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# Pathophysiological role of the glucagon-like peptide-1 system in the regulation of stress-induced impairments of impulsive and compulsive behavior in rats

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**Abstract.** ***Introduction.*** The glucagon-like peptide-1 (GLP-1) system plays an important role not only in the regulation of energy metabolism but also in the control of motivational and reward-related behavior. Recent studies have demonstrated that GLP-1 receptor agonists can modulate the activity of mesolimbic brain structures involved in the development of impulsivity and addictive behavior. However, the effect of GLP-1 system activation on stress-induced disturbances of self-control remains insufficiently studied. ***Aim.*** To determine the role of the glucagon-like peptide-1 (GLP-1) system in regulating impulsive and compulsive behavior that develops in rats following early-life stress (temporary maternal separation), and to evaluate the effects of pharmacological activation of GLP-1 receptors on behavioral manifestations associated with impaired self-control and emotional regulation. ***Materials and methods.*** Experiments were carried out on Wistar rats exposed to maternal separation during the postnatal period. Impulsivity was assessed using a modified decision-making test with different reinforcement probabilities (analogous to the Iowa Gambling Task), and compulsivity was evaluated using the marble burying test. The GLP-1 receptor agonist exenatide (Byetta®, AstraZeneca, UK) was administered subcutaneously at a dose of 10 μg/kg daily for 7 days. Statistical analysis was performed using Student's t-test; data are presented as mean±SEM, and differences were considered significant at $p < 0.05$. ***Results.*** Administration of the GLP-1 agonist resulted in a significant reduction in impulsive behavior, expressed as a decreased frequency of risky arm choices in the probabilistic reinforcement task compared to saline-treated rats ($p < 0.05$). At the same time, no significant effect was observed on compulsive behavior in the marble burying test. ***Conclusions.*** Activation of GLP-1 receptors by exenatide exerts a selective anti-impulsive effect while maintaining the level of compulsive responses, indicating a modulatory role of the GLP-1 system primarily in the regulation of the impulsive component of behavior. The obtained results support the potential of GLP-1 receptor agonists as pharmacological agents for correcting stress-induced impairments of self-control and addiction-related behavioral disorders.

**Keywords:** glucagon-like peptide-1 (GLP-1), exenatide, impulsivity, compulsivity, stress, maternal deprivation, rat, mesolimbic system

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# Патофизиологическая роль системы глюкагоноподобного пептида-1 в регуляции стресс-индуцированных нарушений импульсивного и компульсивного поведения у крыс

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**Резюме.** ***Введение.*** Система глюкагоноподобного пептида-1 (GLP-1) играет важную роль не только в регуляции энергетического обмена, но и в контроле мотивационно-подкрепляющего поведения. В последние годы установлено, что агонисты рецепторов GLP-1 способны модулировать активность мезолимбических структур, участвующих в развитии импульсивности и аддиктивных форм поведения. Однако влияние активации системы GLP-1 на стресс-индуцированные нарушения самоконтроля недостаточно изучено. ***Цель исследования*** — определить роль системы глюкагоноподобного пептида-1 (GLP-1) в регуляции импульсивного и компульсивного поведения, формирующегося у крыс после раннего стрессового воздействия (временной изоляции от матери), а также оценить влияние фармакологической активации рецепторов GLP-1 на поведенческие проявления, связанные с нарушением самоконтроля и эмоциональной регуляции. ***Материалы и методы.*** Эксперименты выполнены на крысах Вистар, подвергшихся временной изоляции от матери в постнатальном периоде. Для оценки импульсивности использовали модифицированный тест выбора с различной вероятностью подкрепления (аналог Iowa Gambling Task), а для оценки компульсивности — тест закапывания шариков. Препарат эксенатид (Byetta®, AstraZeneca, Великобритания) вводили подкожно в дозе 10 мкг/кг ежедневно в течение 7 дней. Статистическую обработку данных проводили с помощью t-критерия Стьюдента; результаты представлены в виде M±SEM, различия считали значимыми при $p < 0,05$. ***Результаты.*** Введение агониста GLP-1 приводило к достоверному снижению импульсивности, выражавшемуся в уменьшении частоты выбора рискованных рукавов в тесте вероятностного подкрепления по сравнению с группой, получавшей изотонический раствор натрия хлорида раствор ($p < 0,05$). При этом достоверного влияния на проявления компульсивного поведения в тесте закапывания шариков не выявлено. ***Выводы.*** Активация рецепторов GLP-1 с помощью эксенатида оказывает селективное антиимпульсивное действие при сохранении уровня компульсивных реакций, что указывает на модулирующую роль системы GLP-1 преимущественно в регуляции импульсивного компонента поведения. Полученные данные подтверждают перспективность агонистов GLP-1 как фармакологических средств для коррекции стресс-индуцированных нарушений самоконтроля и аддиктивных расстройств поведения.

