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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:

the appearance and shape of the food, the taste and smell of the food, and the pleasure obtained by swallowing the food [1]. Food reward is therefore defined as the momentary value of a food at the time of ingestion, while “liking” is defined as pleasantness (tastiness) of food in the mouth [2]. The particular taste of food is the most important factor in eliciting the food reward obtained during ingestion. In contrast with this statement, it has recently been reported that infusing glucose or sucrose solution directly into the stomach via the feeding tube without passing through the oral cavity has a rewarding effect; however, the detailed neural circuits involved in the acquisition of visceral reward are unknown [3].

The brain forms appetite and controls feeding behavior by integrating several factors such as hunger, satiety, and the rewarding effects of food palatability. In other words, feelings of hunger and satiety are visceral sensations that reflect the energy balance in the body, but appetite is a type of desire for a specific behavior (feeding behavior) that leads to the ingestion of specific foods by integrating information including food rewards as well as visceral sensations.

Such feeding behavior is controlled by the neural networks, including the hypothalamus. Specific areas in the hypothalamus and lower brainstem lack the blood-brain barrier; hence, the neural membrane is in direct contact with the blood to monitor humoral information such as nutrients and various hormones released from the digestive system. In addition, the hypothalamus receives information from the digestive system (e.g., stomach extension, chemical nature of ingested

