Review

Aversive Sensation in the Brain after Eating Unpalatable Food

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Summary Taste plays an important role in the regulation of food and fluid intake in animals. Taste information on the tongue is transmitted to the brain, and we feel hedonic or aversive sensation from the taste of a food. Various studies have shown that opioids or the dopamigenic system is deeply related to the hedonic response in the brain. Few studies have been made, however, about the aversion to food, which is an important signal for animals to protect them from poison that usually has a bitter taste and causes an aversive sensation. We recently suggested that diazepam binding inhibitor (DBI) was released in the brain after stimulation by an aversive taste and might be involved in the aversive sensations of taste. In this review we describe the studies on aversive sensation after eating and propose a novel concept that food aversion may be divided into aversion and rejection. Furthermore, we suggest that DBI is involved in aversion.

Key Words aversion, taste, diazepam binding inhibitor (DBI), inverse agonist, rejection

We can distinguish various kinds of tastes. Taste on the tongue is initially transmitted to the nucleus of the solitary tract in the brain through taste nerves in rodents. The second relay nucleus for the ascending taste input is the parabranchial nucleus of the pons. The ascending projection from parabranchial nucleus branches into two pathways. One is the medial parvocellular component of the ventrobasal complex of the thalamus, and the next projects to the cortical gustatory area in the insular cortex. The other goes to the lateral hypothalamus, the central nucleus of the amygdala, and the bed nucleus of the stria terminals. Monkeys have an ascending projection system different from that in rodents; it has nerves from the nucleus of the solitary tract directly projecting to the ventrobasal complex of the thalamus (1, 2). How taste information is transmitted to the brain has been well studied, but what happens in the brain after palatable food or unpalatable food is consumed remains unclear. The rewarding effects, which are also mediated via the dopaminergic and opioidergic systems, have been studied with a sweet taste (such as sucrose) and palatable foods that included high-fat and high-carbohydrate foods (such as cake or chocolate) (3–7). An exogenous injection of benzodiazepine receptor agonists has been reported to increase the palatability of a sweet taste (8–10). In taste-reactivity tests, which can be used to evaluate palatability by intraoral stimuli with tastes without the effects of postdigestion, opioids (morphine) and benzodiazepine agonists increased the palatability to a palatable sucrose solution (10–15), but dopaminergic agents such as pimozide, haloperidol, apomorphine, and amphetamine did not change the taste reactivity (15, 16). The study by Mark et al. using microdialysis revealed that dopamine in the nucleus accumbens increased with the presentation of a taste previously paired with an intragastric infusion of nutrients, though it did not increase with a presentation of taste previously paired with an intragastric infusion of water (no nutrients) (17). From those results, Berridge proposed that a food reward contains two components, liking (pleasure/palatability) and wanting (appetite/incentive motivation) (18). Liking is related to opioids or the GABA/benzodiazepine system, whereas wanting is related to the dopamine system. Nevertheless, the research about aversion to food is quite limited, besides reward to food is advancing. However, it is important to study about the aversion to food to understand the neural mechanism of taste. In this review we will discuss aversion to food from a point of view opposite that of a food reward.

1. What is aversion to food?

What taste is aversive to animals? Animals and infants usually consider that a bitter taste or astringent taste is unpalatable. Human adults, however, prefer strange tastes. Considering these facts, the aversion to food can be divided into two categories: (a) inborn aversion and (b) posteriori aversion.

(a) Inborn aversion

It is well known that animals and infants hate a bitter taste and one that is too sour or salty. Steiner reported that neonate infants before their first feedings showed
facial expressions of satisfaction in response to sweet solutions and frowns in response to bitterness (19), indicating that the response is inborn, not acquired. In his studies of neonate infants born with cephalopelvis, he found them to display similar facial discriminations to various kinds of taste similar to those of normal infants and suggested that these expressions elicited reflexes that he termed gustofacial. He concluded that such a discrimination between pleasant and aversive does not result from cognitive mental processes based on learning, but instead reflects them. Johanson and Shapiro also reported that infant rats responded to strong acid and quinine solutions with aversive responses and suppressed the intake from one day of age (20). These studies suggest that animals innately discriminate between acceptable and unacceptable tastes.