**Ключевые слова:** глюкагоноподобный пептид-1 (GLP-1), эксенатид, импульсивность, компульсивность, стресс, материнская депривация, крыса, мезолимбическая система

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## INTRODUCTION

Characteristic features of many psychiatric disorders, including substance use disorders, gambling disorder, obsessive–compulsive disorder, and binge-eating disorder, include impaired behavioral control [1]. Impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli, with diminished regard for the negative consequences of these actions for oneself or others" [2, 3].

Compulsivity, in contrast, is characterized by "the performance of repetitive and functionally maladaptive behaviors — overt or covert — carried out in a stereotyped manner, according to rigid rules or to prevent subjectively perceived negative consequences" [3].

Contemporary research indicates that both behavioral phenotypes represent multidimensional and multicomponent constructs involving distinct neurobiological and motivational mechanisms. Their relative contribution to the clinical presentation may vary depending on the type of psychopathology, individual personality traits, and the stage of the disorder [4].

In recent years, considerable efforts have been made to investigate the neurobiological basis of impaired self-control, including the development of behavioral tests for assessing impulsivity and compulsivity. Experimental evidence demonstrates pronounced impulsive and compulsive traits in obsessive–compulsive disorder [1], substance use disorders [5], and other addictive behaviors, such as gambling disorder [5].

Considerably less is known about how these processes relate to the pathogenesis of binge-eating disorder (BED). BED is characterized by the consumption of large amounts of food within a limited period of time, accompanied by a subjective loss of control over eating behavior [6]. The disorder is considered to share features with addictive disorders, including a positive correlation with impulsivity [7, 8].

According to current concepts of the neurobiology of addictive disorders, peripheral metabolic factors with central nervous system activity, such as glucagon-like peptide-1 (GLP-1), play an important role in regulating reward circuitry and reinforcement processes associated with psychoactive substances [15].

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to food intake. It lowers blood glucose levels by stimulating insulin secretion from pancreatic β-cells, delays gastric emptying, and enhances satiety [8]. Based on these effects, GLP-1 analogs were developed and are used to improve glycemic control in patients with type 2 diabetes mellitus. In addition to its peripheral effects mediated through vagal afferents, GLP-1 is also synthesized in the brain—primarily by neurons of the nucleus of the solitary tract (NTS)—where it functions as a neuromodulator [10, 11]. GLP-1 receptors (GLP-1R) are expressed in several key brain regions, including the nucleus of the solitary tract, hypothalamus, ventral tegmental area (VTA), and nucleus accumbens (NAc), all of which are involved in the regulation of energy homeostasis, appetite, food reward, and drug-related reward [12].

A number of recent preclinical studies indicate an important role of the GLP-1 system in the regulation of addictive behavior. Publications from the last decade have demonstrated that exendin-4 suppresses conditioned place preference (CPP), cocaine self-administration, and the reinstatement of drug-seeking behavior induced either by the drug itself or by drug-associated cues during abstinence [13–15].

Given current understanding of the neurometabolic mechanisms regulating motivation and reward, investigation of the role of GLP-1 and its receptors in the pathogenesis of behavioral disorders appears highly relevant. While the influence of the GLP-1 system on energy balance, appetite, and glucose metabolism has been extensively studied, its involvement in the development of impulsive and compulsive behavioral patterns, addictive tendencies, and stress-induced disturbances of emotional regulation remains insufficiently explored.

