Neural substrates for the processing of cognitive and affective aspects of taste in the brain

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Summary. Taste is unique among the sensory systems in that, besides its recognition of quality, it is innately associated with hedonic aspects of reward and aversion. This review of the literature will show how taste information is conveyed through the central gustatory pathways to the cortical gustatory area and is processed in terms of qualitative and quantitative aspects. Taste information is also sent to the reward system and feeding center via several brain sites including the prefrontal cortex, insular cortex, and amygdala. The reward system contains the ventral tegmental area, nucleus accumbens, and ventral pallidum; it finally sends information to the lateral hypothalamic area, the feeding center. The dopamine 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. In the last section, the neural substrate of learning and memory of taste is introduced and the biological mechanisms are elucidated.

Introduction

When we start eating our favorite food, we recognize it by discriminating its quality and quantity on the basis of a variety of sensations—including taste—and then evaluate it to be delicious. This positive hedonic characteristic will motivate us to eat more, and the jaw and tongue move rhythmically with salivary secretion and active gastrointestinal functions to ingest the food. Eventually, the ingestive behavior finishes 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 good experiences, e.g., on the basis of association learning between taste perception and nutritive postigestional effects. Conversely, even favorite foods can become aversive and avoided as a consequence of an unpleasant experience including postigestional malaise.

The above-mentioned taste-mediated behaviors are the results of the processing of the sensory information in the brain, especially taste information, arising from the oral cavity. In this article, the literature will be reviewed regarding the cognitive and affective aspects of taste; the underlying anatomy, neural substrates, and chemical mediators in the brain are discussed. Finally, learning and memory processes of taste on the basis of pleasant and unpleasant experiences are also discussed.

1. Anatomy of the taste and reward pathways

Central gustatory pathways have been well studied and documented in monkeys (Rolls, 2004) and rodents, especially in rats (Norgren, 1995). Figure 1 shows a schematic diagram of some of the gustatory and related pathways in rats. Branches of the facial (chorda tympani...
and greater superficial petrosal), glossopharyngeal, and vagus (superior laryngeal) nerves, which synapse with receptor cells in the taste buds, convey taste messages to the first relay nucleus, the rostral part of the nucleus of the tractus solitarius (NTS). The second relay nucleus for ascending taste inputs is the parabrachial nucleus (PBN) of the pons. The third relay station is the parvocellular part of the ventralis posteromedial thalamic nucleus (VPm). This thalamic nucleus projects to the cortical gustatory area in the insular cortex (IC). In monkeys, however, ascending fibers of neurons in the gustatory area of the NTS directly reach the VPm, bypassing the PBN (Beckstead et al., 1980). It is known that general visceral inputs also project in a similar fashion to the brain regions in parallel with the gustatory projections described above.

The neural pathway of the brain reward system has also been well studied and documented (Berridge and Robinson, 1998; Wise, 2002 for reviews). As shown in Figure 1, the essential components are the ventral tegmental area (VTA) of the midbrain, the origin of the mesolimbic dopamine system, the nucleus accumbens (NAc) of the ventral forebrain, an essential interface from motivation (e.g., palatability) to action (e.g., eating), and the ventral pallidum (VP) situated between the NAc and lateral hypothalamus (LH), known as the feeding center.

It is not fully understood how the taste system interacts with the reward and feeding system. The amygdala

**Fig. 1.** Diagram of connections from the taste system to the reward system and feeding center. NTS: nucleus of the tractus solitarius, PBN: parabrachial nucleus, VPm: parvocellular part of the ventralis posteromedial thalamic nucleus, IC: insular cortex, PFC: prefrontal cortex, AMY: amygdala, VTA: ventral tegmental area, NAc: nucleus of accumbens, VP: ventral pallidum, LH: lateral hypothalamic area.

