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Linking peripheral taste processes to behavior

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The act of eating and drinking brings food-related chemicals into contact with taste cells. Activation of these taste cells, in turn, engages neural circuits in the central nervous system that help animals identify foods and fluids, determine what and how much to eat, and prepare the body for digestion and assimilation. Analytically speaking, these neural processes can be divided into at least three categories: *stimulus identification*, *ingestive motivation*, and *digestive preparation*. This review will discuss recent advances in peripheral gustatory mechanisms, primarily from rodent models, in the context of these three major categories of taste function.

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Introduction

Our understanding of peripheral gustatory mechanisms continues to advance at a rapid pace. Ultimately, these neurobiological processes must be linked to behavioral outcomes. At times, such efforts have produced seemingly paradoxical results; for example, knocking out a taste receptor caused severe impairments in one behavioral task but not in another. To explain these apparent disparities, it is important to realize that there are at least three categories of taste processing [1]. *Stimulus identification* is the detection or discrimination of sensory signals arising from taste cell activation. *Ingestive motivation* involves processes that promote or discourage ingestion. *Digestive preparation* refers to feed-forward physiological reflexes that protect oral tissues, aid digestion, and facilitate homeostasis. It must also be recognized that behavioral responses to taste stimuli can be influenced by nongustatory factors, including olfactory, somatosensory, and visceral signals. We propose that integrating these perspectives into studies of taste function will help

establish more logical links between neural processes and taste-related behavior.

Stimulus identification

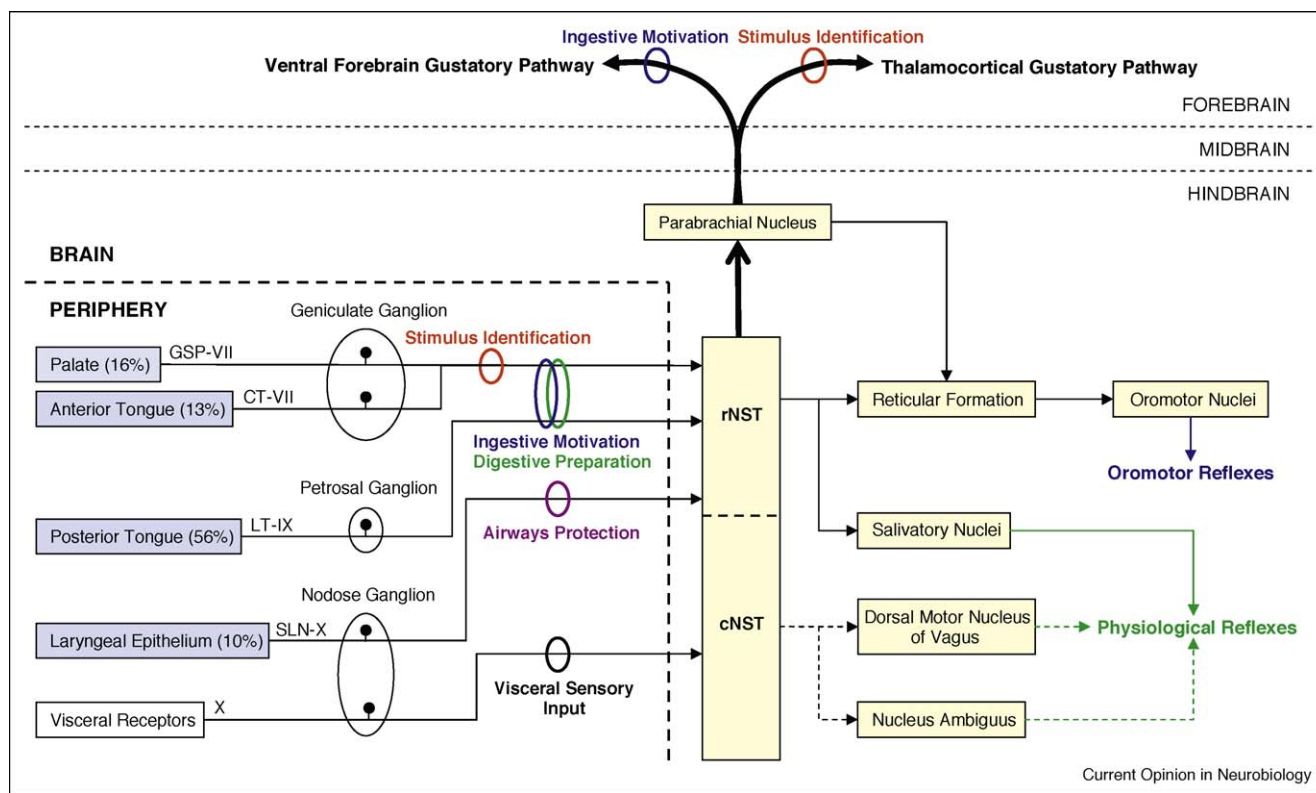
Stimulus identification refers to the ability of animals to discriminate between the gustatory signals generated by different taste stimuli. Such processes allow animals to learn about foods by associating particular tastes with other stimuli and/or outcomes, ultimately facilitating survival. In humans, stimulus identification can be assessed through verbal qualitative descriptors such as ‘sweet,’ ‘sour,’ ‘salty,’ ‘bitter’ and ‘umami.’ In nonverbal animals, more objective approaches, such as operant and classical conditioning procedures, must be used to draw inferences about whether the subject can identify and discriminate among taste compounds. When conditioning techniques are used toward this end, the taste stimuli serve as cues for other events, such as reward or punishment. This ensures that responses are not driven by an animal’s natural preference or aversion for a particular taste stimulus.

