DOI: https://doi.org/10.17816/RCF633931 EDN: VVUXPH

Changes in Gene Expression of *Ntrk2/Pi3k* Pathway Following Vital Stress in Rats With Compulsive Overeating

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ABSTRACT

BACKGROUND: Compulsive overeating, also known as paroxysmal overeating, differs from other eating disorders such as bulimia or anorexia nervosa because it is not associated with compensatory behaviors. Vital psychogenic stress has been demonstrated to be a contributing factor to the development of post-traumatic stress disorders. Despite the available data on the involvement of mediator and cell signaling systems in the effects of post-traumatic stress disorders, there has been a paucity of studies investigating changes in the gene expression following vital stress. This phenomenon is particularly evident in the genes of the NTRK2/PI3K signaling pathway, which is induced by Bdnf and is a component of the neurotrophic mechanism.

AIM: To assess the effect of stress on the brain expression of *Ntrk2* and *Pi3k* genes in response to predator presentation.

METHODS: The experimental study comprised of 86 male Wistar rats, weighing between 200 and 250 g. A high-carbohydrate diet was made available to the experimental groups for one hour, in addition to the standard food granules. Male Wistar rats that exhibited compulsive overeating received a high-carbohydrate diet (a chocolate spread mix) for one hour every third day. Fifteen minutes prior to feeding, the animal was placed at a 5-cm distance from the food, with visual contact maintained throughout the experiment. After becoming food addicted, the rats were placed in a terrarium with an Indian python, where one of them was consumed by the predator. The animals that remained alive after the death of their fellow were subsequently confined within a terrarium, with a transparent partition separating them from the python.

RESULTS: Polymerase chain reaction demonstrated the hypothalamic gene expression in the *Ntrk2/Pi3k* signaling pathway. The gene expression levels were elevated in the group of rats following the predator presentation. However, the *Ntrk2* expression demonstrated a 1.5-fold decrease following stress exposure. However, the *Ntrk2* and *Pi3k* expression was found to be reduced by 2.8 and 5 times, respectively, as compared to non-stressed rats that received chocolate. The *Pi3k* expression increased twofold in stressed rats that did not receive chocolate.

CONCLUSION: The findings from this study offer new insights into the synthesis of pharmacological peptides, which have the potential to address food addiction caused by psychogenic stresses during ontogenesis.

Keywords: compulsive overeating; *Ntrk2/Pi3k*; social isolation; post-traumatic stress disorders; predator presentation.

To cite this article

Lizunov AV, Lebedev AA, Goltz VA, Pyurveev SS, Nadbitova ND, Bychkov ER, Lebedev VA, Evdokimova NR, Shamaeva SA, Tsikunov SG, Yurov AYu, Shabanov PD. Changes in Gene Expression of *Ntrk2/Pi3k* Pathway Following Vital Stress in Rats With Compulsive Overeating. *Reviews on Clinical Pharmacology and Drug Therapy.* 2025;23(1):51–58. DOI: 10.17816/RCF633931 EDN: VVUXPH

Received: 30.06.2024 **Accepted:** 12.02.2025 **Published online:** 31.03.2025

DOI: https://doi.org/10.17816/RCF633931 EDN: VVUXPH

Изменение экспрессии генов сигнального каскада *Ntrk2/Pi3k* при витальном стрессе у крыс при компульсивном переедании

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АННОТАЦИЯ

Обоснование. Расстройство компульсивного (приступообразного) переедания, в отличие от булимии или нервной анорексии, не сопровождается компенсаторным поведением. Витальные психогенные стрессы приводят к посттравматическим стрессовым расстройствам. Несмотря на имеющиеся данные об участии медиаторных систем и систем клеточного сигналинга в эффектах посттравматических стрессовых расстройств, проведено мало исследований по изменению экспрессии генов после витального стресса. В частности, это касается генов сигнального каскада *NTRK2/PI3K*, индуцируемого Bdnf и являющегося частью нейротрофического механизма.

Цель — исследовали влияние стресса при предъявлении хищника на экспрессию генов *Ntrkr2* и *Pi3k* в структурах мозга.