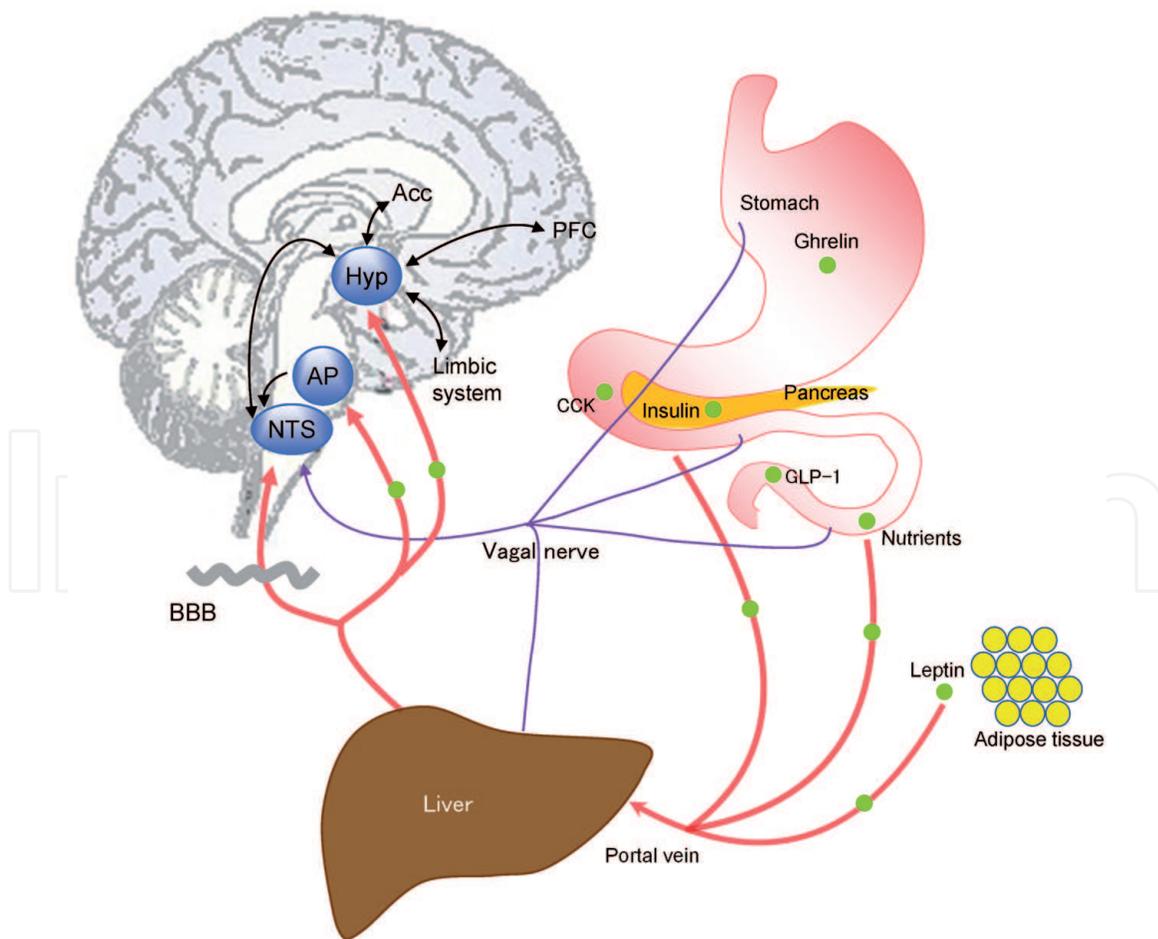


Figure 1. Schematic diagram of the hypothalamic feeding control system that receives information on the internal energy balance (humoral factors in the blood and visceral information from the vagus nerve). The hypothalamic system also receives information from the emotion/reward system (limbic system, prefrontal cortex, and Acc). Hyp, hypothalamus; AP, area postrema; NTS, nucleus tractus solitarius; PFC, prefrontal cortex; Acc, nucleus accumbens; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; BBB, blood-brain barrier.

food in the digestive tract, and metabolic activity of the liver) via the autonomic nervous system and lower brain stem (**Figure 1**). Thus, the hypothalamus monitors the internal environment to control feeding behavior to maintain energy balance and homeostasis (homeostasis-dependent hypothalamic feeding control system). The arcuate nucleus in the hypothalamus plays a crucial role in this control system (**Figure 2**). In addition, the hypothalamus further receives information from the emotion/reward system: (1) information on food rewards and emotions from the nucleus accumbens and the limbic system and (2) higher cognitive information from the prefrontal (orbital) cortex (**Figure 1**). The hypothalamus, especially the lateral hypothalamic area (LHA), integrates these types of information to control feeding behavior [4, 5]. This review focuses on how the emotion/reward system affects feeding behavior.

2. Roles of the emotion/reward system in feeding behavior

2.1 Interaction between the hypothalamic feeding control system and the emotion/reward system

One of the important factors that control human and animal behavior, including feeding behavior, is reward (e.g., food and water required for survival, or conspecific individuals) and punishment (or disgust stimuli) (e.g., pain due to tissue damage, natural enemies, or carnivores that threaten their survival). These rewards and punishments are closely linked to emotions. Emotion is a psychophysical response to the rewarding and punishing stimuli itself or the omission (or suspension) of the rewarding or punishing stimulus [1]. For example, fear and joy are responses to punishing and rewarding stimuli, respectively, while anger and sense of security (relief) are responses to omission (or suspension) of rewarding and punishing stimuli, respectively. These emotions play a motivating role in guiding specific behaviors, including feeding behavior. In other words, animals, including humans, pursue rewarding stimuli that give pleasure or joy (approaching behavior), and avoid punishing stimuli that cause discomfort, anger, fear, or sadness (avoidance or flight behavior) [6]. Based on their influence on behavior, rewarding stimuli are also known as positive reinforcers that strengthen behaviors to seek rewards, while punishing stimuli are also known as negative reinforcers that strengthen behaviors to avoid punishing stimuli. The emotion/reward system evaluates sensory inputs [evaluation of biological value (rewarding or punishing)] from the viewpoint of individual survival, and forms the motivation for a specific survival behavior.

Feeding behavior corresponds to an approaching behavior in which an organism approaches and obtains rewarding stimuli (food) from the viewpoint of emotional behavior. It has been suggested that the emotion/reward system affects the feeding control system in the hypothalamus via the LHA (**Figure 2**) [5, 7, 8]. Reward information is transmitted to the nucleus accumbens by dopaminergic projections from the ventral tegmental area, and is further transmitted to the LHA via the ventral medial part of the pallidum. Injection of various drugs into this pathway has been reported to cause overeating (promotion of feeding behavior) and suppression of feeding behavior [7]. On the other hand, emotional information (especially negative emotions) is transmitted from the amygdala to the LHA. In general, there is a trade-off between feeding behavior and fear-induced emotional behavior. Fear usually suppresses feeding behavior, but in a fasted state, fear or anxiety-induced emotional behavior is suppressed [9, 10]. Conversely, pleasant emotions promote feeding behavior (see below). Furthermore, the