Salt taste transduction and stimulus identification

In rodents, salt taste transduction appears to occur through at least two ion channel receptors. One is specific for sodium (and lithium) salts and is suppressed by the epithelial sodium channel (ENaC) blocker amiloride (e.g. [2,3,4]). The other receptor is less cation-selective and is unaffected by amiloride ([5]; see also [6]). It is widely believed that the amiloride-sensitive receptor is an ENaC [7], and that it mediates the sodium-selective responses of the ‘specialist’ neurons in the chorda tympani nerve and its ganglion (Figure 1). Indeed, although amiloride treatment of the tongue only partially suppresses sodium responses in the whole chorda tympani nerve (because the amiloride-insensitive salt transduction remains), it severely attenuates or abolishes sodium responses in the sodium-specialist neurons in the geniculate ganglion [8–10] and eliminates the ability of rodents to recognize sodium and distinguish it from other cations (e.g. [11–13]). These findings provide a compelling link between peripheral gustatory mechanisms of transduction, neural signaling, and sodium identification (see [14]).

The identification of the ion channel receptor(s) underlying the amiloride-insensitive component of salt taste transduction has been more elusive, but recent reports in rodents implicate a variant of the vanilloid receptor TRPV1 [15]. For instance, amiloride treatment eliminates the tonic portion of the chorda tympani nerve response to NaCl in TRPV1 knock-out (KO) mice; in WT mice it merely reduces the tonic response

Figure 1



Schematic representation of the major gustatory input pathways from the periphery (lower left-hand side) to the rostral nucleus of the solitary tract (rNST) and their associated local hindbrain circuits (right side) and ascending forebrain projections in the rodent model (see [61]). For simplicity, descending projections from forebrain taste structures to hindbrain nuclei are not shown. Percentages in light blue boxes indicate approximate proportion of total oral taste buds found in each oral region with remaining taste buds scattered in other areas of the oropharyngeal epithelium. The gustatory afferent fibers of the VIIth, IXth, and Xth cranial nerves terminate in a rough orotopic fashion with significant overlap in the rNST. The caudal NST (cNST) receives sensory input from the viscera through the vagus nerve (X). The gustatory functions associated with the depicted circuits and structures remain largely speculative. Nerve transection studies indicate that input from the gustatory branches of the facial nerve (VII), but not the IXth cranial nerve, are necessary for stimulus identification (red text and symbols) (see [62,63]). Ingestive motivation (blue text and symbols) appears to depend on input from the VIIth and IXth cranial nerves. There is evidence supporting the necessity of the chorda tympani branch of facial nerve (CT-VII) in the maintenance of cephalic-phase insulin responses [56*], and it is possible that other nerve branches are critical for other taste-evoked physiological reflexes. Recent findings have revealed at least two classes of neurons in the geniculate ganglion. One class synapses on rNST neurons that project to the parabrachial nucleus; the other class synapses on rNST neurons that project to the reticular formation [64*]. This segregated projection pattern is consistent with the hypothesis that different peripheral afferent taste fibers may contribute differentially to various gustatory functions. The taste buds of the laryngeal epithelium are innervated by the superior laryngeal branch of the vagus (SLN-X); based on their response properties and location, the laryngeal taste buds are thought to help protect the airways (e.g. [68]). The efferent limb of such protective reflexes involves several of the medullary structures shown. Neurons in the rNST project to the parabrachial nucleus and also contribute to local medullary circuits that contribute both to salivation (e.g. [66]) and taste-evoked oromotor reflexes (e.g. [65]). The medullary reticular formation also receives forebrain projections (not shown) that play a role in voluntary ingestion (ingestive motivation). The central circuitry subserving other taste-triggered physiological reflexes, including insulin release, remains to be fully described (dashed line). Finally, although there is substantial evidence supporting the role of the ventral forebrain gustatory pathway in ingestive motivation, the hypothesized role of the thalamocortical gustatory pathway in stimulus identification [67] awaits explicit behavioral tests. GSP-VII: greater superficial petrosal branch of the facial nerve; LT-IX: lingual-tonsillar branch of the glossopharyngeal nerve.

[15,16]. Unexpectedly, behaviorally assessed detection thresholds for NaCl [16,17] and KCl [16] in TRPV1 KO mice match those in WT mice, and amiloride treatment raises the NaCl threshold to similar degrees in both genotypes (although see [17]). Thus, even though the chorda tympani nerve response to NaCl + amiloride was more disrupted in TRPV1 KO mice than WT controls, a link to a behavioral outcome was not established. This is likely because there are other receptors in different taste bud fields (i.e. posterior tongue, palate, and laryngeal

epithelium), innervated by other nerves (i.e. glossopharyngeal, greater superficial petrosal, and superior laryngeal; Figure 1), which are sufficient to maintain stimulus detectability. It remains possible, however, that TRPV1 KO mice would display behavioral differences from their WT counterpart if other taste functions were measured, including salt discrimination or salt responsiveness in a brief-access test. For instance, TRPV1 KO mice show altered preference-aversion functions to salts in long-term two-bottle tests, but these tests are often influenced

by postingestive factors [17]. A definitive conclusion awaits further testing.

T1Rs and detection of sugars and amino acids

T1R3 KO mice display severely blunted unconditioned licking responses to L-amino acids and sweeteners [18,19], but normal detection thresholds for both classes of stimuli [20^{••}]. The latter finding was unexpected because the T1R1 + 3 and T1R2 + 3 heterodimers are thought to be the principal taste receptors for L-amino acids and sweeteners, respectively [21[•]]. Thus, while the gene deletion appears to largely eliminate ingestive motivation for the stimuli, either the T1R2 subunit and/or other receptors are sufficient to enable the KO mice to detect these types of compounds (see [22]). This inference is consistent with the observation that the chorda tympani nerve in T1R3 KO mice still displays some responsiveness, albeit severely compromised, to high concentrations of sucrose [18,19,23]. Nevertheless, the finding that C57BL/6J mice did not discriminate sucrose from glucose or fructose [24[•]] supports the view that the T1R2 + 3 heterodimer, which has been shown to bind with all three of these sugars [22,25,26], is the principal receptor for 'sweet-tasting' ligands. This finding also suggests that sucrose, glucose, and fructose generate a unitary qualitative perception, at least from the standpoint of stimulus identification.

