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Research Article

# Role of orexin peptide system in emotional overeating induced by brain reward stimulation in fed rats

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## Abstract

**Introduction:** The purpose of this work was to prove that the reaction of food self-deprivation in “fed up” rats is a suitable model for studying the emotional overeating in the experiment.

**Methods:** The self-deprivation reaction, i.e. self-isolation of an animal from food during electrical self-stimulation of the brain, was studied in animals with food deprivation. To reproduce the self-stimulation of the lateral hypothalamus, the male Wistar rats were trained to press a pedal in a Skinner box. After training, the rats received food deprivation, then a feeder was placed in the Skinner box, and a conditioned food reflex was developed in rats within 5 days.

**Results and discussion:** The food self-deprivation reaction was observed in the ”satiated” rats with a current intensity of 10% and above the threshold for self-stimulation. Hungry animals pressed the pedal for hypothalamic self-stimulation and took no notice of the feeding trough. Sulpiride, a dopamine D2 antagonist (5 and 20 mg/kg i.p.), administered to the “satiated” rats decreased both the eating behavior and self-stimulation in food self-deprivation testing. SB-408124, an orexin A receptor antagonist (0.5 mg/ml, 20 µl intranasally) reduced only the number of pellets eaten, but not the number of pedal presses.

**Conclusion:** The orexin A receptors are preferably involved in emotional eating compared with orexin B (OX2R TCS-OX2-29) and D2 dopamine receptors. Because emotional eating is significantly related to clinical eating disorders, like bulimia and binge eating disorder, it seems promising to use drugs of the orexin system to treat and prevent the issue.

## Keywords

orexin, dopamine, self-stimulation, self-deprivation, overeating, SB-408124, TCS-OX2-29, sulpiride, rats.

## Introduction

Emotional eating is a phenomenon in which a person consumes food for reasons other than being physically hungry. Because emotional eating is significantly related to clinical eating disorders, like bulimia and binge eating disorder (BED), as well as obesity and malnutrition, there is growing interest in learning how to treat and prevent the issue. More specifically, emotional eating is linked to a tendency to overeat in response to negative emotions,

but little is known about emotional eating and positive emotions, like happiness or excitement (Sultson et al. 2017). Negative emotional eaters also increase eating after experiencing positive emotions, suggesting that these emotions may contribute to food consumption in emotional eaters as much as negative emotions (Bongers et al. 2013, 2016). New assessment tools, which in addition to negative emotional eating also address positive emotional eating, could be of potential help in planning intervention. Further, the tendency to overeat in response to positive emotions could be integrated into current models of eating disorders, especially when addressing relapse prevention (Pompili and Laghi 2017; Sultson et al. 2017).

Episodes of binge eating (BE) in humans are characterized by compulsive, non-homeostatic consumption of an unusually large quantity of highly palatable food in a short period of time. Even though they are not hungry, subjects eat more rapidly than normally until feeling uncomfortably full. As described by the DMS-IV-TR (American Psychiatric Association 2000), these episodes are accompanied by a subjective sense of loss of control over eating, and are associated with the feelings of distress, disgust, depression, being guilty about overeating, and eating alone because of embarrassment. Lisdexamfetamine (LDX), a pro-drug of d-amphetamine, is the only pharmaceutical drug currently approved for treatment of BED, and works through modulation of monoamine transmission. LDX has been shown to directly decrease compulsive eating in rats as well as humans, as measured by the Yale–Brown obsessive compulsive scale modified for binge eating (Griffiths et al. 2019). LDX administration produces sustained increases in dopamine in rats, which could recover low dopaminergic states characteristic of compulsive overeating to relieve a negative emotional state (Griffiths et al. 2019). Current medications, like topiramate (McElroy et al. 2009) or sibutramine (Appolinario et al 2003; Wilfley et al. 2008), have been reported to reduce BED in clinical studies. However, their administration is associated with a variety of adverse side effects, which represent serious problems during chronic treatment (Yager 2007; McElroy et al. 2009).

In 1998, two groups independently identified a new class of neuropeptides originating in hypothalamic nuclei (De Lecea et al. 1998; Sakurai et al. 1998). These peptides, called orexin-A (OXA) and orexin-B (OXB), also denoted as hypocretin 1 and hypocretin 2, are produced from proteolytic processing of the pre-pro-OX peptide and bind to two GPCRs, namely OX-1 and OX-2 receptors (OX1R and OX2R), also denoted as HcrtR1 and HcrtR2. OX1R is coupled to Gq/11, whereas studies using neuronal cells suggest that OX2R is coupled to Gq, Gs, and Gi proteins. In the central nervous system, OX1R and OX2R show partially overlapping, but largely distinct and complementary, distribution patterns (Sakurai 2007). Brain areas, such the infralimbic cortex, hippocampus, and locus coeruleus, exhibit high expression of OX1R, whereas OX2R is the only receptor expressed in arcuate nucleus, tuberomammillary nucleus, and dorsomedial and lateral hypothalamus. Both receptors are present in the prefrontal cortex, amygdala, bed nucleus of stria terminalis, paraventricular thalamic nucleus, dorsal raphe, ventral tegmental area, and laterodorsal tegmental nucleus – peduncolo pontine nucleus (Trivedi et al. 1998; Lu et al. 2000; Marcus et al. 2001). These findings suggest that orexins and their receptors are likely to play a broad regulatory role in the central nervous system. Injection of OXA into the lateral ventricle of rats during early light phase induced a dose-related increase in a food intake in rats (Sakurai et al. 1998), which was blocked by pre-treatment with the OX1R antagonist SB-334867 (Haynes et al. 2000; Rodgers et al. 2001). Hypothalamic OX neurons are activated by cues associated with consummatory rewards, such as food (Harris et al. 2005), suggesting a potential role of the orexin system in response to external environmental cues linked to cognitive aspects of feeding. Recent reports support a role for orexin signaling in the neurobehavioral and motivational effects of drugs of abuse (Harris and Anthenelli 2005; Jupp and Dalley 2014; Baimel and Borgland 2015; Matzeu et al. 2018; Schmeichel et al. 2018). Neural systems that motivate and reinforce drug abuse have also been proposed to underlie behaviors associated with compulsive food seeking and food intake (Volkow and Wise 2005; Johnson and Kenny 2010; Corwin et al. 2011; Schulte et al 2019).

