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Anti-addictive potential of the dual incretin receptor agonist tirzepatide in a model of emotional overeating induced by intracranial self-stimulation

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ABSTRACT

Background. The incretin system (GLP-1 and GIP) plays a key role in the regulation of energy metabolism and feeding behavior. Recent research has demonstrated that incretin receptor agonists can modulate not only metabolic processes but also neuronal mechanisms of reward, highlighting their potential use in managing impulsive and addictive disorders.

Aim — to assess the effect of the dual incretin receptor agonist tirzepatide on operant and feeding behavior in rats in the intracranial self-stimulation (ICSS) test.

Material and methods. The experiment involved 24 male Wistar rats. Tirzepatide was administered subcutaneously (s.c.) at doses of 0.05, 0.10, and 0.30 mg/kg once daily for 7 days. Behavioral testing was performed 1 hour after injection, including the ICSS test (number of lever presses per minute) and the feeding test (number of seeds eaten per minute). Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's post hoc test ($p < 0.05$).

Results. A single administration of tirzepatide produced no significant differences compared with control ($H=3.5$; $p=0.38$). On day 3, a significant reduction in lever-pressing was observed at 0.30 mg/kg (approximately 15–20% below control; $H=13.69$; $p < 0.001$; Dunn $p < 0.01$) along with a decrease in food intake ($H=9.64$; $p < 0.05$; Dunn $p < 0.05$). By day 7, a stable dose-dependent suppression of both operant and feeding behavior was recorded (ICSS: $H=13.13$; $p < 0.01$; feeding: $H=14.16$; $p < 0.01$) with significant differences at 0.10 and 0.30 mg/kg.

Conclusion. Repeated administration of tirzepatide, a dual incretin receptor agonist, produces a pronounced dose- and time-dependent reduction in motivational and feeding activity in rats.

Keywords: incretins, tirzepatide, GLP-1, GIP, brain self-stimulation, reward system, impulsive behavior, addictive behavior

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Антиаддиктивный потенциал двойного агониста инкретиновых рецепторов тирзепатида в тесте на эмоциональное переедание, вызванное внутримозговой самостимуляцией

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РЕЗЮМЕ

Актуальность. Инкретиновая система (GLP-1 и GIP) играет ключевую роль в регуляции энергетического обмена и пищевого поведения. Современные исследования показывают, что агонисты инкретиновых рецепторов способны опосредованно изменять не только метаболические процессы, но и нейрональные механизмы вознаграждения, что открывает перспективы их применения при нарушениях импульсивного и аддиктивного поведения.

Цель исследования — оценить влияние двойного агониста инкретиновых рецепторов тирзепатида на показатели оперантной и пищевой активности у крыс в тесте самостимуляции мозга.

Материалы и методы. В эксперименте использованы 24 самца крыс линии Вистар. Препарат вводили подкожно (s.c.) в дозах 0,05; 0,10 и 0,30 мг/кг один раз в сутки в течение 7 дней. Через 1 час после введения проводили тест внутримозговой самостимуляции (ICSS) и тест пищевого поведения (количество съеденных семян за 1 мин). Для статистического анализа применяли непараметрический критерий Краскела–Уоллиса с последующим пост-хок тестом Данна ($p < 0,05$).

Результаты. После однократного введения тирзепатида различий с контролем не выявлено ($H=3,5$; $p=0,38$). На 3-и сутки наблюдалось достоверное снижение количества нажатий на педаль при дозе 0,30 мг/кг (на ~15–20% ниже контроля; $H=13,69$; $p < 0,001$; Dunn $p < 0,01$) и уменьшение потребления пищи ($H=9,64$; $p < 0,05$; Dunn $p < 0,05$). На 7-е сутки выявлено стойкое дозозависимое снижение как оперантной, так и пищевой активности: ICSS ($H=13,13$; $p < 0,01$) и пищевое поведение ($H=14,16$; $p < 0,01$), достоверные различия при дозах 0,10 и 0,30 мг/кг.

Вывод. Повторное введение двойного агониста инкретиновых рецепторов тирзепатида вызывает выраженное дозо- и времезависимое снижение мотивационной и пищевой активности у крыс.

Ключевые слова: инкретины, тирзепатид, GLP-1, GIP, самостимуляция мозга, система вознаграждения, импульсивное поведение, аддиктивное поведение

Как цитировать
Деданишвили Н.С., Пюрвеев С.С., Лебедев А.А., Васильев А.Г., Шабанов П.Д., Лебедев Д.А. Антиаддиктивный потенциал двойного агониста инкретиновых рецепторов тирзепатида в тесте на эмоциональное переедание, вызванное внутримозговой самостимуляцией. *Педиатр*. 2025;16(5):44–55. https://doi.org/10.56871/PED.2025.78.21.005.

