

DOSE- AND TIME-DEPENDENT EFFECTS OF THE DUAL GIP/GLP-1 RECEPTOR AGONIST TIRZEPATIDE ON EMOTIONAL OVEREATING IN A RAT MODEL OF INTRACRANIAL SELF-STIMULATION

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ABSTRACT

Background. Despite the increasing prevalence of emotional overeating and obesity, the specific neurohormonal mechanisms involved in the pathogenesis of these pathological processes remain poorly understood. The incretin system may serve as an important therapeutic target for the correction of these eating disorders.

Aim. To study the effects of the dual GIP/GLP-1 receptor agonist tirzepatide on feeding behavior parameters in a rat model of emotional overeating induced by intracranial self-stimulation (ICSS).

Methods. Experiments were performed on male Wistar rats with electrodes implanted in the ventral tegmental area. Tirzepatide was administered subcutaneously at doses of 0.05, 0.10, and 0.30 mg/kg for 7 days. Food intake (number of seeds consumed) was assessed at 1 minute, 30 minutes, and on days 3 and 7 after administration.

Results. No statistically significant changes in feeding activity were observed 30 minutes after tirzepatide administration. On the third day, a decrease in food intake was observed only at the maximum dose (0.30 mg/kg). On the seventh day, a significant anorexigenic effect was observed at doses of 0.10 and 0.30 mg/kg, indicating a dose- and time-dependent effect.

Conclusion. Tirzepatide does not exert a significant acute effect on feeding activity in the emotional overeating model at 30 minutes after administration. Repeated administration of the drug revealed a dose- and time-dependent anorexigenic effect, manifested by a decrease in food intake on days 3 and 7 of the experiment. The most pronounced decrease in feeding activity was observed at doses of 0.10 and 0.30 mg/kg on day 7.

Keywords: tirzepatide, incretin, GLP-1, GIP, emotional overeating, brain stimulation, VTA, feeding behavior

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ДОЗО- И ВРЕМЯЗАВИСИМОЕ ВЛИЯНИЕ ДВОЙНОГО АГОНИСТА РЕЦЕПТОРОВ GIP/GLP-1 ТИРЗЕПАТИДА НА ЭМОЦИОНАЛЬНОЕ ПЕРЕЕДАНИЕ В МОДЕЛИ ЭЛЕКТРИЧЕСКОЙ САМОСТИМУЛЯЦИИ МОЗГА У КРЫС

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РЕЗЮМЕ

Обоснование. Несмотря на растущую распространенность эмоционального переедания и ожирения, остаются недостаточно изученными конкретные нейрогормональные механизмы в патогенезе данных патологических процессов. Инкретиновая система может служить важной терапевтической мишенью для коррекции этих расстройств пищевого поведения.

Цель исследования. Изучить влияние двойного агониста рецепторов GIP и GLP-1 тирзепатида на показатели пищевого поведения при экспериментальной моделировании эмоционального переедания, вызванного электрической самостимуляцией мозга у крыс.

Методы. Эксперименты выполнены на крысах-самцах линии Вистар с имплантированными электродами в вентральную область покрышки. Тирзепатид вводили подкожно в дозах 0,05; 0,10 и 0,30 мг/кг курсом в течение 7 суток. Оценивали количество семян, потреблённых животными за 1 минуту, 30 минут, а также на 3-и и 7-е сутки после введения препарата.

Результаты. Показано, что на 30-й минуте после введения тирзепатида статистически значимых изменений пищевой активности не выявлялось. На третьи сутки снижение потребления пищи отмечалось только при максимальной дозе (0,30 мг/кг). На седьмые сутки достоверное анорексигенное действие наблюдалось при дозах 0,10 и 0,30 мг/кг, что свидетельствует о дозо- и времязависимом характере эффекта.

Заключение. Тирзепатид не оказывает выраженного острого влияния на пищевую активность в модели эмоционального переедания на 30-й минуте после введения. При повторном введении препарата выявляется дозо- и времязависимый анорексигенный эффект, проявляющийся снижением потребления пищи на 3-и и 7-е сутки эксперимента. Наиболее выраженное снижение пищевой активности наблюдается при дозах 0,10 и 0,30 мг/кг на 7-е сутки введения.

