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Brain Mechanisms of Cognitive, Emotional and Behavioral Aspects of Taste

Takashi Yamamoto

Kio University Faculty of Health Scineces, Department of Health and Nutrition 4-2-2 umaminaka, Kitakatsuragi, Nara 635-0832, Japan

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Taste is associated with hedonic evaluation as well as recognition of quality and intensity. Taste information is sent to the cortical gustatory area in a chemotopical manner to be processed for discrimination of taste quality. It is also conveyed to the reward system and feeding center via the prefrontal cortices. The amygdala, which receives taste inputs, also influences reward and feeding. In terms of neuroactive substances, palatability is closely related to benzodiazepine derivatives and β-endorphin, both of which facilitate consumption of food and fluid. The reward system contains the ventral tegmental area, nucleus accumbens and ventral pallidum and finally sends information to the lateral hypothalamic area, the feeding center. The dopaminergic system originating from the ventral tegmental area mediates the motivation to consume palatable food. The actual ingestive behavior is promoted by the orexigenic neuropeptides from the hypothalamus. Even palatable food can become aversive and avoided as a consequence of postingestional unpleasant experience such as malaise. The brain mechanism of these aspects of taste is elucidated.

Introduction

When we eat a favorite food, we recognize the food by discriminating its quality and quantity on the basis of a variety of sensations including taste, and then evaluate it to be delicious. The positive hedonic characteristic will motivate us to eat more, and the jaw and tongue move rhythmically with active salivary secretion and gastrointestinal functions to ingest the food. The ingestive behavior will finish with the satisfaction of feeling full. Some of our favorite foods may have been innately determined, e.g., cakes and chocolates with innately preferred sweet tastes, but others are acquired after preferable experiences, i.e., on the basis of association learning between taste perception and nutritive postingestional effects. Conversely, even favorite foods will become aversive and avoided as a consequence of an unpleasant experience including postingestional malaise.

The above-mentioned taste-mediated behaviors are the results of processing of sensory information, especially of taste information arising from the oral cavity, in the brain. Neural mechanisms of these taste-mediated behaviors including the brain regions involved and the neurochemical substances activated in the brain will be elucidated in the present article.

*Corresponding author: Kio University Faculty of Health Scineces, Department of Health and Nutrition 4-2-2 umaminaka, Kitakatsuragi, Nara635-0832 Japan Tel.: +0745-54-1601; Fax.: +0745-54-1600; E-mail: ta.yamamoto@kio.ac.jp

Taste information conveyed to the brain

As schematically shown in Fig. 1, each taste cell in taste buds expresses one of the five taste receptors which interact with tastants, such as NaCl, HCl, sucrose, quinine and a umami substance like glutamic acid, representing each of the five basic tastes, such as salty, sour, sweet, bitter and umami, respectively (Lindemann, 2001). Information from each cell is conveyed through each of the five labeled lines of taste nerve fibers to reach the relevant areas in the central nervous system. Such labeled lines are called NaCl-best, HCl-best, sucrose-best, quinine-best or umami-best fibers depending on their best sensitivity to any one of the five basic taste stimuli. These labeled lines terminate to the relatively confined areas within each taste receptive zone, and such a quality-specific projection is called ‘chemotopic