A number of binge eating testing methods are currently being used in animal models (Corwin and Buda-Levin 2004; Corwin et al. 2011). These models are considered within the context of their effects on brain reward systems, including dopamine, opioids, cholinergic systems, serotonin, and GABA. All of the models demonstrate that binge-type consumption of palatable food can occur independently of obesity (Boggiano and Chandler 2006). There are three commonly used models. First, a model of sugar bingeing in which animals with repeated, intermittent access to a sugar solution develop behaviors and brain changes that are similar to the effects of some drugs of abuse, serving as the first animal model of food addiction (Avena et al. 2008). Second, another model in which a history of dieting and stress can perpetuate further binge eating of palatable and non-palatable food (Boggiano and Chandler 2006). Lastly, a limited access model in which non-food deprived rats with sporadic limited access to a high-fat food develop binge-type behaviors (Corwin and Buda-Levin 2004). When using these models, periods of elements of stressful, negative emotional effects are assumed: food deprivation, foot-shock, intermittent access to a sugar solution, or sporadic limited access to a high-fat food. At the same time, models with positive emotional effects, like happiness or excitement, often associated with emotional eating, have not been used previously.

This study used the reaction of self-stimulation of the lateral hypothalamus with the threshold current intensity as a positive emotional component of the environment for eating behavior in fed rats. The self-deprivation phenomenon shown earlier, assessed as a maladaptive preference in a hungry animal, was retrieved after pos-

itively reinforcing electrical stimulation of certain brain areas rather than food. The earliest account of the phenomenon stemmed from the pioneering work of J. Olds (1958), who demonstrated that rats receiving rewarding hypothalamic electric stimulation would self-stimulate to exhaustion, neglecting other bodily needs. According to J. Olds, the highly rewarding properties of the hypothalamic electric stimulation represented the activation of the neural systems that sub serve conventional reward (Margules and Olds 1962). G. Spies (1965) demonstrated that rats having rewarding electrodes in the so-called "feeding center" of the lateral hypothalamus preferred hypothalamic electric stimulation to food in a discrete choice situation even during prolonged periods of food deprivation. The issues of modeling and studying the effects of hypothalamic activation from the point of view of reproducing the non-chemical dependence of emotional overeating, in particular, binge eating, have not been previously conducted. The aim of this work was to prove the role of orexin brain system in mechanisms of BED in the model of food self-deprivation in well-fed rats. To date, the self-deprivation reaction has been studied exclusively in animals with food deprivation (Frank et al. 1982; Frank and Stutz 1984).

# Material and methods

### Animals

The experiments were performed on 29 Wistar male rats weighing 240±30 g (12–13 weeks of age) each, in accordance with EU Directive 2010/63/EU for animal experiments and were approved by the local biomedical ethics committee. The animals were obtained from the Rappolovo laboratory animal nursery (Leningrad region, Russia). At the beginning of the experiment, the rats were housed individually in standard rodent cages (43×28×15 cm, length-width-height) with wood-chip bedding. Standard rat lab chow (Rappolovo) and filtered tap water were freely available throughout the experiment. Artificial light was provided daily from 08.00 am to 08.00 pm; the room temperature and humidity were maintained at 21±21°C and 40–70%, respectively. When food-deprived, the special diet-fed animals daily had limiting access to food for 4 hours, with free access to water. Accordingly, prior to each test, food deprivation was maintained for 20 hours.

### Surgery

The rats were anesthetized with Xyla (Xylazine hydrochloride 20 mg/1 ml, Metaalweg 8, 5804 CG Venray, Netherlends) and Zoletil 100 (tiletamine hydrochloride/zolazepam hydrochloride, 250 mg/5 ml, Valdepharm, France). Bipolar stainless steel electrodes of 0.2 mm thickness (Plastic One), insulated except at the cross section at the tip, were stereotaxically implanted using a micromanipulator (IEM, St. Petersburg, Russia). The electrodes were lowered into the left or right medial forebrain bundle as it passes through the lateral hypothalamic area (coordinates: 2,5 mm posterior to bregma, 2.0 mm lateral to the midline suture, 8.4 mm below the dorsal surface of the skull). The electrodes were attached to the skull with optical screws and dental acrylic, and one week was allowed for recovery from surgery.

### Apparatus

Standard operant conditioning chambers (RITEC, St. Petersburg, Russia) were housed in ventilated, sound-attenuating cubicles, equipped with a 2.8-W house light and a lever. An operant chamber (29.2×30.5×24.1 cm) had a response lever 4.5 cm wide, 2.0 cm inside, 3.0 cm above the floor, with a stimulus light centered 7.6 cm above the lever (Bespalov et al. 1999; Shabanov and Lebedev 2013). The chamber was connected to an IBM clone microcomputer through an MED interface and controlled by MED-PC software (MED Associates Inc., East Fairfield, Vermont, USA). Electrical pulses were produced by the constant current stimulators (PHB-150B; MED Associates Inc.). The electrical stimuli were delivered to the animal through an electrical swivel assembly (Plastic One, Roanoke, Virginia, USA), which extended into the test chamber. Depression of a lever resulted in a single 500-msec of rectangular bipolar waves with a pulse frequency of 100 Hz and a pulse duration of 0.1 ms (FR1). The animals were tested for self-stimulation for 10 min each day for 5 days. During these daily 10-min sessions, the current level was adjusted to produce maximum lever pressing rates in each animal without disruptive motor involvement or convulsions. The animals that did not lever-press for intracranial self-stimulation (ICSS) more than 50 times in the 10-min sessions were dropped from the experiment. The remaining animals were run for 30-min sessions on 5 additional days in order to establish stable base rates of responding.

### ICSS/food competition

After stable self-stimulation rates had been established, the animals were placed on a food-deprivation schedule. They were trained to reach a feeder with a lot of pellets (45-mg Noyes food pellet) within 30 min for 5 days. This training was conducted in the box for self-stimulation testing. The ICSS lever was inactive during this phase of training. Further experiments were carried out using food/ICSS competition: the feeder was placed and the ICSS lever was active with the same current intensity. All the animals were required to maintain a stable weight level for 3 consecutive days.

### Test for stimulus-bound behavior

After a series of ICSS/food competition, the animals were switched for access to a pelleted standard rat chow diet and ad libitum water. The satiated experimental animals

were individually placed into the chamber which contained a dish of food pellets and some small wooden blocks and allowed to explore the chamber for a 5-min period. At the end of this familiarization period, brain stimulation was turned on for 30 sec at the threshold intensities for behavior changes used during ICSS/food competition. The 30-sec train of stimulation was followed by 60 sec of "no-stimulation". In total, 10 stimulation periods were presented. Records were made of any eating or gnawing responses elicited by the stimulation. Although stimulus-bound behaviors are usually controlled by different stimulation parameters, this test was included to ensure that the parameters actually used did not elicit consummatory behaviors.