**Fig. 2.** Photomicrographs showing Fos-LI in the rat parabrachial nucleus (PBN). Representative sections showing (A) the left PBN stained with cresyl violet without Fos-LI, (B) showing Fos-LI after ingestion of 0.1M NaCl mainly in the central medial subnucleus (cms), and (C) after an intraperitoneal injection of 0.15M LiCl (2% volume of the body weight) in the external lateral subnucleus (els). BC: brachium conjunctivum, MeV: mesencephalic nucleus of the trigeminal nerve. Bars = 200 μm (A and C), 100 μm (B)
(AMY)—including the central and basolateral nuclei, the prefrontal cortex (PFC)—including the ventrolateral (or anterior sulcal), and the dorsomedial cortices and IC are the candidates for the interfaces between the two systems. The gustatory IC sends axons to the PFC (Saper, 1982; Shi and Cassell, 1998), and the dorsomedial PFC neurons actually respond to gustatory stimuli (Lukats et al., 2002; Karadi et al., 2005). Among other structures, the PFC is interconnected with the feeding-related subcortical areas such as the basol forebrain (Divac et al., 1978), amygdala (Perez-Jarana and Vives, 1991), LH (Kita and Oomura, 1981), VTA (Divac et al., 1978; Kosobud et al., 1994), and NAc (Brog et al., 1993). Behavioral studies have shown that the PFC is associated with various mechanisms in the central feeding control, e.g., lesions of the dorsomedial PFC result in finickiness (Kolb and Nonneman, 1975) and impairment of conditioned taste aversion (Hernadi et al., 2000; Karadi et al., 2005), while lesion and electrical stimulation of the ventrolateral PFC induce feeding disturbances (Brandez and Johnson, 1978; Kolb and Nonneman, 1975) and feeding (Bielajew and Trzcinska, 1994), respectively.

2. Discrimination of taste quality

One issue concerning the anatomical basis for the discrimination of taste quality is whether neurons responsive to each of the basic tastes are intermingled or spatially localized in each of the cortical and subcortical taste areas.

Using the immunostaining method for the immediate early gene c-fos as an anatomical marker of activated neurons, we have suggested that neurons are functionally located in terms of taste quality and hedonics in the PBN: we localized c-fos-like immunoreactivity (Fos-LI) in the PBN after the ingestion of various taste stimuli with different qualities and different hedonic values (Yamamoto et al., 1993; 1994a). The distribution of the evoked expression of Fos-LI was immunohistochemically examined in the PBN of water-deprived rats after the free ingestion of palatable liquids and after the intraoral infusion of aversive taste solutions including bitter substances. Fos-LI neurons were shown in the external lateral subnucleus (els), external medial subnucleus (ems),
responses (Yamamoto et al., 1988, 1989a; Hanamori et al., 1998), temporal responses (Katz et al., 2001), anticipation (Yamamoto et al., 1988), and familiarity (Bahar et al., 2004).

In an attempt to quantify the single neuron responses and their recorded sites in the GC of anesthetized rats, Yamamoto et al. (1985a) partitioned the GC into 14 blocks. When the mean magnitude of the responses of GC neurons in each block to taste stimulation is rank-ordered in four grades, different patterns of regional responses can be obtained for sucrose, NaCl, HCl, and quinine, indicating a possible existence of chemotopy (Fig. 4). 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 evenly distributed within the GC. Considering that the chemotopy might 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,b).

Yamamoto et al. (1989) further recorded single GC 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 located in this order from rostral to caudal within the GC. Such a relative chemotopic organization of taste responsiveness is similar to the above-mentioned results obtained in anesthetized rats.

The above results from the electrophysiological experiments on the existence of chemotopy and implications of its importance in taste quality discrimination have recently been confirmed with the in vivo optical imaging technique in rats (Accolla et al., 2005) and guinea-pigs (Yoshimura et al., 2005). Sugita and Shiba (2005) used a genetic approach to visualize the neuronal circuitries of bitter and sweet tastes and found that the gustatory positions of neurons in each of the NTS, PBN, VPMPc and GC were organized with sweet inputs rostral and with bitter inputs caudal in mice. In humans, in spite of the limitations of analysis due to the anatomical position and small size of the primary GC in humans, Schoenfeld et al. (2004) have reported the possible existence of chemotopy i.e., a 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.
3. Neural substrate of reward and feeding

It is well documented that the brain reward system is neural substrates for the intracranial self-stimulation phenomena (Olds and Milner, 1954) and the rewarding effects of addictive drugs. The dopamine system, arising from dopaminergic neurons in the VTA to terminate in the NAc, has been shown to play an important role in natural — such as food and sex — as well as drug rewards (Wise, 2002; Berridge and Robinson, 1998 for a review). For the convenience of a better understanding of the following descriptions, essentially the same neural circuitries concerning the taste and reward systems are shown in a cartoon of the rat brain with the representative transmitters in Figure 5.