## AIM

To determine the role of the glucagon-like peptide-1 (GLP-1) system in the regulation of impulsive and compulsive behaviors developing in rats following early-life stress exposure (maternal separation), as well as to evaluate the effects of pharmacological activation of GLP-1 receptors on behavioral manifestations associated with impaired self-control and emotional dysregulation.

## MATERIALS AND METHODS

**Experimental Animals.** The study was conducted on 72 Wistar rats weighing 250–300 g (62 males and 10 females). The animals were obtained from the Rappolovo breeding facility (Tosnensky District, Leningrad Region, Russia) and housed in the animal facility of St. Petersburg State Pediatric Medical University. Animals were maintained in standard

plastic cages (40×50×20 cm) under controlled conditions: temperature 22±2 °C, relative humidity 50–60%, and a reversed light–dark cycle (light: 20:00–08:00; dark: 08:00–20:00). Standard pelleted chow and water were provided *ad libitum*. Upon arrival, the animals underwent a two-week acclimatization period. All experimental procedures complied with Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes and were approved by the Local Ethics Committee of St. Petersburg State Pediatric Medical University (Protocol No. 58/03, September 25, 2025).

**Breeding and Offspring Production.** Female rats were housed in groups of five per cage with free access to food and water. One male was introduced into each cage. Vaginal smears were collected daily and examined under a light microscope. The presence of spermatozoa in a smear during proestrus was considered day 0 of pregnancy. After pregnancy was confirmed, females were housed individually. Gestation lasted 20±2 days.

**Early-Life Stress Model.** Maternal separation was used to model early postnatal stress. From postnatal day 2 to day 12, pups were separated from their mothers daily for 180 min and placed individually in plastic containers. Visual, tactile, and auditory contact with the mother was completely prevented. Following the deprivation period and subsequent nursing, offspring were housed in standard cages with five animals per cage. For behavioral testing, 20 male rats aged 90–100 days and weighing 200–250 g were selected [5]].

**Randomization.** Block randomization was performed at the litter level (1–2 pups from each litter assigned to each group). The experimental groups were: MS+NaCl (n=14); MS+Exenatide (10 μg/kg, s.c., once daily for 7 consecutive days; n=14).

**Assessment of Impulsive Behavior: Probability–Reward Task (Modified Iowa Gambling Task).** ДBehavioral impulsivity was assessed using the Probability–Reward Task, a rodent adaptation of the Iowa Gambling Task. The apparatus consisted of a start platform (33×50×35 cm) connected to three maze arms, each 50 cm long and 15 cm wide. An automatic food dispenser was located at the end of each arm (Fig. 1). Each return to the start platform initiated a new reinforcement cycle.

Animals were trained daily for 21 days under restricted feeding conditions (4 h of food access per day) with free access to water. Prior to each session, rats underwent 20 h of food deprivation.

During the first 5 days, a training reinforcement schedule was used: entry into arm 1 delivered one standard food pellet (0.1 g), arm 2 delivered two pellets, and arm 3 delivered three pellets.

Subsequently, animals proceeded to the main training phase. The reinforcement schedule was modified as follows: Arm 1: FR1 (one pellet on every entry); Arm 2: FR2 (two pellets on every second entry); Arm 3: FR3 (three pellets on every third entry).

Thus, no reward was delivered on 50% of entries into arm 2 and on 66.7% of entries into arm 3. Stable learning was defined as a consistent preference pattern maintained for at least three consecutive days. Animals that failed to enter the maze arms (≤15%) were excluded from the experiment [7].

**Assessment of Compulsive Behavior: Marble Burying Test.** Compulsive and anxiety-related behaviors were evaluated using the Marble Burying Test. Rats were placed individually in standard plastic cages (40×50×20 cm) containing a 5-cm layer of bedding. Twenty glass marbles (1.5 cm in diameter) were evenly distributed across the bedding surface.

Each animal remained in the cage for 30 min, after which the number of partially or completely buried marbles (buried to a depth exceeding two-thirds of their diameter) was recorded [7].

