018.11.001

5. Lazzaroni E, Ben Nasr M, Loretelli C, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharm Res*. 2021;171:105782. doi: 10.1016/j.phrs.2021.105782

6. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143(21):e984–e1010. doi: 10.1161/CIR.0000000000000973

7. Shah MS, Patel ZK, Bharucha R, et al. Sibutramine-induced nonischemic cardiomyopathy. *Cureus*. 2022;14(1):e21650. doi: 10.7759/cureus.21650

8. Nguyen T, Thomas BF, Zhang Y. Overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists: current approaches for therapeutics development. *Curr Top Med Chem*. 2019;19(16):1418–1435. doi: 10.2174/1568026619666190708164841

9. Filippatos TD, Derdemezis CS, Gazi IF, et al. Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Saf*. 2008;31(1):53–65. doi: 10.2165/00002018-200831010-00005

10. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA*. 1999;281(3):235–242. doi: 10.1001/jama.281.3.235

11. O'Meara S, Riemsma R, Shirran L. A systematic review of the clinical effectiveness of orlistat used for the management of obesity. *Obes Rev*. 2004;5(1):51–68. doi: 10.1111/j.1467-789X.2004.00125.x

12. US Food and drug [Internet]. Administration, FDA approves new drug treatment for chronic weight management, first since 2014, 2021 [cited: 21.04.2023]. Available from: https://www.fda.gov/news-event s/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014

13. Beck B, Fernette B, StrickerKrongrad A. Peptide S is a novel potent inhibitor of voluntary and fast-induced food intake in rats. *Biochem Biophys Res Commun*. 2005;332(3):859–865. doi: 10.1016/j.bbrc.2005.05.029

14. Zhang J, Ren P, Avsian-Kretchmer O, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science*. 2005;310(5750):996–999. doi: 10.1126/science.1117255

15. Chen CY, Asakawa M, Fujimiya M, et al. Ghrelin gene products and the regulation of food intake and gut motility. *Pharmacol Rev*. 2009;61(4):430–481. doi: 10.1124/pr.109.001958

16. Gnanapavan S, Kola B, Bustin SA, et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. *J Clin Endocrinol Metabolism*. 2002;87:2988. doi: 10.1210/jcem.87.6.8739

17. Lebedev AA, Karpova IV, Bychkov ER, et al. The ghrelin antagonist [D-LYS3]-GHRP-6 decreases signs of risk behavior in a model of gambling addiction in rats by altering dopamine and serotonin metabolism. *Neurosci Behav Physiol*. 2022;52(3):415–421. doi: 10.19163/MedChemRussia2021-2021-259

18. Nass R, Pezzoli SS, Oliveriet MC, al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: A randomized trial. *Ann Intern Med*. 2008;149(9):601–611 doi: 10.7326/0003-4819-149-9-200811040-00003

19. Huda MSB, Dovey T, Wong SP, et al. Ghrelin restores "lean-type" hunger and energy expenditure profiles in morbidly obese subjects but has no effect on postgastrectomy subjects. *Int J Obes*. 2009;33(3):317–325. doi: 10.1038/ijo.2008.270

20. Broglio F, Arvat E, Benso A, et al. Ghrelin, a natural gh secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. *J Clin Endocrinol Metab*. 2001;86(10):5083–5086. doi: 10.1210/jcem.86.10.8098

21. Reimer MK. Dose-dependent inhibition by ghrelin of insulin secretion in the mouse. *Endocrinology*. 2003;144(3):916–921. doi: 10.1210/en.2002-220819

22. Ducharme R, Anisman H, Abizaid A. Altered metabolic and neurochemical responses to chronic unpredictable stressors in ghrelin receptor-deficient mice. *Eur J Neurosci*. 2010;32(4):632–639. doi: 10.1111/j.1460-9568.2010.07310.x

23. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci*. 2010;13(5):635–641. doi: 10.1038/nn.2519