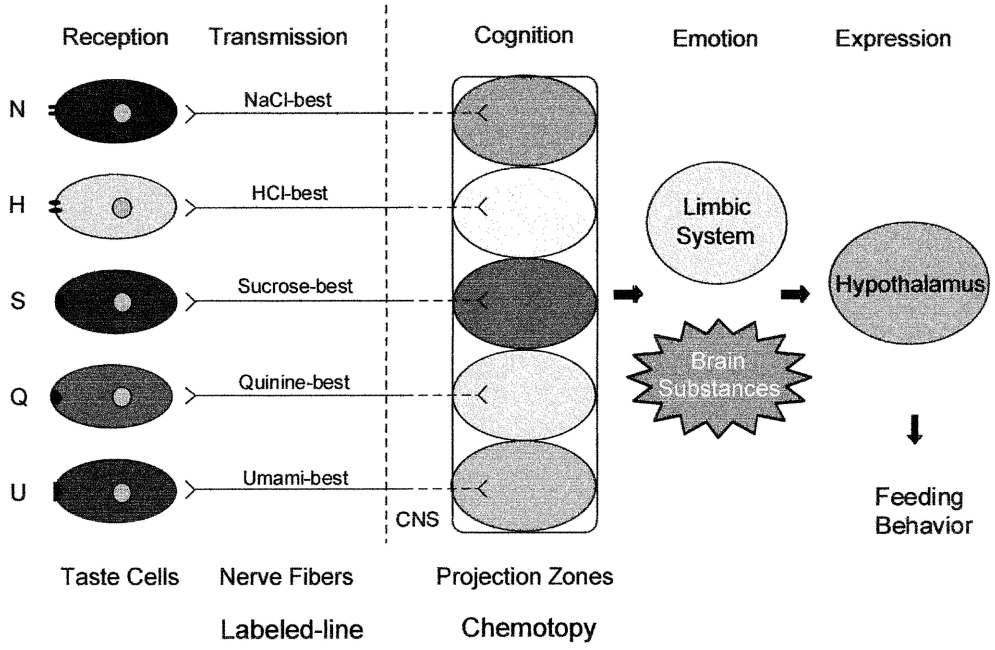

Fig. 1. Schematic drawing of the taste system connecting to feeding behavior. Each taste cell in taste buds expresses one of the five taste receptors which interact with tastants representing each of the five basic tastes such as, NaCl (N), hydrochloric acid (H), sucrose (S), quinine (Q) and umami substances like glutamic acid (U). Information from each cell is conveyed to the central nervous system (CNS) through each of the 5 labeled taste fibers to reach relatively confined areas in the taste receptive zones in a chemotopical manner. Taste information, after sensory perception, is processed in terms of emotional aspect in the limbic system with the participation of brain neuroactive substances. The information is finally sent to the hypothalamus for the regulation of feeding. From Yamamoto (2008).

organization' or 'chemotopy'. After processing of taste for cognition of quality in the cortex, taste information is further processed in terms of emotional aspect in the limbic system of the brain with the participation of brain neuroactive substances. The outcome is finally conveyed to the hypothalamus, the feeding center in the lateral hypothalamic area and the satiety center in the ventromedial nucleus of the hypothalamus.

Taste information processing in the cortical gustatory area (CGA)

Chemotopy, a functional localization of taste-responsive neurons depending on the quality of taste, in the CGA has been suggested by the following electrophysiological experiments. In anesthetized rats, Yamamoto et al. (1985a) found a tendency of different patterns of regional responses within the CGA to each chemical stimulation with sucrose, NaCl, HCl and quinine, i.e., sucrose responses were most dominant in the rostrodorsal region, quinine responses in the caudal region, and NaCl responses in the central and ventral regions, while HCl responses were in the central and dorsal regions within the CGA. In conscious rats, Yamamoto et al. (1989) recorded single CGA neuron activities in response to licking various kinds of taste solutions. When the taste neurons were classified into 'best-stimulus' categories, depending on their best sensitivity to any one of the four basic stimuli, sucrose-best, NaCl-best, HCl-best, and quinine-best neurons were found to be relatively located in this order from rostral to caudal within the CGA. Considering that the chemotopy should be a key to solving the fundamental neural mechanism for quality coding in the cortex, they hypothesized an 'across-region response pattern' for the cortical mechanism of taste quality coding (Yamamoto et al., 1985a; 1985b).

The basis of chemotopy might exist in the columnar information processing of the CGA. Our recent study (Sato et al., 2008) has shown a unique functional column existing in the insular cortex, in which intra-columnar communication between the superficial and deep layers is prominent, and $GABA_A$ action is involved in the inhibition of the intra-columnar communication. In contrast to this finding, $GABA_A$ action is involved in inter-columnar lateral inhibition in the whisker barrel cortex where the columnar organization is most apparent.

