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Involvement of *Bdnf*, *Ntrk2*, and *Pi3k* in the mechanism of binge eating after psychogenic stressors in ontogenesis

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ABSTRACT

BACKGROUND: The study of the neurochemical mechanisms of food addiction provides experimental modeling of some of its clinical manifestations.

AIM: This study aimed to examine the effect of binge eating after maternal deprivation or after rearing in social isolation on the expression of *Bdnf*, *Ntrk2*, and *Pi3k* in the hypothalamus of rats.

MATERIALS AND METHODS: Animals aged 2–12 days were weaned from their mother for 10 days at 180 min, and males aged 90–100 days were used in the experiments. Another group of animals was reared in individual cages from day 21 after birth, and males aged 90–100 days were used in the experiments. To induce binge eating, the animals received a high-carbohydrate feed (chocolate spread) for 1 h every day or every third day within 30 days. Fifteen minutes before feeding, the paste was placed 5 cm within visual contact.

RESULTS: In groups with intermittent exposure to high-calorie food (the animals received pasta every third day), polymerase chain reaction analysis revealed the expression of the *Bdnf*, *Ntrk2*, and *Pi3k* in the hypothalamus. The expression level of *Bdnf* was higher in the maternal deprivation group than in the control group. The expression levels of *Ntrk2* and *Pi3k* in rats taking a high-carbohydrate feed were higher in animals reared in isolation than in those reared in the community.

CONCLUSIONS: The results present new pathways for the synthesis of peptide drugs associated with the PI3K/AKT/mTOR signaling pathway for the correction of food addiction caused by psychogenic stress in ontogenesis.

Keywords: binge eating; *Bdnf*; *Ntrk2*; *Pi3k*; maternal deprivation; social isolation.

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Участие *Bdnf*, *Ntrk2* и *Pi3k* в механизмах компульсивного переедания после действия психогенных стрессоров в онтогенезе

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АННОТАЦИЯ

Актуальность. Исследование нейрохимических механизмов пищевой зависимости дает представление об экспериментальном моделировании ряда его клинических проявлений.

Цель — изучение влияния выработки компульсивного переедания, вызванного материнской депривацией в раннем онтогенезе или выращиванием в условиях социальной изоляции, на экспрессию генов *Bdnf*, *Ntrk2* и *Pi3k* в гипоталамусе крыс.

Материалы и методы. Животных в одной группе со 2-го по 12-й день после рождения на 180 мин отлучали от матери в течение 10 дней, в опытах использовали самцов в возрасте 90–100 дней. Другую группу животных (без отлучения от матери) с 21-го дня после рождения выращивали в индивидуальных клетках, в опытах использовали самцов в возрасте 90–100 дней. При выработке компульсивного переедания животные получали в течение 1 ч диету с высоким содержанием углеводов (шоколадная паста) каждый день или каждый третий день в течение 30 дней. За 15 мин до кормления пасту помещали в 5 см досягаемости при визуальном контакте.

Результаты. В группах с прерывистым воздействием высококалорийной пищи (шоколадную пасту животные получали каждый третий день) ПЦР-анализ показал наличие экспрессии генов *Bdnf*, *Ntrk2* и *Pi3k* в гипоталамусе. Экспрессия гена *Bdnf* при этом была выше у группы крыс после материнской депривации по сравнению с контролем. Показано, что экспрессия генов *Ntrk2* и *Pi3k* на фоне высокоуглеводной пищи была выше у крыс, выращенных в изоляции, по сравнению с животными, выращенными в сообществе.

Заключение. Полученные данные предполагают новые пути синтеза фармакологических средств пептидной природы, связанных с сигнальным каскадом PI3K/AKT/mTOR, для коррекции пищевой зависимости, вызванной психогенными стрессами в онтогенезе.

Ключевые слова: компульсивное переедание; ген *Bdnf*; ген *Ntrk2*; ген *Pi3k*; материнская депривация; социальная изоляция.

