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Effect of antorex, a new antagonist of orexin receptors, on binge eating in rats caused by weaning from the mother in early ontogenesis

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ABSTRACT

BACKGROUND: Research on the elements of food addiction in animal models shows that its manifestations are attributed to intermittent consumption of high-calorie foods. Chronic stress in ontogenesis can cause episodes of binge eating or dietary restrictions such as anorexia.

AIM: This study aimed to investigate the effect of a new orexin receptor antagonist antorex on binge eating in a rat model of maternal neglect.

MATERIALS AND METHODS: Mature male rats weaned from their mothers for 3 h after birth from days 2 to 12 received a high-carbohydrate diet every third day for 1 h for 45 days. Moreover, high-calorie food was placed within 5 cm of visual contact 15 min before feeding. Antorex, an orexin receptor antagonist, was administered intranasally at a dose of 1 μg/1μL for a total of 20 μL for 7 days.

RESULTS: Intermittent consumption of high-calorie food products induced binge eating in rats. The frequency of the signs of binge eating increased after chronic weaning stress. The consumption of standard briquette feed was not altered. Intranasal administration of both the orexin receptor antagonist antorex reduced the manifestations of food addiction in rats after maternal deprivation under conditions of intermittent consumption of high-calorie food compared with controls. Standard food intake did not differ relative to the control group both before and after antorex administration.

CONCLUSIONS: The results suggest new ways to study and synthesize peptide drugs based on orexin and its antagonists for the correction of food addiction caused by chronic stress in ontogenesis.

Keywords: binge eating; maternal neglect; antorex; orexin.

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Влияние анторекса, нового антагониста рецепторов орексина, на компульсивное переедание у крыс, вызванное отлучением от матери в раннем онтогенезе

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АННОТАЦИЯ

Актуальность. При исследовании элементов пищевой зависимости на животных моделях показано, что прерывистое потребление высококалорийной пищи вызывает ее проявления. Хронические стрессы в онтогенезе могут вызывать эпизоды компульсивного переедания или ограничения в питании типа анорексии.

Цель — изучение действия нового пептидного аналога орексина анторекса на компульсивное переедание, вызванное отлучением от матери в раннем онтогенезе, у взрослых крыс.

Материалы и методы. В исследование использовали половозрелых крыс-самцов Вистар, которых после рождения со 2-го по 12-й день на 3 ч отлучали от матери, каждый третий день получали диету с высоким содержанием углеводов на 1 ч/день в течение 45 дней. При этом высококалорийную пищу за 15 мин до кормления помещали в 5 см досягаемости при визуальном контакте. Анторекс вводили интраназально 7 дней в дозе 1 мкг / 1мкл, 20 мкл.

Результаты. Прерывистое потребление продуктов высококалорийной пищи вызывало у крыс компульсивное переедание. После хронического стресса отлучения от матери наблюдалось повышение признаков компульсивного переедания. При этом потребление стандартного брикетированного корма не изменялось. Интраназальные введения антагониста рецепторов орексина анторекса снижало проявления пищевой зависимости у крыс после отлучения от матери в условиях прерывистого потребления высококалорийной пищи по сравнению с контрольной группой. Потребление стандартного корма не отличалось относительно контрольной группы как до курса введения анторекса, так и после его введения.

Заключение. Полученные данные предполагают новые пути изучения и синтеза средств пептидной природы на основе орексина и его антагонистов для коррекции пищевой зависимости, вызванной хроническими стрессами в онтогенезе.

Ключевые слова: компульсивное переедание; материнское пренебрежение; анторекс; орексин.

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BACKGROUND

An animal model of binge eating disorder demonstrates that intermittent consumption of high-calorie foods induces binge eating regardless of body weight gain [1]. Previously, several rodent models of binge eating disorder have been studied. Intermittent exposure to high-calorie foods induces episodes of binge eating [1, 2]. In this case, the mechanism underlying binge eating involves alterations in the metabolism of several neurotransmitter systems particularly, dopamine, serotonin, norepinephrine, opioids, and stress hormones [2].

The hypothalamic neuropeptides orexins A and B are involved in the regulation of the sleep-wake cycle, eating behavior, and reward mechanisms. Orexins are synthesized in the lateral hypothalamus and interact with neurons via G-protein associated orexin receptors types 1 and 2 [3]. OX1R is involved in emotional behavior and avoidance responses, whereas OX2R regulates the circadian rhythm [4, 5]. Experimental and clinical studies have indicated the involvement of the orexin system in response to stress stimulation [6]. The targets of orexin action in the brain are the hypothalamus, the bed nucleus of the stria terminalis, the amygdala, the prefrontal cortex, the hippocampus, and the locus coeruleus [6].

Chronic and acute stress in ontogenesis leads to post-stress disorders [7]. Social deprivation, maternal neglect, and physical and sexual abuse in childhood are associated with long-term disorders of emotional behavior and impaired motivation [8], which, in turn, cause depression, high levels of anxiety, and alcohol and drug abuse issues [9]. Early separation from mother (MS) in ontogenesis causes persistent disturbances in emotional reactions in animals and fosters the development of dependence on psychoactive drugs [10].