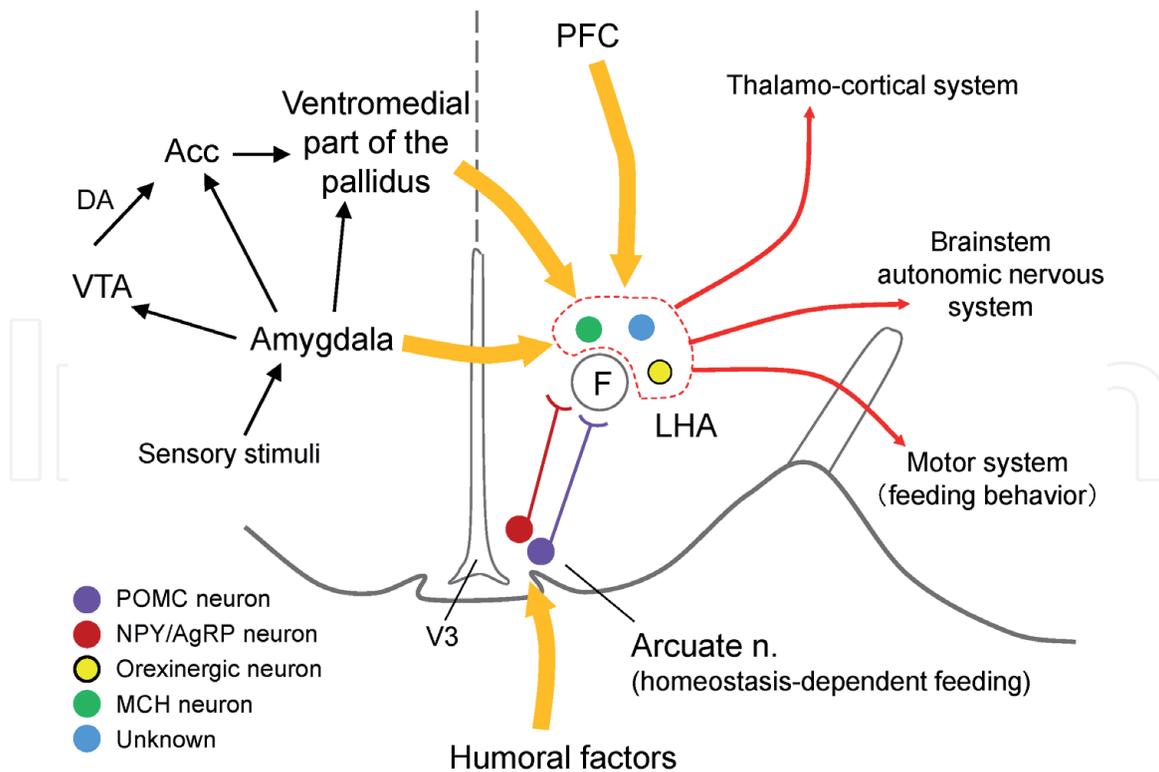


Figure 2. Interaction between the hypothalamic feeding control system and the emotion/reward system in the LHA. F: Fornix; LHA: Lateral hypothalamic area; V3: Third ventricle; PFC: Prefrontal cortex; DA: Dopamine; Acc: Nucleus accumbens; VTA: Ventral tegmental area; PFC: Prefrontal cortex.

prefrontal (orbital) cortex, which is a higher association area of olfaction and taste, sends not only cognitive information but also food information such as taste and smell to the LHA (see below).

2.2 Reward-related information processing in the nucleus accumbens

The nucleus accumbens plays a key role in the dopaminergic reward pathway and is implicated in overeating, leading to obesity. Two hypotheses have been proposed as the mechanisms that implicate the dopaminergic reward pathway in overeating and subsequently obesity [11]. The first hypothesis proposes that in obese subjects, responses to dopamine release during food intake (reward responses) are reduced. In line with this hypothesis, previous positron emission tomography (PET) studies have reported that dopamine D2 receptor utilization was reduced in obese subjects, which suggests a decrease in dopamine D2 receptor density. Thus, obese individuals may consume more food that causes dopamine release to compensate for the reduced reward response. A similar hypothesis (decreased dopamine D2 receptor utilization) has also been proposed as a mechanism for substance abuse. Furthermore, an animal study reported that when a chronic electrode was implanted in a specific brain region such as the medial forebrain bundle and an electric current (rewarding) was applied by a lever press, the animal preferred to press the lever [intracranial self-stimulation (ICSS) behavior]. However, in support of this first hypothesis, injection of a dopamine D2 receptor antagonist into the nucleus accumbens suppressed ICSS behavior due to electrical stimulation of the medial forebrain bundle. The second hypothesis proposes that obese people are more sensitive to cue stimuli (such as food smell and visual appearance, or conditioned stimuli) that predict food availability, rather than food ingestion itself. A higher sensitivity to food cues lead to an increase in food intake, which in turn, gradually reduces the reward response when food is consumed. Thus, food intake is