24. Association AP. *Diagnostic and statistical manual of mental disorders: DSM-5-TR*. Washington; London, 2013.

25. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS ONE*. 2007;2(8):e698. doi: 10.1371/journal.pone.0000698
26. Heo Y-A, Duggan ST. Lisdexamfetamine: a review in binge eating disorder. *CNS Drugs*. 2017;31(11):1015–1022. doi: 10.1007/s40263-017-0477-1
27. Ward K, Citrome L. Lisdexamfetamine: chemistry, pharmacodynamics, pharmacokinetics, and clinical efficacy, safety, and tolerability in the treatment of binge eating disorder. *Expert Opin Drug Metab Toxicol*. 2018;14(2):229–238. doi: 10.1080/17425255.2018.1420163
28. Boggiano MM, Artiga AI, Pritchett CE, et al. High intake of palatable food predicts binge-eating independent of susceptibility to obesity: An animal model of lean vs obese binge-eating and obesity with and without binge-eating. *Int J Obes*. 2007;31(9):1357–1367. doi: 10.1038/sj.ijo.0803614
29. Corwin RL, Wojnicki FHE. Binge eating in rats with limited access to vegetable shortening. *Curr Protoc Neurosci*. 2006;36:9.23B.1–9.23B.11. doi. 10.1002/0471142301.ns0923bs36
30. Moore CF, Leonard MZ, Micovic NM, et al. Reward sensitivity deficits in a rat model of compulsive eating behavior. *Neuropsychopharmacol*. 2020;45:589–596 doi: 10.1038/s41386-019-0550-1
31. Ushakov IB, Bubeev YuA, Krasovets SV, Ivanov AV. Individual psychophysiological mechanisms of adaptation under stress of lethal situations. *Neuroscience and Behavioral Physiology*. 2012;98(1):83–94. EDN: OXHHIZ (In Russ.)
32. Evdokimov VI, Shamrey VK, Pluzhnik MS. Combat stress research prospects in Russian academic publications analyzed using to VOSviewer software (2005–2021). *Medico-Biological and Socio-Psychological Problems of Safety in Emergency Situations*. 2023;(2):99–116. EDN: RUXCZT doi: 10.25016/2541-7487-2023-0-2-99-116
33. Sayin Kasar K, Karaman E. Life in lockdown: Social isolation, loneliness and quality of life in the elderly during the COVID-19 pandemic: A scoping review. *Geriatr Nurs*. 2021;42(5):1222–1229. doi: 10.1016/j.gerinurse.2021.03.010
34. DiLeone RJ, Georgescu D, Nestler EJ. Lateral hypothalamic neuropeptides in reward and drug addiction. *Life Sci*. 2003;73(6):759–768. doi: 10.1016/s0024-3205(03)00408-9
35. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr*. 2009;139(3):629–632. doi: 10.3945/jn.108.097618
36. Colantuoni C, Schwenker J, McCarthy J, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport*. 2001;12(16):3549–3552. doi: 10.1097/00001756-200111160-00035
37. Lebedev AA, Pyurveev SS, Nadbitova ND, et al. Reduction of compulsive overeating in rats caused by maternal deprivation in early ontogenesis with the use of a new ghrelin receptor antagonist agrelax. *Reviews on Clinical Pharmacology and Drug Therapy*. 2023;21(3):255–262. EDN: SLBOTQ doi: 10.17816/RCF562841
38. Shabanov PD, Lebedev AA, Rusanovsky BB, Streltsov VF. Behavioral effects of corticoliberin and its analogs injected into rat brain ventricles. *Medical academic journal*. 2005;5(3):59–67. EDN: VLHVOZ (In Russ.)