Currently, there is a lack of information concerning the role of the orexin system in food addiction. Additionally, the mechanisms through which its receptors influence reinforcement systems and emotional behavior under stressful conditions have not yet been studied. Antorex is a recombinant peptide analogous to orexin with a molecular weight of 6.5 kDa. It was developed at the Institute of Experimental Medicine. Antorex is an innovative compound created based on a genetically engineered protein, an antagonist of orexin A. Antorex blocks OXR1 receptors on dopaminergic terminals, thereby reducing behavioral manifestations of addiction and associated elements of emotional dysphoria [11].

This study *aimed* to investigate the effect of a new peptide analog of orexin antorex on binge eating caused by early ontogenetic weaning in adult rats.

MATERIALS AND METHODS

Experiments were performed using 29 male and 4 female Wistar rats weighing 200–250 g, obtained from the Rappolovo laboratory animal nursery (Leningrad region). The animals were kept under vivarium conditions in standard plastic cages with free access to water and food. They were subjected to inverted light conditions from 8:00 to 20:00 at a temperature of 22 ± 2°C. During the experiment, the principles of humane treatment of laboratory animals were observed in accordance with the "Rules of Laboratory Practice in the Russian Federation" (Order of the Ministry of Health of the Russian Federation of 2003 No. 267).

On arrival from the nursery, the animals underwent a two-week quarantine period in an appropriate vivarium block. Female rats were kept in plastic cages (40 × 50 × 20 cm) in groups of five with access to water and food *ad libitum*. One male was placed in each cage; the next day, vaginal smears were taken from females to screen for sperm and the onset of pregnancy was confirmed using light microscopy. This was considered as day 0. After the onset of pregnancy, the animals were placed in an individual cage. Pregnancy lasted for 20 ± 2 days. The animals were divided into groups, where group 1 consisted of non-stressed animals receiving a chocolate diet three times a week. Group 2MS included animals subjected to maternal deprivation, receiving access to a chocolate diet three times a week.

Model of weaning

Rats of postnatal days 2-12 were placed in individual plastic cups for 180 min for 10 consecutive days. Eye contact with the mother was excluded. After MS and milk feeding, the rats were raised in standard cages with five animals each. Males aged 90–100 days and weighing 200–250 g were used in the experiment.

Method of binge eating of high-calorie foods

The experimental groups were given 1 h access to a high carbohydrate diet (chocolate spread mixture) every third day. Control animals consumed only standard pelleted rat food. The high-energy food was prepared by mixing chocolate spread, crushed rat food pellets and water in the ratio of 52% chocolate spread, 33% food pellets, and 15% water. The calorie content of the diet was 3.63 kcal/g. Standard pelleted rat food was placed inside a metal mesh container suspended from the front wall of the cage. It was removed from this cage to have its weight measured to determine food intake. The chocolate spread mixture was given in a cup suspended by inserting the handle into the metal wall of the cage. The feeder containing the chocolate paste was positioned within 5 cm of reach from the animals and with full visual

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contact 15 min before administration. Within 15 min, the cup containing the chocolate paste was placed inside a container with a metal mesh, which was suspended from the front wall of the cage. The animal could see the paste and also smell it. During this 15-min period, the rat exhibited repeated movements of its forepaws, head, and trunk in attempts to access the paste, albeit unsuccessfully. This manipulation caused an increase in serum corticosterone levels [12]. After 15 min, the cup was placed in the rats' cage so that the paste became available to them. Before the binge session, the standard rodent food in each cage was weighed to estimate food intake over the subsequent 24-h period. Fifteen days after initiating the experiment with the chocolate diet, the rats were placed in single cages to continue feeding for an additional 30 days. The amount of standard food eaten and the amount of chocolate spread eaten during 1 h of access were recorded. The weight of each animals was recorded once a week on a strictly established day.

Using a genetic engineering method, antorex, a peptide analog of the orexin antagonist, was synthesized in the S.V. Anichkov Department of Neurophamacology of the Institute of Experimental Medicine. [11]. On week 6 of the experiment, antorex was administered intranasally (1 μg/1 μl, 20 μl) for 7 days.

The Graph Pad Prizm v.6 software was used for statistical processing of the quantitative data. All data were presented as mean ± standard deviation. The statistical significance of differences between treatment groups was determined using one-way analysis of variance. For comparisons between two groups only, the Student's *t*-test for independent samples was employed.

RESULTS AND DISCUSSION

The analysis of the effect of MS on standard food consumption revealed that the average consumption over a 10-day testing period in the 2MS group remained unchanged relative to that of the control (intact) group 1, both before and after the introduction of antorex (Fig. 1).

MS increased the consumption of high-calorie food when chocolate was provided three times a week in group 2MS ($p < 0.001$) relative to the control (intact) group 1. However, it did not affect the consumption of standard pelleted feed (Fig. 2).