Материалы и методы. Эксперименты проведены на 86 самцах Вистар массой 200–250 г, экспериментальные группы получали в течение 1 ч доступ к диете с высоким содержанием углеводов в дополнение к стандартному гранулированному корму. При выработке компульсивного переедания крысы самцы Вистар получали в течение 1 ч диету с высоким содержанием углеводов (смесь на основе шоколадной пасты) каждый третий день. За 15 мин до кормления животное помещали в 5-см досягаемости от пищи при визуальном контакте. После выработки пищевой зависимости крыс помещали в террариум к тигровому питону, где одно из них становилось жертвой пищевых потребностей хищника. Пережившие гибель партнера животные далее находились в террариуме за прозрачной перегородкой.

Результаты. Анализ полимеразной цепной реакции показал наличие в гипоталамусе экспрессии генов в сигнальном каскаде *Ntrk2/Pi3k*. Экспрессия генов при этом была выше у группы крыс после предъявления хищника. У крыс после стрессирования уровень экспрессии *Ntrkr2* понижался в 1,5 раза. *Ntrkr2* понижался в 2,8 раза, а уровень экспрессии *Pi3k* в 5 раз по сравнению с нестрессированными крысами, получавшими шоколад. Уровень экспрессии *Pi3k* у стрессированных крыс, не получавших шоколад, повышался в 2 раза.

Заключение. Полученные данные предполагают новые пути синтеза фармакологических средств пептидной природы для коррекции пищевой зависимости, вызванной психогенными стрессами в онтогенезе.

Ключевые слова: компульсивное переедание; *Ntrk2/Pi3k*; социальная изоляция; посттравматические стрессовые расстройства; предъявление хищника.

Как цитировать

Лизунов А.В., Лебедев А.А., Гольц В.А., Пюрвеев С.С., Надбитова Н.Д., Бычков Е.Р., Лебедев В.А., Евдокимова Н.Р., Шамаева С.А., Цикунов С.Г., Юров А.Ю., Шабанов П.Д. Изменение экспрессии генов сигнального каскада *Ntrk2/Pi3k* при витальном стрессе у крыс при компульсивном переедании // Обзоры по клинической фармакологии и лекарственной терапии. 2025. Т. 23, № 1. С. 51–58. DOI: 10.17816/RCF633931 EDN: VVUXPH

Рукопись получена: 30.06.2024 **Рукопись одобрена:** 12.02.2025 **Опубликована online:** 31.03.2025

BACKGROUND

Compulsive (paroxysmal) overeating, a form of food addiction, is characterized by intermittent excessive consumption of palatable food within short periods of time. Unlike bulimia or anorexia nervosa, this behavior is not associated with compensatory mechanisms [1]. Factors that may affect compulsive overeating episodes include various stressors (partial food deprivation and intermittent exposure to energy-rich palatable food) [2]. Neuroendocrine processes and several neurotransmitter systems, including the opioid, serotonergic, and dopaminergic pathways and hormones, have been shown to be involved in the mechanisms of food addiction [3]. In our previous research, we demonstrated that higher intermittent intake of fat- and sugar-rich food predicted overeating in rats regardless of body weight gain or obesity, which is a manifestation of compulsive (paroxysmal) overeating [4].

Vital psychogenic stress leads to post-traumatic stress disorder (PTSD). Although the involvement of neurotransmitter and cell signaling systems in the effects of PTSD has been documented, only a few studies have investigated changes in gene expression following vital stress. In particular, this applies to the genes of the *NTRK2/PI3K* signaling pathway, which is induced by Bdnf and is part of the neurotrophic mechanism.

Compulsive overeating, as a form of food addiction, is frequently associated with PTSD [5]. These conditions may have a shared etiology or arise in response to similar environmental antecedents. PTSD is a mental and behavioral disorder that may develop following exposure to extremely traumatic events, such as combat, technological disasters, traffic accidents, sexual assault, child abuse, domestic violence, or other life-threatening experiences (National Institute of Mental Health, 2017).