further increased by the individual to compensate for the reduced reward response. In support of the second hypothesis, in obese individuals as well as obesity-prone rats, responses to cues associated with food are enhanced in certain brain regions, including the nucleus accumbens [12, 13]. The nucleus accumbens is suggested to play a crucial role in incentive motivation: a process that translates expected reward derived from cues into behavioral manifestation for food acquisition [14]. A functional magnetic resonance imaging (fMRI) study on alcohol-dependent patients reported that activity in the ventral striatum, including the nucleus accumbens, increased in response to visual cues associated with alcohol [15]. It must be noted that obese individuals might have already experienced high-reward foods such as high fat or high calorie foods. Therefore, it is difficult to clarify which hypothetical mechanism causes a decrease in the reward response [11]. However, a human genetic study reported that obese subjects had a genetic polymorphism, called *Taq1A*, with decreased dopamine D2 receptor density [16]. These findings suggest that there are multiple underlying mechanisms for obesity.

A study analyzed neuronal responses in the ventral striatum, including the nucleus accumbens during discrimination of foods from nonfoods in a lever-press feeding task, in monkeys (unpublished data). This task consisted of three phases: (1) a visual recognition phase during which various objects including food and nonfood were presented to the monkey by opening an opaque shutter in front of an object, (2) a lever-press phase during which the monkey pressed the lever by a predetermined number of times if food was presented, and (3) an ingestion phase during which the monkey could take food after the last lever press opened a transparent shutter in front of the object [17–19]. In this task, white and red cylinders were associated with drops of juice and water, respectively. A predetermined number of lever presses opened a valve to deliver a drop of juice and water, respectively. When a brown cylinder was presented, the monkey had to press the lever a predetermined number of times to avoid electric shock. An example of a ventral striatum neuron in the monkey that selectively responded to rewarding objects has been shown in **Figure 3A**. This neuron responded to the rewarding objects, including orange and white cylinders associated with juice and water, but not to the brown cylinder and aversive syringe associated with electric shock. It should be noted that the responses to the rewarding objects were not related to simple lever-pressing movements, since the neuron did not respond to the brown cylinder even though the monkey pressed the lever. The response magnitudes of this neuron to various objects have been shown in **Figure 3B**. The results showed that this neuron was highly responsive to the monkeys' favorite (highly rewarding) objects. The existence of this type of neuron in the ventral striatum suggests that the ventral striatum is involved in incentive motivation for rewarding objects.

Previous studies have suggested that dopamine release in the ventral striatum is involved in the motivation for appetitive behaviors. Tonic (slow) increases in dopamine levels were shown to be involved in motivation [20, 21]. A positive correlation between reward-seeking behavior and dopamine levels was also reported [21]. Another study analyzed the activity of medium spiny neurons (MSNs), the major output neurons in the nucleus accumbens that receive dopaminergic projections [22] in the rat nucleus accumbens [23]. In this study, water-deprived rats were trained with an operant conditioning task in which the licking of a spout was associated with intragastric glucose (glucose group) or water (water group) infusion. After training, it was observed that rats in the glucose group were more vigorous in licking the spout in the absence of intragastric infusion. The inter-spike interval variability of MSNs, which reflects dopamine release in the striatum, was higher in the glucose group than in the water group [23]. These findings suggest that dopamine release in the nucleus accumbens plays a crucial role in motivation.

