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Neural Mechanisms of Feeding Behavior and Its Disorders

Hisao Nishijo and Taketoshi Ono

Abstract

There are two forms of feeding behavior. The hypothalamus and the lower brainstem monitor the internal environment of the body and are involved in the control of feeding behavior to maintain energy balance and homeostasis (homeostasis-dependent feeding behavior). On the other hand, humans and animals, when placed in an environment similar to modern society (e.g., cafeterias), where organisms can easily ingest highly preferred foods, consume more than necessary (homeostasis-independent feeding behavior). The emotion/reward system, including the amygdala and nucleus accumbens, is involved in this type of feeding behavior. These two control systems interact in the lateral hypothalamic area (LHA), where feeding behavior is controlled by systems with higher activity. In modern society, there is abundant information on food, and high-calorie foods such as snacks are readily available. Thus, in modern society, the homeostasis-independent control system easily surpasses the homeostasis-dependent control system, which results in obesity. Various feeding and eating disorders might be ascribed to dysregulations in the two control systems. In the future, more effective treatments for feeding and eating disorders can be developed by elucidating the mechanisms of these two control systems.

Keywords: feeding behaviors, hypothalamus, LHA, homeostasis, energy balance, reward, motivation

1. Introduction

Feeding behavior is a series of actions that includes food acquisition, food intake into the oral cavity, taste perception, chewing, and swallowing. Feeding behavior is affected by a number of factors such as the internal state of the body (hunger or satiety), the taste of the food as well as health, mood, as well as the atmosphere around an individual. Hunger and satiety, appetite, and food reward are the most important factors that regulate feeding behavior.

Both humans and animals engage in feeding behaviors to obtain pleasure (food reward: pleasure when ingesting food), and the desire for this food reward is driven by appetite. When a gastric tube was placed in an animal to discharge ingested food, the animal continued to eat to obtain a food reward; however, when the gastric tube was closed, the feeding stopped with the extension of the stomach [1]. This finding suggests that food reward is obtained by a series of feeding behaviors up to the swallowing stage, and the satiety that terminates feeding is dependent on the stomach extension and the subsequent digestive absorption processes. Thus, food reward is elicited by several events that occur before it passes through the esophagus:

food-specific satiety [35]. In humans, frontotemporal dementia with atrophy of the ventral frontal lobe leads to overeating even with awareness of satiety [36, 37]. Third, knowledge about specific foods or previous experience of eating certain foods may affect the reward values of it [34, 38]. Humans simulate the expected reward of foods using this cognitive information. For example, a famous food brand or food at a famous restaurant may have a high expected reward value. Fourth, the expected reward value of food decreases as the time for acquiring food (or food reward) increases (temporal discounting). For example, healthy foods that lead to longevity and slimming seem to be highly rewarding, but it takes a long time for the effects to be observed. Due to temporal discounting, the expected reward value of healthy foods may decrease. In contrast, junk food, which can provide an immediate reward when ingested, has a higher reward value than healthy

Figure 5.
Representation of taste solutions in the orbital cortex of rats. (A) An example of a response profile of a taste neuron to four basic and umami tastes. MSG, 0.1 M monosodium glutamate; GMP, 0.5 mM guanylic acid. Filled bars indicate significant taste responses (2.5 SD above or below the water response). The top bars indicate excitatory responses, and the down bars indicate inhibitory responses. (B) Distribution of taste solutions and water in a two-dimensional space.

foods. The orbital cortex is suggested to comprehensively evaluate and integrate this food-related multiple sensory, visceral, and cognitive information, and is involved in the final decision of food selection based on these factors [34, 39].