T2R coexpression patterns and discrimination of bitter-tasting ligands

The mere existence of separate molecular receptors does not guarantee that the ligands for those receptors will be behaviorally discriminable. For example, in rats and humans there are over two dozen taste receptors (T2Rs) that are thought to bind with bitter-tasting ligands. If a taste cell expresses one T2R, then it is likely that it expresses many others [27]. The degree of coexpression of T2Rs, although extensive, may not be complete ([28,29], but see [30]). For example, in rats, bitter-tasting ligands, such as quinine and denatonium, do not activate identical subsets of taste bud cells [31]. On the basis of these cellular data, one might predict that rats should be able to behaviorally discriminate between quinine and denatonium. This, however, does not appear to be the case [32]. Behavioral discrimination tasks suggest that the initial signals differentiating quinine from denatonium in the periphery converge downstream in the gustatory pathway, resulting in a unitary signal. Indeed, in rats, at the level of the parabrachial nucleus (Figure 1), a brainstem gustatory relay to forebrain structures, quinine and denatonium appear to stimulate activity in a similar subset of taste-responsive neurons [33]. Clearly, more behavioral work is needed with a broader array of compounds before definitive conclusions can be reached about whether rodents can discriminate bitter-tasting ligands [34].

It was recently reported that rats can discriminate nicotine from quinine in an operant taste discrimination task

[35]. These latter findings do not necessarily conflict with those from the study testing discrimination of quinine and denatonium [32]. Because nicotine can both stimulate nicotinic acetylcholine receptors and modulate certain ion channels [36], it may be activating a variety of taste receptor cell types, gustatory afferent fibers, and trigeminal free nerve endings. Accordingly, nicotine could generate a more complex oral sensation than quinine. This example illustrates two important points. When an animal successfully discriminates two taste stimuli, it is difficult to attribute the discrimination unambiguously to central taste processing. On the other hand, when an animal fails to discriminate two taste stimuli (provided that learning and concentration effects can be ruled out), this suggests that an equivalence exists between the indiscriminable stimuli somewhere in the nervous system.

Peripheral gustatory mechanisms and taste quality of fat

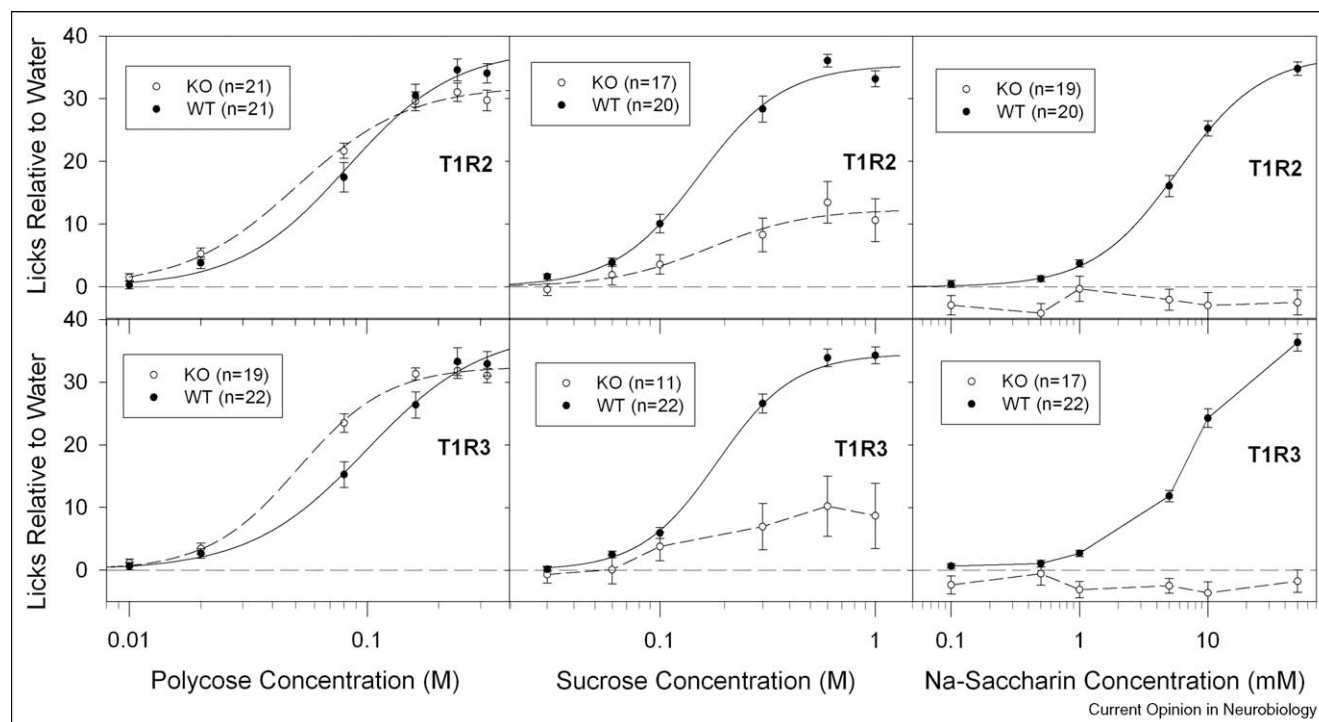
One of the growing controversies is whether fats generate a distinct taste quality. Prior work indicated that detection of fat was based on its ability to both alter the tactile properties of foods and retain food-related odors. There is accumulating evidence, however, supporting the involvement of the gustatory system. For instance, the CD36 fatty acid translocator is expressed in murine taste cells, and may serve as a receptor. This protein is necessary for normal responsiveness to fatty acids at both the cellular and behavioral (i.e. 30 min or 24-hour intake) levels [37,38^{••},39[•]]. Likewise, there is evidence that long chain unsaturated fatty acids can block delayed rectifying potassium (DRK) channels, which, in turn may bring taste cells closer to threshold and make them more responsive to other taste stimuli such as sugars and salts [40].