### Test for ICSS induced emotional overeating

The current threshold for pedal pressings was used for ICSS-induced emotional overeating in well-fed rats. ICSS blocks of three trials are presented to the rat for evaluating a threshold at a given stimulation intensity (Koob et al. 1993), and the intensity is altered systematically between blocks of trials by 5 μA steps. The initial stimulus intensity is set 40 μA above the baseline current threshold for each animal. Each test session typically lasts 30–40 min. The current threshold for a descending series was defined as the midpoint between stimulation intensities that supported responding (i.e. positive responses to at least two of the three trials) and current intensities that failed to support responding. The threshold for an ascending series was defined as the midpoint between stimulation intensities that did not support responding and current intensities that supported responding for two consecutive blocks of trials. Four threshold estimates were recorded, and the mean of these values was taken as the final threshold (Koob et al. 1993). After the stimulation threshold were found, the feeder was placed in an experimental box, and the ICSS lever was active. The number of approaches to the feeding trough, the number of pellets eaten, and the number of pedal pressings at a fixed threshold current intensity were determined, and the parameters of eating behavior and self-stimulation reactions at various current intensities were determined for 10 min. On the following days, drugs were injected to an animals in an individual cage 20 minutes before testing, and then the rat was placed into a chamber to study overeating caused by self-stimulation of the brain; the threshold current in the satiated rats was used.

### Histology

When the tests were completed, the animals were sacrified with an overdose of Nembutal and perfused with saline followed by Formalin. The brains were removed, embedded in celloidin, sliced and stained with cresylfast violet (Fig. 1). The electrode placements were determined using the atlas (Konig and Klippel 1963).

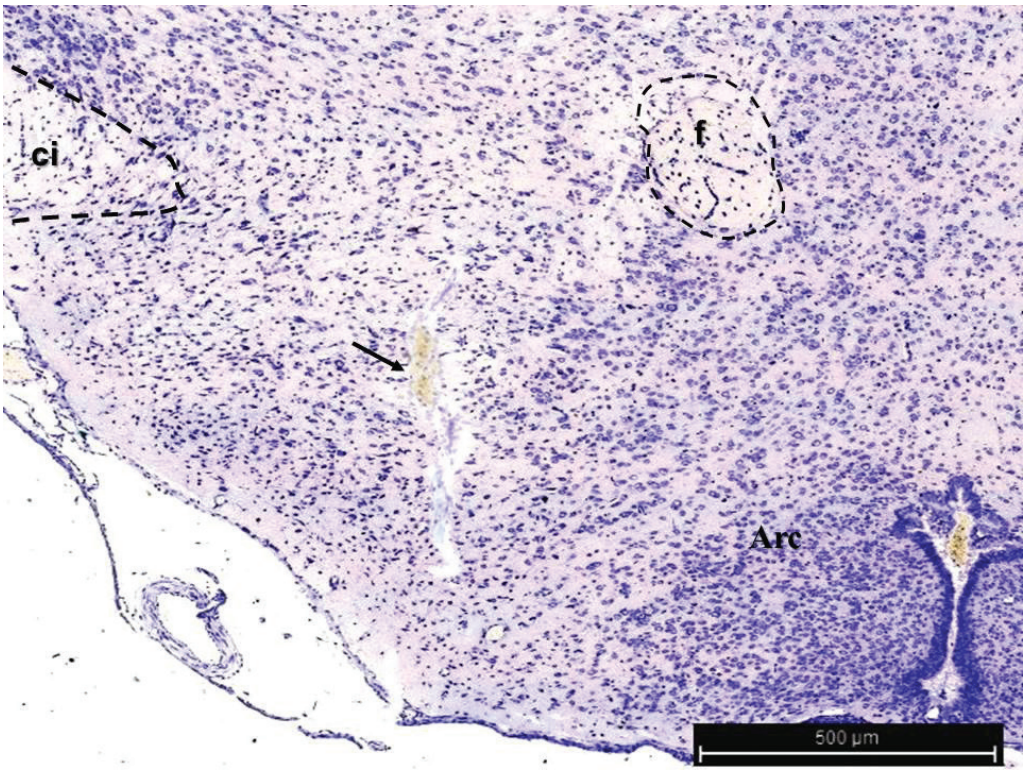


**Figure 1.** The trace after the electrode in the lateral hypothalamus (**arrow**), located below the conditional border between fornix (**f**) and the forebrain inner capsule (**ci**). Note: A line drawn from the fornix down to the brain surface separates the lateral hypothalamus from the medial hypothalamus with an extended complex of the arcuate nucleus (Arc). Stained by cresyl violet. The scale bar is 500 μm.

### Drugs and chemicals

A dopamine D2 antagonist sulpiride (Sigma, USA) at doses of 5 and 20 mg/kg i.p., a selective orexin A receptor (OX1R) antagonist SB-408124 (N-(6,8-Difluoro-2)-methyl-4-quinolinyl)-N′-[4-(dimethylamino) phenyl]urea, cat. No. S2694) and a selective antagonist of the orexin B receptors (OX2R) TCS-OX2-29 (2S)-1-(3,4-Dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)-3,3-dimethyl-2-[(4-pyridinylmethyl)amino]-1-butanone hydrochloride (Sigma, USA), diluted in distilled water, 0.5 mg/ml, were used as pharmacological analyzers. Solutions of orexin antagonists were administered intranasally at a dose of 20 µl (10 µl in each nostril). As a control, the intranasal administration of a 0.9% sodium chloride solution (isotonic solution) was used.

### Statistical analysis

The data were expressed as the mean ± standard error of the mean (SEM). Differences among groups were statistically tested by oneway analysis of variance (ANOVA) followed by the Tukey-Kramer post hoc multiple comparisons test. The behavior data were presented as the median (interquartile range) and analysed using a non-parametric Kruskal-Wallis test followed by Dunn's post-test for multiple comparisons. All statistical analyses were conducted using Graph Pad Prism version 6.0 (Graph Pad Software, San Diego, California, USA). Statistical significance was assumed at $P<0.05$.

## Results

The five animals that did not lever-press for ICSS more than 50 times in the 10-min sessions were dropped from the experiment. In food/ICSS competition test, the food-deprived animals were classed as self-deprivers when using current strength causing maximum lever-pressing rates without disruptive motor involvement or convulsions. All 18 animals deprived themselves of food during the food/ICSS competition: the animals almost totally neglected food during the competition phases. Eating behavior was not observed after an increase in the duration of the experiment for 1.5 hours. A food reaction with self-stimulation reaction intervals was observed only when threshold currents were used.

The rats that had completed an extensive series of competition tests over 3 days were later tested for stimulation-bound feeding using the procedure described above. Twelve of the 18 tested animals showed evidence of any of the three responses measured during the tests for stimulus-bound behavior. Neither eating, nor gnawing could be elicited by the administration of long durations (30 sec) of stimulation adjusted to the current level used in the self-deprivation tests. Subsequently, these 12 rats were taken for experiments with overeating induced by self-stimulation.