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family, which interacts with receptor tyrosine kinases such as tropomyosin receptor kinase B (TrkB, NTRK2). BDNF expression is regulated by neuronal activity or peripheral hormones. Neurotrophins regulate neuronal survival and differentiation during development; however, accumulating evidence suggests they are also involved in numerous adult brain functions, including plasticity processes [6, 7]. Tropomyosin receptor kinase B (TrkB) is a catalytic receptor for certain neurotrophins, including BDNF. TrkB influences neuronal differentiation and survival. Studies have demonstrated that TrkB activation by BDNF inhibits KCC2, a chloride ion transporter protein in neurons [7, 8]. The expression of both TrkB and BDNF is reduced in the brain of patients with early-stage Alzheimer disease and mild cognitive impairment, and mouse models have shown that reduced TrkB levels in the brain are associated with pronounced memory deficits [9–11]. Phosphoinositide 3-kinase IB (PI3K) activates the PI3K/AKT/mTOR signaling cascade, which regulates the cell cycle and enhances neural cell proliferation and differentiation. Accelerated proliferation has been shown to result from the effect of the PI3K/AKT/mTOR cascade on the BDNF/TrkB signaling system [12, 13]. Thus, the BDNF/TrkB/PI3K/AKT/mTOR signaling system plays a role in proliferative and regenerative processes in the central nervous system. These mechanisms are activated in response to stress and the development of compulsive overeating, as demonstrated in previous studies [14, 15].

This work aimed to assess the effect of compulsive overeating development on the expression of *Ntrk2* and *Pi3k* genes in the hypothalamus of rats following vital stress induced by predator exposure.

METHODS

The experiments were conducted in 86 male Wistar rats weighing 200–250 g, obtained from the Rappolovo laboratory animal breeding facility (Leningrad Region, Russia). The animals were housed in a vivarium in standard plastic cages, with ad libitum access to water and food, under an inverted light/dark cycle (08:00 am-08:00 pm) at a controlled temperature of 22±2°C. All experimental procedures complied with the principles of humane treatment of laboratory animals in accordance with the "Good Laboratory Practice Rules of the Russian Federation" (Order of the Ministry of Health of the Russian Federation No. 267, 2003).

The animals were randomized into four groups: non-stressed animals with no access to chocolate-based diet (Group 1); non-stressed animals with access to chocolate-based diet every third day (Group 2); animals exposed to predator stress with no access to chocolate-based diet (Group 3); and animals exposed to predator stress with access to chocolate-based diet every third day (Group 4).

Modeling of predator stress. Rats were placed into a terrarium with a reticulated python, where one of the animals was consumed by the predator. The surviving animals were subsequently kept in the terrarium behind a transparent partition for 30–40 minutes [16]. During the traumatic event, the rats exhibited pronounced fear responses, including behavioral manifestations such as freezing, huddling, rearing, and prolonged and altered grooming. Some animals displayed agitated and uncontrolled movement in the terrarium [17]. The control group of rats (n=10) was not subjected to stress.

Modeling of compulsive overeating with high-calorie food. The experimental groups (Groups 2 and 4) were given access to a high-carbohydrate diet (a chocolate spread-based mixture) for 1 hour every third day over a 6-week period. The intact and control animals (Groups 1 and 3,

respectively) received only standard pelleted feed for rats. The high-calorie diet consisted of a paste prepared by mixing chocolate spread, crushed rat chow pellets (4RF18; Mucedola; Settimo Milanese), and water in the following weight/weight ratio: 52% chocolate spread, 33% chow pellets, and 15% water. The caloric density of the diet was 3.63 kcal/g. Standard pellet chow for rats was placed in a container with a metal grid suspended on the front wall of the cage. The container was removed to weigh and measure food intake. The chocolate mixture was served in a coffee cup, with the handle inserted through the cage's metal wall. Fifteen minutes prior to access, the cup with the chocolate paste was placed 5 cm away from the animals, in full visual contact. During this 15-minute period, the cup was placed inside a container with a metal grid suspended on the front wall of the cage. In this setup, the animals could see the cup containing the paste and smell it, but were unable to access it. During this 15-minute period, the animals made repetitive movements with their forelegs, head, and torso in an attempt to get the paste, but were unable to reach it. This induced a mild stress state, which led to an increase in serum corticosterone levels. After 15 minutes, the cup was placed inside the cage, allowing the animals access to the paste [18]. Before each overeating session, the standard rodent chow present in each cage was weighed to assess the 24-hour food intake on the following day. Fifteen days after the start of the chocolate diet experiment, the rats were housed individually and continued to receive the diet for another 30 days. The following parameters were recorded: the amount of standard chow consumed and the amount of chocolate paste consumed within the 1-hour access period. Body weight was measured weekly on a fixed day.