Ключевые слова: тирзепатид, инкретин, GLP-1, GIP, эмоциональное переедание, самостимуляция мозга, VTA, пищевое поведение

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BACKGROUND

Pharmacological intervention strategies involving simultaneous targeting of multiple regulatory signaling pathways are being extensively explored in modern medicine for the treatment of polyetiological chronic diseases, including metabolic disorders, obesity, and type 2 diabetes mellitus. The concept of polypharmacology involves the development of agents that act on multiple biological targets to enhance therapeutic efficacy and broaden the spectrum of action compared to monotargeted drugs [1, 2].

The underlying rationale of such approaches is to improve treatment outcomes through synergy arising from the concurrent activation of complementary mechanisms. Traditionally, this has been achieved via polypharmacotherapy, where patients receive a combination of several drugs [2]. However, advances in peptide engineering have enabled the transition to the creation of “multifunctional” molecules capable of acting on multiple pharmacological targets simultaneously within a single compound [2].

Most such hybrid peptides target G protein-coupled receptors (GPCRs). In recent years, a number of multi-receptor agonists have entered clinical trials as potential therapies for type 2 diabetes, obesity, and non-alcoholic steatohepatitis. The most advanced representative of this class to date is the dual GIP and GLP-1 receptor agonist – tirzepatide [3].

Initial clinical trials of tirzepatide have demonstrated unprecedented efficacy in lowering blood glucose levels and body weight in patients with type 2 diabetes [4]. Approximately one-third of patients receiving the maximum dose (15 mg) achieved normoglycemia, and about 25 % of participants lost at least 15 % of their baseline body weight within 26 weeks of therapy [5, 6]. Additionally, a marked reduction in fasting triglyceride levels was observed, and analysis of the insulin resistance index (HOMA2-IR) indicated improved tissue insulin sensitivity, which was only partially explained by weight loss [7, 8].

Such comprehensive metabolic improvement is consistent with the hypothesis that adding GIP activity to classical GLP-1 agonist therapy enhances glycemic control through several mechanisms: stimulation of insulin secretion by pancreatic β -cells, normalization of white adipose tissue function, and a pronounced anorexigenic effect mediated through integration of signals from both receptors at the level of the central nervous system [6, 8]. It is hypothesized that the high clinical efficacy of tirzepatide is largely determined by its specific pharmacological properties at each receptor.

The incretin system plays a key role in the regulation of energy homeostasis and feeding behavior. The major incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), secreted by enteroendocrine cells of the intestine in response to food intake. GLP-1 receptors have been shown to be expressed in brain centers

regulating behavior and reward, including the ventral tegmental area and the nucleus accumbens, which may influence motivation for food and other rewards [4]. Activation of GLP-1R in these structures leads to reduced food intake and modulation of dopaminergic transmission, indicating the involvement of the incretin system in the regulation of the hedonic component of feeding [5]. GIP receptors are also expressed in the CNS, and their co-activation with GLP-1R is considered a promising mechanism for enhancing metabolic and behavioral effects [8]. GLP-1 receptor agonists have been shown to reduce engagement of reward systems, decreasing addictive-like behavior in models of nicotine use disorders [5].

However, experimental data on the effects of dual GIP/GLP-1 agonists, such as tirzepatide, on behavior under conditions of hyperactivation of the reward system remain extremely limited. Tirzepatide has been shown to attenuate dopaminergic signals associated with alcohol and reduce reward-related behavioral manifestations, indicating an impact on central reward mechanisms [5].

Therefore, the relevance of this study lies in the experimental evaluation of the effects of tirzepatide on emotional overeating in a model induced by brain self-stimulation. Since this disorder is characterized by combined dysregulation of reward systems, food motivation, and energy homeostasis, it is fundamentally sensitive to drugs with a multimodal mechanism of action.

AIM

To investigate the effects of the dual GIP/GLP-1 receptor agonist tirzepatide on feeding behavior parameters in an experimental model of emotional overeating induced by electrical self-stimulation of the brain in rats.

METHODS

The study was conducted in accordance with the requirements of the European Convention for the care, maintenance, and euthanasia of laboratory animals and was approved by the local ethics committee of Saint Petersburg State Pediatric Medical University (Protocol No. 58/03, dated September 25, 2025).

Animals. A total of 24 male Wistar rats obtained from the Rappolovo laboratory animal breeding facility (Leningrad Region) were used in the study. Animals were housed in standard plastic cages, 5 per cage, with free access to water and food, under an inverted light cycle (8:00 AM – 8:00 PM) at a temperature of $22 \pm 2^\circ\text{C}$. All experiments were conducted during the autumn-winter period.