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BACKGROUND

Incretins are a group of hormonal peptides of the gastrointestinal tract that are secreted in response to food intake and enhance glucose-dependent insulin secretion by pancreatic β-cells [1]. The main representatives of the incretin system are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are synthesized by enteroendocrine L- and K-cells of the small intestine, respectively [2]. After being secreted into the bloodstream, incretins provide fine regulation of energy and carbohydrate metabolism by coordinating the interaction between the gastrointestinal tract, pancreas, central nervous system, and peripheral target organs [3].

Incretins increase insulin release in response to oral glucose administration compared with intravenous administration at the same blood glucose concentration. This effect is observed due to the combined action of GLP-1 and GIP (Fig. 1), which enhances insulin secretion and decreases glucagon production. These effects contribute to the homeostatic control of blood glucose levels [2].

Glucagon-like peptide-1 (GLP-1) is synthesized by proteolytic cleavage of the precursor proglucagon (PPG), which is expressed in enteroendocrine cells of the distal small intestine and the pancreas. Glucose-dependent insulinotropic polypeptide (GIP) is encoded by a separate gene and is synthesized in the proximal intestine [2]. Both peptides belong to the glucagon-like peptide family and act through specific G protein-coupled receptors (GPCRs): GLP-1R and GIPR (Fig. 2) [4].

Activation of GLP-1R and GIPR triggers an intracellular cascade that includes increased cAMP levels and activation of protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K). In β-cells, these processes lead to potentiation of insulin secretion [5]. At the same time, glucagon secretion by α-cells is inhibited, and hepatic glucose production is reduced. As a result, postprandial glucose homeostasis is maintained [5]. Additionally, GLP-1 has anorexigenic and gastrointestinal effects: it slows gastric emptying, reduces intestinal motility, and induces a feeling of satiety. These effects underlie the therapeutic use of GLP-1R agonists for weight reduction and the treatment of obesity [6].

Receptors such as GLP-1R and GIPR are expressed in various tissues, reflecting the systemic nature of incretin axis regulation (Fig. 2). Peripheral expression of GLP-1R has been found in the pancreatic islets (on β- and δ-cells), in the heart, kidneys, lungs, liver, adipose tissue, and gastrointestinal tract. GIPRs are predominantly expressed in the pancreas, adipose tissue, bones, and adrenal glands [3].

In addition to peripheral organs, GLP-1R is widely represented in the central nervous system, where it mediates the interaction between metabolic and neurobiological processes. A high density of receptors is observed in the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve, which are key centers for visceral signal integrations, as well as in structures that cross the blood-brain barrier, such as the lateral septum, ventral tegmental area (VTA), nucleus accumbens (NAc),

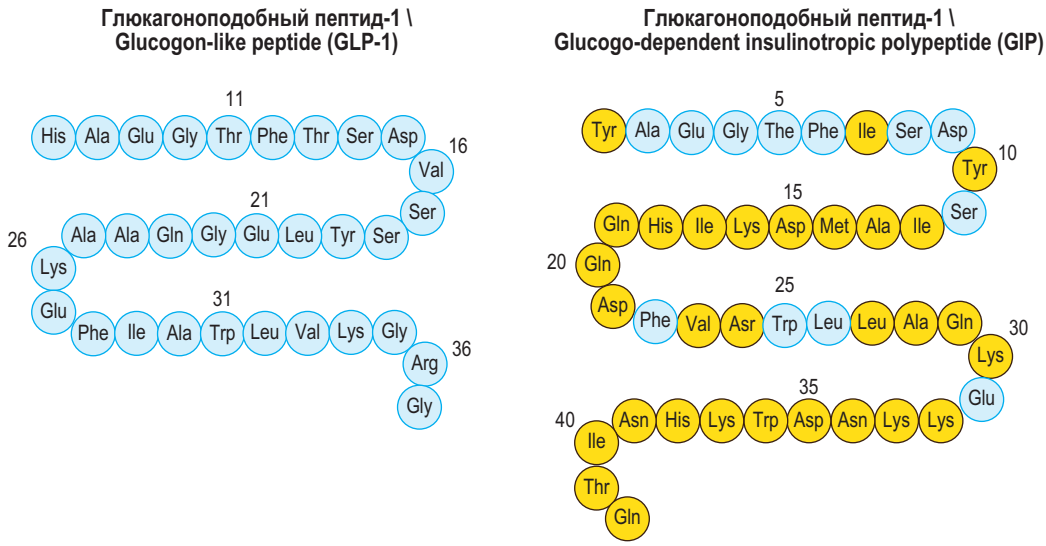


Fig. 1. Structure of incretin peptides: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Amino acid sequences of GLP-1 (left) and GIP (right) are shown, both representing key components of the incretin system that regulates insulin secretion and energy homeostasis