39. Piccoli L, Micioni Di Bonaventura MV, Cifani C, et al. Role of orexin-1 receptor mechanisms on compulsive food consumption in a model of binge eating in female rats. *Neuropsychopharmacology*. 2012;37(9):1999–2011. doi: 10.1038/npp.2012.48
40. Craft RM, Howard JL, Pollard GT. Conditioned defensive burying as a model for identifying anxiolytics. *Pharmacol Biochem Behav*. 1988;30(3):775–780. doi: 10.1016/0091-3057(88)90098-6
41. Kalinina T, Kudryashov N, Naplekova P, et al. P.1.h.032 Interaction of antidepressants with mild chronic stress: behavioural effects and content of monoamines and their metabolites in mouse brain. *Eur Neuropsychopharmacol*. 2014;24:288. doi: 10.1016/s0924-977x(14)70455-9
42. Naumenko VS, Bazovkina DV, Semenova AA, et al. Effect of glial cell line-derived neurotrophic factor on behaviorand key members of the brain serotonin system in mouse strains genetically predisposed to behavioral disorders. *J Neurosci Res*. 2013;91(12):1628–1638. doi: 10.1002/jnr.23286
43. Bali A, Jaggi AS. Electric foot shock stress: A useful tool in neuropsychiatric studies. *Rev Neurosci*. 2015;26(6):655–677. doi: 10.1515/revneuro-2015-0015
44. Tsikunov SG, Klyueva NN, Kusov AG, et al. Changes in the lipid composition of blood plasma and liver in rats induced by severe psychic trauma. *Bulletin of Experimental Biology and Medicine*. 2006;141(5):575–578. EDN: HTPYLD
45. Yakushina ND, Tissen IYu, Lebedev AA, et al. Effect of intranasal ghrelin administration on the compulsive behavior patterns and the level of anxiety after the vital stress exposure to rats. *Reviews on Clinical Pharmacology and Drug Therapy*. 2017;15(3):28–37. EDN: ZHRRKX doi: 10.17816/RCF15328-37
46. Veale D, Roberts A. Obsessive-compulsive disorder. *Biomed J*. 2014;348:2183. doi: 10.1136/bmj.g2183
47. Decloedt EH, Stein DJ. Current trends in drug treatment of obsessive-compulsive disorder. *Neuropsychiatr Dis Treat*. 2010;6(1):233–242. doi: 10.2147/NDT.S3149
48. Koob GF. Dynamics of neuronal circuits in addiction: reward, antireward and emotional memory. *Pharmacopsychiatry*. 2009;42(10):32–41. doi: 10.1055/s-0029-1216356
49. Shabanov PD, Lebedev AA, Yakushina ND, et al. Modeling the obsessive-compulsive and addictive gambling behavior in a rat marble test by means of amphetamine administration. *Narcology*. 2017;16(1):32–38. EDN: XWNOMF
50. Shabanov PD, Lebedev AA, Yakushina ND, et al. Effect of amphetamine on behavioral patterns of obsessive-compulsive and addictive gambling in a rat marble test. *Reviews on Clinical Pharmacology and Drug Therapy*. 2016;14(3):46–52. EDN: WWUKGT doi: 10.17816/RCF14346-52
51. Shabanov PD, Yakushina ND, Lebedev AA. Pharmacology of peptide mechanisms of gambling behavior in rats. *Journal of addiction problems*. 2020;(4):24–44. EDN: JBUQJN doi: 10.47877/0234-0623_2020_4_24
52. Geliebter A, Marci EG, Sami AH. Plasma ghrelin concentrations are lower in binge-eating disorder. *J Nutr*. 2005;135(5):1326–1330. doi: 10.1093/jn/135.5.1326
53. Alvarez-Crespo M, Skibicka KP, Farkas I, et al. The amygdala as a neurobiological target for ghrelin in rats: neuroanatomical, electrophysiological and behavioral evidence. *PloS one*. 2012;7(10):e46321. doi: 10.1371/journal.pone.0046321

