Brain Mechanisms of Sweetness and Palatability of Sugars

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Sugars are sweet and palatable. Sweetness is detected by the neural system, whereas palatability may be detected within the neural and chemical systems in the brain. Sweetness is discriminated from other tastes by different receptor sites on taste bud cells, a different subset of fibers in the taste nerves, and different projection zones in the brain. The benzodiazepine and opioid systems are related to palatability, and the dopaminergic system mediates the motivation to consume palatable food.

Key words: taste, brain, benzodiazepine, β-endorphin, dopamine

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The sensation of taste has both cognitive and hedonic aspects. The former involves qualitative discrimination among the tastes such as sweet, salty, sour, bitter, and umami, and their perceived intensity, whereas the latter is concerned with the development of preference or aversion to a taste. The hedonics of taste may accompany the appropriate ingestive behaviors such as initiation, enhancement, or cessation of eating and drinking. Sugars including glucose, fructose, maltose, and sucrose are sweet and very palatable. In this article, recent advances of peripheral and central neural mechanisms of sweet sensation and brain mechanisms of palatability are reviewed.

Reception and Transmission of Sweetness

It is well accepted that taste substances combine or interact with specific receptor sites on the apical membrane of taste bud cells. Treatment of the tongue with gymnemic acid, an extract from leaves of plants, *Gymnema sylvestre*, selectively inhibits the sensation of sweetness. This finding suggests that the sweet-taste receptors on the surface of taste bud cells are different from the receptors for other taste stimuli. Another important finding was that a proteolytic enzyme applied to the dorsal tongue almost completely suppressed sweet taste,[1] indicating that the sweet-taste receptors consist of proteins. In accordance with these suggestions, recent progress in molecular biology and genetics has finally revealed a candidate, T1R3 (a member of T1R family), for the sweet-taste receptors in 2001.[2] More recently, Nelson et al.[3] showed that the Sac locus (a single principal locus in mice chromosome that influences the responses to sweet substances including saccharin) encodes T1R3; further they demonstrated that T1R2 and T1R3 combine to function as a sweet-taste receptor.

Sweet-tasting substances, including various sugars, synthetic sweeteners such as saccharin and cyclamate, and some amino acids such as glycine and alanine, bind to the sweet-taste receptors that are coupled to guanine-nucleotide-binding proteins (G-proteins). When activated, G-proteins stimulate second-messenger systems in the cytoplasm to depolarize receptor cells.[4] Depolarization of cells induces a rise in intracellular free Ca^{2+}, which is crucial for releasing neurotransmitters. Afferent fibers in the taste nerves, which have synaptic contacts with taste cells, are then excited to transfer sensory information of sweetness to the central nervous system. According to the labeled-line theory,[5] this information is encoded and transmitted by a specific subgroup of fibers that are more responsive to sucrose than to the four other basic taste stimuli (NaCl [salty], HCl [sour], quinine [bitter], and monosodium glutamate [umami]). These fibers are called sucrose-best fibers. Sweetness and palatability are perceived after the brain processes the information conveyed via the sucrose-best fibers.

Central Projections of Sweet-Taste Information in Rats

c-Fos Immunohistochemical Study

Based on c-fos studies, Yamamoto et al.[6] found that neurons are functionally located in terms of taste quality and hedonics. c-Fos-like protein is localized in the pontine parabrachial nucleus (PBN), the second-order taste relay station, as an anatomic marker after ingestion of

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various taste stimuli with different qualities and different hedonic values.[6] c-Fos is a proto-oncogene, which is expressed in neurons following voltage-gated calcium entry into the cell. Neuronal excitation induces immunoreactivity to c-fos-like proteins in nuclei as a result of a rapid induction of c-fos. The distribution of evoked expression of c-fos was immunohistochemically examined in the PBN of water-deprived rats after free ingestion of palatable liquids and after intra-oral infusion of aversive taste solutions including bitter substances. c-Fos-like immunoreactive neurons were densely packed in the external lateral subnucleus (els), external medial subnucleus (ems), dorsal lateral subnucleus (dls), central lateral subnucleus (cls), and the central medial subnucleus (cms) depending on the kind of stimulation. The rostral part of the els may be related to general visceral input; the caudal part of the els, negative hedonics or aversive behavior; the dls, positive hedonics or ingestive behavior. Both the ems and the els may be related to taste information for bitter-tasting compounds and acids; the cls, for sucrose and saccharin; and the cms, for NaCl (Figure 1).

Electrophysiologic Study

Electrophysiologic studies provide evidence that sweetness is discriminated from other tastes in the primary taste area (PTA) of the cerebral cortex. The PTA receives gustatory inputs from the thalamic taste area. This thalamo-cortical network may be important for an epicritic aspect of taste sensation. In addition to the thalamic input, neurons in the parabrachial nucleus, central nucleus of the amygdala, and the lateral hypothalamic area project directly and indirectly to the PTA. These inputs suggest involvement of hedonic or affective aspects of taste perception in the PTA.