Рис. 1. Структура инкретиновых пептидов: глюкагоноподобного пептида-1 (GLP-1) и глюкозозависимого инсулинотропного полипептида (GIP). Показаны аминокислотные последовательности GLP-1 (слева) и GIP (справа), являющихся основными представителями инкретиновой системы, регулирующей секрецию инсулина и энергетический гомеостаз

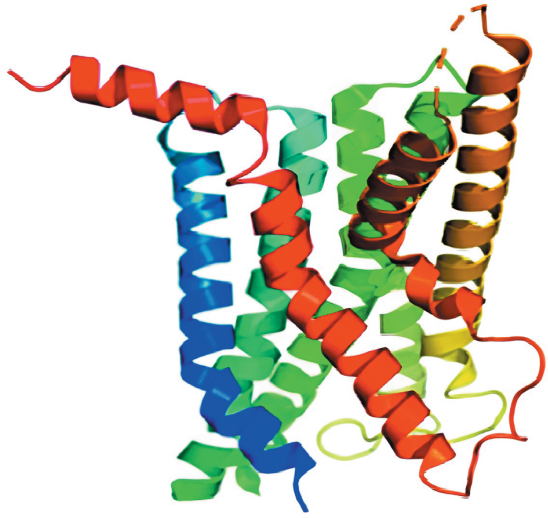


Fig. 2. Three-dimensional structure of the glucagon-like peptide-1 receptor (GLP-1R). Spatial organization of GLP-1R, a G protein-coupled receptor (GPCR) composed of seven transmembrane α-helices that mediate ligand (GLP-1) binding and intracellular signal transduction

Рис. 2. Трехмерная структура рецептора глюкагоноподобного пептида-1 (GLP-1R). Изображена пространственная организация GLP-1R — мембранного рецептора, относящегося к семейству рецепторов, сопряженных с G-белками (GPCR). Рецептор состоит из семи трансмембранных α-спиралей, обеспечивающих связывание лиганда (GLP-1) и передачу сигнала внутрь клетки

hippocampus, amygdala, and bed nucleus of the stria terminalis [4, 7].

Such a distribution of receptors indicates that GLP-1 is involved not only in glycemic control but also in the regulation of appetite, food motivation, reward, cognitive function, and stress responses. Collectively, the effects of incretins provide integration of metabolic, behavioral, and cognitive processes, making the incretin system a unique link between energy metabolism and the central regulation of behavior [8].

The rapid enzymatic degradation of endogenous GLP-1 by dipeptidyl peptidase-IV (DPP-IV) and neutral endopeptidase 24.11 limits its bioavailability, so that only a small fraction of the circulating peptide reaches brain structures [8]. This fact has stimulated the development of degradation-resistant GLP-1 analogues with prolonged action, such as exendin-4, liraglutide, dulaglutide, and semaglutide, which are administered subcutaneously at varying intervals. In clinical practice, DPP-IV inhibitors (sitagliptin, linagliptin) are also used, whereas the GLP-1 receptor antagonist exendin-9-39 is mainly used in experimental studies [9, 10].

In recent years, considerable attention has been paid to the role of the GLP-1 signalling pathway in regulating neurobiological processes beyond metabolism, including the development of addictive behavior. The results of preclinical and clinical studies indicate the involvement of the GLP-1 system in regulating responses associated with alcohol consumption, allowing it to be considered a potential therapeutic target for disorders related to addictive behavior.

AIM

The aim of the study was to evaluate the effect of the dual incretin receptor agonist tirzepatide on measures of operant and feeding activity in rats using the brain self-stimulation test.

MATERIALS AND METHODS

Animal selection. A total of 24 male Wistar rats (Rappolovo Laboratory Animal Nursery, Leningrad region) were used in the study. Animals were housed in standard plastic cages with 8–10 animals per cage with free access to water and food under inverted light from 8:00 to 20:00 at a temperature of 22±2 °C. All experiments were conducted during the autumn-winter period.