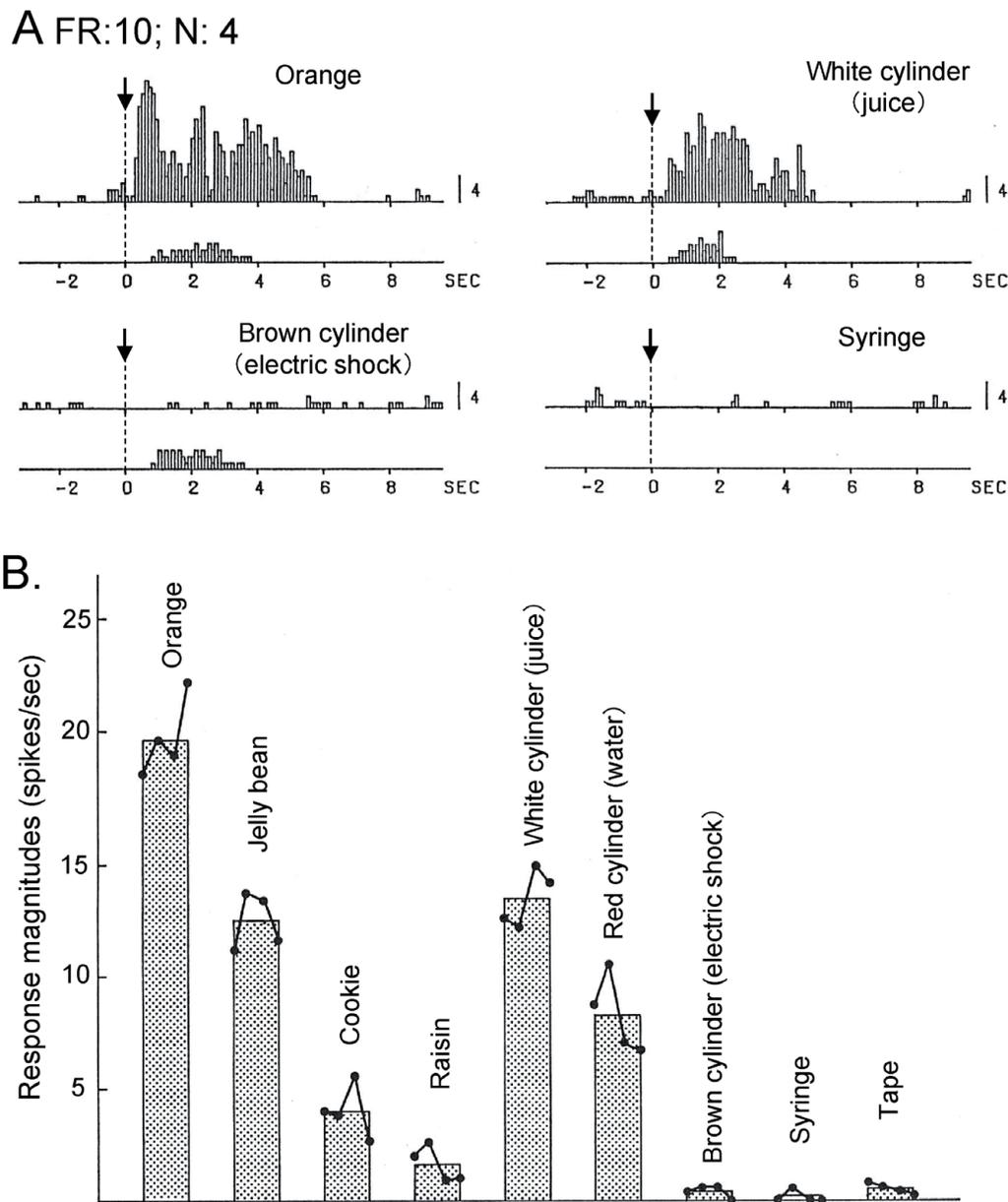


Figure 3. Response of a monkey ventral striatal neuron to various objects. (A) Responses of a ventral striatal neuron to various objects. Upper histogram: Summed histogram of neuronal activity (bin width, 100 ms bin); lower histogram: Summed histograms of lever-press signals. Zero on time axis: Onset of object presentation. Calibration shown at the right of each histogram (4 spikes/bin). FR, number of lever presses; N, number of trials. (B) Average response magnitudes for various objects. Closed circle, response magnitude in each trial.

However, the actual roles of dopamine and other neurotransmitters in motivation (wanting) and hedonic pleasure (liking) is still under debate [24–26].

2.3 Food valuation in the amygdala

Food is a rewarding object that induces pleasant emotions. The amygdala is involved in evaluating the biological (motivational) values of objects such as food. The activity of amygdala neurons has been reported to correlate with the biological value of sensory stimuli in monkeys as well as humans [17–19, 27, 28]. Therefore, it can be said that humans select an object with a high reward value based on value evaluation in the amygdala [27]. Thus, when the reward value of food decreases (devaluation), approaching behavior to the conditioned stimulus associated with that food also decreases. For example, the injection of lithium after eating causes discomfort, which reduces the reward value of the food to induce appetitive

behaviors. However, it has been reported that basolateral amygdala lesions in rats abolished these changes in behaviors after devaluation [29]. Similarly, in another study, monkeys were trained to form an association between two pairs of specific objects with specific foods. They were then allowed to eat only one of the foods to satisfaction (i.e., devaluation of one of the foods) after which it was observed that the monkeys chose the specific object associated with the other food (food-specific satiety) when given the option. However, lesions to the amygdala or surgical disconnection of neural fibers between the amygdala and orbital cortex reduced such behavioral changes associated with devaluation [30, 31]. Also, in a human fMRI study, devaluation of a specific food after eating it reduced brain hemodynamic responses to the odor of that specific food in the amygdala and orbital cortex [32]. These findings suggest that the amygdala receives information about the internal state of the body from the hypothalamus and evaluates the expected reward. Since stimulation of the amygdala increases dopamine release in the nucleus accumbens [33], value information from the amygdala may modulate dopamine release in the nucleus accumbens. This further suggests that an interaction between the amygdala and the nucleus accumbens is crucial in behavioral alterations in devaluation or food-specific satiety.