Human fMRI studies have reported that activity in the orbital cortex correlates with the subjective pleasantness of liquid foods, including umami solutions [40, 41]. To investigate the representation of taste solutions in the orbital cortex, a study analyzed neuronal responses to various taste solutions in the rat orbital cortex after infusing the solutions into the oral cavity of awake rats through implanted chronic intraoral cannulae (unpublished data). **Figure 5A** shows an example of the neuronal activity recorded from the rat orbital cortex during ingestion of various taste solutions including monosodium glutamate (MSG). This neuron responded to 0.1 M MSG, but not to 0.1 M sodium chloride (NaCl). The neuron had an inhibitory response to sucrose solution. **Figure 5B** shows a representation of these taste solutions resulting from a multidimensional scaling analysis of response patterns of 21 orbital cortical taste neurons. Each taste solution is arranged almost in a straight line from the left, where the most aversive quinine and citric acid are located. On the right side, there are rewarding solutions including sucrose, GMP (0.5 mM guanylic acid, a kind of umami), and MSG + GMP (mixture of MSG and GMP). In addition, the MSG and water are located in the center of the space. These orders are fairly consistent with the orders of the rats' preference for taste solutions. These results suggest that the rat orbital cortical neurons represent reward values based on sensory information derived from food.

3. Eating disorders in neuropsychiatric disorders

3.1 Feeding and eating disorders

Feeding and eating disorders are classified into several subtypes including anorexia nervosa, bulimia nervosa, binge-eating disorder, and others. Patients with anorexia nervosa show reduced dietary intake, weight loss, increased activity, hypothermia, and often present with symptoms of compulsive behavior. Since patients with anorexia nervosa have a fear of food or its intake, they restrict themselves from eating. The arcuate nucleus of the hypothalamus contains two groups of neurons that reciprocally regulate feeding behavior in response to blood hormones [42]. One is a group of neurons that produce neuropeptide Y and agouti-related peptide (NPY/AgRP neurons), which promotes feeding behavior. The other group of neurons produces α -melanocyte-stimulating hormone (α -MSH), which suppresses feeding behavior. Since α -MSH is a neurotransmitter produced by processing the precursor protein proopiomelanocortin (POMC), α -MSH-producing neurons are called POMC neurons. The hunger state that occurs due to this restriction of food intake leads to excessive NPY/AgRP neuronal activity, which in turn suppresses the activity of POMC neurons. A recent study using chemogenetic methods showed that selective enhancement of NPY/AgRP neuronal activity in mice increases behavioral activity and repetitive behaviors, which is similar to the compulsive behavior exhibited in human anorexia nervosa [43]. Furthermore, since POMC neurons promote oxytocin production in the paraventricular and supraoptic nuclei in the hypothalamus [44, 45], the reduction of POMC neuronal activity in fasting states may reduce oxytocin production and lead to the development of autistic traits. Reduced oxytocin production and autistic traits are also traits that are hallmarks of anorexia nervosa [46].

Bulimia nervosa is characterized by the repetition of eating large amounts of food in a short period of time (binge eating). To prevent weight gain, patients

restrict their diet, vomiting, and abuse laxatives. Clinical studies have reported that there are reduced levels of dopamine metabolites in the cerebrospinal fluid of bulimia patients. Administration of alpha-methyl-para-tyrosine (AMPT), an inhibitor of tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis), causes binge eating to reoccur in patients who have remitted binge eating [47]. Therefore, it can be suggested that the dopamine release (which reflects food reward when ingesting food) is reduced in bulimia nervosa; thus, patients overeat to compensate for a shortage of dopamine. It has also been reported that patients with anorexia nervosa and bulimia nervosa are more likely to have autoantibodies to α -MSH and adrenocorticotrophic hormone (ACTH) in their blood, suggesting that these autoantibodies may disrupt the functions of hypothalamic neurons in the feeding control system [48]. Taken together, it is likely that patients with feeding and eating disorders have some deficits in the feeding control system of the hypothalamus and/or the emotion/reward system.

3.2 Eating disorders in autism

In recent years, the prevalence of autism spectrum disorder has increased: 1 in 68 children have autism in the United States. It has been suggested that the orbital cortex and amygdala are involved in the development of autism [49]. These brain regions play important roles in information processing and in assessing food reward for taste (see above). Thus, it can be suggested that autism might present with some eating disorders. In line with this, patients with autism spectrum disorders have been shown to prefer eating limited kinds of foods (less than five foods at the lowest) [50], and their ability to identify sweetness, sourness, and bitterness is reduced [51].