The average threshold intensity capable of evoking eating was 26 µA, and the average number of times when the animals ate out of the 20 stimulations at optimal current intensities was 13.2. Self-stimulation rates for the animals ranged between 62 and 350 presses per 10 minutes and averaged 135.4 and 154.2 for the 6 positive and 12 negative stimulation-bound feeders, respectively. This difference was not statistically significant. The slight trend being in the opposite direction to that seen in the rats supports the conclusion that there is no relationship between behavior in the competition and stimulus-bound eating tests.

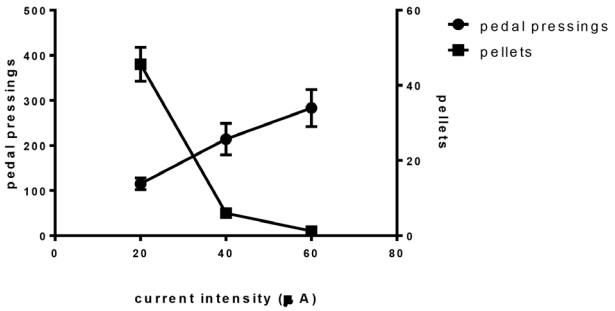


**Figure 2.** The effect of current intensity on the number of pedal pressings for self-stimulation and pellets eaten in the self-deprivation test in "well-fed" rats.

In the next series of experiments, 12 non food-deprived, negative stimulus-bound eaters were used in ICSS/food competition. Mean lever press rates for ICSS and the number of pellets eaten during competition are shown in Figure 2. It is apparent from this figure that the animals almost totally neglected food, even during the competition phases. At the same time, when assessing ICSS/food competition by threshold currents for the self-stimulation reaction, there were observed transitions from the pedal to the feeder, and the animals ate up to 60 pellets in 10 minutes of the experiment.

### Drug investigation

After administration of a D2 dopamine antagonist sulpiride at a dose of 5 mg/kg i.p., the number of approaches to the feeder practically did not change, the number of pellets eaten and the number of pedal pressings did not decrease significantly. After administration of sulpiride at a dose of 20 mg/kg, the number of approaches to the feeder and the number of pellets eaten decreased by more than 2 times, and the number of pedal-pressings by more than 3 times (Fig. 3).

After intranasal administration of a selective antagonist of orexin A receptor (OX1R) SB-408124 (20 µl, 0.5 µg), there was a significant decrease in the number of pellets eaten – from 54.2 to 32.1, and the number of pedal-pressings significantly increased from 97.6 to 138.2 (Figs 3, 4). The number of approaches to the feeding trough did not change significantly. After intranasal administration of a selective antagonist of the orexin B receptor (OX2R) TCS OX2 29 (20 µl, 0.5 mg/ml), there was no decrease in the number of pellets eaten, and the number of pedal pressings did not change (Fig. 5). Neither significantly changed the number of approaches to the feeder.

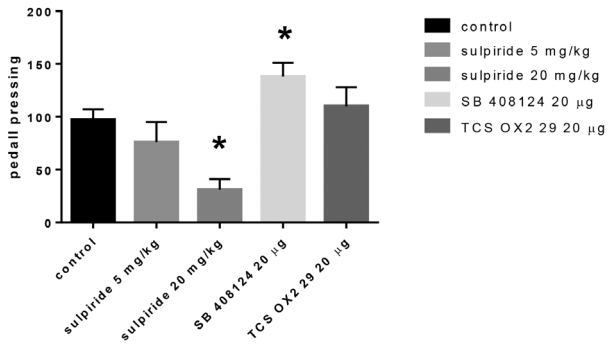


**Figure 3.** The effect of sulpiride, SB-408124 and TCS OX2 29 on the number of pedal pressings for self-stimulation in the self-deprivation test at a threshold current strength in "well-fed" rats. Note: * p≤0.05 – compared with the control group of animals.

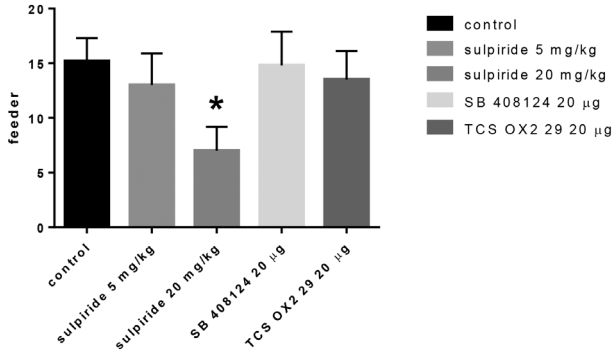


**Figure 4.** The effect of sulpiride, SB-408124 and TCS OX2 29 on the number of approaches to the feeder in the self-deprivation test at a threshold current strength in "well-fed" rats. Note: * p≤0.05 – compared with the control group of animals.

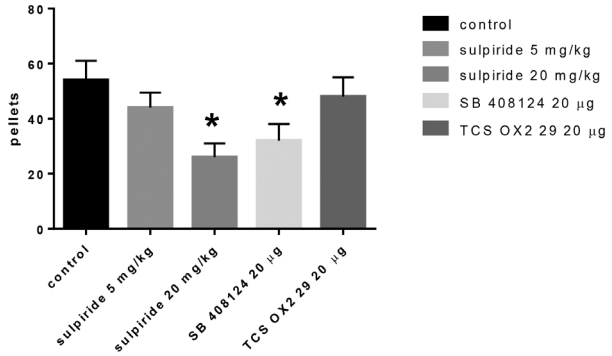


**Figure 5.** The effect of sulpiride, SB-408124 and TCS OX2 29 on the number of pellets eaten in the self-deprivation test at a threshold current strength in "satiated" rats. Note: * p≤0.05 – compared with the control group of animals.

# Discussion

The current studies of ICSS/food competition are consistent with the results of the studies conducted by a number of authors. The self-deprivation phenomenon was demonstrated when ICSS was placed in competition with food reward in food-deprived animals (Spies 1965; Routtenberg 1968; Frank et al. 1982; Wise 2005). No effect from the noncontingently administered electrical stimulation of the brain (ESB) on food intake in 12 experimental rats indicated that self-deprivation was not due to drive-reducing, transient satiety, or consummatory response suppression functions of the ESB. At the same time, in 6 out of 18 rats, noncontingently administered ESB caused food intake. The slight trend being in the opposite direction to that seen in the rats supports the conclusion that there is no relationship between behavior in the competition and stimulus-bound eating tests, which is consistent with other research (Frank et al. 1982).