Surgery. Upon reaching a body weight of 250 g, rats underwent stereotaxic surgery. Rats were anesthetized with Zoletil® 100 at a dose of 50 mg/kg

(tiletamine, zolazepam; Virbac, France). Bipolar stainless steel electrodes (0.2 mm diameter) were implanted using a stereotaxic apparatus (Harvard Apparatus, USA) under aseptic conditions. Electrodes were implanted into the right ventral tegmental area (VTA) at the following coordinates relative to Bregma: AP = -5.3 mm, L = 0.8 mm, H = 8.2 mm.

Self-stimulation response study. 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 software (Institute of Experimental Medicine). Each lever press delivered a train of rectangular pulses (500 ms duration, 100 Hz pulse frequency, 1 ms pulse duration). Animals were trained for 10 minutes daily over 5 days. During these sessions, current intensity was adjusted to achieve maximum lever-pressing rates without impairing motor function or inducing seizures. Animals that failed to press the lever more than 50 times during 10-minute sessions were excluded from the experiment. The remaining animals were tested during 30-minute sessions over 5 additional days to establish a stable baseline response rate [9].

Self-stimulation and feeding behavior competition test. After stable self-stimulation parameters were established, animals were placed on a food deprivation schedule. Rats were trained for 30 minutes daily to access a feeder containing abundant shelled sunflower seeds over 5 days in the self-stimulation testing chamber. The self-stimulation lever was disabled during this phase. Subsequent experiments were conducted under choice conditions between self-stimulation and food consumption: a feeder was placed in the Skinner box, and the lever was activated with a fixed current intensity. All animals were required to maintain stable body weight [9].

Hypothalamic stimulation-induced behavior test. Following the competition test, animals were returned to ad libitum access to standard pelleted chow and water. Each animal was placed in a specialized chamber for 5 minutes containing a feeder with sunflower seeds and several wooden chips. At the end of this habituation period, forced hypothalamic stimulation (10 periods of 30 seconds each) was applied at the current intensity used during the competition test. Food-directed responses or chewing induced by stimulation were recorded [10].

Self-stimulation-induced emotional overeating test. In the emotional overeating test in satiated rats, the threshold current intensity required for lever presses during self-stimulation was used. Threshold determination was performed by varying current intensity in 5 μ A increments. Following threshold determination, a feeder was placed in the Skinner box and the self-stimulation lever was activated. The number of approaches to the feeder, number of seeds consumed, number of lever presses at fixed threshold current intensity, and feeding behavior parameters were recorded over 10 minutes. On subsequent days, drugs were administered

20 minutes prior to testing, and then the rat was placed in the chamber to assess self-stimulation-induced overeating [10].

Initially, 28 animals were included in the study. Following postoperative recovery and the self-stimulation training phase, 4 animals failed to develop a stable behavioral response (did not press the lever) and were consequently excluded from further experimentation. Thus, 24 rats were included in the final analysis.

Randomization was performed using simple random sampling with a random number generator. Prior to group allocation, animals were stratified by body weight (250 g) to ensure group comparability at baseline. Each animal was then assigned an individual number, and group allocation was performed by an independent investigator not involved in subsequent behavioral testing.

Drugs. Tirzepatide, a synthetic peptide, an unbalanced dual agonist of the glucose-dependent insulinotropic polypeptide (GIPR) and glucagon-like peptide-1 (GLP-1R) receptors, was used in the study. Tirzepatide (PROMOMED JSC, Russian Federation) was administered subcutaneously in the scruff region at doses of 0.05, 0.1, and 0.3 mg/kg body weight in a volume of 1 mL/kg, calculated individually based on animal weight, over a 7-day course. A 0.9 % sterile sodium chloride solution was used as a control solution administered subcutaneously. Rats were tested 20 minutes after the last administration.

A schematic representation of the experimental design is provided in Figure 1.

Statistical analysis. Statistical significance was assessed using GraphPad Prism 10. Data were tested for normality (Shapiro – Wilk test). As distributions deviated from normality, the non-parametric Kruskal – Wallis test was used with subsequent Dunn's post-hoc test. For analysis of parameter dynamics over time, the Friedman test with Wilcoxon – Holm pairwise comparisons was applied. The significance level was set at $p < 0.05$.