54. Carroll ME, France CP, Meisch RA, at al. Food deprivation increases oral and intravenous drug intake in rats. *Science (New York)*. 1979;205(4403):319–321. doi: 10.1126/science.36665
55. Kharbanda KK, Farokhnia M, Deschaine SL, at al. Role of the ghrelin system in alcohol use disorder and alcohol-associated liver disease. A narrative review. *Alcohol Clin Exp Res*. 2022;46(12):2149–2159. doi: 10.1111/acer.14967
56. Goeders NE. The impact of stress on addiction. *Eur Neuropsychopharmacol*. 2003;13(6):435–441. doi: 10.1016/j.euroneuro.2003.08.004

СПИСОК ЛИТЕРАТУРЫ

1. www.who.int [Электронный ресурс]. Obesity and overweight, 2021 [дата обращения: 21.04.2023]. Режим доступа: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Westbury S., Oyebode O., van Rens T., Barber T.M. Obesity stigma: causes, consequences, and potential solutions // Curr Obes Rep. 2023. Vol. 12, N 1. P. 10–23. doi: 10.1007/s13679-023-00495-3
3. Al-Sulaiti H., Diboun I., Agha M.V., et al. Metabolic signature of obesity-associated insulin resistance and type 2 diabetes // J Transl Med. 2019. Vol. 17, N 1. ID 348. doi: 10.1186/s12967-019-2096-8
4. Avgerinos K.I., Spyrou N., Mantzoros C.S., Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives // Metabolism. 2019. Vol. 92. P. 121–135. doi: 10.1016/j.metabol.2018.11.001
5. Lazzaroni E., Ben Nasr M., Loretelli C., et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes // Pharm Res. 2021. Vol. 171. ID 105782. doi: 10.1016/j.phrs.2021.105782
6. Powell-Wiley T.M., Poirier P., Burke L.E., et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association // Circulation. 2021. Vol. 143, N 21. P. e984–e1010. doi: 10.1161/CIR.0000000000000973
7. Shah M.S., Patel Z.K., Bharucha R., et al. Sibutramine-induced nonischemic cardiomyopathy // Cureus. 2022. Vol. 14, N 1. ID e21650. doi: 10.7759/cureus.21650
8. Nguyen T., Thomas B.F., Zhang Y. Overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists: current approaches for therapeutics development // Curr Top Med Chem. 2019. Vol. 19, N 16. P. 1418–1435. doi: 10.2174/1568026619666190708164841
9. Filippatos T.D., Derdemezis C.S., Gazi I.F., et al. Orlistat-associated adverse effects and drug interactions: a critical review // Drug Saf. 2008. Vol. 31, N 1. P. 53–65. doi: 10.2165/00002018-200831010-00005
10. Davidson M.H., Hauptman J., DiGirolamo M., et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial // JAMA. 1999. Vol. 281, N 3. P. 235–242. doi: 10.1001/jama.281.3.235
11. O'Meara S., Riemsma R., Shirran L. A systematic review of the clinical effectiveness of orlistat used for the management of obesity // Obes Rev. 2004. Vol. 5, N 1. P. 51–68. doi: 10.1111/j.1467-789X.2004.00125.x
12. US Food and drug [Электронный ресурс]. Administration, FDA approves new drug treatment for chronic weight management, first since 2014, 2021 [дата обращения: 21.04.2023]. Режим доступа: https://www.fda.gov/news-event s/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014