Analysis of the effects of vital stress and overeating on gene expression. To assess the expression levels of *Ntrk2* and *Pi3k* genes, mRNA was isolated from dissected hypothalamic tissue using a standard protocol. A ground hypothalamic fragment was placed in 1,000 µL of TRIzol and incubated at 40°C for 5 minutes. Subsequently, 200 µL of chloroform was added to each sample, followed by gentle mixing and a 5-minute incubation. Samples were then centrifuged at 13,000g for 10 minutes, and the upper aqueous phase was collected. An equal volume of isopropanol was added to the collected phase, mixed, and incubated at –20°C for 24 hours. The samples were centrifuged again at 13,000g for 10 minutes to collect the precipitate. The supernatant was removed, and the pellet was washed with 70% ethanol and dried in a thermostat at 40°C. The dried pellet was then dissolved in 50 µL of dH_2O with 1% RNase inhibitor (RNasin). After mRNA extraction, reverse transcription reactions were performed, followed by real-time PCR using primers specific for *Ntrk2* and *Pi3k* mRNA. *Beta-actin* and glyceraldehyde 3-phosphate dehydrogenase (*Gapdh*) were used as housekeeping genes (Table 1).

Statistical analysis. Statistical processing of the obtained quantitative data was performed using GraphPad Prism v6.0. All data are presented as mean±standard deviation. One-way analysis of variance (ANOVA) was used to assess significant intergroup differences. For comparisons between two independent groups, the unpaired Student's *t*-test was applied. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Chocolate consumption in these experiments was described in detail in our previous publication [15]. In the present study on the development of food addiction, we examined the expression levels of the *Ntrk2* and *Pi3k* genes under conditions of carbohydrate dependence in stressed rats (following predator exposure) and non-stressed rats. In stressed rats, *Ntrk2* gene expression was reduced 1.5-fold compared to non-stressed animals. In stressed rats that received the chocolate-based mixture, *Ntrk2* expression decreased by 2.8 times, and *Pi3k* expression decreased by 5 times compared to non-stressed rats that also received the chocolate diet. In stressed rats without access to the chocolate diet, *Pi3k* expression increased 2-fold compared to non-stressed rats not receiving the chocolate diet (Fig. 1).

Despite recent advances in understanding the neurochemical mechanisms regulating body weight, obesity remains a major global public health concern, associated with numerous complications including metabolic and endocrine disorders, malignancies, and psychosocial issues [2]. The global "epidemic" of obesity suggests that it

Table 1. Experiment design
Таблица 1. Дизайн эксперимента

Gene	Forward primer (5'–3')	Reverse primer (3'–5')
Gapdh	AGACAGCCGCATCTTCTTGT	CTTGCCGTGGGTAGAGTCAT
Beta-actin	TGTCACCAACTGGGACGATA	AACACAGCCTGGATGGCTAC
Pi3k(Pi3kcb)	GCGGTGGGAGTGATCTTCAA	GCGATTGTCTCAGAGGTGCT
Ntrkr2	GAACCAACCACGCTCTGAGA	TGCAGGCCTATTCACACTGG