RESULTS

According to the Kruskal – Wallis test, differences between the four groups were non-significant at 30 minutes post-administration ($H = 2.097$, $p = 0.5525$), indicating no overall dose effect on the number of seeds consumed. Dunn's post-hoc analysis also revealed no significant differences between the control group and the groups receiving the compound at 0.05, 0.10, and 0.30 mg/kg ($p > 0.05$) (Fig. 2).

The Kruskal – Wallis test revealed an overall dose effect on day 3 of administration ($H = 9.641$, $p = 0.0219$), indicating significant variability in median values between groups. Dunn's post-hoc analysis showed a significant difference only between the control group and the group receiving the compound at 0.30 mg/kg ($p = 0.0265$). No significant differences were found

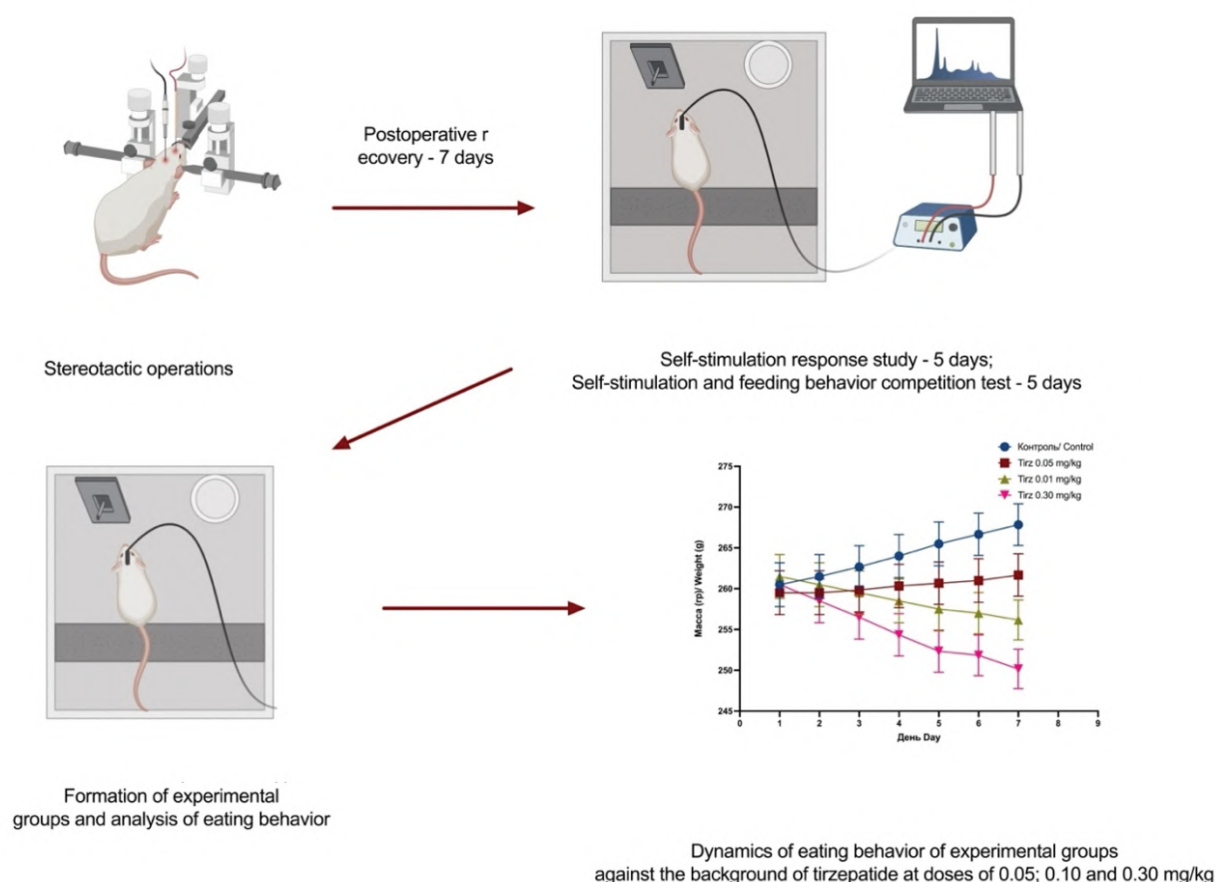


FIG. 1.
Study design scheme

between the control and the 0.05 mg/kg and 0.10 mg/kg groups (Fig. 3).