Как цитировать

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BACKGROUND

The study of the neurochemical mechanisms of food addiction provides insight into the experimental modeling of some of its clinical manifestations. Neuroendocrine processes and certain neurotransmitter systems, particularly opioids, serotonin, dopamine, and hormones, have been involved in the mechanisms of food addiction [1]. Compulsive overeating disorder, a form of food addiction, is characterized by intermittent and excessive consumption of palatable food in brief periods. Unlike bulimia or anorexia nervosa, this behavior is not accompanied by a compensatory behavior [1]. Various stressors may contribute to compulsive overeating, including partial deprivation of food and intermittent exposure to energy-rich, palatable food [2]. A previous study demonstrated that higher intermittent intake of sugar- and fat-rich foods predicts overeating in rats, irrespective of increased body weight or obesity, as evidenced by compulsive (binge) overeating [3].

Early psychogenic stressors can result in chronic post-traumatic stress disorder (PTSD) [4]. The experience of maternal separation (MS) and growing up in isolation (IS) has been linked to the development of behavior disorders, poor motivation, depression, increased anxiety, and substance abuse [5–7]. Previously, the involvement of genes in MS-related behavioral disorders has been identified, including the serotonin transporter (*5-HTTLPR*), serotonin receptor (*5HT2A, 5HT2C*), MAOA monoamine oxidase A, tryptophan hydroxylase TPH1, dopamine receptors (*DRD2* and *DRD4*), and dopamine transporter *SLC6A3* [8, 9]. Despite evidence on the involvement of mediator systems in the delayed effects of MS [10–12], no studies have examined the involvement of peptide genes after chronic stress induced by MS and IS, particularly the brain-derived neurotrophic factor gene *Bdnf* [13–15].

Compulsive overeating as the basis of food addiction is often combined with PTSD [16]. These conditions may have a common etiology or arise in response to similar antecedent environmental factors. PTSD, a mental and behavioral disorder, can result from exposure to a super-intense traumatic event such as combat, man-made disasters, traffic accidents, sexual assault, child abuse, domestic violence, or other threats to a person's life (National Institute of Mental Health, 2017).

BDNF belongs to the family of neurotrophins that interact with high-affinity protein kinase (Trk) receptors and the nonselective p75NGFR receptor. *Bdnf* has a complex structure comprising multiple regulatory elements and four promoters that are differentially expressed in the central or peripheral tissue [17–19]. The expression of BDNF is regulated by neuronal activity or peripheral hormones. During development, neurotrophins regulate neuronal survival and differentiation; however, they are also involved in certain functions in adulthood, including plasticity. The expression of *Bdnf* in the central nervous system (CNS) is altered in various brain injuries, including stress, ischemia, seizures, and hypoglycemia. Alterations in *Bdnf* expression may contribute to the development of pathologies such as depression, epilepsy, Alzheimer's disease, and Parkinson's disease [19]. Appetite-regulating peptides such as BDNF have been shown to play a modulatory role in reward-related behavior through pathways that control energy intake and body weight [20]. Appetite-regulating peptides, such as BDNF, were found to exert a modulatory influence on reward-related behavior through pathways that regulate energy intake and body weight [20]. BDNF serves as an activator of tropomyosin tyrosine kinase receptor B (TrkB, BDNF/NT growth factor receptor 3), a protein encoded by *NTRK2*. *TrkB* activation was found to result in the inhibition of *KCC2*, a chloride ion transporter protein present in CNS cells [13]. TrkB ligands (tyrosine kinases) were observed to activate the PI3K/AKT/mTOR signaling pathway, an intracellular signaling pathway. This pathway contains one of its central components, namely, phosphoinositide 3-kinase (PI3K) enzymes [21]. The PI3K/AKT/mTOR pathway represents an intracellular signaling cascade that triggers the mechanism of food addiction.

This study aimed to examine the effect of maternal deprivation during early ontogeny or rearing in social isolation on the expression of *Bdnf, Ntrk2*, and *Pi3k* in the rat hypothalamus, specifically in relation to compulsive overeating.