The results of the competition test indicate that stimulation of the medial forebrain bundle in the lateral hypothalamic-ventral tegmental area has a greater reward value than primary food reward, thus producing a general self-deprivation phenomenon. In ICSS/food competition test, 18 of the animals were classed as self-deprivers. The animals deprived themselves of food during the ICSS/food competition.

The current work evaluated for the first time the self-derivation reaction in "well-fed" rats, using threshold current values. When current was reduced to a threshold value for the self-stimulation reaction, ICSS/food competition was transformed into ICSS/food cooperation. In this case, excessive food intake is modelled under conditions of an emotiogenic environment looking like production of binge eating (DMS-V-TR) in humans. This study used the self-stimulation reaction to the lateral hypothalamus of the threshold current intensity in the satiated rats as an additional positive emotional component of the environment for food reinforcement.

Research on positive emotional eating is largely based on data on its effects in humans. The Positive-Negative Emotional Eating Scale (PNEES) was constructed and tested on 531 women, who also completed Eating Disorders Assessment Scale. The results showed that a two-factor model constituting Positive emotional eating (PNEES-P) and Negative emotional eating (PNEES-N) fit the data well (Sultson et al. 2017). The analysis showed that after controlling for the mediating effect of PNEES-N, PNEES-P continued to significantly predict binge eating. The tendency to overeat in response to positive emotions could be integrated into current models of eating disorders, especially when addressing relapse prevention (Pompili and Laghi 2017; Sultson et al. 2017). In the present experiments, out of 18 animals, only 12 were used in which direct stimulation of the hypothalamus did not cause a food reaction, but only an exploratory reaction. Thus, the feeding of the satiated rats in ICSS/food cooperation was not observed as a result of direct electrical stimulation of the hypothalamus. The feeder and pedal turn out to be pragmatically different environmental signals causing a general activation background of the emotional-motivational arousal. It can be assumed that this condition is similar to that which occurs during the

development of emotional overeating in humans. Multiple runs to the feeder during self-stimulation reaction with threshold current in the satiated rats were seen (Fig. 4).

As currently known, BED refers to non-chemical dependence and, apparently, is formed like other types of addictive behavior (Iemolo et al. 2012; Pompili and Laghi 2017). It was shown that an activating effect of post-training lateral hypothalamic self-stimulation on aversive and appetitive classical conditioning (Ettenberg and White 1978), as well as post-training ICSS could also be an effective treatment for improving implicit visual discrimination learning and memory (Garcia-Brito et al. 2017). Stimulation of the medial forebrain bundle was linked to activation of general arousal systems, due to activity of dopaminergic, noradrenergic and serotoninergic ascendant fibers (Wise 2005). Only indirect evidence exists for addictive behavior on natural environmental stimuli. In particular, conditioned taste preferences were observed in rats which drank flavored water, followed by a session of self-stimulation. The control groups neither self-stimulated, nor exhibited conditioned taste preferences (Ettenberg and White 1978). It was shown that self-stimulation of brain zones with higher thresholds and lower pedal presses than medial forebrain bundle, lateral hypothalamus and ventral tegmental area activated feeding, contributing to obesity. In particular, prefrontal cortex self-stimulation induced feeding and weight gain over several weeks of exposure to stimulation. Overall, it appears that prefrontal cortex self-stimulation modulates energy balance (McGregor and Atrens 1991). The use of moderate stimulation by threshold currents in the present work confirms the data obtained.

In the present work, it was shown that after administration of D2 dopamine receptors antagonist sulpiride, the number of approaches to the feeder, the number of pellets eaten and the number of pedal pressings during self-stimulation decreased dose-dependently. In other words, both feeding and reinforcing properties of electrical stimulation decreased during food self-deprivation. It was demonstrated that another D2 antagonist raclopride reduced pedal-pressing responses reinforced with electrical stimulation of the ventral tegmental area and those reinforced with food within 30 min after injection. An increase in the frequency of brain-stimulation pulses and a change in the schedule of food reinforcement, which respectively increased the baseline rate of responding, did not alter the effectiveness of raclopride (Nakajima and Baker 1989).

At the same time, after administration of orexin A receptor (OX1R) antagonist SB-408124 (but not after administration of orexin B receptor antagonist TCS OX2 29) only a decrease in the number of eaten pellets was observed, whereas the number of pedal pressings was not significantly changed or mainly increased (see Figs 3, 5).

Thus, the current studies have shown the selectivity of OX1R (SB-408124) in relation to food reactions during self-deprivation in the well-fed rats. This is largely consistent with the literature. It is known that orexins and their receptors modulate food intake, arousal, stress and the use of addictive drugs (Shabanov et al. 2016; Ayrapetov et al. 2018; Thyssen et al. 2018). OX1R antagonist GSK1059865 and OX1/OX2R antagonist SB-649868, but not the OX2R antagonist JNJ-10397049, have been shown to reduce binge eating in female rats at doses that do not cause sleep. However, in this work, the highly preferred food was served in the regime (Boggiano and Chandler 2006), with three cycles of food restriction and a foot-shock, i.e. negative emotional influences were summarized (Piccoli et al. 2012).

Appropriate responding to aversive and rewarding stimuli is essential for survival, and subcortical neural systems for regulating emotions are evolutionarily conserved (Coulombe and White 1980). The precise mechanisms underlying approach and avoidance behaviors are beginning to be uncovered, with efforts focused on the intricate connectivity of the lateral hypothalamus (Giardino 2018). The lateral hypothalamus receives dense synaptic inputs from the amygdala, a brain region critical for emotional processing. Multiple distinct cell types are co-mingled in the lateral hypothalamus, and posterodorsal lateral hypothalamic neurons expressing the neuropeptide hypocretin (Hcrt) are particularly important for motivated behaviors. HcrtR signaling has been hypothesized to promote both negative and positive emotional states, but a nuanced theory for how Hcrt-lateral hypothalamic neurons process oppositely-valenced stimuli remains under development. Inputs to the lateral hypothalamus originating from the extended amygdala may govern complex behavioral responses to emotional stimuli. Bed nuclei of stria terminalis (BNST) is sufficient to drive emotion-related behaviors (Giardino 2018). Corticoliberin and cholecystokinin neurons of BNST respectively provide abundant and sparse inputs onto orexin lateral hypothalamic neurons, display discrete physiological responses to salient stimuli, drive opposite emotionally valenced behaviors, and receive different proportions of inputs from upstream networks. The data provide an advanced model for how parallel BNST-lateral hypothalamus pathways promote divergent emotional states via connectivity patterns of genetically defined, circuit-specific neuronal subpopulations (Giardino 2018).