Surgical procedure. When the rats reached a body weight of 250 g, stereotaxic surgery was performed. The rats were anesthetized with Zoletil 100 (tiletamine, zolazepam, Virbac, France) at a dose of 50 mg/kg. Bipolar stainless steel electrodes (0.2 mm in diameter) were implanted under aseptic and antiseptic conditions using a stereotaxic apparatus (Harvard Apparatus, USA). The electrodes were implanted into the right VTA at the following coordinates relative to bregma: AP=–5.3 mm, L=0.8 mm, V=8.2 mm.

Study of self-stimulation response. In a Skinner box (29.2×30.5×24.1 cm), a lever (4.5×2.0 cm) was positioned 3.0 cm above the floor. The chamber was connected to a computer via an interface and controlled by proprietary software (Institute of Experimental Medicine, Russia). Each lever press triggered a train of rectangular pulses lasting 500 ms, with a pulse frequency of 100 Hz and a pulse duration of 1 ms. The animals were trained for 10 min daily over 5 days. During these sessions, the current intensity was adjusted to ensure the maximum rate of lever pressing for each animal without impairing motor function or inducing seizures. Animals that failed to press the lever more than 50 times during the 10-minute sessions were excluded from the experiment. The remaining animals were tested during 30-minute sessions for an additional 5 days to establish a stable baseline response rate [11].

Competition between Self-Stimulation and Eating Behaviour Test. After stabilization of the self-stimulation parameters, a food deprivation regime was introduced. Rats were trained to reach a feeder containing a large number of shelled sunflower seeds for 30 min daily for 5 days in a self-stimulation testing chamber. The self-stimulation lever was deactivated.

Subsequent experiments were conducted under choice conditions between self-stimulation and food consumption: a feeder was placed in the Skinner chamber, and the pedal with a fixed current was activated. All animals were maintained at a stable body weight.

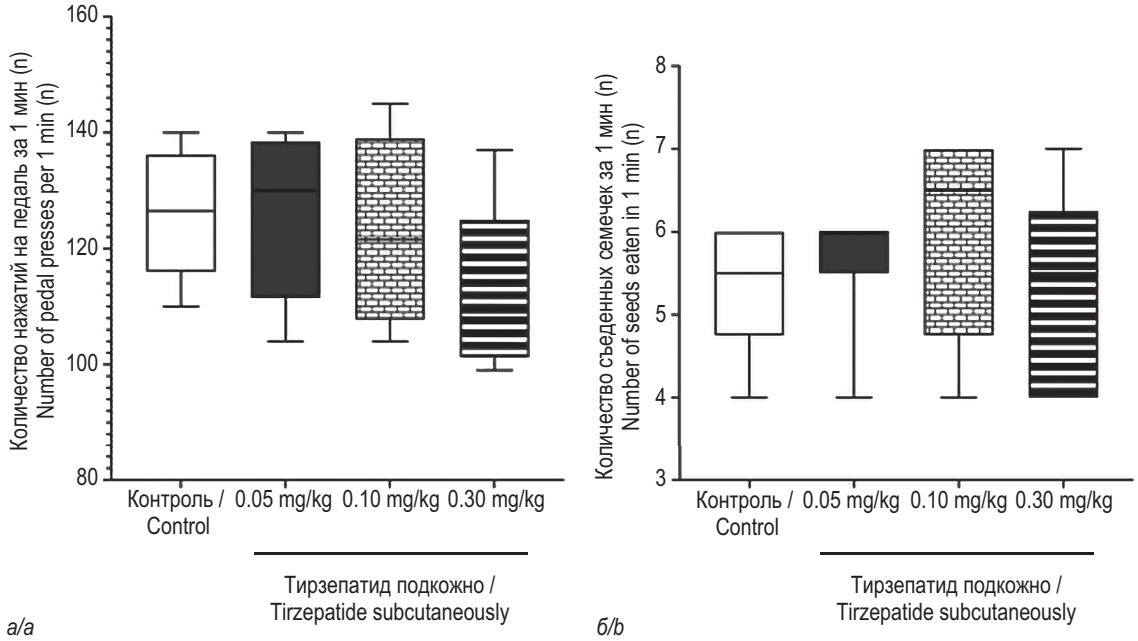
Hypothalamic Stimulation-Induced Behavior Test. After competition of the self-stimulation and eating behaviour tests, the animals were returned to ad libitum access to standard pelleted chow and water. Animals were placed in a special chamber for 5 min. This chamber contained a feeder with sunflower seeds and a small amount of wood shavings. At the end of the habituation period, forced hypothalamic stimulation was applied at the same intensity (10 periods of 30 s) used during the competition test between self-stimulation and feeding behavior. Stimulation-induced feeding responses or chewing were recorded [11, 12].