13. Beck B., Fernette B., StrickerKrongrad A. Peptide S is a novel potent inhibitor of voluntary and fast-induced food intake in rats // Biochem Biophys Res Commun. 2005. Vol. 332, N 3. P. 859–865. doi: 10.1016/j.bbrc.2005.05.029
14. Zhang J., Ren P., Avsian-Kretchmer O., et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake // Science. 2005. Vol. 310, N 5750. P. 996–999. doi: 10.1126/science.1117255
15. Chen C.Y., Asakawa M., Fujimiya M., et al. Ghrelin gene products and the regulation of food intake and gut motility // Pharmacol Rev. 2009. Vol. 61, N 4. P. 430–481. doi: 10.1124/pr.109.001958
16. Gnanapavan S., Kola B., Bustin S.A., et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans // J Clin Endocrinol Metabolism. 2002. Vol. 87. ID 2988. doi: 10.1210/jcem.87.6.8739
17. Lebedev A.A., Karpova I.V., Bychkov E.R., et al. The ghrelin antagonist [D-LYS3]-GHRP-6 decreases signs of risk behavior in a model of gambling addiction in rats by altering dopamine and serotonin metabolism // Neurosci Behav Physiol. 2022. Vol. 52, N 3. P. 415–421. doi: 10.19163/MedChemRussia2021-2021-259
18. Nass R., Pezzoli S.S., Oliveriet M.C., al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: A randomized trial // Ann Intern Med. 2008. Vol. 149, N 9. P. 601–611. doi: 10.7326/0003-4819-149-9-200811040-00003
19. Huda M.S.B., Dovey T., Wong S.P., et al. Ghrelin restores "lean-type" hunger and energy expenditure profiles in morbidly obese subjects but has no effect on postgastrectomy subjects // Int J Obes. 2009. Vol. 33, N 3. P. 317–325. doi: 10.1038/ijo.2008.270
20. Broglio F., Arvat E., Benso A., et al. Ghrelin, a natural gh secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans // J Clin Endocrinol Metab. 2001. Vol. 86, N 10. P.5083–5086. doi: 10.1210/jcem.86.10.8098
21. Reimer M.K. Dose-dependent inhibition by ghrelin of insulin secretion in the mouse // Endocrinology. 2003. Vol. 144, N 3. P. 916–921. doi: 10.1210/en.2002-220819
22. Ducharme R., Anisman H., Abizaid A. Altered metabolic and neurochemical responses to chronic unpredictable stressors in ghrelin receptor-deficient mice // Eur J Neurosci. 2010. Vol. 32, N 4. P. 632–639. doi: 10.1111/j.1460-9568.2010.07310.x
23. Johnson P.M., Kenny P.J. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats // Nat Neurosci. 2010. Vol. 13, N 5. P. 635–641. doi: 10.1038/nn.2519
24. Association A.P. Diagnostic and statistical manual of mental disorders: DSM-5-TR. Washington; London, 2013.
25. Lenoir M., Serre F., Cantin L., Ahmed S.H. Intense sweetness surpasses cocaine reward // PLoS ONE. 2007. Vol. 2, N 8. ID e698. doi: 10.1371/journal.pone.0000698
26. Heo Y.-A., Duggan S.T. Lisdexamfetamine: a review in binge eating disorder // CNS Drugs. 2017. Vol. 31, N 11. P. 1015–1022. doi: 10.1007/s40263-017-0477-1
27. Ward K., Citrome L. Lisdexamfetamine: chemistry, pharmacodynamics, pharmacokinetics, and clinical efficacy, safety, and tolerability in the treatment of binge eating disorder // Expert Opin Drug Metab Toxicol. 2018. Vol. 14, N 2. P. 229–238. doi: 10.1080/17425255.2018.1420163