From a behavioral standpoint, rodents and humans can detect long chain fatty acids through oral mechanisms [41–43]. If a taste aversion is conditioned to linoleic acid, both rats and mice will avoid ingesting the same compound on future occasions [39[•],42,43]. Further, transection of the chorda tympani nerve in rats impairs long chain unsaturated fatty acid detection in rats [42,44]. Although these findings indicate that information in the chorda tympani nerve is necessary for detection to take place, it is unclear why the stimulation of the anterior tongue with linoleic acid fails to activate gustatory afferents in the chorda tympani nerve or geniculate ganglion [45,46]. Another conundrum is the exact definition of the perceptual qualitative nature of fatty acid taste. Although speculative, it is possible that there is no fat taste quality *per se*. Instead, the effects of fats on the gustatory system may be limited to activating the central neural circuits that subservise ingestive motivation and digestive preparation (see Figure 1 and below).

Ingestive motivation

The motivational function of taste has been referred to as affect, hedonics, palatability, and reward. All of these processes share the same fundamental property of facil-

Figure 2



Mean (\pm SE) licking responses (after subtracting responses to water) during 5-s trials to various concentrations of Polycose, sucrose, and sodium saccharin in a brief-access test by mice lacking either the T1R2 (top panels) or T1R3 (bottom panels) protein (KO: open circles) as well as by their wild-type controls (WT: closed circles) (from [48^{*}]). Knocking out the *Tas1r2* or *Tas1r3* genes eliminated concentration-dependent responses to sodium saccharin. The responses of the KO mice to sucrose were severely blunted relative to WT mice, but the KO mice did show some degree of responsiveness to high concentrations which were more evident in the subset of animals that were previously tested with Polycose. In contrast, KO mice displayed relatively normal concentration-dependent licking to Polycose. This latter finding suggests that either the T1R2 or T1R3 subunits alone are sufficient or that other receptors are involved in the maintenance of responses to some glucose polymers in the absence of either T1R2 or T1R3 (see also [47^{*}]). Reprinted with permission from the American Physiological Society.

itating or inhibiting ingestion. It is important to recognize that two taste compounds can be equally preferred or avoided but have distinct taste qualities. For instance, even though rats avoid high concentrations of quinine and NaCl, they can nevertheless discriminate the tastes of these stimuli.

T1Rs and the acceptability of carbohydrate stimuli

Deleting the genes encoding the T1R2 or T1R3 receptor subunits leads to profound deficits in responsiveness to sweeteners, as measured in brief-access lick tests [18]. Recently, however, it has become clear that not all carbohydrates require T1R2 or T1R3 to support normal taste-related acceptability. T1R2 KO and T1R3 KO mice each display normal concentration-dependent responsiveness to Polycose, a glucose polymer mixture, in brief-access tests [47^{*},48^{*}] (Figure 2). This indicates that glucose polymers can either bind with T1R2 (or T1R3) alone, or bind with a yet-to-be-identified taste receptor(s), and stimulate intake. Tests with T1R2 and T1R3 double-KO mice would help distinguish between these possibilities.

Peripheral gustatory mechanisms and the acceptability of fats

It is clear that the orosensory characteristics of fats have motivational salience to rodents. Indeed, rodents will lick for fats in a concentration-dependent manner [49]. An intact olfactory system is not required for those responses to be displayed [50], but the presence of CD36 and TRPM5 is necessary initially [39^{*},51^{*}]. Following repeated testing, however, CD36 KO or TRPM5 KO mice will begin to display responsiveness to fat stimuli presumably through an associative learning process by which the positive consequences of fat ingestion are paired with some detectable oral cue associated with the stimuli [39^{*},51^{*}].

When low concentrations of long chain unsaturated fatty acids (e.g. linoleic acid) were added to prototypical taste stimuli in brief-access tests, concentration–response functions of rats were shifted leftward, indicating that stimulus acceptability was enhanced [52]. This supports the hypothesis that fatty acids sensitize taste cells to other taste stimuli through their action on DRK channels. In

humans, however, long chain unsaturated fatty acids do not appear to alter threshold or suprathreshold sensitivity to taste stimuli [53]. It would be instructive to determine whether firstly, the addition of linoleic acid changes the hedonic ratings of taste stimuli so as to bring the human taste testing more in register with the brief-access lick tests in rats; or secondly, linoleic acid improves the detection thresholds for prototypical taste stimuli in rats when operant psychophysical procedures are used.

Digestive preparation

A third function of gustatory input is the activation of physiological reflexes that produce effects like delaying gastric emptying, protecting the oral cavity, facilitating digestion, and maintaining homeostasis. These are commonly referred to as cephalic-phase reflexes because they are triggered by the stimulation of head receptors. For instance, a recent study documented that bitter taste alone can delay gastric emptying in human subjects [54[•]]. This could have adaptive value in that it would both slow the rate at which an ingested toxin was absorbed and allow more time for emetic processes to expel the chemical culprit. These taste-triggered physiological effects have the potential to alter behavior.