Some previous studies have shown that recordings from the amygdala neurons of monkeys were made during performance of the same lever-press feeding task (as shown in **Figure 3**) [17–19]. About one-fourth of the recorded amygdala neurons responded differentially to various rewarding and aversive objects with biological value (differential neurons). An example of such differential neurons has been shown in **Figure 4A**. These neurons responded strongly to orange, which was highly preferred (**Figure 4Aa**) in the visual discrimination and ingestion phases, but had a weak response to raisin, which was less preferred (**Figure 4Af**). The neuron had no response to tape, which had no biological value (**Figure 4Ag**). The neurons also responded to an aversive spider model (**Figure 4Ad**) and a brown column associated with electric shock (**Figure 4Ae**). Furthermore, this neuron responded more strongly to the preferred white cylinder associated with juice compared with the less preferred red cylinder associated with water, in the visual discrimination and ingestion phases (**Figure 4Ab, c**). These results suggest that the activity of the amygdala neuron reflects the biological values of objects. Similar types of amygdala neurons have been reported in a human study [27]. In this study, recordings from the amygdala neurons of a patient were made, while the patient rated specific foods displayed on a monitor by bidding. It was observed that the activities of some amygdala neurons positively correlated with food evaluation (bid price).

In the same studies done by Nishijo et al. [17–19], the monkeys drank 80 mL of water after the initial recording, which reduced the values of the red cylinder. The same neuron in **Figure 4A** was again tested with the white and red cylinders. **Figure 4B** shows altered neuronal responses in the amygdala after drinking. Although the neuron responded similarly to the white cylinder in the visual discrimination and ingestion phases, its responses to the red cylinder were attenuated (**Figure 4B**). These findings suggest that neuronal activity in the amygdala changes online based on the biological significance of objects.

2.4 Comprehensive food valuation in the frontal orbital cortex

Delicious food is highly rewarding. Both humans and animals consume foods with high reward values. Several factors can affect the expected reward value of a specific food when cues associated with that food are presented. Several factors can also affect food reward when food is ingested. Factors that can affect the expected reward value and food reward includes the following: (1) sensory factors derived