In recent years, excessive food consumption in an emotiogenic environment (contributing to the development of binge eating) has been associated with changes in the brain, similar to those observed during the formation of dependence (Gearhardt et al. 2011). It has been shown that in patients with bulimia nervosa and BED in the striatum, the dopamine content can change, similar to that observed after taking the drug of abuse (Wang et al. 2011). The release of dopamine and its receptor binding in animals with binge eating also resembles a response to drug administration (Avena et al. 2008). Orexigenic neuropeptides, which are synthesized in the lateral hypothalamus, can modulate the activity of neurons in the ventral tegmental region and ventral striatum. In particular, orexin-containing neurons send projections from the lat-

eral hypothalamus to the ventral tegmental region, where OX1R play a key role in regulating the release of dopamine by the mesolimbic system of the brain and are thus involved in the effects of various drugs and mechanisms of dependence (Cason et al. 2010). In addition, episodes of binge eating can be controlled through the influence on the processes of reward and reinforcement of highly preferred food (goodies). In this regard, neurons of the lateral hypothalamus containing orexin are a key link for food reward (Koob 2008) and are activated by reward signals, such as food or drugs. Moreover, stimulation of neurons of the lateral hypothalamus containing orexin leads to the reinstatement of drug use in rats (Stuber and Wise 2016).

In terms of practical orientation, the intranasal introduction that was used in the work has obvious prospects. One of the most challenging problems facing modern medicine is how to deliver a given drug to a specific target at the exclusion of other regions. For example, a variety of compounds have beneficial effects within the central nervous system (CNS), but unwanted side effects in the periphery. For such compounds, traditional oral or intravenous drug delivery fails to provide benefit without cost. However, intranasal delivery is emerging as a noninvasive option for delivering drugs to the CNS with minimal peripheral exposure. Additionally, this method facilitates the delivery of large and/or charged therapeutics, which fail to effectively cross the blood-brain barrier. Thus, for a variety of growth factors, hormones, neuropeptides and therapeutics including insulin, oxytocin, orexin, and even stem cells, intranasal delivery is emerging as an efficient method of administration, and represents a promising therapeutic strategy for the treatment of diseases with CNS involvement, such as obesity, Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, autism spectrum disorders, seizures, drug addiction, eating disorders, and stroke. In 2004, intranasal hypocretin-1 (orexin-A) was first shown to be delivered from the nose to the brain and proposed as a new strategy to treat narcolepsy (Scranton et al. 2011). A study in non-human primates demonstrated that intranasal hypocretin-1 reduces cognitive performance deficits resulting from sleep deprivation (Deadwyler et al. 2017). However, intranasal hypocretin-1 administration is just starting to be explored in humans. This line of research has focused on narcolepsy, a disorder characterized by impaired or absent CNS hypocretin signaling and has shown promising results (Baier et al. 2008). Animal studies have demonstrated that intranasal administration of hypocretin-1 leads to significantly greater tissue-to-blood concentration ratios in all brain regions over 2 h as compared to intravenous administration. Intranasal administration also increased drug targeting to the brain and spinal cord 5- to 8-fold (Dhuria et al. 2009).

## Conclusion

Thus, it is necessary to conclude the selectivity of the orexin A antagonist SB-408124 with respect to binge eating compared with the action of orexin B antagonist TCS OX2 29 and dopamine D2 receptors antagonist sulpiride, i.e. blockade of only one dopaminergic link in the regulation of brain supporting mechanisms (Lebedev et al. 2013). Food self-deprivation caused by electrical self-stimulation of the lateral hypothalamus in well-fed rats is a promising and adequate model for studying the mechanisms of binge eating in an experiment.

## Conflict of interests

The authors declare no competing financial interests and no conflict of interests.

## References


- American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association.
- Appolinario JC, Bacaltchuk J, Sichieri R, Claudino AM, Godoy-Matos A, Morgan C, Zanella MT, Coutinho W (2003) A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Archives of General Psychiatry 60(11): 1109–1116. https://doi.org/10.1001/archpsyc.60.11.1109 [PubMed]
- Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neuroscience and Biobehavioral Reviews 32(1): 29–39. https://doi.org/10.1016/j.neubiorev.2007.04.019 [PubMed] [PMC]
- Ayrapetov MI, Sexte EA, Eresko SO, Bychkov ER, Lebedev AA, Shabanov PD (2018) The type 1 orexin receptor mRNA level (OX1R) in the emotional brain structures of rats during their chronic alcoholization. Journal of Addiction Problems [Voprosy narkologii] 8(168): 18–25. [in Russian]
- Baier PC, Weinhold SL, Huth V, Gottwald B, Ferstl R, Hinze-Selch D (2008) Olfactory dysfunction in patients with narcolepsy with cataplexy is restored by intranasal Orexin A (Hypocretin-1). Brain 131(10): 2734–2741. https://doi.org/10.1093/brain/awn193 [PubMed]
- Baimel C, Borgland SL (2015) Orexin signaling in the VTA gates morphine-induced synaptic plasticity. The Journal of Neuroscience 35(18): 7295–7303. https://doi.org/10.1523/JNEUROSCI.4385-14.2015 [PubMed] [PMC]
- Bespalov A, Lebedev A, Panchenko G, Zvartau E (1999) Effects of abused drugs on thresholds and breaking points of intracranial self-stimulation in rats. European Neuropsychopharmacology 9(5): 377–383. https://doi.org/10.1016/S0924-977X(99)00008-5 [PubMed]
- Boggiano MM, Chandler PC (2006) Binge eating in rats produced by combining dieting with stress. Current Protocols in Neuroscience 36(1): 9–23. https://doi.org/10.1002/0471142301.ns0923as36 [PubMed]
- Bongers P, De Graaff A, Jansen A (2016) 'Emotional' does not even start to cover it: Generalization of overeating in emotional eaters. Appetite 96: 611–616. https://doi.org/10.1016/j.appet.2015.11.004 [PubMed]