It has been suggested that environmental pollution is partly involved in increasing the prevalence of brain development disorders, including autism. According to a study investigating the brain development of infants in dioxin-contaminated areas in Vietnam, the concentration of dioxins (particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) in the breast milk of mothers at 1 month of age was significantly correlated with that in autistic traits of children at 3 years of age [52]. In another study, a single dose of TCDD was administered to pregnant female rats. Analyses of the offspring indicated that there were disorders of social behaviors and alteration of synaptic activity as well as altered levels and/or activity of calcium ion (Ca^{2+})/calmodulin-dependent protein kinase II α (CaMKII α) in the amygdala and orbital cortex [53]. As shown in human patients, deficits of parvalbumin-positive neurons were also observed in the offspring of the rats [54]. These epidemiological and experimental reports suggest that rats that are administered TCDD during the fetal period can be used as animal models of autism.

Parvalbumin-positive neurons are known to be sensitive to endoplasmic reticulum (ER) stress, while TCDD has been suggested to cause ER stress. Furthermore, POMC neurons are parvalbumin-positive neurons [55], suggesting that they are impaired by TDCC. It has also been reported that TDCC reduces parvalbumin-positive neurons in the amygdala [54]. These findings suggest that parvalbumin-positive neuronal damage is caused by TDCC, and that TCDD may induce abnormal eating. Consequently, a clinical study reported that patients with anorexia nervosa, bulimia nervosa, and binge-eating disorder showed more symptoms of subthreshold autism compared with healthy controls [56]. In order to examine the effects of TCDD on feeding behavior, TCDD was administered to pregnant female rats and the intake of amino acid solutions of the pups was investigated after weaning [57]. The pups could freely take in eight kinds of solutions (histidine, sodium glutamate, glycine, arginine, lysine hydrochloride, threonine, salt, and distilled water). **Figure 6** shows

Figure 6. Effects of fetal TCDD exposure on amino acid intake behavior. Average intake rates of eight solutions (0.05 M histidine, 0.15 M MSG, 0.5 M glycine, 0.05 M arginine, 0.2 M lysine hydrochloride, 0.4 M threonine, 0.15 M salt, and distilled water) from 29 to 35 days after birth are shown. The ordinate indicates the intake rate (percentage of each solution in total liquid consumption). In the TCDD-administered group, the intake of lysine solution increased significantly and that of MSG decreased significantly compared with the control group. TCDD, tetrachlorodibenzo-*p*-dioxin.

the mean intake rate of each solution (the ratio of each solution to the total liquid consumption) between 29 and 34 days after birth. The control group took almost no lysine solution, while the TCDD-treated group took more lysine than the control group. Conversely, the intake of MSG solution was significantly reduced in the TCDD-treated group compared with that in the control group. These findings suggest that abnormalities in the hypothalamus, orbital cortex, and amygdala caused by TCDD administration may induce these eating disorders. Future studies in human autistic patients are required to draw valid conclusions.

4. Conclusions

The hypothalamus and the lower brain stem monitor the internal state of the body and control feeding behavior to maintain energy balance and homeostasis (homeostasis-dependent feeding behavior). A disruption in this system could lead to obesity. For a review of how molecular mechanisms of the central nervous system (CNS) regulate energy homeostasis in the hypothalamus and mechanisms of obesity due to their dysregulation, see Timper and Brüning (2017) [42]. On the other hand, when humans and animals are placed in a similar cafeteria-style environment, ingestion of unnecessary high-preference food occurs, which leads to becoming obese (homeostasis-independent eating behavior, or hedonic feeding). Hedonic feeding behaviors are controlled by an emotion/reward system. Both systems interact in the LHA (Figure 2), and feeding behavior is governed by the system with higher activity. In modern society, even when the energy balance of a body is positive, feeding behavior may be elicited by decision-making information in the cerebral cortex. Furthermore, there is an overflow of information about food in modern society, and high-calorie foods such as snacks can be easily obtained. A recent study reported that after watching TV food commercials, children became more dependent on tastiness rather than health benefits when choosing foods. Those TV commercials were suggested to have activated the ventromedial prefrontal cortex involved in

reward valuation [58]. Thus, in a modern society, the homeostasis-independent control system of feeding behavior easily surpasses the homeostasis-dependent control system of feeding behavior, which leads to obesity. In addition, various feeding and eating disorders are also presumed to be caused by disorders of both control systems. We hope that the elucidation of the mechanisms of these two control systems will lead to the development of more effective treatments for feeding and eating disorders.

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