VTA

It is well known that dopamine affects feeding behavior (Blackburn et al., 1992 for a review). Early studies suggested that the dopamine receptor blockade reduced the rewarding impact of hedonic stimuli, including food (Wise, 1982). However, taste reactivity analyses have shown that dopamine is less likely involved in modifying the palatability. Positive hedonic reactions to sucrose were not suppressed relative to control levels even in aphagic rats in which dopamine was depleted by 95-99% (Berridge et al., 1989; Berridge, 1996). Conversely, aversive reactions to bitter solutions were unaltered by the selective dopaminergic lesions.

Electrophysiological experiments also suggest that dopamine neurons in the mesolimbic system are less related to the evaluation of taste palatability, i.e., dopamine neurons in the midbrain including the VTA of the monkey appear to encode a reward prediction rather than reward per se (Ljungberg et al., 1992). Recently, we have found that more than half of the neurons recorded in the VTA of freely behaving rats change their firing during the licking of a liquid reward (Shimura et al., 2005). Since there is no difference in the responsiveness to taste solutions and water, these neurons may be involved in fluid reward rather than the hedonic evaluation of taste.

Shimura et al. (2002) showed that the dopamine system interacts with benzodiazepine and/or opioid systems to exhibit the normal intake pattern of palatable fluid. Lesions of the VTA suppressed the consumption of a preferred sucrose or NaCl solution without influencing the intake of other tastes or water. Systemic injections of the benzodiazepine agonist, midazolam, significantly facilitated the consumption of a preferred sucrose in sham control but not in VTA-lesioned rats. Midazolam did not affect the intake of an aversive quinine solution in both lesioned and sham animals. Moreover, while the systemic administration of morphine, an opioid agonist, selectively increased the intake of a sucrose solution without affecting the intake of a quinine solution in control rats, the intake of both sucrose and quinine solutions remained unchanged by morphine injections in lesioned rats. These results suggest that the dopaminergic mediation is required for the normal expression of both benzodiazepine- and opioid-induced overconsumption of
palatable fluid. 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. In fact, hyperdopaminergic dopamine transporter knockdown mutant mice have a stronger "wanting" for a sweet reward in a runway task (Pecina et al., 2003). However, a sucrose taste fails to elicit higher orofacial "liking" reactions from mutant mice in an affective taste reactivity test. On the other hand, since sucrose sham-feeding proportionally increases dopamine levels in the NAcB depending on the concentration of sucrose (Hajnal et al., 2004), the dopamine system seems to be implicated in a reward effect of taste palatability.

**NAcB**

The NAcB is composed of two major subregions, the core, and the shell extending medially, ventrally, and laterally around the core. The functions of core and shell subregions are suggested to be different on the basis of distinctive anatomical profiles (Heimer et al., 1991).

The NAcB is 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. For example, microinjections of an opioid agonist, DAMGO, induce a robust, dose-dependent increase in food intake (Bakshi and Kelley, 1993). It is noted that the hyperphagic effects of DAMGO are selective to highly palatable taste stimuli such as a high-fat diet (Zhang et al., 1998; Zhang and Kelley, 2000), sucrose solution (Zhang and Kelley, 1997), saccharin, NaCl, and ethanol solutions (Zhang and Kelley, 2002). In addition, the taste reactivity test of hedonic palatability has shown that morphine microinjections into the NAcB shell not only facilitate feeding but also selectively increase positive hedonic patterns of a behavioral affective reaction elicited by oral sucrose (Pecina and Berridge, 2000).

The NAcB receives afferent inputs from PFC and amygdaloid structures, which are primarily coded by glutamic acid (Robinson and Beart, 1988). Moreover, the feeding response is completely inhibited by the concurrent infusion of the GABA agonist muscimol into the LH, a major projection area of the NAcB shell (Maldonado-Irizarry et al., 1995). These findings demonstrate a selective role for non-NMDA receptors in the NAcB shell in ingestive behavior, and suggest an important functional link between the NAcB and LH. In addition, opioid mechanisms mainly in the NAcB are critically involved in the enhancement of taste palatability.