Protection of the oral cavity

Many foods and beverages can damage the hard and soft tissues in the oral cavity. Taste-induced salivation plays a central role in mitigating these negative effects by reducing irritation to soft tissues, frictional wear of the tooth enamel, and acidic dissolution of tooth mineral. Damage to oral tissues is also reduced by the secretion of salivary proteins (e.g. proline-rich, anti-bacterial, and anti-fungal proteins) that help neutralize reactive chemicals and microorganisms in foods. A recent study [55] revealed that oral stimulation with chemicals representing different taste qualities stimulates the secretion of different quantities and types of proteins. More work is needed to determine the neural basis and functional significance of this latter observation.

Maintenance of homeostasis

Taste activates several physiological reflexes, which serve both to facilitate digestion and maintain homeostasis. For instance, oral stimulation with sweeteners but not salts, monosodium glutamate, or quinine activates a cephalic-phase insulin release (CPIR) in rats [56[•]] and humans [57]. Likewise, lingual stimulation with fats or fatty acids activates a pancreato-biliary response in wild-type mice, but not CD36 KO mice [37], and in humans elevates serum triglyceride levels [58] and induces release of pancreatic polypeptide [59]. Investigators recently demonstrated that the stimulation of the anterior tongue with glucose increased the sympathetic stimulation of the interscapular brown adipose tissue (BAT) depot in rats [60]. Given that BAT stimulation increases energy expenditure, it may aid in body weight regulation.

Conclusion

The three categories of taste function discussed here must have dissociable neural substrates at some level in the gustatory neuraxis (Figure 1) [61]. Although these substrates have yet to be clearly delineated, there are hints in the literature. For example, in rats, stimulus identification relies on input from the gustatory branches of the facial nerve, whereas taste signals carried by the glossopharyngeal nerve appear unnecessary to support this function [see [62,63]]. Neurons in the geniculate ganglion of the facial nerve of the rat can be divided into those that contribute input to the ascending gustatory pathway and those that contribute input to local brain-stem circuits through the reticular formation [64[•]]. Perhaps the former are involved largely with stimulus identification and ingestive motivation and the latter are involved with oromotor (e.g. [65]) and physiological reflexes (e.g. [66]). It remains to be seen whether taste-related neurons in the petrosal ganglion of the glossopharyngeal nerve can be similarly subdivided on the basis of their central anatomical fates. Finally, the ascending gustatory system of the rodent bifurcates at the level of the forebrain, and it has been a longstanding hypothesis that the thalamocortical branch is more involved with stimulus identification whereas the ventral forebrain branch is more involved with ingestive motivation [67]. While there is growing evidence supporting the latter, the former awaits to be explicitly tested.

As more is revealed about the neurobiological hardware of the gustatory system, it will be important for investigators to consider the multidimensional nature of taste function in their analysis and interpretation. Accordingly the use of a variety of complementary experimental approaches to study gustatory function will optimize the formation of links between neural processes and taste-related behavior.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Spector AC: **Linking gustatory neurobiology to behavior in vertebrates.** *Neurosci Biobehav Rev* 2000, **24**:391-416.
 2. Heck GI, Mierson S, DeSimone JA: **Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway.** *Science* 1984, **223**:403-405.
 3. Brand JG, Teeter JH, Silver WL: **Inhibition by amiloride of chorda tympani responses evoked by monovalent salts.** *Brain Res* 1985, **334**:207-214.
 4. Vandenbeuch A, Clapp TR, Kinnamon SC: **Amiloride-sensitive channels in type I fungiform taste cells in mouse.** *BMC Neurosci* 2008, **9**:1.

Using ion current signatures coupled with targeted expression of green fluorescent protein to distinguish between the three cell types in taste buds, the authors show that the taste bud cells (in the anterior tongue) with amiloride-sensitive currents are Type I. The fact that Type II cells, independent subsets of which express T2Rs (bitter) and T1Rs (sweeteners and amino acids), do not possess amiloride-sensitive currents provides an anatomical basis for the segregation of sodium-specific signals from the signals generated by ligands for these other taste receptors.