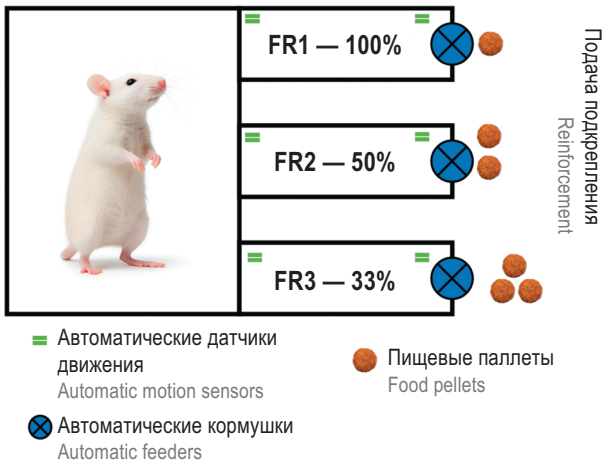



**Fig. 1.** **Experimental setup for the probability–reward task (modified Iowa Gambling Task). FR1 — one pallet per pass; FR2 — two pallets per every second pass; FR3 — three pallets per every third pass. (compiled by the authors)**

**Рис. 1.** Схема экспериментальной установки для теста вероятности и величины подкрепления (модифицированный Iowa Gambling Task). FR1 — одна паллета при каждом заходе; FR2 — две паллеты при каждом втором заходе; FR3 — три паллеты при каждом третьем заходе (рисунок составлен авторами)

The number of buried marbles was used as an indicator of compulsive behavior. Following each test session, both the bedding and marbles were replaced to eliminate olfactory influences.

**Pharmacological Agents.** The GLP-1 receptor agonist exenatide (Exendin-4; Byetta®, AstraZeneca, United Kingdom), a synthetic analogue of endogenous incretin with high affinity for GLP-1 receptors and resistance to degradation by dipeptidyl peptidase-IV, was used as the pharmacological agent.

According to published preclinical studies, exenatide is commonly administered to rodents at doses ranging from 2.4 to 10 μg/kg, producing pronounced behavioral and neurochemical effects without significant somatic adverse effects.

In the present study, exenatide was administered subcutaneously (s.c.) at a dose of 10 μg/kg in a volume of 1 mL/kg once daily for 7 days. Treatment began after the adaptation period. The selected dose and administration regimen were based on previously published data demonstrating the efficacy of GLP-1 receptor agonists in correcting stress-induced and addiction-related behavioral disturbances.

**Statistical Analysis.** Statistical analyses were performed using GraphPad Prism 10.1 (USA). Data distribution was assessed using the Kolmogorov–Smirnov test. Differences between groups were evaluated using Student's t-test.

Data are presented as mean ± standard error of the mean (M±SEM). Differences were considered statistically significant at $p < 0.05$.

## RESULTS

A comparison of the proportion of visits to the first arm in groups subjected to maternal separation and treated either with isotonic sodium chloride solution (MS+NaCl) or a GLP-1 receptor agonist (exenatide, MS+GLP-1 agonist) revealed statistically significant differences.

Figure 2 presents the results of the Probability-Reward Task in rats after maternal separation (MS). Two groups of animals were compared: MS+NaCl rats receiving isotonic sodium chloride solution; and MS+GLP-1 agonist rats treated with a GLP-1 receptor agonist.

In the MS+Ex4 group, the proportion of visits to the first arm was 36.01±2.90%, which was significantly higher than in rats receiving isotonic sodium chloride solution (21.61±1.76%, $t(26)=4.238$, $p=0.0003$). The mean difference was 14.40% with a 95% confidence interval of 7.42–21.38. The coefficient of determination ($\eta^2=0.4085$) indicates that approximately 41% of the variance in this parameter is explained by GLP-1 receptor agonist administration.

When comparing the proportion of visits to the third arm between the same groups, a significant decrease was observed in animals treated with the GLP-1 receptor agonist. The mean proportion of visits to the third arm in the MS+NaCl group was 44.43±2.90%, whereas in the exenatide-treated group this value decreased to 24.40±2.90% ($t(26)=4.803$, $p < 0.0001$). The mean difference was −20.03% with a 95% confidence interval of −28.60 to −11.46. The coefficient of determination ($\eta^2=0.4702$) indicates that approximately 47% of behavioral variability is explained by the effect of GLP-1 receptor activation.