The Kruskal – Wallis test revealed an overall dose effect on day 7 of administration ($H = 14.16$, $p = 0.0027$), indicating significant variability in median values between groups. Dunn's post-hoc analysis showed significant differences between the control group and the groups receiving the compound at 0.10 mg/kg and 0.30 mg/kg ($p = 0.0442$). No differences were found between the control and the 0.05 mg/kg group (Fig. 4).

Analysis of body weight dynamics revealed differential changes depending on the tirzepatide dose. In the control group, physiological weight gain was observed throughout the observation period. In the group receiving tirzepatide at 0.05 mg/kg, weight gain was slower compared to controls. In the 0.10 mg/kg group, a trend toward gradual weight loss was observed, while at 0.30 mg/kg, pronounced weight loss was registered from day 2–3 of the experiment (Fig. 5A).

By day 7, intergroup differences in body weight were statistically significant. The Kruskal – Wallis test revealed an overall dose effect ($H = 13.19$, $p < 0.01$). Post-hoc comparison showed significant weight loss in the tirzepatide 0.30 mg/kg group compared to controls ($p < 0.01$).

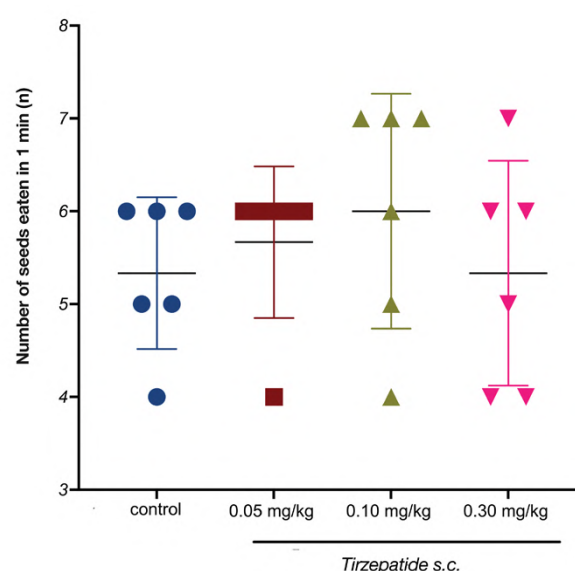


FIG. 2.
Feeding activity, defined as the number of seeds consumed per minute, in the control group and in groups receiving the test compound at various doses, assessed at 30 minutes post-administration. Each dot represents an individual animal

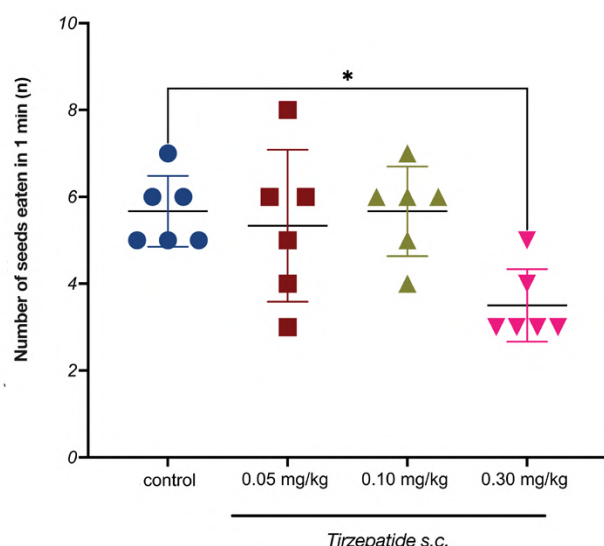


FIG. 3.

Feeding activity, defined as the number of seeds consumed per minute, in the control group and in groups treated with the test compound at various doses on day 3 post-administration (Mean $\pm$ SD). Each dot represents an individual animal. * $p < 0.05$ (Kruskal-Wallis test followed by Dunn's post-hoc test)

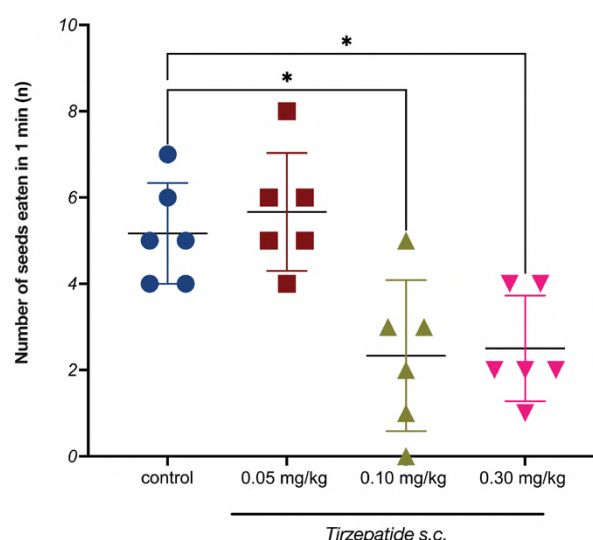


FIG. 4.