5. Yoshida R, Horio N, Murata Y, Yasumatsu K, Shigemura N, Ninomiya Y: **NaCl responsive taste cells in the mouse fungiform taste buds**. *Neuroscience* 2009, **159**:795-803.
 6. Lindemann B, Gilbertson TA, Kinnamon SC: **Amiloride-sensitive sodium channels in taste**. *Curr Top Membr* 1999, **47**:315-336.
 7. Shigemura N, Ohkuri T, Sadamitsu C, Yasumatsu K, Yoshida R, Beauchamp GK, Bachmanov AA, Ninomiya Y: **Amiloride-sensitive NaCl taste responses are associated with genetic variation of ENaC alpha-subunit in mice**. *Am J Physiol Regul Integr Comp Physiol* 2008, **294**:R66-R75.
- Amiloride treatment suppresses the integrated chorda tympani nerve response to NaCl much more in C57BL/6J mice compared with 129P3/J mice. This paper links this difference to a single nucleotide polymorphism in the gene encoding the α -subunit of the epithelial sodium channel (ENaC). This finding further implicates the ENaC as the principal sodium-specific receptor in rodents.
8. Ninomiya Y, Funakoshi M: **Amiloride inhibition of responses of rat single chorda tympani fibers to chemical and electrical tongue stimulations**. *Brain Res* 1988, **451**:319-325.
 9. Lundy RF Jr, Contreras RJ: **Gustatory neuron types in rat geniculate ganglion**. *J Neurophysiol* 1999, **82**:2970-2988.
 10. Hettlinger TP, Frank ME: **Specificity of amiloride inhibition of hamster taste responses**. *Brain Res* 1990, **513**:24-34.
 11. Spector AC, Guagliardo NA, St John SJ: **Amiloride disrupts NaCl versus KCl discrimination performance: implications for salt taste coding in rats**. *J Neurosci* 1996, **16**:8115-8122.
 12. Geran LC, Spector AC: **Anion size does not compromise sodium recognition by rats after acute sodium depletion**. *Behav Neurosci* 2004, **118**:178-183.
 13. Bernstein IL, Hennessy CJ: **Amiloride-sensitive sodium channels and expression of sodium appetite in rats**. *Am J Physiol Regul Integr Comp Physiol* 1987, **253**:R371-R374.
 14. Spector AC, Travers SP: **The representation of taste quality in the mammalian nervous system**. *Behav Cogn Neurosci Rev* 2005, **4**:143-191.
 15. Lyall V, Heck GL, Vinnikova AK, Ghosh S, Phan TH, Alam RI, Russell OF, Malik SA, Bigbee JW, DeSimone JA: **The mammalian amiloride-insensitive non-specific salt taste receptor is a vanilloid receptor-1 variant**. *J Physiol* 2004, **558**:147-159.
 16. Treesukosol Y, Lyall V, Heck GL, DeSimone JA, Spector AC: **A psychophysical and electrophysiological analysis of salt taste in Trpv1 null mice**. *Am J Physiol Regul Integr Comp Physiol* 2007, **292**:R1799-R1809.
 17. Ruiz C, Gutknecht S, Delay E, Kinnamon S: **Detection of NaCl and KCl in TRPV1 knockout mice**. *Chem Senses* 2006, **31**:813-820.
 18. Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, Ryba NJ, Zuker CS: **The receptors for mammalian sweet and umami taste**. *Cell* 2003, **115**:255-266.
 19. Damak S, Rong M, Yasumatsu K, Kokrashvili Z, Varadarajan V, Zou S, Jiang P, Ninomiya Y, Margolske RF: **Detection of sweet and umami taste in the absence of taste receptor T1r3**. *Science* 2003, **301**:850-853.
 20. Delay ER, Hernandez NP, Bromley K, Margolske RF: **Sucrose and monosodium glutamate taste thresholds and discrimination ability of T1R3 knockout mice**. *Chem Senses* 2006, **31**:351-357.

T1R3 knock-out mice had normal detection thresholds for sucrose and MSG (as assessed in a shock avoidance paradigm), and were able to discriminate between the two stimuli even when firstly, amiloride was added to the solutions to minimize sodium taste, and secondly, NaCl was added to sucrose to minimize the contribution of sodium ion in perfor-

mance. These findings suggest either that the T1R1 and T1R2 subunits of the T1R1 + 3 and T1R2 + 3 heterodimers, respectively, can provide a sufficient signal to maintain some taste function or that non-T1R receptors are guiding performance in this detection and discrimination task.

21. Chandrashekar J, Hoon MA, Ryba NJP, Zuker CS: **The receptors and cells for mammalian taste**. *Nature* 2006, **444**:288-294.
- This article offers a concise and well-written review of the major molecular discoveries of taste receptors and transduction intermediaries in the first half of this decade, as well as a discussion of their functional significance.
22. Nie Y, Vignes S, Hobbs JR, Conn GL, Munger SD: **Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli**. *Curr Biol* 2005, **15**:1948-1952.
 23. Ohkuri T, Yasumatsu K, Horio N, Jyotaki M, Margolske RF, Ninomiya Y: **Multiple sweet receptors and transduction pathways revealed in knockout mice by temperature dependence and gurnarin sensitivity**. *Am J Physiol Regul Integr Comp Physiol* 2009, **296**:R960-R971.
 24. Dotson CD, Spector AC: **Behavioral discrimination between sucrose and other natural sweeteners in mice: implications for the neural coding of T1R ligands**. *J Neurosci* 2007, **27**:11242-11253.
- A two-response operant taste discrimination procedure was used to show that C57BL/6J mice could distinguish sucrose from NaCl, L-serine, and L-threonine, but could not discriminate sucrose from fructose or glucose. The finding suggests that these three sugars produce a single qualitative taste perception.
25. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS: **Mammalian sweet taste receptors**. *Cell* 2001, **106**:381-390.
 26. Li XD, Staszewski L, Xu H, Durick K, Zoller M, Adler E: **Human receptors for sweet and umami taste**. *Proc Natl Acad Sci U S A* 2002, **99**:4692-4696.
 27. Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS: **A novel family of mammalian taste receptors**. *Cell* 2000, **100**:693-702.
 28. Matsunami H, Montmayeur JP, Buck LB: **A family of candidate taste receptors in human and mouse [see comments]**. *Nature* 2000, **404**:601-604.
 29. Behrens M, Foerster S, Staehler F, Raguse JD, Meyerhof W: **Gustatory expression pattern of the human TAS2R bitter receptor gene family reveals a heterogeneous population of bitter responsive taste receptor cells**. *J Neurosci* 2007, **27**:12630-12640.
 30. Mueller KL, Hoon MA, Erlenbach I, Chandrashekar J, Zuker CS, Ryba NJP: **The receptors and coding logic for bitter taste**. *Nature* 2005, **434**:225-229.
 31. Caicedo A, Roper SD: **Taste receptor cells that discriminate between bitter stimuli**. *Science* 2001, **291**:1557-1560.
 32. Spector AC, Kopka SL: **Rats fail to discriminate quinine from denatonium: implications for the neural coding of bitter-tasting compounds**. *J Neurosci* 2002, **22**:1937-1941.
 33. Geran LC, Travers SP: **Bitter-responsive gustatory neurons in the rat parabrachial nucleus**. *J Neurophysiol* 2009, **101**:1598-1612.
 34. Travers SP, Geran LC: **Bitter-responsive brainstem neurons: characteristics and functions**. *Physiol Behav* 2009, **97**:592-603.
 35. Oliveira-Maia AJ, Stapleton-Kotloski JR, Lyall V, Phan TH, Mummalaneni S, Melone P, DeSimone JA, Nicoletis MA, Simon SA: **Nicotine activates TRPM5-dependent and independent taste pathways**. *Proc Natl Acad Sci U S A* 2009, **106**:1596-1601.
 36. Liu L, Zhu W, Zhang ZS, Yang T, Grant A, Oxford G, Simon SA: **Nicotine inhibits voltage-dependent sodium channels and sensitizes vanilloid receptors**. *J Neurophysiol* 2004, **91**:1482-1491.
 37. Laugerette F, Passilly-Degrace P, Patris B, Niot I, Febbraio M, Montmayeur JP, Besnard P: **CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions**. *J Clin Invest* 2005, **115**:3177-3184.