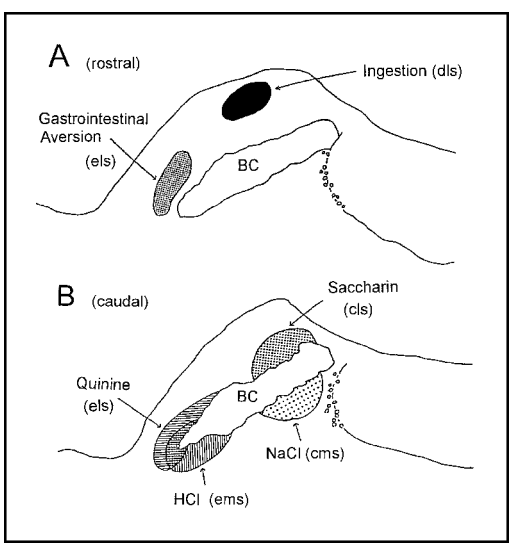

Figure 1. Schematic representation of functional segregation within the parabrachial nucleus of the rat. Els = external lateral subnucleus, ems = external medial subnucleus, dls = dorsal lateral subnucleus, cls = central lateral subnucleus, cms = central medial subnucleus, BC = brachium conjunctivum. Modified from Yamamoto et al.[6]

The PTA is in and/or near the insular cortex, which has direct relations with the viscero-autonomic system and motor system, both of which relate to feeding behavior in rats.[7] Recording of single neuron activities in the tongue somatosensory area and PTA revealed the existence of different types of neurons relating to various components of ingestive behavior such as attention, anticipation, jaw and tongue movements, and somatosensory inputs from the oral cavity, as well as qualitative and hedonic aspects of taste sensation.[8]

Taste-responsive neurons in the PTA show increasing or decreasing discharge rates while licking particular taste solutions. Their responsiveness differs greatly depending on the quality of the solutions the animal ingests.[9] When the taste-responsive neurons are 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 are located in this order from anterior to posterior within the PTA. Such a relative chemotopic organization in the PTA, or the anatomic separation of taste responsiveness among the four basic taste qualities, may play an important role in the cortical mechanism of taste quality discrimination. The "across-region response pattern" hypothesis,[10,11] assumes that taste-quality coding is based on the chemotopic organization (i.e., taste quality is coded by the pattern of relative amount of neural responses across the anatomically discrete areas rather than across the individual neurons).

Central Mechanisms of Palatability of Sucrose

To elucidate the brain mechanisms of palatability in animals, the authors employed pharmacobehavioral experiments in rats.[12] An intraperitoneal (i.p.) injection of midazolam, a benzodiazepine agonist, increased the intake of sucrose compared with saline-injected control rats in a dose-dependent manner, but had no effects on intake of a quinine solution. The same effect was observed after an i.p. injection of morphine. As shown in the next section, the level of beta-endorphin, an endogenous opioid, in rat cerebrospinal fluid increased markedly by ingestion of sucrose, but not quinine. Sucrose intake was decreased by naloxone, an opioid antagonist. These results suggest that intrinsic opioids play an important role in induction of palatability. The increasing effect of midazolam and morphine on sucrose intake was impaired by lesions of the ventral tegmental area (VTA), which contains dopaminergic cells. Lesions of interpeduncular pontine nucleus, which sends cholinergic fibers to the VTA, showed the similar lesion effects.

With these findings, we could propose the following possible brain mechanism (Figure 2). Taste information of sucrose reaches the amygdala through the taste pathway; the information is then conveyed to the arcuate nucleus of the hypothalamus to release beta-endorphin. One of the main targets of beta-endorphin is the nucleus accumbens. Output information from the nucleus accumbens finally reaches the VTA through the ventral pallidum and interpeduncular pontine nucleus. Dopaminergic fibers from the VTA project widely to the forebrain structures. Palatability and motivation to consume may occur within these chemical and neural systems.

Effects of Taste Stimulation on β-Endorphin Levels

Opioids are suggested to be involved in generation of palatability and facilitation of consumption of food and fluid. Yamamoto et al. measured the level of β-endorphin in the cerebrospinal fluid (CSF) and plasma after free drinking of water and taste solutions in rats.[13] When the water-deprived animals were allowed to drink 10 mL of water, the level of β-endorphin increased significantly 60 and 90 minutes after the start of drinking in both samples. Ingestion of 0.5 M sucrose or 0.005 M saccharin induced the strongest release of β-endorphin in CSF followed by 0.1 M NaCl, 0.1 mM quinine, and water. An intragastric infusion of 7 mL of water did not change the β-endorphin level. Essentially the same results were obtained for plasma samples except that NaCl and quinine solutions did not increase β-endorphin levels. In correspondence with these results, sucrose intake was accompanied by the increase of pro-opiomelanocortin messenger RNA in the arcuate nucleus of the hypothalamus.[14]

Sucrose became ineffective in releasing β-endorphin in both samples after the establishment of conditioned taste aversions to this taste stimulus. Consequently, it is obvious that the release of β-endorphin is positively correlated with the palatability of taste stimuli.