Feeding activity, defined as the number of seeds consumed per minute, in the control group and in groups treated with the test compound at various doses on day 7 post-administration (Mean $\pm$ SD). Each dot represents an individual animal. * $p < 0.05$ (Kruskal – Wallis test followed by Dunn's post-hoc test)

The 0.10 mg/kg group also showed a statistically significant difference relative to controls ($p < 0.05$), while the 0.05 mg/kg dose did not differ from controls (Fig. 5B).

Thus, tirzepatide administration was associated with dose-dependent weight loss, most pronounced at 0.30 mg/kg, confirming the pharmacological activity of the drug under repeated administration conditions.

DISCUSSION

The present study demonstrated that tirzepatide exerts dose- and time-dependent effects on feeding behavior in a model of emotional overeating induced by electrical self-stimulation of the brain. The observed gradual development of the anorexigenic effect confirms that the influence of dual GIP/GLP-1 receptor activation on behavioral parameters requires repeated administration and is not immediate. This profile is consistent with clinical data on the gradual reduction of appetite and body weight during tirzepatide therapy [11, 12].

The absence of a statistically significant effect 30 minutes after a single drug administration may indicate that short-term incretin receptor activation does not lead to immediate behavioral changes under conditions of an activated reward system. This aligns with data showing that central GLP-1 receptor effects develop gradually and are associated with changes in hypothalamic and mesolimbic neuronal activity [13]. It has been shown that blockade of endogenous GLP-1R signaling in the ventral tegmental area (VTA) and nucleus

accumbens (NAc) led to a significant increase in food intake, establishing the physiological significance of GLP-1 signaling in the mesolimbic reward system [14]. Our hypothesis is supported by functional magnetic resonance imaging studies in patients receiving GLP-1 agonists, demonstrating reduced reward center reactivity to food stimuli after several weeks of therapy, but not in the first days of treatment [15–17].

The reduction in food intake observed on day 3 only at the maximum dose indicates the existence of a threshold level of receptor activation required to achieve the behavioral effect. Similar data on dose-dependency of incretin effects have been demonstrated in preclinical models for GLP-1R agonists. Activation of central GLP-1Rs has been shown to suppress reward and motivation for food intake, interacting with the mesolimbic system [17]. Concurrent activation of GIPR and GLP-1R has been shown to enhance metabolic and behavioral effects compared to isolated stimulation of a single receptor, supporting the concept of synergy of dual agonists [18].

The most pronounced reduction in feeding activity by day 7 of drug administration indicates the establishment of a stable pharmacological effect. Clinical studies demonstrate a similar dynamic of gradual intensification of tirzepatide's anorexigenic action during the first weeks of therapy [11, 12]. In patients with type 2 diabetes mellitus, tirzepatide was non-inferior to semaglutide and superior in terms of mean change in glycated hemoglobin and body weight from baseline at 40 weeks [19]. Furthermore, changes in eating behavior patterns in patients during long-term drug administration have been demonstrated [20].