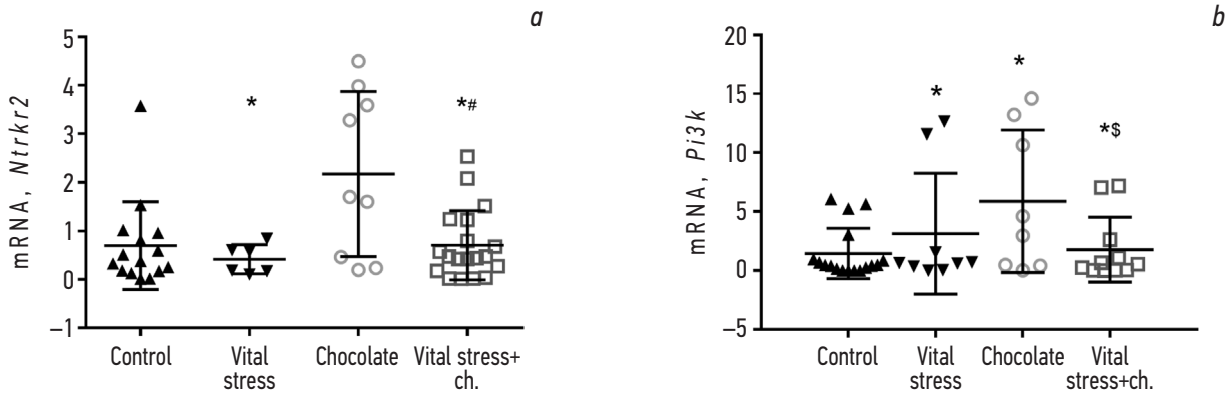

Fig. 1. Hypothalamic gene expression as an effect of the predator presentation to experimental rats: *a*, *Ntrkr2*. The data are expressed in conventional units, normalized to the beta-actin (*Beta-actin*) and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) gene expression, and calculated in relative units as a percentage of the mean *Ntrkr2* expression in the study groups. *b*, *Pi3k*. The data are expressed in conventional units, normalized to the beta-actin (*Beta-actin*) and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) gene expression, and calculated in relative units as a percentage of the mean *Pi3k* expression in the study groups. **p* <0.01 for non-stressed rats that did not receive chocolate; $^{\#}p$ <0.01 for non-stressed rats that received chocolate. The data were aligned using the geometric mean of the two reference genes (*Beta-actin* and *Gapdh*). The data are presented as mean±standard error of the mean. Control, non-stressed rats that did not receive chocolate; Vital stress, stressed rats (python presentation); Chocolate, non-stressed rats that received chocolate; Vital stress+ch., stressed rats that received chocolate.

Рис. 1. Экспрессия генов в гипоталамусе крыс после предъявления хищника: *a* — *Ntrkr2*, данные выражены в условных единицах и нормированы к уровню экспрессии генов бета-актина (*Beta-actin*) и глицеральдегид-3-фосфатдегидрогеназы (*Gapdh*) и рассчитаны в относительных единицах по отношению к средней величине экспрессии гена *Ntrkr2* в группах; *b* — *Pi3k*, данные выражены в условных единицах и нормированы к уровню экспрессии генов бета-актина (*Beta-actin*) и глицеральдегид-3-фосфатдегидрогеназы (*Gapdh*) и рассчитаны в относительных единицах по отношению к средней величине экспрессии гена *Pi3k* в группах. **p* <0,01 по отношению к группе нестрессированных крыс, не получавших шоколад; $^{\#}p$ <0,01 по отношению к группе нестрессированных крыс, получавших шоколад. Выравнивание производилось по среднему геометрическому двух референсных генов (*Beta-actin* и *Gapdh*). Данные представлены как среднее±стандартная ошибка среднего. Control — нестрессированные крысы, не получавшие шоколад; Vital stress — стрессированные крысы (предъявление удава); Chocolate — нестрессированные крысы, получавшие шоколад; Vital stress+ch. — стрессированные крысы, получавшие шоколад.

is caused not only by a lack of motivation to lose weight, but also by a loss of control over food intake and the persistence of excessive eating despite being aware of its adverse consequences. This condition may affect a large portion of the population [2]. The term “food addiction” has been used to describe compulsive eating behavior associated with loss of control over food consumption, with a reported prevalence ranging from 19% to 56.8% in different populations [19, 20]. Eating behavior may be regulated by both homeostatic mechanisms (related to energy needs/stores) and hedonic pathways (involving the brain’s dopaminergic reward system), which jointly control energy intake and body weight [19, 21]. Investigating the mechanisms underlying eating behavior may help identify more effective approaches to combat obesity.