In humans, in spite of the limitations of analysis due to the anatomical position and small size of the primary CGA, Schoenfeld et al. (2004) have reported the possible existence of chemotopy i.e., topographic arrangement of taste responsiveness to each of the 5 basic tastes, sweet, umami, salty, sour and bitter, with a high inter-individual variability, although with some considerable overlap. They reported that the taste specific patterns were stable over time in each subject.

Neurochemical substances related to palatability

Several neurochemicals are related to the reinforcing aspect of taste. The resulting perceived palatability (or taste pleasure) is believed to be evaluated finally in the orbitofrontal cortex in primates.

Benzodiazepine

Benzodiazepines such as chlordiazepoxide and diazepam, which facilitate the opening of Cl^- channels in response to $GABA_A$ receptor activation, are widely described for the treatment of anxiety disorders. It has been shown that these benzodiazepine agonists promote food intake (Berridge and Pecina, 1995). Benzodiazepine-induced hyperphagia is not due to its secondary effects of anxiety or arousal, but is due to its action of enhancement of the palatability of food. It is suggested that benzodiazepines act on the particular receptors in the lower brainstem and enhance taste palatability. The PBN is the most probable region on which benzodiazepines act to influence food intake (Higgs and Cooper, 1996). Shimura et al. (2004) found that systemic injection of midazolam increased intake of a sucrose solution in wild-type mice but not in mice deficient in the 65-kDa isoform of glutamate decarboxylase (GAD65), an enzyme for synthesis of GABA in the central nervous system, suggesting that GAD65-generated GABA is necessary for benzodiazepines to enhance taste palatability.

Opioids

Opioid agonists facilitate and antagonists diminish food consumption. Opioids may enhance palatability of food, leading to increased food intake. Opioid antagonists, such as naloxone and naltrexone, abolish the preference to a highly palatable saccharin solution in rats with no effect on water intake. In fact, levels of β-endorphin in the blood and cerebrospinal increase after the consumption of palatable sweeteners and decrease following the intake of aversive quinine in thirsty rats (Yamamoto et al., 2000).

Reward system

It is well documented that the brain reward system is the neural substrate for the intracranial self-stimulation phenomenon which was originally found by Olds and Milner (1954) and the rewarding effects of addictive drugs. Essentially the same neural circuitries are concerned with the taste reward system.

Ventral tegmental area (VTA)

The VTA in the midbrain sends dopaminergic fibers to the forebrain structures including the nucleus accumbens, and affects feeding behavior. Shimura et al. (2002) showed that lesions of the VTA suppressed the consumption of a preferred sucrose or NaCl solutions without influencing the intake of less- or non-preferred tastes or water. According to the current concept that food reward contains separate functional components, "liking" (palatability) and "wanting" (incentive motivation) (Berridge, 1996), the dopamine system seems to mediate "wanting" rather than "liking" for food and fluid reward.

Nucleus accumbens (NAcb)

The NAcb is known to be involved in palatability-induced feeding behavior. The hyperphagic effect of opioids has been shown to be most prominent when opioids are injected into the NAcb, especially into the shell subdivision. Opioid mechanisms mainly in the NAcb are critically involved in enhancement of taste palatability. The NAcb receives afferent inputs from the prefrontal cortex and amygdaloid structures, which are primarily coded by glutamic acid. Although the information transmitted through these glutamatergic inputs has not yet been identified, if it activates the GABAergic neurons, which constitute about 90% of the NAcb, then these neurons would suppress feeding responses by inhibiting VP neurons as described below. This possibility is partly suggested by the findings that strong c-*fos* expression was shown in the NAcb neurons (Yasoshima et al, 2006) and significantly larger GABA release was observed in the VP (Inui et al., 2009) after acquisition of conditioned taste aversion.

Ventral pallidum (VP)

The VP is a main target of the GABAergic neurons in the NAcb. From the VP, efferents project to the lateral hypothalamus (LH), indicating that the VP is anatomically interposed between the NAcb and LH. Blockade of $GABA_A$ receptors in the VP with bicuculline elicits a strong feeding response in satiated rats without affecting water intake (Stratford and Kelley, 1999). Recently we have found that microinjection of bicuculline into the VP enhances the intake of a preferred saccharin but not quinine solution and water, suggesting that the over-consumption by GABA blockade in the VP is confined to palatable tastes (Shimura et al., 2006).