MATERIALS AND METHODS

The experiments were conducted on 86 male and 9 female Wistar rats, with an average weight of 200–250 g, obtained from the laboratory animal nursery "Rappolovo" (Leningrad Region). They were maintained in accordance with standard vivarium conditions, housed in plastic cages with unrestricted access to water and food, and subjected to inverted light conditions from 8:00 to 20:00 at 22 ± 2°C. In accordance with the Rules of Laboratory Practice in the Russian Federation (Order of the Ministry of Health of Russia, 2003, No. 267), the principles of humane treatment of laboratory animals were observed throughout the experiment.

After the arrival of the animals from the nursery, they were quarantined for 2 weeks in the appropriate section of the vivarium. Female Wistar rats were housed in 40 × 50 × 20 cm plastic cages, with five per cage, and provided *ad libitum* access to water and food. One male was placed in each cage, and the following day, vaginal swabs were taken from the females to detect the presence of spermatozoa. The onset of pregnancy was recorded by light microscopy, which was considered day 0.

Following the onset of pregnancy, the animals were transferred to individual cages, and the gestation period was 20 ± 2 days.

Animals were randomly divided into six groups: the e.ch. group included nonstressed animals with a daily chocolate diet, the e.ch.+MD group comprised animals subjected to maternal deprivation with a daily chocolate diet, the i.ch group included nonstressed animals accessing the chocolate diet three times per week (Tuesday, Thursday, and Saturday), the i.ch+MD group consisted of animals subjected to maternal deprivation accessing chocolate diet three times per week (Tuesday, Thursday, and Saturday), the i.ch+MD group included nonstressed animals not receiving a chocolate diet, and the control group included animals subjected to maternal deprivation not receiving chocolate diet. In the second experiment, the animals were also randomly divided into four groups: grouped (intact control, non-isolated rats), grouped+ch. (non-isolated rats that received carbohydrate feeding every other day), isolated (isolated rats), and isolated+ch. (isolated rats that received carbohydrate feeding every other day).

MS model

The rats were placed in individual plastic cups for 180 min for 10 consecutive days, from postnatal days 2 to 12. The experimenter made every effort to avoid eye contact with the mother. After MS and milk feeding, rats were reared in standardized cages, with five rats per cage. The experiment was conducted using male rats aged 90–100 days and weighing 200–250 g [22].

SI model

On postnatal day 21 (immediately after milk feeding), males were placed in individual cages. At the age of 90–100 days, the animals were used for behavioral studies, and after each experiment, they were returned to their cages [22].

Compulsive overeating of high-energy food [23, 24]

The experimental groups were provided with access to a high-carbohydrate diet (chocolate paste mix) for 1 h each day (e.ch. and e.ch.+MD groups) or 1 h every third day (i.ch. and i.ch.+MD groups; grouped.+ch and isolated.+ch every other day, in the second experiment). The control animals (intact and control, and grouped groups, in the second experiment) only received standard pelleted rat food. The high-energy food was a paste prepared by mixing 52% chocolate paste, 33% ground rat food pellets, and 15% water. The caloric value of the diet was 3.63 kcal/g. The standard pelleted rat food was placed inside a metal mesh container that was suspended from the front wall of the cage. The container was removed from the cage for weight measurement to determine feed intake. The chocolate paste mixture was served in a coffee cup, with the cup handle inserted into the metal wall of the cage. The chocolate paste feeder was placed within 5-cm reach of the animals and in full visual contact 15 min before feeding. The cup containing the chocolate paste was inaccessible to the animal for 15 min; however, the animal could see the cup containing the paste and smell its contents. During this 15-min period, the rat made repetitive movements of its front paws, head, and trunk to retrieve the paste; however, it was unable to reach it. This event resulted in a mild stress condition, which led to an increase in serum corticosterone levels. Subsequently, the cup was placed within the rat's cage to ensure it had access to the paste [25, 26]. Before the overeating session, the standard rodent food present in each cage was weighed to estimate the 24-h food intake for the following day. Fifteen days after the commencement of the chocolate diet experiment, the rats were placed in individual cages, and their feeding regimen was continued for 30 days. The following variables were recorded: quantity of standard food consumed and quantity of chocolate paste ingested in 1 h. The weight of the animals was recorded weekly on the same day of the week.