Self-Stimulation-Induced Emotional Eating Test. In the emotional overeating test conducted in satiated rats, the threshold current intensity required to maintain lever pressing during self-stimulation was used. To determine the threshold, the current intensity was adjusted in 5 μA increments. After determination of the stimulation threshold, a feeder was placed in the Skinner chamber and the self-stimulation pedal was activated. The number of approaches to the feeder, the number of seeds eaten, the number of pedal presses at a fixed threshold current, and feeding behavior parameters were recorded over a 10-minute period. On subsequent days, the drugs were administered 20 min before testing, after which the rats were placed in the chamber to assess self-stimulation induced overeating [13, 14].

Tirzepatide (PROMOMED PJSC, Russian Federation) was used in the study. Tirzepatide was administered subcutaneously in the scruff at doses of 0.05, 0.1, and 0.3 mg/kg body weight, in a volume of 1 ml/kg, calculated individually according to body weight, for 7-day course. A sterile 0.9% sodium chloride solution served as a control solution, administered subcutaneously.

Rats were tested 20 minutes after the final administration.

Statistical processing. Statistical significance was assessed using GraphPad Prism 10. Data were tested for normality using the Shapiro–Wilk test. As the data were not normally distributed, the nonparametric Kruskal–Wallis test was used, followed by Dunn's post hoc test and Holm's correction. To analyze the dynamics of the parameters over time, the Friedman test was used, followed by pairwise comparisons using the Wilcoxon–Holm test. Results are presented as the median [25th; 75th percentiles], and statistical significance was set at $p < 0.05$. Additionally, the effect size (ε2) and Spearman's correlation coefficient (rs) were calculated to assess the relationship between the number of lever presses and the amount of food consumed.



а/a *б/b*

Fig. 3. Effect of tirzepatide on behavioral parameters in rats: *a* — number of pedal presses per 1 min during intracranial self-stimulation test; *b* — number of seeds eaten per 1 min. Data presented as median with 25th and 75th percentiles. Kruskal–Wallis nonparametric test followed by Dunn's post hoc test ($p > 0.05$)

Рис. 3. Влияние тирзепатида на поведенческие показатели у крыс: *а* — количество нажатий на педаль за 1 мин при тесте самостимуляции; *б* — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскела–Уоллиса с пост-хок тестом Данна ($p > 0,05$)

RESULTS

The effects of tirzepatide on self-stimulation and feeding activity parameters were assessed 1 hour after a single subcutaneous administration of tirzepatide at doses of 0.05, 0.1, and 0.3 mg/kg.

Administration of tirzepatide within the studied dose range did not have a statistically significant effect on the number of pedal presses compared to the control group (Fig. 3, a). The activity ranged from 120 to 140 presses per minute, with no significant dose dependence.

Statistical analysis using the nonparametric Kruskal–Wallis test revealed no significant differences between groups (H=3.5, p=0.38). To clarify intergroup differences, Dunn's test was used as a post-hoc comparison, which also revealed no statistically significant differences (p>0.05 for all pairwise comparisons).

The effect of tirzepatide on the number of seeds consumed per minute is presented. The median valuesranged from 4–7 seeds/min (Fig. 3b). A slight increase in consumption was observed at a dose of 0.1 mg/kg. However, the differences compared with the control group did not reach statistical significance. The Kruskal-Wallis test also revealed no statistically significant differences between groups (H=2.09, p=0.55). Dunn's post hoc test revealed no significant differences between individual dose groups (p>0.05).

Effects of tirzepatide on self-stimulation and feeding behavior on day 3 of the experiment. Behavioral testing was conducted 1 h after drug administration on day 3 of the experiment.

On day 3, a dose-dependent reduction in the number of pedal presses was observed. The most pronounced effect was observed at a dose of 0.3 mg/kg, where the median number of presses decreased by approximately 15–20% compared with the control group (Fig. 4, a).

Statistical analysis using the nonparametric Kruskal–Wallis test revealed significant differences between the groups (H=13.69; p <0.001). Dunn's post hoc test revealed that the 0.3 mg/kg tirzepatide group differed significantly from the control group (p <0.01). Doses of 0.05 and 0.1 mg/kg did not have a significant effect (p >0.05).