**VP**

The VP is a main output target of the GABAerigic neuron in the NAcB. From the VP, GABAergic efferents project to the LH (Groenewegen et al., 1993). Thus, the VP is anatomically interposed between the NAcB and LH. A blockade of GABA_A receptors in the VP with bicuculline elicits a strong feeding response in satiated rats without affecting water intake (Stratford et al., 1999). We have recently found that a microinjection of bicuculline into the VP enhances the intake of a preferred saccharin but not quinine solution and water, suggesting that the overconsumption by GABA blockade in the VP is specific to palatable tastes (Shimura et al., 2005).

The NAcB receives taste and visceral information through direct input from the NTS (Ricardo and Koh, 1978; Saper, 1982). The NAcB also receives taste information from the IC (Brog et al., 1993). The amygdala is likely an important source of information about taste and visceral functions to the NAcB. The IC-BLA-NAcB pathway has also been suggested in rats (McDonald and Jackson, 1987; McDonald et al., 1999).

**Hypothalamus**

Deliciousness of food plays an important role in the regulation of ingestion (Saper et al., 2002). It is known that animals prefer sweet and fatty edibles and often consume more than is needed for homeostatic repletion. A key site involved in the regulation for regulating ingestive behavior is the hypothalamus, where a number of neuropeptides that regulate appetite have been identified (Schwartz et al., 2000). 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. The 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 induced by central orexin-A and NPY are well known; however, MCH did not induce such responses. The central administration of orexin-A facilitated gastric emptying. These results suggest that the overconsumption promoted by sweet and palatable tastes is attributed to the activation of orexigenic neuropeptides—such as orexin and NPY—and a downstream opioid system together with enhanced
digestive functions (Kobashi et al., 2002; 2006).

4. Learning and memory of taste

Feeding behavior can be modified by learned associations between the gustatory experience of food following pleasant or unpleasant feelings.

Preference learning

Taste preference is classified into two types: attenuation of neophobia and conditioned taste preference. When an animal ingests a harmless new substance or liquid, it shows neophobia, i.e., cautious intake toward the first experience of new edibles, and it increases the consumption at subsequent exposures after learning that the substance is safe to consume. Through this process of the attenuation of neophobia (or learned-safety), foods can be classified as familiar-safe (Domjan, 1976; Nachman and Jones, 1974). Recent studies (Gutierrez et al., 2003; Bahar et al., 2004) show that the IC plays an important role in recognition whether the taste is familiar or novel.

When the ingestion of neutral or mildly aversive foods is associated with good postingestive visceral sensation, those foods become hedonically positive and preferred. This phenomenon is documented as conditioned taste preference (Fanselow and Birk, 1982). Previous studies demonstrated that rats could learn to prefer a taste solution paired with intragastric nutrient infusion (Elizalde and Sclafani, 1990), opiate administration (Mucha and Herz, 1986), or intracranial self-stimulation (Olds and Milner, 1954). Nutrients can have positive postingestive actions that influence food selection and increase consumption (Sclafani, 2004). The rewarding properties of food that promote eating and influence food choice result from the central association of orosensory and visceroeysory stimuli. Although the central neural mechanism of the association of taste with post-ingestive food reward is not fully understood, it is suggested that the PBN and LH play important roles in flavor preference learning (Sclafani et al., 2001; Touzani and Sclafani, 2001) with the involvement of the dopamine system (Azzara et al., 2001) and the opioid system (Azzara et al., 2000).
Aversion learning

In contrast to preference learning, when the ingestion of a substance is followed by a malaise such as gastrointestinal disorders and nausea, a learned association between the ingested substance and internal consequences is quickly established; animals remember the taste for a long time and reject its ingestion at subsequent exposures (Garcia et al., 1955). This phenomenon is called conditioned taste aversion (CTA) or taste aversion learning.

CTA has the following characteristics which are distinguished from classical Pavlovian conditioning or associative conditioning of flavor preferences (Bures et al., 1988): 1) Strong and long-lasting CTAs to novel taste stimuli can be established after a single pairing of conditioned stimulus (CS, taste) and unconditioned stimulus (US, nausea or illness). 2) Successful CTA can develop to the CS after a delay of as long as 4-12 h between exposure to the CS and delivery of the US. 3) CTA can be considered as a kind of fear learning and serves as a defense mechanism of the organisms to avoid the ingestion of potentially harmful toxins.