In accordance with the established protocol, mRNAs were isolated from the dissected hypothalamus to evaluate the expression of *Bdnf, Ntrk2*, and *Pi3k*. The minced hypothalamic fragment was placed in 1,000 µL of Trizol and incubated for 5 min at 40°C. Subsequently, 200 µL of chloroform was added to each sample, mixed, and incubated for 5 min with gentle stirring. The resulting solution was then subjected to centrifugation at 13,000 rpm for 10 min, and the upper phase was then collected. Subsequently, an equal volume of isopropyl alcohol was added to the selected upper phase, mixed, and incubated for 24 h at –20°C. It was then centrifuged at 13,000 g for 10 min, and the precipitate was collected. The alcohol was removed, and the precipitate was washed with 70% ethyl alcohol and dried in a thermostat at 40°C. The dried precipitate was dissolved in 50 µL of dH_2O with the addition of 1% RNasein. After mRNA isolation, reverse-transcription reactions were performed. After real-time polymerase chain reaction, reactions were performed with primers against the mRNAs of *Bdnf, Ntrk2,* and *Pi3k*; the housekeeping genes beta-actin and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) were used as reference genes (Table).

Statistical analysis

The statistical processing of quantitative data was conducted using GraphPad Prism v.6.0. All data were presented as means ± standard deviations. The significance of differences between groups was determined using the one-factor analysis of variance. For comparison between two groups, Student's *t*-test for independent samples was used, with the level of significance of differences set at $p < 0.05$.

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Table. Primer sequence
Таблица. Последовательность праймеров

Gene	Primers	
	forward (5'–3')	reverse (3'–5')
Gapdh	AGACAGCCGCATCTTCTTGT	CTTGCCGTGGGTAGAGTCAT
Beta-actin	TGTCACCAACTGGGACGATA	AACACAGCCTGGATGGCTAC
Bdnf	GACGGCGTGAACAGAGATCA	TGGCCTTTTGATACCGGGAC
Pi3k(Pi3kcb)	GCGGTGGGAGTGATCTTCAA	GCGATTGTCTCAGAGGTGCT
Ntrk2	GAACCAACCACGCTCTGAGA	TGCAGGCCTATTCACACTGG

RESULTS AND DISCUSSION

Exploring the development of food addiction

The study of chocolate consumption was described in a previous article. The study revealed that maternal deprivation caused compulsive overeating of high-energy food in sexually mature rats [4].

In the first experiment, the level of *Bdnf* expression on the background of carbohydrate dependence in stressed and nonstressed rats and its mRNA levels in the hypothalamus of experimental rats were investigated. In the control group (stressed animals), the gene expression level in the hypothalamus of experimental animals did not change significantly compared with that in the intact group (intact animals). In nonstressed animals receiving constant carbohydrate nutrition (e.ch. group), the expression of *Bdnf* increased 150-fold compared with that in intact animals (iptast group) and animals subjected to maternal deprivation (control group). In nonstressed animals that received carbohydrate nutrition every other day (i.ch. group), the expression level of *Bdnf* increased 39-fold relative to that of the control group (intact animals) and the control group (with maternal deprivation). In stressed animals constantly fed carbohydrates (e.ch.+MD group), the expression level *Bdnf* did not change significantly compared with that in the intact (intact animals) and control (with maternal deprivation) groups. In stressed animals fed carbohydrates every other day (i.ch.+MD group), the expression level of *Bdnf* expression increased 230-fold relative to that in the intact and control groups (with maternal deprivation).

In the second experiment, the expression of *Ntrk2* and *Pi3k* induced by carbohydrate addiction in isolated rats was examined. In non-isolated rats receiving a chocolate diet, the expression level of *Ntrk2* increased threefold relative to that in intact animals. In isolated rats, *Ntrk2* expression was upregulated threefold compared with that in intact animals. In isolated rats taking a chocolate diet, *Ntrkr2* expression was upregulated 1.5-fold compared with that in isolated rats that did not receive chocolate. The expression level of *Pi3k* in non-isolated rats taking a chocolate diet increased fivefold compared with that in intact animals. The expression level of *Pi3k* tended to decrease in isolated rats compared with intact animals. Moreover, the expression level of *Pi3k* in isolated rats receiving chocolate increased compared with that in isolated rats not receiving chocolate (1.7-fold) and intact animals (1.8-fold). Data are presented in Figs. 1–3.