Hypothalamus

A key site involved in the regulation of ingestive behavior is the hypothalamus, where a number of neuropeptides that regulate appetite have been identified. To elucidate the brain mechanisms of the palatability-induced ingestion, Furudono et al. (2006) explored the roles of six hypothalamic orexigenic neuropeptides, orexin, melanin-concentrating hormone (MCH), neuropeptide Y (NPY), agouti-related protein, ghrelin and dynorphin, in the intake of a palatable solution, saccharin. Of the six peptides, intracerebroventricular administrations of orexin, MCH and NPY increased the intake of saccharin. Drinking of saccharin in turn elevated the mRNA levels of

orexin and NPY, but not MCH. Pre-treatments of naloxone, an opioid antagonist, blocked the orexigenic effects of orexin and NPY. Specific gastric motor responses were induced by central administration of orexin-A and NPY (Kobashi et al., 2003; 2006), however, MCH did not induce such responses. These results suggest that the over-consumption promoted by sweet and palatable tastes is attributed to 1) the activation of orexigenic neuropeptides, such as orexin and NPY, 2) the involvement of the opioid system, and 3) the enhanced activation of digestive functions.

A model of overeating

Fig. 2 summarizes the interconnections among the phases of palatability-induced ingestive behavior. The neural information of preferable taste, most typically sweet taste, is hedonically evaluated as palatable with the participation of brain substances such as benzodiazepine derivatives, β-endorphin and cannabinoids. Then the reward system is activated for motivation to acquire the palatable edible with the participation of various neurotransmitters mostly including dopamine. The output of the reward system is sent to the hypothalamus, mainly to the feeding center, releasing orexigenic neuropeptides (especailly NPY and orexin). The ingestion stops eventually with the activation of the satiety center accompanying the actions of various chemical mediators such as insulin, leptin, histamine, anorexigenic neuropeptides and blood glucose. The flow, however, is not in such a simple one-way direction. It is known that chemicals interact with each other especially within the top three phases in the figure as indicated by arrows. Moreover, sweet taste information may activate each of the upper 3 phases in parallel to release directly the chemicals concerning palatability, motivation and eating. Consequently, the information goes round and round before reaching the satiety center, which is a major reason why animals are highly motivated to over-consume palatable foods and/or fluids.

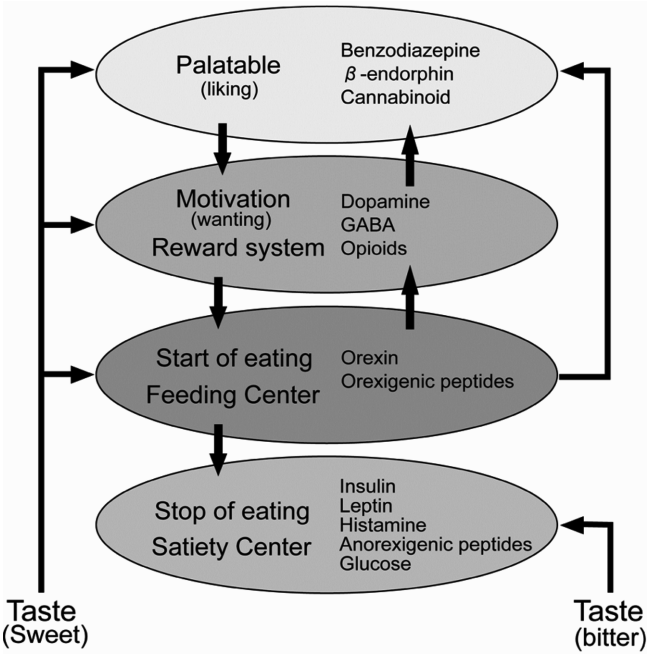

Fig. 2. Involvement of different neuroacitive substances in the brain in phases of taste-elicited ingestive behavior such as liking, wanting, feeding and satiety. Information of palatable taste (e.g., sweet) is related to liking, wanting and feeding, while aversive taste (e.g., bitter) is sent to the satiety center to stop ingestion. From Yamamoto (2008).