Thus, activation of GLP-1 receptors led to a redistribution of behavioral activity toward arms associated with guaranteed reinforcement, reflecting a shift in motivational decision-making patterns following early-life stress exposure.

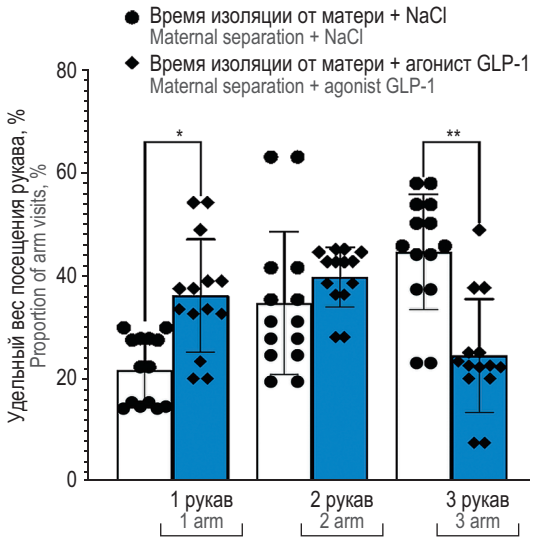



**Fig. 2.** **Changes in the proportion of arm visits with different reinforcement probabilities in rats after maternal separation following administration of saline or a GLP-1 agonist. Data are presented as mean ± SEM; statistical analysis was performed using Student's t-test; *p <0.01, **p <0.001 (compiled by the authors)**

**Рис. 2.** Изменение удельного веса посещения рукавов с различной вероятностью подкрепления у крыс после временной изоляции от матери при введении изотонического раствора натрия хлорида и агониста GLP-1. Данные представлены в виде средних значений ± SEM; статистическая обработка — t-критерий Стьюдента; * p <0,01, ** p <0,001 (рисунок составлен авторами)

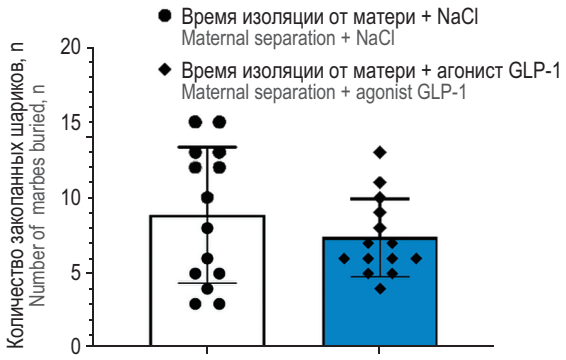



**Fig. 3.** **Number of marbles buried in the marble burying test in rats after maternal separation following administration of saline or a GLP-1 agonist. Data are presented as mean ± SEM (compiled by the authors)**

**Рис. 3.** Количество закопанных шариков в тесте закапывания шариков у крыс после временной изоляции от матери при введении изотонического раствора натрия хлорида и агониста GLP-1. Данные представлены как средние ± SEM (рисунок составлен авторами)

Figure 3 presents the results of the Marble Burying Test in rats subjected to maternal separation and treated with either isotonic sodium chloride solution (MS+NaCl) or a GLP-1 receptor agonist (MS+GLP-1 agonist). Both groups demonstrated a similar behavioral trend: animals actively interacted with the environment and buried marbles; however, administration of the GLP-1 receptor agonist did not produce statistically significant changes in the number of buried marbles compared with the control group ($p > 0.05$, Student's t-test).

The mean number of buried marbles was 8.2±0.7 in the MS+NaCl group and 7.1±0.6 in the MS+GLP-1 agonist group. Despite a slight trend toward reduction in the treated group, the differences were not statistically significant.

## DISCUSSION

The maternal separation model used in this study represents one of the most valid and reproducible experimental approaches for modelling stress-induced disturbances of emotional and behavioral regulation [16, 17]. Prolonged separation of pups from the mother during the early postnatal period is accompanied by activation of the hypothalamic–pituitary–adrenal axis and the development of persistent alterations in dopaminergic and serotonergic brain systems, leading to increased impulsivity, anxiety, and the emergence of rigid behavioral patterns in adulthood [18].