Animals prefer a familiar food more than a new food when the familiar food has no strange taste because they have no way of knowing whether the new food is toxic or safe. This avoidance of a new food is termed food neophobia, which is also a form of inborn aversion by which animals protect themselves from harmful ingredients. After they have learned that the new food is safe, it becomes a familiar food to them (attenuation of neophobia). Buresova and Bures reported that in rats, the attenuation of neophobia to the first presentation of apple juice was prevented by treatment with pentobarbital anesthesia within 1 h after the first presentation, and intake doubled during the second presentation 2 d later without anesthesia (21). The attenuation of neophobia was also disrupted by hypothermia, bilateral cortical spreading depression, and electroconvulsive shock within 1 h after the first presentation of apple juice (21). In consideration of these facts, a memory of foods seems to be important for an attenuation of neophobia. In the brain, amygdala is related to neophobia, two opinions exist about amygdala. One is that a lesion of the amygdala increases neophobia (22). The other is that a lesion of it decreases neophobia (23–25). These discrepancies are due to the differences in the animals used and the conditioned environment. Nevertheless, the amygdala seems to play an important role in neophobia, since it receives gustatory information from the parabrachial nuclei (PBN) and from the insular cortex.

(b) *Posteriori aversion*

If we eat some foods and happen to develop digestive malaise or some disease, we come to avoid those foods, even when we know that they are safe. This phenomenon is termed as conditioned taste aversion (CTA). Animals retain the memory of the aversion for a long time after experiencing newly tasted food followed by digestive malaise. This phenomenon has been experimentally mimicked in animals. CTA could arise from association learning between conditioned stimulus (taste) and unconditioned stimulus (illness). Various kinds of substances such as toxins, psychoactive drugs, endogenous substances, and immune effectors induce CTA (26). Physical treatment such as radiation (27) and rotation (28–30) also induce it. Bernstein et al. suggested that CTA was induced in tumor-bearing rats during the growth of the tumor (31). Anorexia and weight loss induced by the growth of a tumor might be another cause of CTA. Many studies have shown that insular cortex (32–34), parabrachial nuclei (PBN) (35, 36), amygdala (37, 38) and area postrema (39) play important roles in the formation of CTA, which has been reviewed in detail (2, 40).

2. The appraisal method of palatability in animals

It is hard to determine whether the animal prefers the food it is given. One way to study a preference of food is to measure ingestive volume with a one-bottle test or a two-bottle choice test. These tests are based on the assumption that the acceptable fluid more drinkable, and we cannot know whether the animals actually prefer the fluid given to them. Furthermore, these ways cannot be applied to taste stimuli, which were not acceptable fluid spontaneously. Another way to interpret a food preference is by the use of the taste-reactivity test (41). Grill and Norgren examined the response to 4 taste stimuli (sucrose, NaCl, HCl, and quinine-HCl) in rats. The response to sucrose, NaCl, and HCl elicited mouth movements followed by rhythmic tongue protrusions, then lateral tongue movements without body movements. On the other hand, the response to quinine elicited gaping, and body movements increased. These behaviors are assumed to reflect the palatability of a gustatory stimulus. The measure of palatability by the use of a taste-reactivity test can be applied not only to rats, but also to mice (42) and hamsters (43). Taste reactivity can be used as an exploring taste factor, except for the effect of digestion.