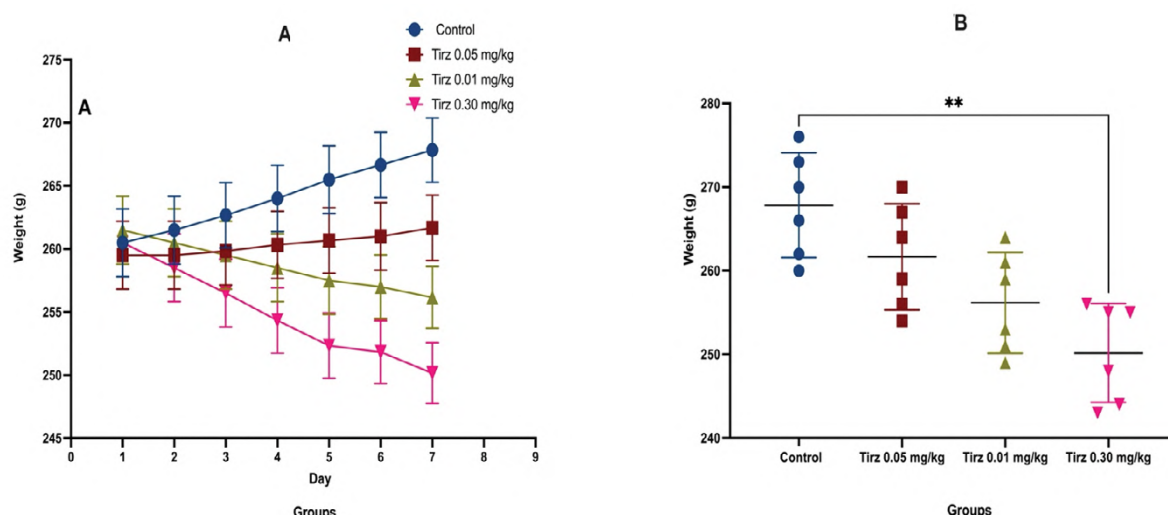


FIG. 5.
Dynamics of body weight changes in rats during 7 days of tirzepatide administration
A – Body weight changes (Mean $\pm$ SD) in the control group and in groups treated with tirzepatide at doses of 0.05, 0.10, and 0.30 mg/kg.
B – Individual body weight values on day 7 of the experiment, with the group mean indicated by a horizontal line. Each dot represents an individual animal. ** $p < 0.01$ (Kruskal – Wallis test followed by Dunn’s post-hoc test).

From a neurobiological perspective, it is well established that GLP-1 receptors are expressed in structures involved in the regulation of both homeostatic and hedonic feeding, including the hypothalamic arcuate nucleus, ventral tegmental area, and nucleus accumbens [13, 14]. GLP-1R activation in the VTA reduces dopaminergic activity and diminishes the motivational salience of food stimuli. Central delivery of the GLP-1R agonist exendin-4 has been shown to suppress phasic dopamine release induced by intravenous cocaine administration. This effect was selective for dopamine signaling in the NAc [21].

The influence of GIP receptors on central mechanisms has been studied less extensively. However, it has been shown that their co-activation may enhance GLP-1 effects through alterations in intracellular signaling and potentiation of metabolic responses [18, 22]. The hypothesis that dual GIP/GLP-1 activation leads to more pronounced modulation of mesolimbic circuits compared to selective GLP-1R stimulation appears biologically plausible but requires direct neurochemical confirmation.

The present study demonstrates the effect of tirzepatide on feeding behavior in a model of artificial hyperactivation of the reward system. In contrast to most preclinical studies evaluating hyperphagia in diet-induced obesity models, this model allows investigation of the hedonic component of feeding associated with activation of the mesolimbic dopaminergic system. Therefore, this work expands the mechanistic understanding of the clinical effects of tirzepatide.

The data obtained suggest that tirzepatide may be considered a potential tool for correcting not only

metabolic disorders but also conditions characterized by pathologically enhanced food motivation. Clinical data indicate the presence of a pronounced hedonic component of feeding and elements of compulsive behavior in a subset of patients with obesity [23–25]. If the hypothesis of central modulation of the reward system is confirmed, this may expand the therapeutic potential of dual incretin agonists in patients with emotional overeating and comorbid impulse control disorders [26].

Therefore, the present study confirms the dose- and time-dependent nature of tirzepatide’s anorexigenic effect in an experimental model of emotional overeating, demonstrates the potential involvement of central mechanisms of motivational regulation, and establishes a foundation for further translational research.

CONCLUSION

The obtained data confirm that tirzepatide, upon repeated administration, reduces feeding activity in a model of emotional overeating and exhibits a dose- and time-dependent effect. However, to demonstrate a primarily central (motivational) mechanism of action, additional studies with control of locomotion/somatic status and an extended panel of behavioral and neurobiological markers of the reward system are required. The potential role of dual incretin activation in the correction of feeding behavior relevant to clinical forms of obesity with a pronounced hedonic component is substantiated, while simultaneously indicating the limitations of interpretation necessary for clinical translation.

Conflict of interest

The authors declare no conflict of interest.

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