Learning and memory of taste

Once the flavor of the ingested food is associated with an appetitive (e.g., satiation with pleasure) or aversive (e.g., malaise with displeasure) signal, the animal reacts to its subsequent exposure by increasing or decreasing ingestion to the food. These two types of association learning (preference learning vs. aversion learning) are basic learning and memory phenomena, leading selection of food and proper food intake. Neural mechanisms of the aversion learning will be described.

Conditioned taste aversion (CTA)

When ingestion of food (conditioned stimulus, CS) is followed by malaise (unconditioned stimulus, US) such as gastrointestinal disorders and/or nausea, the association learning between the CS and US is quickly established, and animals remember the taste for a long time, and reject its ingestion at subsequent exposures (Garcia et al., 1955; Bures et al., 1998), a phenomenon called CTA. After the acquisition of CTA to a CS, the taste quality may not change, but the hedonic aspect changes drastically from positive to negative. According to previous findings, behavioral and neural characteristics of CTA can be expressed by the following 5 items: 1) alertness (novelty of the CS), 2) association between the CS and US, 3) avoidance, 4) aversion (hedonic shift from positive to negative) and 5) augmentation of responses to the CS.

Alertness (novelty of the CS)

It is well documented that strong CTA can be acquired when the CS is novel rather than familiar. Our recent study suggests that the CGA plays an important role in judging whether the CS is novel or familiar. Familiarity information is stored in the CGA which sends the information to the subcortical taste relay stations (Yamamoto et al., 2009). Novelty plays a key role in alerting animals to be cautious toward the food (neophobia).

Association between the CS and US

Long-term potentiation occurs in the basolateral nucleus of the amygdala (BLA) in response to a single electrical stimulation of the parabrachial nucleus (PBN). When we use fairly a large electrode, both gustatory and general visceral

routes are stimulated, and activity of mass neurons can be recorded as evoked potentials. After repetitive stimulation of the PBN, the evoked potential to single stimulation of the PBN is potentiated by more than 50% of the original response (Yamamoto and Yasoshima, 2007). Once a paring of the CS and US occurs, the established long-term potentiation to the CS is the basis of the aversive learning. In fact, FOS immunohistochemistry analysis also shows that sucrose CS induced strong activation of BLA neurons to re-exposure of the CS after the acquisition of CTA (Yasoshima et al., 2006).

Concerning the role of amygdala in CTA, a number of studies have dealt with the functions of the amygdaloid subnuclei in the formation of CTA. Although the studies have yielded inconsistent behavioral results, overall electrolytic or excitotoxic lesions show little, if any, involvement of the CeA in CTA (Yamamoto et al., 1995; Morris et al., 1999). Our previous lesion-behavioral studies (Yamamoto et al., 1995) showed that lesions of the CeA had little effects on CTA, and lesions of the BLA severely impaired CTA.

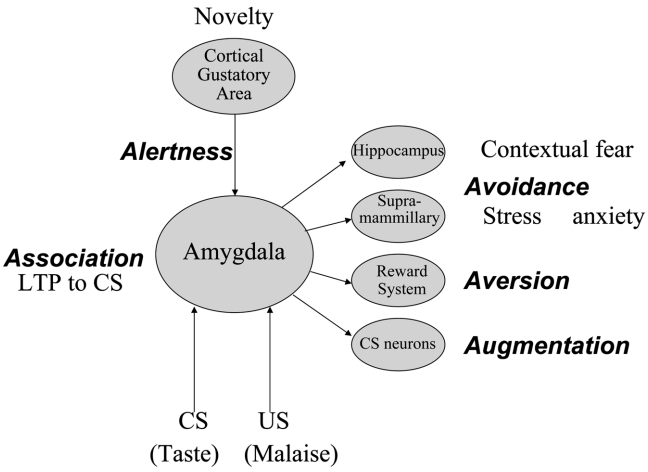

Fig. 3. Behavioral and neural characteristics of conditioned taste aversion. CS, conditioned stimulus; US, unconditioned stimulus. See text for details.