3. The brain region related to discrimination of palatability

3-1. The brain region where food palatability is judged

The lesions of various parts of the brain cause changes of feeding behavior. The area postrema (AP) is in the hindbrain circumventricular organ and is connected with the nucleus of the solitary tract (SOL). The rats with AP-lesions overingested the preferred foods and did not respond to lab food (44). Lesions of amygdala altered taste reactivity (45–48). Furthermore, the aversive value toward quinine in rats with lesions of the central amygdaloid nucleus by ibotenic acid increased in the two-bottle choice test (49). Electrolytic lesions of the lateral hypothalamus area (LHA) have been known to lead to aphasia and adipsia (50). LHA is well known as the feeding center, and the ventromedial nucleus of the hypothalamus (VMH) is referred to as a satiety center (50). Moreover, LHA is also studied from the point of view that hypothalamus is related to palatability or aversion. The lesion of LHA by ibotenic acid increased the preference-aversion threshold for saccharin solution (51, 52). Cromwell and Berridge reported that the crucial region for aversion is ventral and medial to the globus pallidus and dorsal in LHA, shown by the use of a taste reactivity test after the lesion of various sites in LHA (53). On the other hand, Teitelbaum studied the
effect of a negative taste (quinine taste) on food intake among three groups—normal, obese (hypothalamic lesions), and dynamic hyperphagic, which was prevented from becoming obese by restricted feeding after hypothalamic lesion. The results of his experiments showed that a negative taste yields an exaggerated negative response in the obese group, but it had no effect in the normal and dynamic hyperphagic groups (54). He concluded that a hypothalamic lesion was not important for determining the quality of diet, but that the obesity caused the hyperphagia. Furthermore, Yamamoto et al. examined the activity of 58 single neurons in LHA. About half increased their activity in anticipatory periods just before injection and decreased it in rewarding periods during an injection of water or sapid solutions (55). These results indicate that LHA does not directly discriminate the quality of taste.

In many recent studies, taste palatability has been evaluated within the brain stem. Grill and Norgren demonstrated that the gustatory response in the chronic decerebrate rat is similar to that in intact rats, and the rats with thalamic surgery showed an increased rejection response for quinine, suggesting that discriminative responses to taste are sufficient in the mid- or hindbrain (56). The results of many studies that used benzodiazepine receptor agonists usually used as antianxiolytic drugs and that also increase the intake of palatable food and fluid, support this finding (8–10). Benzodiazepine receptor agonists enhanced not only feeding, but also ingestive reactions in taste reactivity tests (57). Berridge reported that the increasing effect of chlordiazepoxide, a benzodiazepine agonist, on the ingestive response in taste reactivity using chronic mesencephalic decerebrate rats (11). A microinjection of midazolam into the 4th ventricle increases the consumption of palatable mash (58) and hedonic reactions in taste reactivity tests (59). Furthermore, the direct administration of midazolam into the PBN of the pons increases mash intake (60). These results suggest that the brain stem is a key site to recognize the taste. Although benzodiazepine receptors are distributed in the lowest densities in parts of the thalamus, pons, and medulla (61, 62), benzodiazepine receptors in the PBN may be an important site of action for the effects of benzodiazepines. Because the brain stem appears to be an important site for benzodiazepine to increase palatability, the benzodiazepine receptor in the hindbrain may play an important role for palatability. This is supported by the immunohistochemical studies on the distribution of the evoked expression of c-fos in the PBN of rat after an intraoral infusion of various tastes and test stimuli followed by the i.p. injection of LiCl reported by Yamamoto et al. (63). The c-fos neurons expressed in the PBN were seen in the external lateral subnucleus (els) after stimulation with aversive stimuli such as 0.001 M quinine-HCl, 0.03 M HCl, and 0.2 M NaCl after CTA and were seen in the dorsal lateral subnucleus (dls) and central medial subnucleus (cms) after ingestive stimuli (63). 3-2. Substances related to aversive taste