The present data demonstrate that pharmacological activation of GLP-1 receptors with exenatide in animals exposed to early postnatal stress selectively corrects the impulsive component of decision-making, shifting behaviour from risky strategies toward predictable reinforcement. This is directly reflected in the redistribution of arm choices in the modified Probability–Reward Task: in rats treated with exenatide, the proportion of visits to the arm with guaranteed reinforcement (FR1) was significantly higher than in animals receiving isotonic sodium chloride solution (36.01±2.90% vs. 21.61±1.76%; $t(26)=4.238$; $p=0.0003$), whereas the number of visits to the "risky" arm (FR3) was significantly reduced (24.40±2.90% vs. 44.43±2.90%; $t(26)=4.803$; $p < 0.0001$). The absence of significant changes in the marble burying test highlights the selectivity of exenatide's effect: the intervention modulates impulsivity but does not affect compulsive or stereotyped behavioral patterns, where rigidity and perseveration play a dominant role. It should be noted that the marble burying test integrates an anxiety-related component as well, which limits its sensitivity to changes in cognitive rigidity; thus, the observed dissociation between impulsivity and compulsivity is not only methodologically plausible but also conceptually expected, supporting the relative independence of these constructs within a broader impulsive–compulsive spectrum.

These findings are consistent with evidence on the central role of the GLP-1 system in regulating motivational and reward-related behaviour. GLP-1 receptors are expressed in key reward-processing structures (NAc, VTA, amygdala, hypothalamus), and GLP-1 agonists are capable of modulating mesolimbic pathway activity [20, 21]. Inhibition of the GLP-1 system during early ontogenesis also produces significant behavioral changes: neonatal administration of the dipeptidyl peptidase IV inhibitor diprotin A, which blocks degradation of endogenous incretins, leads to a hyperactive phenotype and persistent increases in aggression in adult rats [22].

Against this background, the observed shift from risky to predictable behavioral strategies following exenatide administration extends the known effects of GLP-1 agonists (suppression of conditioned place preference, cocaine self-administration, and reinstatement of drug seeking) from the domain of "drug-related motivation" to stress-induced decision-making impulsivity [23–27].

Thus, the combined experimental and literature data support the view of the GLP-1 system as an important neuropeptidergic component integrating metabolic and motivational mechanisms of behavioral regulation.

## CONCLUSION

1. The GLP-1 receptor agonist exenatide demonstrates a pronounced anti-impulsive effect, manifested by a reduction in risky choices and an increased preference for stable reinforcement in rats subjected to early-life stress, thereby supporting the regulatory role of the GLP-1 system in mechanisms of impulse control.

2. Administration of a GLP-1 receptor agonist does not significantly affect measures of compulsive behaviour in the marble burying test, which may indicate a selective action of the GLP-1 system predominantly on impulsivity-related behavioral components.

## ADDITIONAL INFORMATION

**Author contributions.** N.S. Dedanishvili — experimentation, writing and editing; S.S. Purveev — experimentation, writing and editing, and study concept; A.A. Lebedev, A.G. Vasiliev, A.V. Vasilyeva, M.A. Pakhomova— writing and editing; P.D. Shabanov — writing and editing, and supervision.

All authors made a significant contribution to the concept development, study execution, and preparation of the article, and read and approved the final version prior to publication.

**Conflict of interest.** The authors declare no actual or potential conflicts of interest related to the publication of this article.

**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).

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** Н.С. Деданишвили — проведение экспериментов, написание и редактирование текста; С.С. Пюрвеев — проведение экспериментов, написание и редактирование текста, концепция исследования; А.А. Лебедев, А.Г. Васильев, А.В. Васильева, М.А. Пахомова — написание и редактирование текста; П.Д. Шабанов — написание и редактирование текста, руководство.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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**Эксперименты с животными** проводили в соответствии с международными правилами (Директивой 2010/63/EU Европейского парламента и Совета Европейского союза от 22 сентября 2010 г. по охране животных, используемых в научных целях).

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