RESULTS

Despite recent advances in the neurochemical mechanisms that regulate body weight, obesity remains a significant global public health concern and is associated with various consequences including metabolic and endocrine complications, malignant diseases, and psychosocial issues [23]. Its global prevalence implies that it is not only attributable to a lack of motivation to lose weight, but is also associated with a loss of control over food intake and prolonged overconsumption despite awareness of adverse consequences. This may be observed in a significant proportion of the population [23]. The term “food addiction” has been employed to describe compulsive eating behaviors associated with a lack of control over food, with rates ranging from 19% to 56.8% in different populations [10]. The regulation of eating behavior is dependent on both homeostatic (energy needs and storage) and hedonic (dopaminergic brain reward system) pathways, which control energy intake and body weight [24]. A deeper understanding of the mechanisms that regulate eating behavior may ease the development of more effective strategies for battling obesity.

This study demonstrates the involvement of the BDNF peptide and the appetite-regulating Trkb/Pi3k signaling cascade triggered by it in the formation of compulsive overeating after chronic MS, IS, and social isolation. Previously, we demonstrated that an intermittent chocolate diet resulted in increased episodes of compulsive overeating in animals subjected to maternal deprivation and induced an increase in compulsivity and behavioral anxiety levels in animals on withdrawal of a high-calorie diet. Furthermore, our results indicate a reduction in the consumption of high-energy food in rats after maternal deprivation with a daily chocolate diet [4]. Furthermore, the involvement of neuroendocrine processes, particularly testosterone, neurotransmitter systems, serotonin,

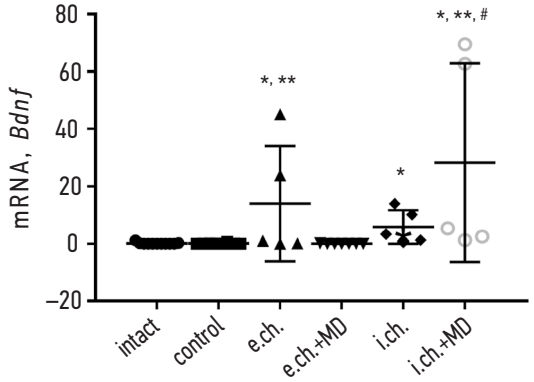

Fig. 1. *Bdnf* expression at the mRNA level. *$p < 0.01$ in relation to the control group; **$p < 0.01$ in relation to the stress group; #$p < 0.01$ in relation to the non-stress group given chocolate every other day. Data are expressed in arbitrary units and normalized to the expression level of beta-actin (*Beta-actin*) and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) genes and calculated in relative units in relation to the average value of *Bdnf* expression in the groups. Alignment was made using the geometric mean of two reference genes (*Beta-actin* and *Gapdh*). Data are presented as the mean ± standard error of the mean. Intact, intact control; control , stressed rats (maternal deprivation); e.ch., non-stressed rats given a carbohydrate feed every day; e.ch.+MD , stressed rats given a carbohydrate feed every day; i.ch., non-stressed rats given a carbohydrate feed every other day; i.ch.+MD, stressed rats given a carbohydrate feed every other day

Рис. 1. Экспрессия *Bdnf*, уровень мРНК. *$p < 0,01$ по отношению к группе интактного контроля; **$p < 0,01$ по отношению к группе стрессированных крыс; #$p < 0,01$ по отношению к группе нестрессированных крыс, получавших шоколад через день. 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 *Bdnf* в группах. Выравнивание производилось по среднему геометрическому двух референсных генов (*Beta-actin* и *Gapdh*). Данные представлены как среднее ± стандартная ошибка среднего. intact — интактный контроль; control — стрессированные крысы (материнская депривация); e.ch. — нестрессированные крысы, углеводное кормление давали каждый день; e.ch.+MD — стрессированные крысы, углеводное кормление давали каждый день; i.ch. — нестрессированные крысы, углеводное кормление давали через день; i.ch+MD — стрессированные крысы, углеводное кормление давали через день