- Bongers P, Jansen A, Havermans R, Roefs A, Nederkoorn C (2013) Happy eating: the underestimated role of overeating in a positive mood. Appetite 67: 74–80. https://doi.org/10.1016/j.appet.2013.03.017 [PubMed]
- Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G (2010) Role of orexin/hypocretin in reward seeking and addiction: implications for obesity. Physiology and Behavior 100(5): 419–428. https://doi.org/10.1016/j.physbeh.2010.03.009 [PubMed] [PMC]
- Corwin RL, Avena NM, Boggiano MM (2011) Feeding and reward: perspectives from three rat models of binge eating. Physiology and Behavior 104(1): 87–97. https://doi.org/10.1016/j.physbeh.2011.04.041 [PubMed] [PMC]
- Corwin RL, Buda-Levin A (2004) Behavioral models of binge-type eating. Physiology and Behavior 82(1): 123–130. https://doi.org/10.1016/j.physbeh.2004.04.036 [PubMed]
- Coulombe D, White N (1980) The effect of post-training lateral hypothalamic self-stimulation on aversive and appetitive classical conditioning. Physiology and Behavior 25(2): 267–272. https://doi.org/10.1016/0031-9384(80)90215-2 [PubMed]
- De Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proceedings of the National Academy of Sciences of the United States of America 95(1): 322–327. https://doi.org/10.1073/pnas.95.1.322 [PubMed] [PMC]
- Deadwyler SA, Porrino L, Siegel JM, Hampson RE (2007) Systemic and nasal delivery of orexin-A (Hypocretin-1) reduces the effects of sleep deprivation on cognitive performance in nonhuman primates. The Journal of Neuroscience 27(52): 14239–14247. https://doi.org/10.1523/JNEUROSCI.3878-07.2007 [PubMed] [PMC]
- Dhuria SV, Hanson LR, Frey II WH (2009) Intranasal drug targeting of hypocretin-1 (orexin-A) to the central nervous system. Journal of Pharmaceutical Sciences 98(7): 2501–2515. https://doi.org/10.17816/RCF16134-42 [PubMed]
- Ettenberg A, White N (1978) Conditioned taste preferences in the rat induced by self-stimulation. Physiology and Behavior 21(3): 363–368. https://doi.org/10.1016/0031-9384(78)90095-1 [PubMed]
- Frank RA, Preshaw RL, Stutz RM, Valenstein ES (1982) Lateral hypothalamic stimulation: stimulus-bound eating and self-deprivation. Physiology and Behavior 29(1): 17–21. https://doi.org/10.1016/0031-9384(82)90359-6 [Pubmed]
- Frank RA, Stutz RM (1984) Self-deprivation: a review. Psychological Bulletin 96(2): 384–393. https://doi.org/10.1037/0033-2909.96.2.384 [PubMed]
- Garcia-Brito S, Morgado-Bernal I, Biosca-Simon N, Segura-Torres P (2017) Intracranial self-stimulation also facilitates learning in a visual discrimination task in the Morris water maze in rats. Behavioural Brain Research 317: 360–366. https://doi.org/10.1016/j.bbr.2016.09.069 [PubMed]
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD (2011) Neural correlates of food addiction. Archives of General Psychiatry 68(8): 808–816. https://doi.org/10.1001/archgenpsychiatry.2011.32 [PubMed] [PMC]
- Giardino WJ (2018) Parallel circuits from the bed nuclei of stria terminalis to the lateral hypothalamus drive opposing emotional states. Nature Neuroscience 21(8): 1084–1095. https://doi.org/10.1038/s41593-018-0198-x [PubMed] [PMC]
- Griffiths KR, Yang J, Touyz SW, Hay PJ, Clarke SD, Korgaonkar MS, Gomes L, Anderson G, Foster S, Kohn MR (2019) Understanding the neural mechanisms of lisdexamfetamine dimesylate (LDX) pharmacotherapy in Binge Eating Disorder (BED): a study protocol. Journal of Eating Disorders 7: 23. https://doi.org/10.1186/s40337-019-0253-3 [PubMed] [PMC]
- Harris DS, Anthenelli RM (2005) Expanding treatment of tobacco dependence. Current Psychiatry Reports 7(5): 344–351. https://doi.org/10.1007/s11920-005-0034-3 [PubMed]
- Harris GC, Wimmer M, Aston-Jones G (2005) A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 437(7058): 556–559. https://doi.org/10.1038/nature04071 [PubMed]
- Haynes AC, Jackson B, Chapman H, Tadayyon M, Johns A, Porter RA (2000) A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. Regulatory Peptides 96(1–2): 45–51. https://doi.org/10.1016/S0167-0115(00)00199-3 [PubMed]
- Iemolo A, Valenza M, Tozier L, Knapp CM, Kornetsky C, Steardo L, Sabino V, Cottone P (2012) Withdrawal from chronic, intermittent access to a highly palatable food induces depressive-like behavior in compulsive eating rats. Behavioural Pharmacology 23(5–6): 593–602. https://doi.org/10.1097/FBP.0b013e328357697f [PubMed] [PMC]
- Johnson PM, Kenny PJ (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nature Neuroscience 13(5): 635–641. https://doi.org/10.1038/nn.2519 [PubMed] [PMC]
- Jupp B, Dalley JW (2014) Convergent pharmacological mechanisms in impulsivity and addiction: insights from rodent models. British Journal of Pharmacology 171(20): 4729–4766. https://doi.org/10.1111/bph.12787 [PubMed] [PMC]
- Konig KP, Klippel AA (1963) The rat brain: a stereotaxic atlas of the forebrain and lower parts of the brain stem. Williams and Wilkins, Baltimore, 214 pp.
- Koob G, Markou A, Weiss F, Schulteis G (1993) Opponent process and drug dependence: neurobiological mechanisms. Seminars in Neuroscience 5(5): 351–358. https://doi.org/10.1016/S1044-5765(05)80043-0
- Koob GF (2008) A role for brain stress system in addiction. Neuron 59(1): 11–34. https://doi.org/10.1016/j.neuron.2008.06.012 [PubMed] [PMC]
- Lebedev AA, Bychkov ER, Shabanov PD (2013) Orexin A receptor antagonist SB-408124 attenuates the effect of amphetamine on the brain reward system. European Neuropsychopharmacol 23(S2): S244–244. https://doi.org/10.1016/S0924-977X(13)70379-1
- Lu XY, Bagnol D, Burke S, Akil H, Watson SJ (2000) Differential distribution and regulation of OX1 and OX2 orexin/hypocretin receptor messenger RNA in the brain upon fasting. Hormones and Behavior 37(4): 335–344. https://doi.org/10.1006/hbeh.2000.1584 [PubMed]
- Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M (2001) Differential expression of orexin receptors 1 and 2 in the rat brain. The Journal of Comparative Neurology 435(1): 6–25. https://doi.org/10.1002/cne.1190 [PubMed]
- Margules DL, Olds J (1962) Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats. Science 135(3501): 374–385. https://doi.org/10.1126/science.135.3501.374 [PubMed]
- Matzeu A, Koebel P, Vendruscolo LF, Sidhu H, Shahryari R, Kieffer BL, Koob GF, Martin-Fardon R, Contet C (2018) Knockdown of hypocretin attenuates extended access of cocaine self-administration

in rats. Neuropsychopharmacology 43(12): 2373–2382. https://doi.org/10.1038/s41386-018-0054-4 [PubMed] [PMC]