What substances in the brain are actually related to aversive taste? Calcitonin gene-related peptide (CGRP)-like immunoreactivity levels in the gustatory part of the insular cortex were increased significantly by strongly aversive taste stimuli, such as quinine hydrochloride, and by conditioned taste stimuli that animals had been taught to avoid (38). An infusion of 0.001 M quinine-HCl produced a marked increase in the release of acetylcholine up to more than triple the baseline level in the insular gustatory cortex with a microdialysis study. After a treatment of CTA to 0.01 M saccharin, an infusion of saccharin in rats caused a marked increase in acetylcholine similar to an infusion of quinine (64). These substances are related to some aversive state. However, many lines of evidence support the notion that discrimination of taste seems to start in the hindbrain, as above. This suggests that additional factors are related to aversion in the hindbrain, but little is known about aversive taste in the hindbrain. We therefore postulate that some substances are released in the hindbrain after an unpleasant taste is encountered. We did an experiment that cerebrospinal fluid from rats after stimulation by quinine-HCl (quinine CSF) injected into the fourth ventricle of mice to confirm this assumption. As a result, the mice injected with the quinine CSF suppressed a 5% sucrose intake [(65) and Fig. 1]. This result implies that some substances increase in the quinine CSF. We searched for the substance responsible for suppressing sucrose intake in mice by using a hydra bioassay (66–69), and diazepam binding inhibitor (DBI) emerged as a candidate. The administration of benzodiazepines is reported to be related to the increase in the intake of palatable foods (8–10), though their effects

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**Fig. 1.** The effect of an injection of rat CSF on 5% sucrose intake in mice. CSF taken from rats stimulated with quinine-HCl (quinine CSF) was injected into the fourth ventricle of mice, and the sucrose intake was examined 15, 30, and 60 min later. Quinine CSF significantly decreased the intake of sucrose solution (*p<0.05, **p<0.01, the paired t-test). Values are means±SE (n=16) (65).
Fig. 2. Ligands for benzodiazepine receptor. Benzodiazepine receptor ligands divide into three categories: an agonist such as diazepam, clonazepam, or midazolam; an antagonist such as flumazenil or CGS8216; and an inverse agonist such as FG7142, β-CCE, or DMCM. Agonists act as a positive allosteric modulator of benzodiazepine receptors and enhance Cl⁻ flux. Inverse agonists decrease receptor activity and act as negative allosteric effectors. Antagonists only block receptor activity (16–18). Benzodiazepine agonists are related to an increase of the consumption of palatable food (12, 22, 41). We are proposing that DBI is related to aversion.

are only exogenous (Fig. 2). It is interesting that the benzodiazepine receptor is widely distributed in the brain (61, 62) and that the benzodiazepine receptor agonist has not yet been found. DBI is the only known endogenous ligand to this receptor, which is a 10-kDa neuropeptide present in the brain (70, 71). It binds to the benzodiazepine binding site on the GABA<sub>A</sub> receptor complex (72, 73) and acts as an inverse agonist, which elicits effects opposite to those of benzodiazepines (70, 74, 75). An injection of DBI into the brain reportedly produced anxiogenic effects in the conflict test (73). Furthermore, an increase in DBI-like immunoreactive compounds has been reported in depressive patients (76, 77) and in alcohol-dependent rats (78, 79). Katsura et al. also reported that the expression of DBI mRNA was elevated in the brain of ethanol-withdrawn mice after chronic treatment (80).

However, the relationship between DBI and feeding remains unknown. As a drug, N-methyl-β-carboline-3-carboxiamide (FG7142), a benzodiazepine receptor inverse agonist, dose-dependently reduced the intake of fluid and the preference for a saccharin solution (81–83). Taken together, DBI might be related to an aversive sensation as a biologically active molecule. Since the injection of benzodiazepine agonists into the brain enhances palatability sensation, a benzodiazepine inverse agonist DBI may be involved in the aversive feeling in regard to taste. Therefore we examined the effects of injection of DBI into the brain on the intake of mice as a candidate for the peptide related to aversive taste (84). An injection of DBI peptide fragment significantly suppressed the intake of 5% sucrose in mice (84). An administration (i.p.) of flumazenil, benzodiazepine receptor antagonist, 20 min before the injection of DBI (i.c.v.) antagonized the suppressive effect of DBI on the intake and the preference for saccharin. Furthermore, the injection of DBI increased the aversive response in a reactivity test. These results suggest that DBI is related to aversive taste (84). Immunoreactive somata were found throughout the gustatory NST, indicating an inhibition of the processing of taste information at the first level of the relay in the brain stem (85). Kobashi and Bradley reported that GABA functions as an inhibitory neurotransmitter through the GABA<sub>A</sub> receptor in both the gustatory and the visceral part of PBN (86). Thus DBI may modulate GABA action through a GABA<sub>A</sub> receptor in the hindbrain because DBI modulates Cl⁻ channels by the GABA<sub>A</sub> receptor (72, 87). The mechanism and the meaning underlying the increase of DBI and the intake of quinine are unclear. However, higher CSF levels of DBI may be related to disgust after the intake of a disliked food. An increase of DBI in the quinine-CSF we report here could explain why the intake of a disliked food induces a feeling of disgust.