Human Cortical Responses to Taste Stimuli

Responses to taste in the central neurons system in humans can be recorded with the magnetoencephalography (MEG) technique, one of the noninvasive techniques monitoring brain functions.[15] A computer-controlled stimulus delivery system was used to apply taste solutions (0.5M sucrose [very sweet and palatable] and 0.05 M citric acid [very sour and aversive]) and rinsing water to a flow chamber covering the anterior part of the subject's tongue. Taste responses were localized in the operculoinsular cortex known as the PTA in primates,[16,17] and the mean latency of the response was approximately 260 msec and 440 msec after onset of stimulation with citric acid and sucrose, respectively. This statistically significant difference in latency may reflect the different transduction mechanism between sucrose and acid in taste cells. When the subject was stimulated with citric acid after chewing a piece of miracle fruit, which has the unusual property of changing sour taste of acids to sweet taste,[18] for 3 minutes and perceived sweet, the activity was also localization in the PTA, but with a longer latency of 410 milliseconds. This longer response latency after miracle fruit treatment corresponds to that of sucrose, suggesting that sweetness is detected in the PTA, that is, taste inputs to the PTA are directly related to the perception of the taste quality.

Taste-elicited MEG activities were also detected in the caudolateral orbitofrontal cortex (OFC) known as the

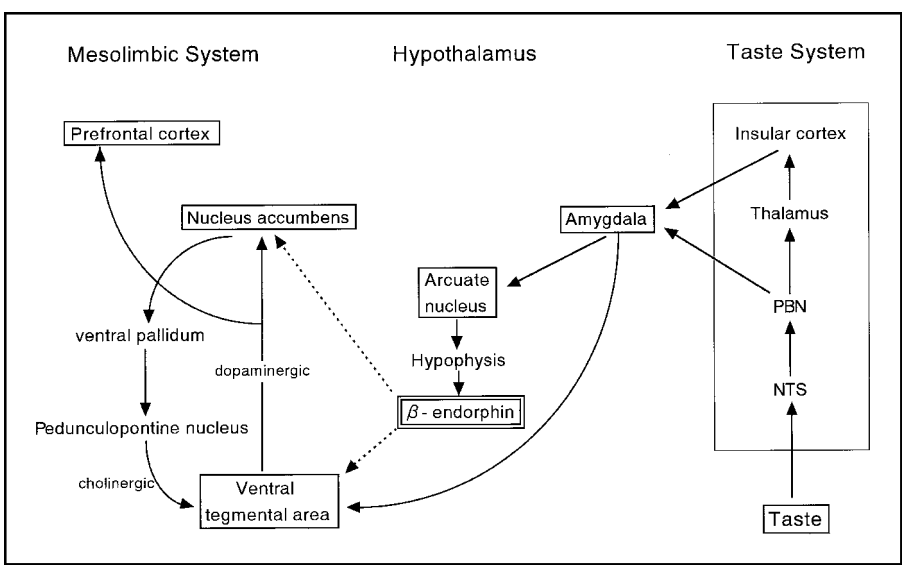

Figure 2. Possible neural networks concerning taste, palatability, motivation, and food intake. NTS = nucleus tractus solitarius, PBN = parabrachial nucleus.

secondary taste area.[16] Sucrose elicited the response with a latency of approximately 800 milliseconds in the right OFC and citric acid elicited the responses with a latency of approximately 500 milliseconds in the left OFC. When the subjects' to citric acid was sweet and pleasant after miracle fruit treatment, MEG activity was detected in the right OFC. Taste quality is perceived soon after the onset of stimulation and hedonic judgment comes later. Given the notion that the PTA is responsible for the perception of taste quality and the OFC is related to the hedonics of taste,[16,19] this phenomenon may correspond with brain function in that the PTA responds quickly depending on the kind of taste stimuli and the OFC responds rather slowly reflecting the hedonic assessment.

One other interesting finding is that various regions of the cortex besides the PTA and OFC are activated by taste stimuli.[20] Because the pattern of activation across the regions differs between sucrose and citric acid, there is a possibility that the palatability is reflected by the pattern of activity across several areas of the cerebral cortex. Activation of various parts of the brain may reflect the involvement of chemical systems influencing widespread areas of the brain.

The subcortical areas including the amygdala may also play important roles in evaluation and expression of taste hedonics.[19,21] The information is finally sent to the lateral hypothalamic area (i.e., feeding center) to enhance food intake or to the paraventricular and ventromedial hypothalamic nuclei (i.e., satiety center) to stop eating. Neurons containing orexins, neuroactive peptides known to increase food intake, are localized within and near the lateral hypothalamus.[22] We found recently that orexins increased fluid intake as well as food intake and that orexins elicited far more dominant intake of sucrose and saccharin solutions than other sapid solutions.[23] This suggests that orexins are concerned with a craving for sweet-tasting drinks and foods.

Conclusion

Sweetness is discriminated from other tastes by different receptor sites on taste bud cells, a different subset of fibers in the taste nerves, and different projection zones in the brain. The benzodiazepine and opioid systems are related to palatability, and the dopaminergic system mediates the motivation to consume palatable food. Glycemic carbohydrates represented by sucrose are highly caloric and very palatable. It is no wonder that most organisms accept these eagerly. Humans must have a strong will to control themselves to avoid over-consumption.

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