After the acquisition of CTA to an artificial sweetener, saccharin, this sweet and palatable substance still tastes sweet but changes to an aversive one. Taste quality may not change, but the hedonic aspect changes drastically. This fact may indicate that there exist separate neural representations of the sensory aspect and the hedonic aspect in the structures in the gustatory pathway (Sowards, 2004 for a review). The neural substrate and the molecular mechanisms of CTA have recently been well studied (Yamamoto et al., 1994b; Bures et al., 1998; Bermudez-Rattoni, 2004 for reviews; Yasoshima et al., 2006a,b).
Intensity change

Shimura et al. (1997) recorded neuronal responses to taste stimuli from the PBN of the rat under deep urethane anesthesia. Animals were separated into two groups: a 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 a 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) 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. Electrical stimulation of the central amygdaloid nucleus (CeA), but not the GC, produced an excitatory effect in significantly more neurons in the CTA group than in the control group. They have suggested that CTA conditioning uses an effective CeA input to modulate the activity of gustatory neurons in the PBN, and further 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 GC neurons (Yamamoto et al., 1989; Yasosima and Yamamoto, 1998) and amygdaloid neurons (Yamamoto and Fujimoto, 1991; Yasosima et al., 1995) exhibit enhanced responses to the CS after CTA acquisition.

Hedonic shift

We have been exploring which brain regions are selectively activated by re-exposure to the CS in conditioned rats by mapping Fos-LI as markers of neuronal activation (Yasosima et al., 2005; Yasosima et al., 2006a). The supramammillary nucleus (Yasosima et al., 2005), thalamic paraventricular nucleus (Yasosima et al., 2006a), extended amygdala (Yasosima et al., 2006a), and NAc (Yasosima et al., 2006a), are activated by retrieval of (or the first re-exposure to) the CS after the acquisition of CTA. The former two regions are suggested to be involved in the expression of anxiety and psychological stress (Beck and Fisiger, 1995; Ryabinin et al., 1995; Wirtshafter et al., 1998; Bulser and Deutch, 1999; Spencer and Houpt, 2001), and Yasosima et al. (2005) have suggested that the supramammillary nucleus is activated by memory-elicted discomfort during the retrieval of CTA. The latter two regions are involved in the reward system where CS information from the basolateral nucleus of the amygdala (BLA) reaches the NAc directly or via the extended amygdala (Groenewegen et al., 1999; Shammah-Lagnado et al., 1999; 2001). As shown in Figure 6, the CS induces strong Fos-LI in the BLA where little Fos-LI is induced by the CS in sham control animals, although the CS elicits Fos-LI in the CeA in both CTA and control groups, suggesting a key role for the BLA in the formations of CTA.

The NAc-VP-LH circuit is suggested to be involved in the acquisition and retrieval of CTAs (Mark et al., 1991; Turgeon and Reishstein, 2002; Fenu and Di Chiara, 2003; Ramirez-Lugo et al., 2006). To elucidate the role of the VP in the expression of CTA, Inui et al. (2005) examined the effects of microinjections of a GABAA receptor antagonist, bicuculline, on the intake of CS in a retrieval test. They showed that the blockade of GABAA receptors in the VP by microinjections of bicuculline disrupted the retrieval of CTA, and have suggested that this is due to the elimination of aversive responses to the saccharin CS.

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 (e.g., Kemble et al., 1979; Bermudez-Rattoni and McGaugh 1991; Yamamoto, 1994; Yamamoto et al., 1995; Morris et al., 1999), whereas the lesions of BLA in many cases disrupted or attenuated CTA (e.g., Aggleton, 1981; Fitzgerald and Burton, 1983; Simba et al., 1986; Yamamoto, 1994; Yamamoto et al., 1995; Rollins et al., 2001). The BLA may play an important role in CS-US association, and this nucleus is also suggested to be involved in neophobia requisite for CTA formation (Reilly and Bornova, 2005). Our previous lesion-behavioral studies showed that lesions of the CeA had little effect on CTA, and lesions of the BLA severely impaired CTA. (Fig.7)

Taking these results together with those from other literature, it is plausible that the BLA, which is known to be involved in the formation of fear learning (Maren and Fanselow, 1996 for a review), is important in the hedonic shift from palatable to aversive, and the central nucleus, which is known to receive taste inputs together with other sensory inputs, contributes to the enhancement of gustatory response to the CS (Shimura at al., 1997, 2002; Tokita et al., 2004), which enables the animal to facilitate detecting and avoiding harmful substances.

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