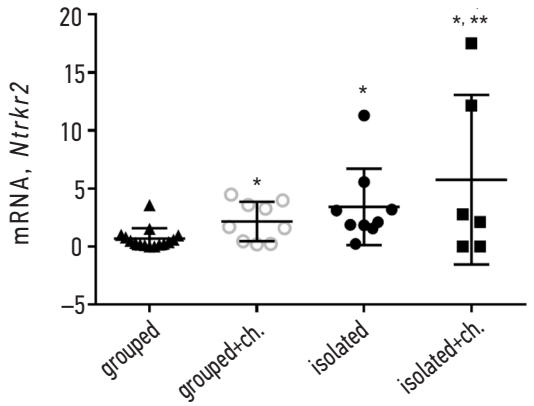

Fig. 2. *Ntrkr2* expression at the mRNA level. *$p < 0.01$ relative to the control group; **$p < 0.05$ relative to the isolated group. Data are expressed in arbitrary units and normalized to the expression level of beta-actin and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) genes and calculated in relative units relative to the average value of *Ntrk2* expression in the groups. Alignment was performed using the geometric mean of two reference genes (*Beta-actin* and *Gapdh*). Data are presented as mean ± standard error of the mean. Grouped, intact control, grouped+ch., non-isolated rats given a carbohydrate feed every other day; isolated, isolated rats; isolated+ch., isolated rats given a carbohydrate feed every other day

Рис. 2. Экспрессия *Ntrkr2*, уровень мРНК. *$p < 0,01$ по отношению к группе интактного контроля; **$p < 0,05$ по отношению к группе изолированных крыс. 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 *Ntrk2* в группах. Выравнивание производилось по среднему геометрическому двух референсных генов (*Beta-actin* и *Gapdh*). Данные представлены как среднее ± стандартная ошибка среднего. grouped — интактный контроль; grouped+ch. — неизолированные крысы, углеводное кормление давали через день; isolated — крысы-изолянты; isolated+ch. — крысы-изолянты, углеводное кормление давали через день

opioids, and dopamine systems, in the mechanisms of compulsive overeating was established [25].

MS and IS caused an increase in *Bdnf* expression in the hypothalamus of adult rats. *Bdnf* was expressed in animals with intermittent exposure to high-energy food (receiving chocolate paste three times per week) and with signs of compulsive overeating. In addition, the expression level of *Bdnf* was higher in the maternal deprivation

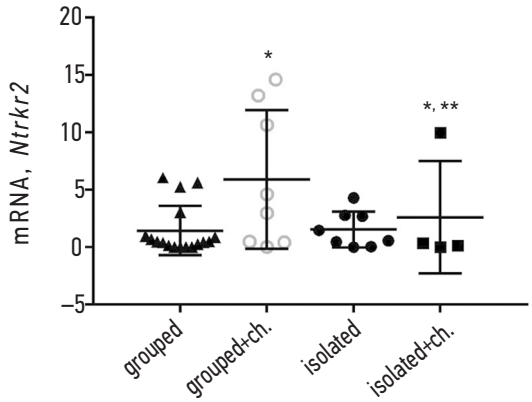

Fig. 3. *Pi3k* expression at the mRNA level. *$p < 0.01$ relative to the control group; **$p < 0.05$ relative to the isolated group. Data are expressed in arbitrary units and normalized to the expression level of beta-actin and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) genes and calculated in relative units relative to the average *Pi3k* expression in the groups. Alignment was performed using the geometric mean of two reference genes (*Beta-actin* and *Gapdh*). Data are presented as mean ± standard error of the mean. Grouped, intact control; grouped+ch., non-isolated rats given a carbohydrate feed every other day; isolated, isolated rats; isolated+ch., isolated rats given a carbohydrate feed every other day