- McElroy SL, Guerdjikova AI, Martens B, Keck PEJr, Pope HG, Hudson JI (2009) Role of antiepileptic drugs in the management of eating disorders. CNS Drugs 23(2): 139–156. https://doi.org/10.2165/00023210-200923020-00004 [PubMed]
- McGregor IS, Atrens DM (1991) Prefrontal cortex self-stimulation and energy balance. Behavioral Neuroscience 105(6): 870–883. https://doi.org/10.1037/0735-7044.105.6.870 [PubMed]
- Nakajima S, Baker JD (1989) Effects of D2 dopamine receptor blockade with raclopride on intracranial self-stimulation and food-reinforced operant behaviour. Psychopharmacology 98(3): 330–333. https://doi.org/10.1007/BF00451683 [PubMed]
- Olds J (1958) Effects of hunger and male sex hormone on self-stimulation of the brain. Journal of Comparative and Physiological Psychology 51(3): 320–324. https://doi.org/10.1037/h0040783 [PubMed]
- Piccoli L, Di Bonaventura MV, Cifani C, Costantini VJ (2012) Role of Orexin-1 receptor mechanisms on compulsive food consumption in a model of binge eating in female rats. Neuropsychopharmacology 37(9): 1999–2011. https://doi.org/10.1038/npp.2012.48 [PubMed] [PMC]
- Pompili S, Laghi F (2017) Binge eating and binge drinking among adolescents: The role of drinking and eating motives. Journal of Health Psychology 24(11): 1505–1516. https://doi.org/10.1177/1359105317713359 [PubMed]
- Rodgers RJ, Halford JC, Nunes de Souza RL, Canto de Souza AL, Piper DC, Arch JR, Upton N, Porter RA, Johns A, Blundell JE (2001) SB-334867, a selective orexin-1receptor antagonist, enhances behavioural satiety and blocksthe hyperphagic effect of orexin-A in rats. The European Journal of Neuroscience. 13(7): 1444–1452. https://doi.org/10.1046/j.0953-816x.2001.01518.x [PubMed]
- Routtenberg A (1968) "Self-starvation" of rats living in activity wheels: adaptation effects. Journal of Comparative and Physiological Psychology 66(1): 234–238. https://doi.org/10.1037/h0025977 [PubMed]
- Sakurai T (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nature reviews. Neuroscience 8(3): 171–181. https://doi.org/10.1038/nrn2092 [PubMed]
- Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92(4): 573–585. https://doi.org/10.1016/S0092-8674(00)80949-6 [PubMed]
- Schmeichel BE, Matzeu A, Koebel P, Vendruscolo LF, Sidhu H, Shahryari R, Kieffer BL, Koob GF, Martin-Fardon R, Contet C (2018) Knockdown of hypocretin attenuates extended access of cocaine self-administration in rats. Neuropsychopharmacology. 43(12): 2373–2382. https://doi.org/10.1038/s41386-018-0054-4 [PubMed] [PMC]
- Schulte EM, Sonneville KR, Gearhardt AN (2019) Subjective experiences of highly processed food consumption in individuals with food addiction. Psychology of Addictive Behaviors 33(2): 144–153. https://doi.org/10.1037/adb0000441 [PubMed]
- Scranton RA, Fletcher L, Sprague S, Jimenez DF, Digicaylioglu M (2011) The rostral migratory stream plays a key role in intranasal delivery of drugs into the CNS. PLoS One 6(4): e18711. https://doi.org/10.1371/journal.pone.0018711 [PubMed] [PMC]
- Shabanov PD, Lebedev AA (2013) Involvement of GABA- and dopaminergic mechanisms of the bed nucleus of the stria terminalis in the reinforcing effects of psychotropic substances mediated via the lateral hypothalamus. Neuroscience and Behavioral Physiology 43(4): 485–491. https://doi.org/10.1007/s11055-013-9759-3
- Shabanov PD, Lebedev AA, Morozov VI, Roik RO (2016) The reinforcing properties of psychoactive substances are modulated by the brain orexin peptide system. Narcology [Narkologiya] 4(172): 27–33. [in Russian]
- Spies G (1965) Food versus intracranial self-stimulation reinforcement in food-deprived rats. Journal of Comparative and Physiological Psychology 60(2): 153–157. https://doi.org/10.1037/h0022367 [PubMed]
- Stuber GD, Wise RA (2016) Lateral hypothalamic circuits for feeding and reward. Nature Neuroscience 19(2): 198–205. https://doi.org/10.1038/nn.4220 [PubMed] [PMC]
- Sultson H, Kukk K, Akkermann K (2017) Positive and negative emotional eating have different associations with overeating and binge eating: construction and validation of the positive-negative emotional eating scale. Appetite 116: 423–430. https://doi.org/10.1016/j.appet.2017.05.035 [PubMed]
- Thyssen IYu, Yakushina ND, Lebedev AA, Pshenichnaya AG, Bychkov ER, Tsikunov SG, Shabanov PD (2018) Effects of OX1R Orexin A receptor antagonist SB-408124 on compulsive behavior and anxiety level after vital stress in rats. Reviews on Clinical Pharmacology and Drug Therapy [Obzory po klinicheskoi farmakologii I lekarstvennoi terapii] 16(1): 34–42. https://doi.org/10.17816/RCF16134-42 [in Russian]
- Trivedi P, Yu H, MacNeil DJ, Van der Ploeg LH, Guan XM (1998) Distribution of orexin receptor mRNA in the rat brain. FEBS Letters 438(1): 71–75. https://doi.org/10.1016/S0014-5793(98)01266-6 [PubMed]
- Volkow ND, Wise RA (2005) How can drug addiction help us understand obesity? Nature Neuroscience 8(5): 555–560. https://doi.org/10.1038/nn1452 [PubMed]
- Wang GJ, Geliebter A, Volkow ND, Telang FW, Logan J, Jayne MC (2011) Enhanced striatal dopamine release during food stimulation during binge eating disorder. Obesity 19(8): 1601–1608. https://doi.org/10.1038/oby.2011.27 [PubMed] [PMC]
- Wilfley DE, Crow SJ, Hudson JI, Mitchell JE, Berkowitz RI, Blakesley V, Walsh BT, Sibutramine Binge Eating Disorder Research Group (2008) Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. The American Journal of Psychiatry 165(1): 51–58. https://doi.org/10.1176/appi.ajp.2007.06121970 [PubMed]
- Wise RA (2005) Forebrain substrates of reward and motivation. The Journal of Comparative Neurology 493(1): 115–121. https://doi.org/10.1002/cne.20689 [PubMed] [PMC]
- Yager J (2008) Binge eating disorder: the search for better treatments. The American Journal of Psychiatry 165(1): 4–6. https://doi.org/10.1176/appi.ajp.2007.07101541 [PubMed]

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