On day 3, a decrease in feeding activity was also observed following the administration of tirzepatide at a dose of 0.3 mg/kg (Fig. 4, b). The median number of seeds consumed per 1 min decreased compared with the control group. According to the Kruskal–Wallis test, the differences between groups were statistically significant (H=9.64; p <0.05). Dunn's post hoc test showed a significant decrease in feeding activity in the 0.3 mg/kg group compared with the control group (p <0.05), whereas no significant differences were observed at doses of 0.05 and 0.1 mg/kg (p >0.05).

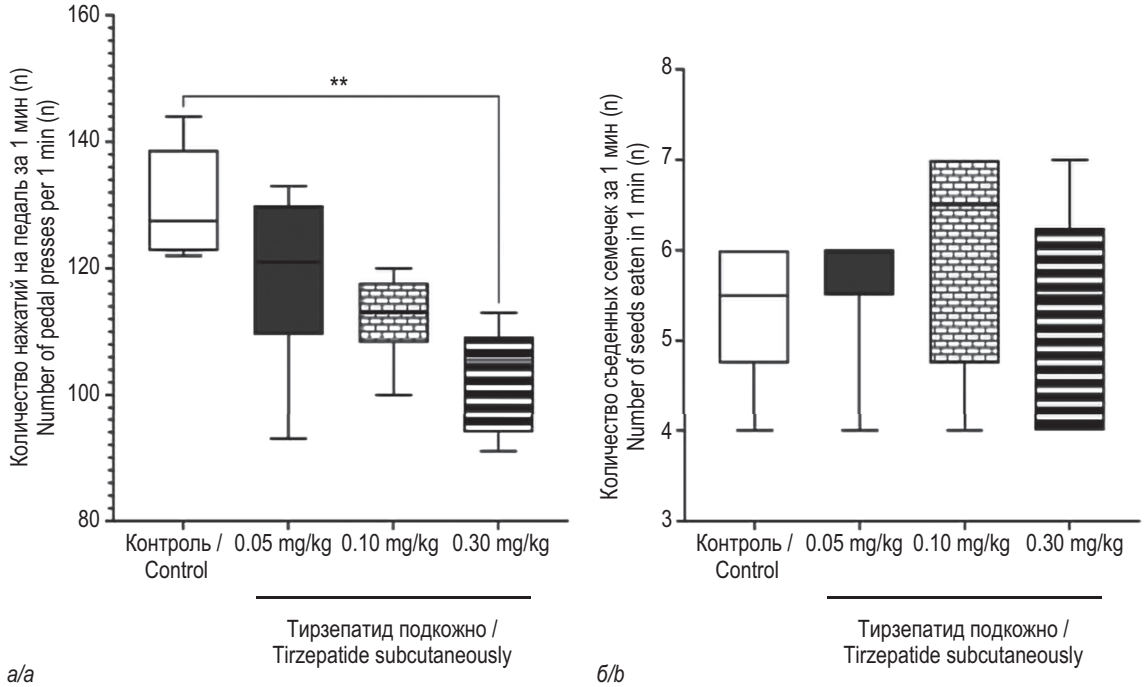


Fig. 4. Effect of tirzepatide on behavioral measures in rats on day 3 of the experiment: *a* — number of lever presses per 1 min in the intracranial self-stimulation (ICSS) test; *b* — number of seeds consumed per 1 min. Data are presented as the median and interquartile range (25th–75th percentiles). Kruskal–Wallis test with Dunn's post hoc test for pairwise comparisons. ** — p <0.01

Рис. 4. Влияние тирзепатида на поведенческие показатели у крыс на 3-и сутки эксперимента: *а* — количество нажатий на педаль за 1 мин при тесте самостимуляции; *б* — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскела–Уоллиса, с пост-хок тестом Данна для парных сравнений. ** — p <0.01