Avoidance

We found that the supramammillary nucleus (Yasoshima et al., 2005), thalamic paraventricular nucleus (Yasoshima et al., 2007), extended amygdala (Yasoshima et al., 2006) and NAcb (Yasoshima et al., 2006) were activated by retrieval of the CS after the acquisition of CTA. The former two regions are suggested to be involved in the expression of anxiety and psychological stress, and Yasoshima et al. (2005) have suggested that the supramammillary nucleus is activated by memory-elicited discomfort during retrieval of CTA.

Aversion (hedonic shift from positive to negative)

The latter two regions, the extended amygdala and NAcb, are involved in the reward system where CS information from the BLA reaches the NAcb directly or via the extended amygdala. The CS induced strong activity in the BLA where little activity was induced by the CS in control animals, suggesting a key role of the BLA in the formation of CTA. The reward system may be involved in aversive reactions to the CS after the acquisition of CTA. To elucidate the role of the VP in the expression of CTA, Inui et al. (2007) examined the effects of microinjections of a $GABA_A$ receptor antagonist, bicuculline, on the intake of CS in a retrieval test. They showed that the blockade of $GABA_A$ receptors in the VP by microinjections of bicuculline disrupted the retrieval of CTA, and have suggested that this is due to elimination of aversive responses to the CS. This finding suggests that the GABAergic neurotransmission in the VP is involved in expression of aversive responses to CS, we actually confirmed the increase of the level of extracellular GABA release in the VP using microdialysis technique (Inui et al., 2009). We conclude from these findings that the CS presentation after acquisition of CTA increase the extracellular GABA release in the VP through the activation of the NAcb receiving the amygdaloid input, inducing the expression of aversive responses to the CS and the inhibition of consumption of the CS.

Augmentation

Perceived intensity of the CS becomes stronger after the acquisition of CTA. Shimura et al. (1997) recorded neuronal responses to taste stimuli from the PBN of anesthetized rats. Animals were separated into two groups: the CTA group that had acquired a taste aversion to 0.1 M NaCl (CS) by paired presentation of an i.p. injection of LiCl (US), and the control group without CTA experience. Taste-responsive neurons in the CTA group showed larger responses to NaCl than in the control group. Tokita et al. (2004; 2007) found that the enhanced responses to the CS (0.1 M NaCl) were observed exclusively in amiloride-sensitive NaCl-best neurons, but neither in amiloride-insensitive NaCl-best nor any other best neurons. They have suggested that amiloride-sensitive components of NaCl-best neurons play a critical role in the recognition of the distinctive taste of NaCl. Not only PBN neurons, but CGA neurons (Yamamoto et al., 1989; Yasoshima and Yamamoto, 1998) and amygdaloid neurons (Yamamoto and Fujimoto, 1991; Yasoshima et al., 1995) exhibit enhanced responses to the CS after CTA acquisition. Augmentation of CS responses enables the animal to facilitate detecting and avoiding the harmful substance.

Summary

As shown in Fig. 3, CS-US association leading to long-term potentiation in the amygdala, especially in the BLA, is the basis of establishment of CTA. The novelty of the CS detected by the CGA may be supportive in CS-US association. After the association, CS input is conveyed through the amygdala to different brain regions including the hippocampus for contextual fear formation, to the supramammilary and thalamic paraventricular nuclei for stressful anxiety or memory dependent fearful or stressful emotion, to the reward

system to induce aversive expression to the CS, or hedonic shift from positive to negative, and to the CS-responsive neurons in the gustatory system to enhance the resposiveness to facilitate to detect the harmful stimlus.

Conclusion

Taste information is processed neurally in each taste-related region of the brain for rapid recognition of its quality, intensity and reflex reactions. Taste information also influences levels of neurochemicals in the brain such as β-endorphin, dopamine and orexigenic neuropeptides corresponding to palatability evaluation (liking), motivation (wanting) and ingestion (eating), respectively. Although a basic framework has been disclosed as summarized in this article, further studies are necessary for more profound understanding of the taste-mediated behaviors.

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