38. Gaillard D, Laugerette F, Darcel N, El-Yassimi A, Passilly-
 • Degrace P, Hichami A, Khan NA, Montmayeur JP, Besnard P: **The gustatory pathway is involved in CD36-mediated orosensory perception of long-chain fatty acids in the mouse.** *FASEB J* 2008, **22**:1458-1468.
 The authors found that the linoleic acid-elicited increase in $[Ca^{2+}]_i$ within taste cells was correlated with the presence of CD36 in mice. Further, transection of gustatory nerves impaired: firstly, the preference for linoleic acid; secondly, the expression of a presurgically conditioned aversion to linoleic acid, and thirdly, the pancreato-biliary response to lingually applied linoleic acid. Finally, knocking out CD36 eliminated the induction of c-fos expression within neurons in the rostral nucleus of the solitary tract following lingual stimulation with linoleic acid. These findings support the hypothesis that CD36 is a necessary component of the taste-mediated response to long-chain unsaturated fatty acids.
39. Sclafani A, Ackroff K, Abumrad NA: **CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice.** *Am J Physiol Regul Integr Comp Physiol* 2007, **293**:R1823-R1832.
 In 24-hour tests, CD36 knock-out (KO) mice expressed little or no preference for linoleic acid, a noncaloric oil, and a dilute soybean oil emulsion. The KO mice did prefer high soybean oil concentrations, however, indicating that post-oral stimulation can condition intake. This inference was supported by KO mice learning to prefer a flavored solution paired with intragastric infusions of soybean oil. These findings suggest that CD36 is necessary to promote taste-mediated intake of caloric oils, but that conditioned intake of oils as a result of post-oral stimulation does not require CD36.
40. Gilbertson TA, Liu L, Kim I, Burks CA, Hansen DR: **Fatty acid responses in taste cells from obesity-prone and -resistant rats.** *Physiol Behav* 2005, **86**:681-690.
41. Chale-Rush A, Burgess JR, Mattes RD: **Evidence for human orosensory (taste?) sensitivity to free fatty acids.** *Chem Senses* 2007, **32**:423-431.
42. Pittman D, Crawley ME, Corbin CH, Smith KR: **Chorda tympani nerve transection impairs the gustatory detection of free fatty acids in male and female rats.** *Brain Res* 2007, **1151**:74-83.
43. Pittman DW, Smith KR, Crawley ME, Corbin CH, Hansen DR, Watson KJ, Gilbertson TA: **Orosensory detection of fatty acids by obesity-prone and obesity-resistant rats: strain and sex differences.** *Chem Senses* 2008, **33**:449-460.
44. Stratford JM, Curtis KS, Contreras RJ: **Chorda tympani nerve transection alters linoleic acid taste discrimination by male and female rats.** *Physiol Behav* 2006, **89**:311-319.
45. Stratford JM, Curtis KS, Contreras RJ: **Linoleic acid increases chorda tympani nerve responses to and behavioral preferences for monosodium glutamate by male and female rats.** *Am J Physiol Regul Integr Comp Physiol* 2008, **295**:R764-R772.
46. Breza JM, Curtis KS, Contreras RJ: **Monosodium glutamate but not linoleic acid differentially activates gustatory neurons in the rat geniculate ganglion.** *Chem Senses* 2007, **32**:833-846.
47. Zukerman S, Glendinning JI, Margolskee RF, Sclafani A: **T1R3 taste receptor is critical for sucrose but not Polycose taste.** *Am J Physiol Regul Integr Comp Physiol* 2009, **296**:R866-R876.
 In 60-s preference tests, T1R3 KO mice preferred Polycose (a starch-derived polysaccharide), but not sucrose. In 24-hour preference tests, the KO mice preferred high but not low concentrations of sucrose, perhaps reflecting post-oral stimulation by sucrose. The chorda tympani nerve response of KO mice to sucrose was abolished, but that to Polycose was completely normal. These results show that the T1R3 receptor is not necessary for the taste-mediated response to Polycose.
48. Treesukosol Y, Blonde GD, Spector AC: **The T1R2 and T1R3 subunits are individually unnecessary for normal affective licking responses to Polycose: implications for saccharide taste receptors in mice.** *Am J Physiol Regul Integr Comp Physiol* 2009, **296**:R855-R865.
 Brief-access taste tests were used to examine concentration-dependent appetitive licking for sucrose, saccharin, and Polycose (a starch-derived polysaccharide) in both T1R2 KO and T1R3 KO mice. The authors found that both types of KO mice display normal concentration-dependent licking for Polycose, but severely blunted licking for sucrose and saccharin. These results indicate that neither T1R2 nor T1R3 are individually necessary for normal appetitive licking for Polycose.
49. Glendinning JI, Feld N, Goodman L, Bayor R: **Contribution of orosensory stimulation to strain differences in oil intake by mice.** *Physiol Behav* 2008, **95**:476-483.
50. Saitou K, Yoneda T, Mizushige T, Asano H, Okamura M, Matsumura S, Eguchi A, Manabe Y, Tsuzuki S, Inoue K, Fushiki T: **Contribution of gustation to the palatability of linoleic acid.** *Physiol Behav* 2009, **96**:142-148.