Antorex did not change the consumption of high-calorie feed, as well as standard pelleted feed in group 2MS relative to the control (intact) group 1.

The term "food addiction" is used to describe binge eating. Binge eating is usually associated with loss of control over feed intake [1, 2]. Eating activity can be influenced by mechanisms related to the regulation of energy reserves in the body, and by motivational and hedonic needs, which are mediated through the activation of the brain's reward system [13].

In this study, a high-calorie food binge development method was used. Maternal neglect increased the manifestations of elements of overeating. Episodes of binge eating occurred due to the intermittent feeding of high-calorie foods. This phenomenon can be further elucidated through experiments investigating the development of food addiction in animals subjected to a 15-min delay in food reinforcement, while maintaining visual proximity to the food source, which is consistent with other studies [12].

Weaning stress in rodents serves as a model of maternal deprivation in humans. Analysis of the model of early maternal deprivation indicates significant effects, indicating that stress stimulation significantly contributes to the development of binge eating [9]. Mental stress in ontogenesis causes disturbances in human development and socialization and influences the development of eating disorders, particularly, binge eating. Puberty induces endocrine shifts and alterations in excitatory–inhibitory balance, with neuropeptides and monoamines crucially involved in the development of eating disorders [10].

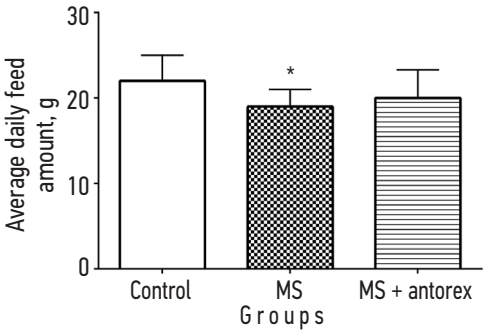

Fig. 1. Effect of maternal deprivation on the consumption of standard food when given chocolate three times a week. *$p < 0.001$ compared with the control (intact) group of animals

Рис. 1. Влияние материнской депривации (MS) на потребление стандартного корма при выдаче шоколада 3 раза в неделю. *$p < 0{,}001$ относительно контрольной (интактной) группы животных

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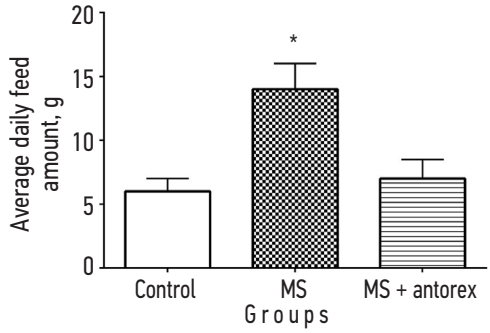

Fig. 2. Effect of maternal deprivation on the consumption of high-calorie foods when chocolate is provided three times a week. *$p < 0.001$ compared with the control (intact) group of animals
Рис. 2. Влияние материнской депривации (MS) на потребление высококалорийной пищи при выдаче шоколада 3 раза в неделю. *$p < 0,001$ относительно контрольной (интактной) группы животных

Examining the clinical manifestations of binge eating disorder in animal models improves the understanding of the mechanisms of eating behavior. The involvement of hormonal and mediator mechanisms in the formation of positive emotional states during binge eating has been demonstrated. This involves the dopamine and serotonin systems, as well as brain peptides [12]. The findings of this study show that the orexigenic peptide system is also involved in the mechanism of binge eating through orexin. Orexin acts primarily on the metabolic nutrition regulation system in the hypothalamus, where it is formed, and activates feeding behavior [13]. The role of orexin in the extrahypothalamic areas of the brain manifests in its influence on higher brain functions, reinforcement and motivation, and fear and depression. The targets of orexin action during stress are hypothalamic neurons that synthesize corticotropin-releasing hormone (CRH) [5], as well as the extended amygdala system, which includes the bed nucleus of stria terminalis, the substantia innominata, the central nucleus of the amygdala, and the nucleus accumbens [14]. The structures of the extended amygdala form a functional system that reinforces the effects of psychotropic drugs. Antagonists of CRH receptors in these structures reduce the effects of narcogens [14].

CONCLUSION

The findings of this study show that chronic stress due to maternal weaning in early ontogenesis causes an increase in elements of binge eating in adult rats. Intranasal administration of a new orexin receptor antagonist, antorex, reduced the manifestations of binge eating in rats after weaning under conditions of intermittent consumption of high-calorie food. This highlights the necessity for innovative strategies in studying and synthesizing orexin receptor antagonists to address eating disorders triggered by psychogenic stress during early ontogenesis.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: A.A. Lebedev, S.S. Pyurveev, N.D. Nadbitova, A.V. Lizunov, E.R. Bychkov, V.V. Lukashkova, N.R. Evdokimova, V.A. Lebedev — writing an article, data analysis; P.D. Shabanov — editing an article, developing a general concept.

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Competing interests. The authors declare that they have no competing interests.

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