Рис. 3. Экспрессия *Pi3k*, уровень мРНК. *$p < 0,01$ по отношению к группе интактного контроля; **$p < 0,05$ по отношению к группе изолированных крыс. 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. Выравнивание производилось по среднему геометрическому двух референсных генов (*Beta-actin* и *Gapdh*). Данные представлены как среднее ± стандартная ошибка среднего. grouped — интактный контроль; grouped+ch. — неизолированные крысы, углеводное кормление давали через день; isolated — крысы-изолянты; isolated+ch. — крысы-изолянты, углеводное кормление давали через день

group compared with the nonstressed group. The disruption of the neurochemical mechanisms of food addiction in the maternal deprivation model of animals was also reflected by the increased expression of *Bdnf* in the hypothalamus. The expression levels of *Ntrk2* and *Pi3k* were also increased in the hypothalamus during chocolate consumption but increased more significantly in rats exposed to isolation-induced stress. Thus, the results of this study show that different ontogenetic stress factors systemically disrupt the molecular mechanisms regulating neurochemical processes that trigger compulsive overeating. This is reflected in the increased expression of genes encoding *Trkb* and *Pi3k* receptors.

Chronic stress related to maternal deprivation in animals is a model of maternal neglect in humans. Results of analysis of data from an experimental model of maternal deprivation in early ontogenesis prove the significant influence of stress on the development of compulsive overeating [26]. Early psychological stress has a long-term effect on the development, maturation, and socialization of children and adolescents and on the risk of developing eating disorders and compulsive overeating. During adolescence, hormonal restructuring and imbalance in excitation and inhibition processes occur, when the important role of neurochemical intracerebral processes in the formation of compulsive overeating becomes critical [26].

Experimental modeling of certain clinical manifestations of compulsive overeating provides opportunities for direct investigations of the neurochemical mechanisms of compulsive overeating. Experiments have implicated certain neuroendocrine processes and brain mediator systems, particularly serotonin and testosterone, in the development of overeating [3]. Opioid and dopamine systems are involved in the generation of positive emotions in compulsive overeating [25, 27]. In the experimental model of compulsive overeating, the involvement of the brain opioid system was observed [28, 29]. In the present study, BDNF is involved in the development of compulsive overeating and processes of neuronal growth and differentiation, plasticity mechanisms, and neuroprotection. It may also play an important role in the development of compulsive overeating by acting on the food intake control systems in the hypothalamus and midbrain and on monoaminergic reinforcement systems.

Previously, in a model of maternal neglect in animals, neurochemical mechanisms of food addiction were impaired, manifested by increased compulsive overeating [30, 31], compulsivity, and anxiety 32, 33]. Weaning from the mother induced compulsive overeating in adult rats with the participation of appetite-regulating peptides, BDNF, and implied new ways to synthesize pharmacological peptides for the correction of food addiction induced by psychogenic stress in early ontogenesis. Isolation of adult rats also resulted in impaired expression of *Bdnf, Ntrk2,* and *Pi3k*. The identification of the link between this signaling cascade and food addiction reflects new ways to synthesize pharmacological peptides related to the PI3K/AKT/mTOR signaling cascade for the correction of food addiction induced by psychogenic stress.

CONCLUSIONS

1. Intermittent consumption of high-energy foods during the development of compulsive overeating is accompanied by expression of *Bdnf, Ntrk2*, and *Pi3k* in the hypothalamus, regardless of the animal's rearing conditions.

2. The expression level of *Bdnf* during the development of compulsive overeating was higher in rats subjected to maternal deprivation than in animals not exposed to maternal deprivation.

3. The expression levels of *Ntrk2* and *Pi3k* in the background of intermittent consumption of high-calorie food during the development of compulsive overeating were higher in isolation-raised rats than in community-raised animals.

4. The results present new ways to synthesize pharmacological peptides related to the PI3K/AKT/mTOR signaling cascade for the correction of food addiction induced by psychogenic stress in ontogenesis.

ADDITIONAL INFORMATION

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