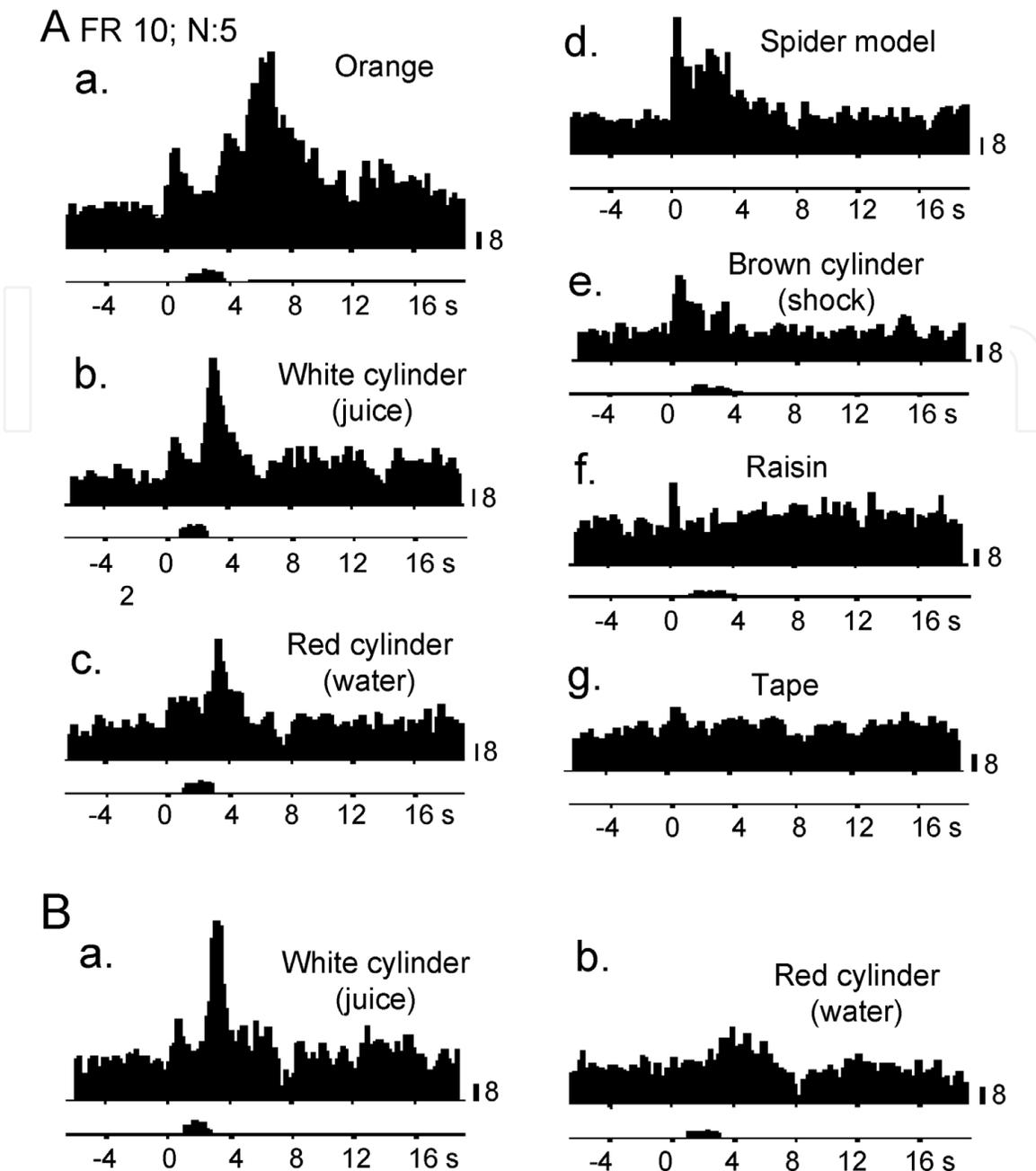


Figure 4. Changes in responsiveness of amygdala neurons in a monkey before and after drinking. (A) Responses of an amygdala neuron to various objects with and without biological significance. (B) Changes in neuronal responses to the white and red cylinders after drinking 80 mL of water. Upper and lower histograms indicate summed histograms of neuronal activity and lever-press signals (bin width, 200 ms), respectively. Calibration is shown on the right of each histogram (8 spikes/bin). FR, number of lever presses; N, number of trials. A zero on the time scale indicates stimulus onset.

from foods such as taste and smell, (2) internal states such as hunger and satiety, (3) previous experience of ingesting foods, (4) cognitive factors, and (5) temporal factors such as immediate availability of foods [11, 34]. The orbital cortex receives multisensory inputs, such as visual and auditory inputs, and also functions as a secondary taste and olfactory area. This brain region also receives inputs from the somatosensory cortex and is involved in processing food texture in the oral cavity. Thus, the orbital cortex receives all food-related sensory inputs and is involved in the valuation of food reward. Second, the orbital cortex receives information on the internal states and other visceral information from the hypothalamus and amygdala and is involved in food-specific satiety (see above). It has been shown in monkeys that lesions of the orbital cortex as well as the amygdala impair