3-3. Two phases of aversion to food in the brain

Food rewards are believed to distinguish two components: liking (pleasure/palatability) and wanting (appetite/incentive motivation) (18). This idea is based on whether the animal considers a food palatable and whether it wants to eat more being separable events (Fig. 3). Liking is the sensory of pleasure for eating. Wanting is the motivational process of appetite. Benzodiazepine receptor agonists (8, 10, 18) and opioids (12, 14, 88) are considered to be the substances related to liking. Dopamine is reported as the neurotransmitter related to wanting (3, 15, 17, 89, 90). There are
many studies about the mechanism in the brain related to food reward, but the aversive mechanism has not been studied well. Can this mechanism be classified into two processes? We argue that the aversive process of food consists of two phases: aversion and rejection (eating is stopped). In this review, aversion is defined as reflecting unpleasantness or dislike. Rejection is refusal to eat or passive dropping of food from the mouth. Berridge has already proposed that aversion is different from rejection from the results of a taste reactivity test (91). However, his view was based only in consideration of a taste reactivity test. In this part, we also describe the difference between aversion and rejection in detail. Food aversion is considered a condition opposite to a food reward. The first phase is that the animal feels an unconquerable aversion. The second is that the animal rejects the food and stops eating. Since research has been done from this viewpoint, it is difficult to argue about the aversive process. However, many suppressive substances for feeding have been reported, such as calcitonin (92), glucagon (93), insulin (94, 95), leptine (96, 97), corticotropin-releasing factor (CRF) (98), thyrotropin-releasing hormone (TRH) (99), oxytocin (100), cholecystokinin octapeptide (CCK-8) (101), bombesin (102), neuropeptin (103), satietine (104), and interleukin-1(IL-1) (105, 106). Some might act on the hypothalamus and in energy regulation in the hypothalamus, but some might act as suppressive factors for rejection independent of energy regulation. As an example, central injections of glucagon-like peptide-1-amide (GLP-1) (107, 108) and leptine (96, 97) reduce food intake and body weight. GLP-1 produces CTA in rats, although leptin produces no CTA (109). These results imply that GLP-1 has not only a suppressive effect of feeding, but also an aversive effect. Satietin has also been reported to have a suppressive effect without causing CTA (104, 110–112). These results suggest that suppressive substances of feeding that have already been reported may also be responsible for aversion. It is hard to distinguish between aversion and rejection by studies that use animals. Taste reactivity is one way to study aversive substances. This method is designed to evaluate taste apart from digestion in animals. The other way to study aversive substances is CTA. If an injection of a substance into the brain produces CTA, at least we could consider that substance as being related to aversion. However, an i.c.v. injection at a higher dose of amphetamine than brain levels after peripheral administration is insufficient to induce CTA (113). Therefore the candidate substance cannot be considered to be unrelated to aversion for the simple reason that the substance did not cause CTA.

**Conclusion**

The aversive mechanism to food in the brain is still unclear. However, the discrimination of taste starts in the brain stem, which is also a crucial area for food aversion. We proposed that in the brain, the aversive mechanism to food consists of two phases from a viewpoint opposite to a food reward (liking and wanting). The first phase is an aversive sensation, next to a rejection of the food. The factors related to each phase need to be studied further for a detailed elucidation of the mechanism aversion to food.

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