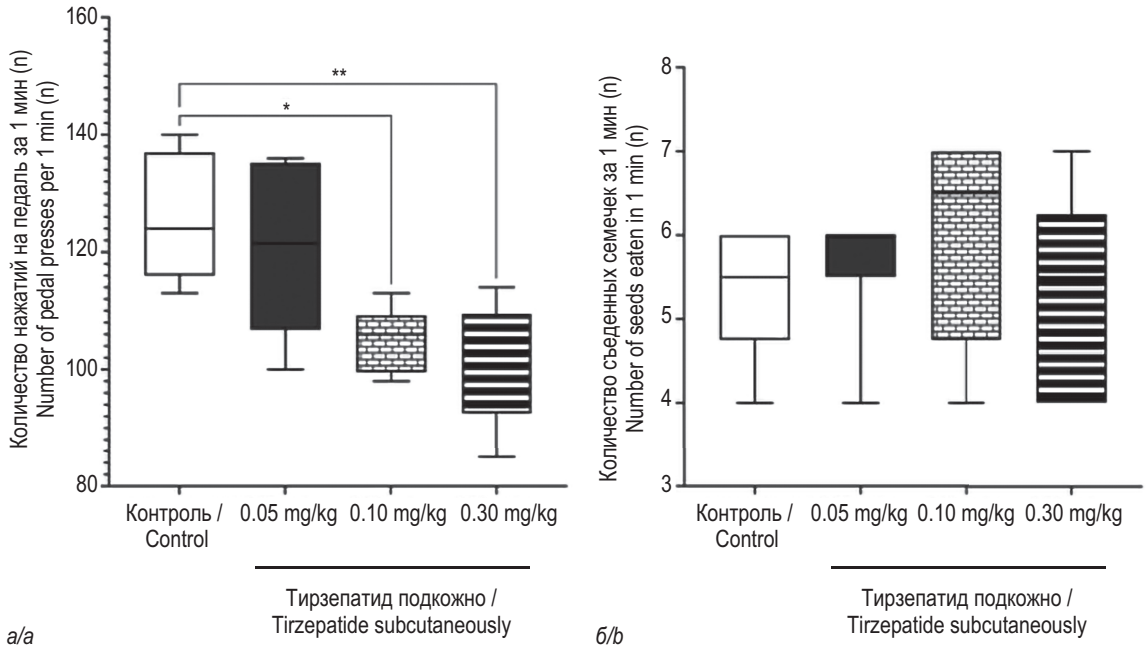


Fig. 5. Effect of tirzepatide on behavioral measures in rats on day 7 of the experiment: *a* — number of lever presses per 1 min in the intracranial self-stimulation (ICSS) test; *b* — number of seeds consumed per 1 min. Data are presented as the median and interquartile range (25^{th}–75^{th} percentiles). Kruskal–Wallis test with Dunn's post hoc test for pairwise comparisons. * — p <0.05; ** — p <0.01

Рис. 5. Влияние тирзепатида на поведенческие показатели у крыс на 7-и сутки эксперимента: *а* — количество нажатий на педаль за 1 мин при тесте самостимуляции; *б* — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскела–Уоллиса с пост-хок тестом Данна для парных сравнений. * — p <0,05; ** — p <0,01

Effect of tirzepatide on self-stimulation and feeding behavior on day 7 of the experiment. Behavioral testing was conducted 1 h after subcutaneous administration of tirzepatide at doses of 0.05, 0.1, and 0.30 mg/kg on day 7 of the experiment. A significant dose-dependent decrease in behavioral activity was observed.

Tirzepatide administration caused a gradual decrease in lever presses, reflecting a reduction in the motivational component of behavior (Fig. 5, a). A moderate decrease in activity was observed at a dose of 0.05 mg/kg, while the effect was more pronounced at doses of 0.1 and 0.3 mg/kg. According to the nonparametric Kruskal–Wallis test, the differences between groups were statistically significant ($H = 13.13$; $p < 0.01$).

Additional analysis using Dunn's post hoc test showed a significant difference between the 0.1 mg/kg group and the control ($p < 0.01$) with the most pronounced decrease in the number of presses at a dose of 0.3 mg/kg ($p < 0.01$).

In parallel, the feeding behavior test also revealed a significant dose-dependent reduction in the number of seeds consumed (Fig. 5b). At doses of 0.1 and 0.3 mg/kg, food intake was almost halved compared to the control group. Statistical analysis using the Kruskal–Wallis test confirmed significant differences between groups ($H=14.16$; $p < 0.01$), and subsequent Dunn's test showed a significant reduction in food intake at doses of 0.10 mg/kg ($p < 0.05$) and 0.3 mg/kg ($p < 0.05$).