This study demonstrates the involvement of *Ntrk2* and *Pi3k*, components of the *TRKB/PI3K* signaling cascade. This cascade plays a regulatory role in appetite and is implicated in the development of compulsive overeating following chronic maternal separation, isolation, and acute predator stress. We previously showed that intermittent access to a chocolate-based diet promotes compulsive overeating in animals subjected to maternal separation, increasing compulsive behavior and anxiety levels upon withdrawal from the high-calorie diet [15]. We also demonstrated alterations in the expression of *Bdnf*, the ligand that activates the *TRKB/PI3K* cascade, in rats developing food addiction in a maternal neglect model [15].

Experimental modeling of various clinical manifestations of compulsive overeating provides opportunities for directly investigating its neurochemical mechanisms. Experimental studies have demonstrated the involvement of neuroendocrine processes and several neurotransmitter systems, particularly serotonin and testosterone, in its development [22, 23]. The opioid and dopaminergic systems are implicated in generating positive emotional responses during compulsive overeating. The brain’s opioid system plays a role in experimental models of compulsive overeating [23]. In the present study, we demonstrated that the development of compulsive overeating following vital stress involves *Ntrk2* and *Pi3k*, genes of the *TRKB/PI3K* cascade. This cascade is known to be involved in neuronal growth and differentiation, synaptic plasticity, and neuroprotection. Consequently, changes in the expression of genes encoding peptides of this cascade

may play an important role in compensatory mechanisms associated with the onset of compulsive overeating.

CONCLUSION

Thus, vital stress induced by predator exposure leads to compulsive overeating in adult rats. The *TRKB/PI3K* signaling cascade, which regulates neuronal differentiation and regeneration, is involved in the response to vital stress. The findings suggest new avenues for the synthesis of peptide-based pharmacological agents based on the regulation of gene activity within the *TRKB/PI3K* system, aimed at managing food addiction induced by acute psychogenic stress and providing long-term support for the recovery of the central nervous system following acute stress and PTSD.

ADDITIONAL INFO

Authors' contribution. A.V. Lizunov, A.A. Lebedev, V.A. Goltz, S.S. Pyurveev, N.D. Nadbitova, E.R. Bychkov, V.A. Lebedev, N.R. Evdokimova, S.A. Shamaeva, S.G. Tsikunov, A.Yu. Yurov: manuscript drafting, writing and pilot data analyses; P.D. Shabanov: paper reconceptualization and general concept discussion. The authors have approved the version for publication and have also agreed to be responsible for all aspects of the work, ensuring that issues relating to the accuracy and integrity of any part of it are properly considered and addressed.

Ethics approval. The conduct of the study was approved by the local ethical committee of the Institute of Experimental Medicine (protocol No. № 2/23 of 15.06.2023).

Funding sources. The work was carried out within the framework of the state assignment of the Institute of Experimental Medicine FGWG-2025-0020 and the World-class Scientific Center "Center for Personalized Medicine", agreement No. 075-15-2022-302 dated 2022 April 20 (Shamaeva S.A.).

Disclosure of interests. The authors have no relationships, activities or interests for the last three years related with for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

Statement of originality. The authors did not use previously published information (text, illustrations, data) to create this paper.

Data availability statement. All data obtained in the present study are available in the article.

Generative AI. Generative AI technologies were not used for this article creation.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.В. Лизунов, А.А. Лебедев, В.А. Гольц, С.С. Пюрвеев, Н.Д. Надбитова, Е.Р. Бычков, В.А. Лебедев, Н.Р. Евдокимова, С.А. Шамаева, С.Г. Цикунов, А.Ю. Юров — написание статьи, анализ данных; П.Д. Шабанов — разработка общей концепции, написание статьи. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Проведение исследования одобрено локальным этическим комитетом ФГБНУ «Институт экспериментальной медицины» (протокол № 2/23 от 15.06.2023).

Источники финансирования. Работа выполнена в рамках государственного задания ФГБНУ «Институт экспериментальной медицины» FGWG-2025-0020 и НЦМУ «Центр персонализированной медицины», соглашение № 075-15-2022-302 от 20.04.2022 (Шамаева С.А.).

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Все данные, полученные в настоящем исследовании, доступны в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

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