28. Boggiano M.M., Artiga A.I., Pritchett C.E., et al. High intake of palatable food predicts binge-eating independent of susceptibility to obesity: An animal model of lean vs obese binge-eating and obesity with and without binge-eating // Int J Obes. 2007. Vol. 31, N 9. P. 1357–1367. doi: 10.1038/sj.ijo.0803614
29. Corwin R.L., Wojnicki F.H.E. Binge eating in rats with limited access to vegetable shortening // Curr Protoc Neurosci. 2006. Vol. 36. P. 9.23B.1–9.23B.11. doi. 10.1002/0471142301.ns0923bs36
30. Moore C.F., Leonard M.Z., Micovic N.M., et al. Reward sensitivity deficits in a rat model of compulsive eating behavior // Neuropsychopharmacol. 2020. Vol. 45. P. 589–596 doi: 10.1038/s41386-019-0550-1
31. Ушаков И.Б., Бубеев Ю.А., Красовец С.В., Иванов А.В. Индивидуальные психофизиологические механизмы адаптации при стрессе смертельно опасных ситуаций // Российский физиологический журнал им. И.М. Сеченова. 2012. Т. 98, № 1. С. 83–94. EDN: OXHHIZ
32. Евдокимов В.И., Шамрей В.К., Плужник М.С. Развитие направлений научных исследований по боевому стрессу в отечественных статьях с использованием программы VOSviewer (2005–2021 гг.) // Медико-биологические и социально-психологические проблемы безопасности в чрезвычайных ситуациях. 2023. № 2. С. 99–115. EDN: RUXCZT doi: 10.25016/2541-7487-2023-0-2-99-116
33. Sayin Kasar K., Karaman E. Life in lockdown: Social isolation, loneliness and quality of life in the elderly during the COVID-19 pandemic: A scoping review // Geriatr Nurs. 2021. Vol. 42, N 5. P. 1222–1229. doi: 10.1016/j.gerinurse.2021.03.010
34. DiLeone R.J., Georgescu D., Nestler E.J. Lateral hypothalamic neuropeptides in reward and drug addiction // Life Sci. 2003. Vol. 73, N 6. P. 759–768. doi: 10.1016/s0024-3205(03)00408-9
35. Lutter M., Nestler E.J. Homeostatic and hedonic signals interact in the regulation of food intake // J Nutr. 2009. Vol. 139, N 3. P. 629–632. doi: 10.3945/jn.108.097618
36. Colantuoni C., Schwenker J., McCarthy J., et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain // Neuroreport. 2001. Vol. 12, N 16. P. 3549–3552. doi: 10.1097/00001756-200111160-00035
37. Лебедев А.А., Пюрвеев С.С., Надбитова Н.Д., и др. Снижение компульсивного переедания у крыс, вызванного материнской депривацией в раннем отногенезе, с применением нового антагониста рецепторов грелина агрелакс // Обзоры по клинической фармакологии и лекарственной терапии. 2023. Т. 21, № 3. С. 255–262. EDN: SLBOTQ doi: 10.17816/RCF562841
38. Шабанов П.Д., Лебедев А.А., Русановский В.В., Стрельцов В.Ф. Поведенческие эффекты кортиколиберина и его аналогов, вводимых в желудочки мозга крыс // Медицинский академический журнал. 2005. Т. 5, № 3. С. 59–67. EDN: VLHVOZ
39. Piccoli L., Micioni Di Bonaventura M.V., Cifani C., et al. Role of orexin-1 receptor mechanisms on compulsive food consumption in a model of binge eating in female rats // Neuropsychopharmacology. 2012. Vol. 37, N 9. P. 1999–2011. doi: 10.1038/npp.2012.48
40. Craft R.M., Howard J.L., Pollard G.T. Conditioned defensive burying as a model for identifying anxiolytics // Pharmacol Biochem Behav. 1988. Vol. 30, N 3. P. 775–780. doi: 10.1016/0091-3057(88)90098-6
41. Kalinina T., Kudryashov N., Naplekova P., et al. P.1.h.032 Interaction of antidepressants with mild chronic stress: behavioural effects and content of monoamines and their metabolites in mouse brain // Eur Neuropsychopharmacol. 2014. Vol. 24. ID 288. doi: 10.1016/s0924-977x(14)70455-9