DISCUSSION

The study revealed that administration of tirzepatide induces pronounced dose-dependent and time-dependent changes in behavioral activity of rats. On day 1 after a single administration of the drug, no statistically significant changes were observed in the lever-pressing frequency or feeding activity, indicating the absence of an immediate effect on the reward system and food motivation. However, by day 3 of the experiment, a significant decrease in the number of lever presses in the self-stimulation test, along with the reduction in seed consumption, was observed at the dose of 0.3 mg/kg. On day 7, a persistent and pronounced dose-dependent decrease in both motivational activity and feeding behavior was observed, with significant differences found for the 0.1 and 0.3 mg/kg doses compared to the control group. These results confirm the cumulative effect of tirzepatide and its ability to gradually modulate behavioral patterns associated with the reward system.

The obtained data reflect both the peripheral and central action of the drug [15]. Tirzepatide is a dual agonist of GLP-1R and GIPR, allowing it to simultaneously activate two incretin pathways. Peripherally, tirzepatide slows gastric emptying, reduces intestinal motility, and enhances satiety signals, leading to decreased food intake [16]. However, much more interesting are the central effects mediated by GLP-1R activation in brain structures involved in reward and

motivation regulation. GLP-1-producing neurons in the nucleus tractus solitarius (NTS) are known to project to the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, and hippocampus — areas involved in the regulation of dopaminergic reinforcement [17, 18]. Activation of GLP-1R in these regions suppresses dopaminergic activity, reducing the attractiveness of rewarding stimuli and diminishing motivationally driven behavior [19, 20]. These mechanisms may explain the observed decrease in self-stimulation frequency, which is a model for assessing dopaminergic activity and positive reinforcement.

The observed anorexigenic effect of tirzepatide is consistent with known data on the role of GLP-1 in the regulation of appetite and energy metabolism [21]. Stimulation of GLP-1R in the hypothalamus and brainstem has been shown to enhance satiety and reduce food cravings, as supported by data from both experimental models and clinical observations [4]. Concurrent activation of GIPR can enhance or prolong these actions through synergistic effects on pancreatic β-cells and modulation of peripheral metabolism. Thus, the combined activation of GLP-1R and GIPR generates a more stable and potent regulatory response at both the level of glucose homeostasis and within the reward system [10].

The temporal profile of the drug's action deserves special attention. The absence of an effect after a single administration and its gradual increase by days 3 and 7 indicate the cumulative nature of tirzepatide's action. This may be due to the pharmacokinetic properties of the drug, including a long half-life and a gradual increase in concentration with repeated injections, as well as to the gradual restructuring of neuronal circuits [22]. Repeated activation of GLP-1R can induce plastic changes in dopaminergic synapses, reducing the sensitivity of the mesolimbic system to external reward stimuli [23]. From a functional point of view, this is manifested as a decrease in motivational activity, reflected by a reduced number of lever presses in the ICSS, as well as a decrease in spontaneous food intake, indicating suppression of behavioral responses associated with positive reinforcement.

These data are consistent with the current understanding of the incretin system as a neurometabolic regulator integrating energy balance and motivational behavior [24]. A number of studies have shown that GLP-1R agonists (liraglutide, semaglutide) reduce both body weight and appetite and the desire to consume psychoactive substances and alcohol, which is explained by a common effect on the mesolimbic dopaminergic system. In this context, tirzepatide, which combines GLP-1R and GIPR activation, may have similar but more pronounced effects, making it a promising agent for treatment of obesity, diabetes, as well as for the modulation of impulsive and addictive behavior [15, 25, 26].

Thus, the results of this study demonstrate that repeated administration of tirzepatide leads to a consistent and statistically significant reduction in operant behavior and food intake in rats. The effect is dose-dependent and increases over time, reflecting both the peripheral (metabolic) and central (neuromodulatory) mechanisms of the drug's action.

The reduction in lever pressing and food intake can be viewed as a behavioral equivalent of decreased reward motivation and appetite, consistent with the known properties of incretin receptor agonists. These data confirm the involvement of GLP-1/GIP-dependent mechanisms in the regulation of the reward system and open up the prospect of further study of tirzepatide as a therapeutic agent for the treatment of motivational and impulsive behavior disorders.

CONCLUSION

Repeated administration of the dual incretin receptor agonist tirzepatide induces a pronounced dose- and time-dependent reduction in motivational and food-directed activity in rats, indicating the involvement of GLP-1/GIP-dependent neuromodulatory mechanisms in the regulation of motivational-reinforcement processes (reward system) and the control of feeding behavior. This supports the potential of tirzepatide as a therapeutic agent for the correction of disorders associated with impulsive and addictive behavior.

ADDITIONAL INFORMATION

Author contributions. All authors made a significant contribution to the conception, design, execution, and interpretation of the study, read, and approved the final version of the manuscript before publication.

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Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU

of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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