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

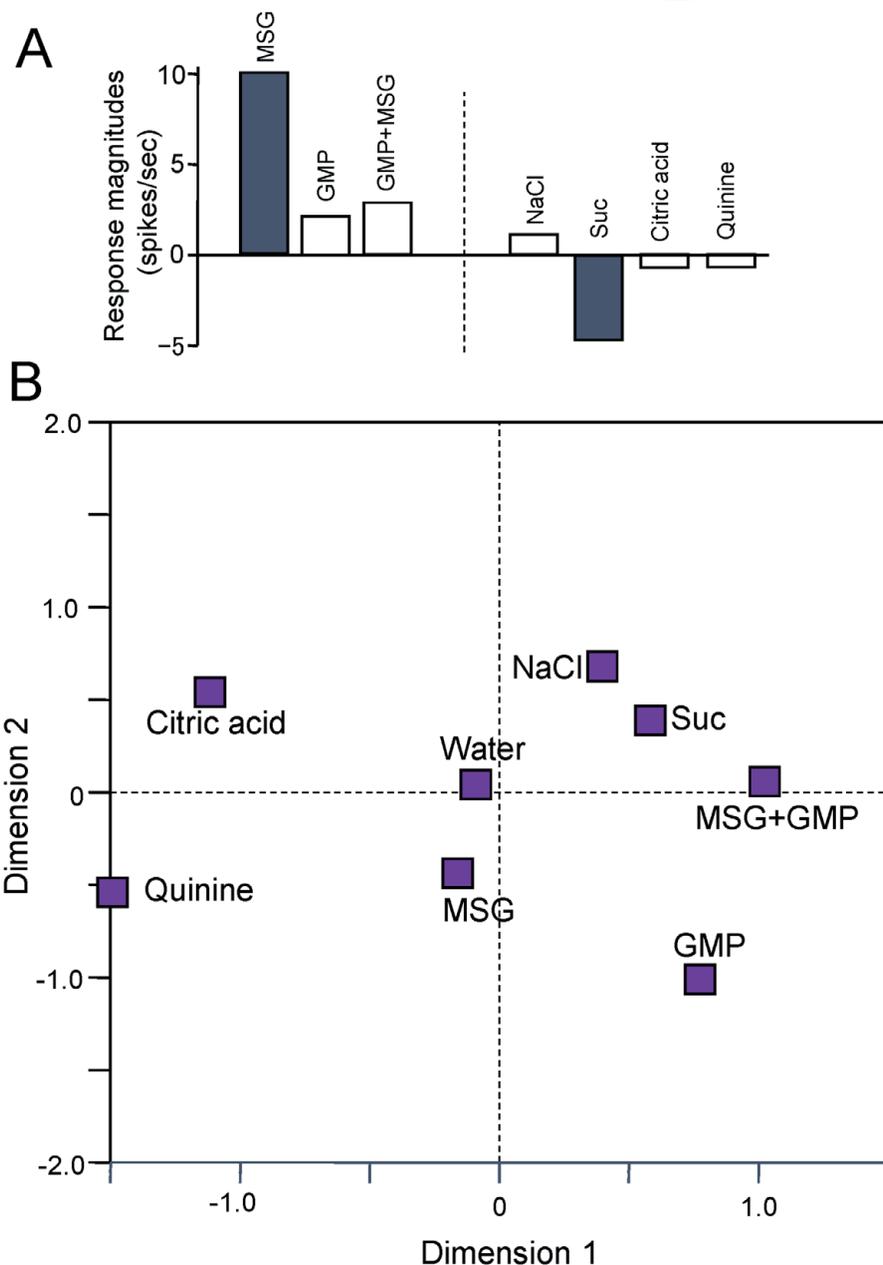


Figure 5. Representation of taste solutions in the orbital cortex of rats. (A) An example of a response profile of a taste neuron to four basic and umami tastes. MSG, 0.1 M monosodium glutamate; GMP, 0.5 mM guanylic acid. Filled bars indicate significant taste responses (2.5 SD above or below the water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

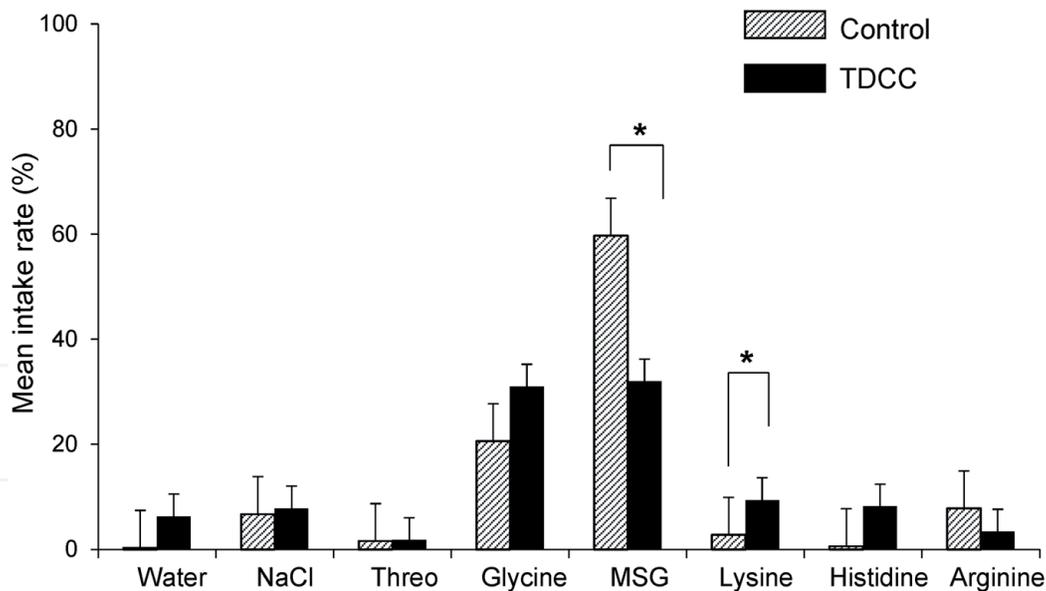


Figure 6.

*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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