42. Naumenko V.S., Bazovkina D.V., Semenova A.A., et al. Effect of glial cell line-derived neurotrophic factor on behaviorand key members of the brain serotonin system in mouse strains genetically predisposed to behavioral disorders // J Neurosci Res. 2013. Vol. 91, N 12. P. 1628–1638. doi: 10.1002/jnr.23286
43. Bali A., Jaggi A.S. Electric foot shock stress: A useful tool in neuropsychiatric studies // Rev Neurosci. 2015. Vol. 26, N 6. P. 655–677. doi: 10.1515/revneuro-2015-0015
44. Цикунов С.Г., Клюева Н.Н., Кусов А.Г., и др. Изменение липидного спектра сыворотки крови и печени крыс, вызванное тяжелой психогенной травмой // Бюллетень экспериментальной биологии и медицины. 2006. Т. 141, № 5. С. 575–578. EDN: HTPYLD
45. Якушина Н.Д., Тиссен И.Ю., Лебедев А.А., и др. Влияние интраназально вводимого грелина на проявления компульсивного поведения и уровень тревожности у крыс после витального стрессорного воздействия // Обзоры по клинической фармакологии и лекарственной терапии. 2017. Т. 15, № 3. С. 28–37. EDN: ZHRRKX doi: 10.17816/RCF15328-37
46. Veale D., Roberts A. Obsessive-compulsive disorder // Biomed J. 2014. Vol. 348. ID 2183. doi: 10.1136/bmj.g2183
47. Decloedt E.H., Stein D.J. Current trends in drug treatment of obsessive-compulsive disorder // Neuropsychiatr Dis Treat. 2010. Vol. 6, N 1. P. 233–242. doi: 10.2147/NDT.S3149
48. Koob G.F. Dynamics of neuronal circuits in addiction: reward, antireward and emotional memory // Pharmacopsychiatry. 2009. Vol. 42, N 10. P. 32–41. doi: 10.1055/s-0029-1216356
49. Шабанов П.Д., Лебедев А.А., Якушина Н.Д., и др. Моделирование обсессивно-компульсивного и аддиктивного игрового поведения у крыс введением фенамина в тесте закапывания шариков // Наркология. 2017. Т. 16, № 1. С. 32–38. EDN: XWNOMF
50. Шабанов П.Д., Лебедев А.А., Якушина Н.Д., и др. Влияние фенамина на поведенческие компоненты обсессивно-компульсивного и аддиктивного игрового поведения в тесте закапывания шариков у крыс // Обзоры по клинической фармакологии и лекарственной терапии. 2016. Т. 14, № 3. С. 46–52. EDN: WWUKGT doi: 10.17816/RCF14346-52
51. Шабанов П.Д., Якушина Н.Д., Лебедев А.А. Фармакология пептидных механизмов игрового поведения у крыс // Вопросы наркологии. 2020. № 4. С. 24–44. EDN: JBUQJN doi: 10.47877/0234-0623_2020_4_24
52. Geliebter A., Marci E.G., Sami A.H. Plasma ghrelin concentrations are lower in binge-eating disorder // J Nutr. 2005. Vol. 135, N 5. P. 1326–1330. doi: 10.1093/jn/135.5.1326
53. Alvarez-Crespo M., Skibicka K.P., Farkas I., et al. The amygdala as a neurobiological target for ghrelin in rats: neuroanatomical, electrophysiological and behavioral evidence // PloS one. 2012. Vol. 7, N 10. ID e46321. doi: 10.1371/journal.pone.0046321
54. Carroll M.E., France C.P., Meisch R.A., at al. Food deprivation increases oral and intravenous drug intake in rats // Science (New York).1979. Vol. 205, N 4403. P. 319–321. doi: 10.1126/science.36665
55. Kharbanda K.K., Farokhnia M., Deschaine S.L., at al. Role of the ghrelin system in alcohol use disorder and alcohol-associated liver disease. A narrative review // Alcohol Clin Exp Res. 2022. Vol. 46, N 12. P. 2149–2159. doi: 10.1111/acer.14967
56. Goeders N.E. The impact of stress on addiction // Eur Neuropsychopharmacol. 2003. Vol. 13, N 6. P. 435–441. doi: 10.1016/j.euroneuro.2003.08.004

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