51. Sclafani A, Zukerman S, Glendinning JI, Margolskee RF: **Fat and carbohydrate preferences in mice: the contribution of alpha-gustducin and Trpm5 taste-signaling proteins.** *Am J Physiol Regul Integr Comp Physiol* 2007, **293**:R1504-R1513.
 Using 24-hour intake tests, the authors examined preference for and intake of oil, starch, and starch-derived polysaccharides (Polycose) in Trpm5 KO and alpha-gustducin KO mice. The results implicated both alpha-gustducin and Trpm5 in the preference for polysaccharide taste, but only Trpm5 in the preference for oil. The fact that the preference for Polycose, but not starch, was disrupted in alpha-gustducin KO mice suggests that the response to each of these carbohydrates is mediated by a different signaling pathway.
52. Pittman DW, Labban CE, Anderson AA, O'Connor HE: **Linoleic and oleic acids alter the licking responses to sweet, salt, sour, and bitter tastants in rats.** *Chem Senses* 2006, **31**:835-843.
53. Mattes RD: **Effects of linoleic acid on sweet, sour, salty, and bitter taste thresholds and intensity ratings of adults.** *Am J Physiol Gastrointest Liver Physiol* 2007, **292**:G1243-G1248.
54. Wicks D, Wright J, Rayment P, Spiller R: **Impact of bitter taste on gastric motility.** *Eur J Gastroenterol Hepatol* 2005, **17**:961-965.
 The authors sham fed human subjects a bitter or a nonbitter taste stimulus and monitored gastric emptying rate and gastric motility. They found that the bitter taste significantly delayed gastric emptying, but had no impact on gastric motility.
55. Neyraud E, Sayd T, Morzel M, Dransfield E: **Proteomic analysis of human whole and parotid salivas following stimulation by different tastes.** *J Proteome Res* 2006, **5**:2474-2480.
56. Tonosaki K, Hori Y, Shimizu Y, Tonosaki K: **Relationships between insulin release and taste.** *Biomed Res* 2007, **28**:79-83.
 The authors examined insulin release in rats, immediately following oral stimulation with sucrose, starch, NaCl, HCl, quinine, and MSG. Sucrose was the only taste stimulus that elicited a CPIR. The observation that bilateral transection of the chorda tympani nerve eliminated the CPIR for sucrose indicates that taste input from the chorda tympani nerve is necessary to elicit CPIR in rats.
57. Just T, Pau HW, Engel U, Hummel T: **Cephalic phase insulin release in healthy humans after taste stimulation?** *Appetite* 2008, **51**:622-627.
58. Mattes RD: **Brief oral stimulation, but especially oral fat exposure, elevates serum triglycerides in humans.** *Am J Physiol Gastrointest Liver Physiol* 2009, **296**:G365-G371.
59. Crystal SR, Teff KL: **Tasting fat: cephalic phase hormonal responses and food intake in restrained and unrestrained eaters.** *Physiol Behav* 2006, **89**:213-220.
60. Shinozaki K, Shimizu Y, Shiina T, Morita H, Takewaki T: **Relationship between taste-induced physiological reflexes and temperature of sweet taste.** *Physiol Behav* 2008, **93**:1000-1004.
61. Lundy RF, Norgren R: **Gustatory system.** *The Rat Nervous System*. edn 3. Elsevier; 2004. pp. 891-921.
62. St. John SJ, Spector AC: **Behavioral discrimination between quinine and KCl is dependent on input from the seventh cranial nerve: implications for the functional roles of the gustatory nerves in rats.** *J Neurosci* 1998, **18**:4353-4362.
63. Spector AC: **The functional organization of the peripheral gustatory system: lessons from behavior.** In *Progress in Psychobiology and Physiological Psychology*, vol. 18. Edited by Fluharty SJ, Grill HJ. San Diego: Academic Press; 2003:101-161.
64. Zaidi FN, Todd K, Enquist L, Whitehead MC: **Types of taste circuits synaptically linked to a few geniculate ganglion neurons.** *J Comp Neurol* 2008, **511**:753-772.
 Pseudorabies virus was injected into anterior tongue taste buds of mice to label cells in the geniculate ganglion. The goal was to transynaptically label their central connections. After these afferent fibers synapse with

neurons in the rostral nucleus of the solitary tract, the projection patterns become anatomically heterogeneous. That is, some neurons contribute to the ascending gustatory pathway and others contribute to local medullary connections. This raises the possibility that different taste functions could have distinct anatomical substrates, each of which is already segregated in the peripheral gustatory system.

65. Nasse J, Terman D, Venugopal S, Hermann G, Rogers R, Travers JB: **Local circuit input to the medullary reticular formation from the rostral nucleus of the solitary tract.** *Am J Physiol Regul Integr Comp Physiol* 2008, **295**:R1391-R1408.
66. Suwabe T, Fukami H, Bradley RM: **Synaptic responses of neurons controlling the parotid and von Ebner salivary glands in rats to stimulation of the solitary nucleus and tract.** *J Neurophysiol* 2008, **99**:1267-1273.
67. Pfaffmann C, Norgren R, Grill HJ: **Sensory affect and motivation.** In *Tonic Functions of Sensory Systems*, edn 290. Edited by Wenzel BM, Zeigler HP. Ann. N.Y. Acad. Sci.; 1977:18-34.
68. Smith DV, Hanamori T: **Organization of gustatory sensitivities in hamster superior laryngeal nerve fibers.** *J Neurophysiol* 1991, **65**:1098-1113.