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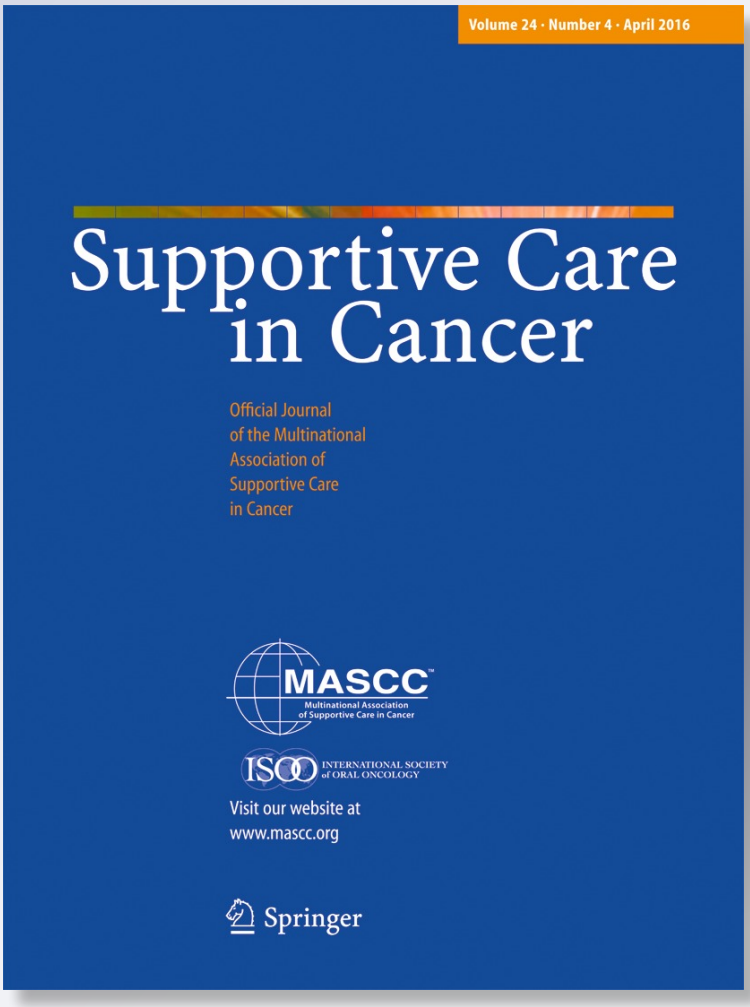

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REVIEW ARTICLE

Understanding the impact of taste changes in oncology care

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Abstract
Purpose Taste perception is frequently altered in cancer patients. The purpose of this review is to provide an update on advances in understanding of the basic biology and physiology of taste and how taste and flavor may be impacted in cancer and its treatment.
Methods A succinct review of the literature on the biology and neurology of taste, taste evaluation, and the impact in oncology is provided.
Results Advances have occurred in the study of the gustatory system. Taste and smell are commonly affected during cancer care, and specific chemosensory complaints may persist in large numbers of cancer survivors. Limited study in oncology patients is available despite the significant impact that taste and smell have on oral intake and general physical and social well-being.
Conclusions Taste and flavor has had limited study in cancer therapy. Impact on taste and flavor can result in changes ranging from elimination of taste to taste distortions that may be associated with taste aversions, nausea, and dietary compromise. New therapeutics and new approaches in oncology may have additional impact upon taste that requires further study. This paper reviews the current understanding of taste function, taste testing, and its potential impact on cancer care, to serve as a guide for directing further research.

Keywords Taste · Smell · Flavor · Oral sensory function · Taste testing

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Introduction

Taste is an important sense that serves to evaluate the content of food, support food selection and intake, and identify and prevent ingestion of potentially toxic substances [1, 2]. Flavor is a combination of several sensory mechanisms including taste, smell, texture, and temperature. Flavor impacts food choices, food intake, and the desire to eat. Taste sensation, per se, is based primarily upon a limited number of basic qualities, namely, sweet, bitter, salt, sour, savory (*umami*), and possibly fat taste and metallic taste [2, 3]. *Umami*, of which monosodium L-glutamate is a representative stimulus, is likely associated with assessing a food's protein content and the enjoyment and pleasure that enhance interest in eating. Changes in taste intensity, quality, or loss can be assessed with patient-reported outcomes (PRO), as well as by quantitative taste tests. Dysgeusia or phantogeusia (distortions or phantom taste sensations), may present in the form of metallic, bitter, sour, salty, or, more rarely, sweet taste sensations that may be triggered, reduced, or unaffected by eating.

Current estimates suggest that approximately 0.6 % of the US population experience taste disturbances [4]. Importantly, numerous diseases and disorders are associated with taste

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dysfunction [5], up to 85 % of cancer therapy patients report taste changes [1]. These taste disturbances may be caused by damage to the gustatory system, loss or distortions of olfactory function, systemic disease, or local oropharyngeal conditions. Importantly, such disturbances have a significant impact on the quality of life and oral intake of foods.

In this paper, we provide an updated review of the anatomy and physiology of the human taste system. We review factors that alter its function and how taste function can be quantitatively measured. Our primary purpose is to provide a basis for better understanding how taste (sensations derived from stimulation of taste buds) is impacted by cancer and other disorders, ultimately directing the way for palliative and therapeutic strategies for enhancing the eating experience of persons suffering from taste disturbances. Olfaction, which significantly contributes to the flavor of foods via stimulation from volatiles that traverse the nasopharynx from the oral cavity to reach the olfactory epithelium, is not reviewed. More detailed information on the roles of olfaction, taste, and somatosensation that contribute to flavor and the palatability of food and drinks is available elsewhere [6, 7].

Anatomy and physiology of the taste system

Taste buds

The experience of taste perception begins with activation of taste receptors located on microvillae of taste receptor cells that are clustered together to form taste buds. These taste receptor cells are modified epithelial cells that detect a variety of taste stimuli. Taste buds are structures that resemble segments of a grapefruit or a rosebud.[1] Each taste bud, which contains 60 to 120 cells, has an apical opening, termed the taste pore, into which liquids enter from the oral epithelial surface into the bud's lumen, termed the taste pit (Fig. 1). Based on morphological features, the elongated cells within the taste bud are classified as types I (dark), II (light), or III (intermediate) [11, 12]. The cells at the base and margin of the bud are termed types IV and V, respectively. The gross morphological features of type I, II, and III cells are shown in Fig. 2. Type I cells have a narrow neck that entwine type II cells, whereas type II cells have a straight short thick neck. The microvillae of type I cells are located in close proximity to the taste pore, unlike those of type II cells, which are located deeper within the taste pit.

[1] Receptors in the gut have been identified that respond to amino acids, peptides, sugars, and bitter compounds by either releasing local peptides or by activating vagal afferents [8–10]. Since such extraoral structures do not contribute to taste perception per se, they are not discussed, as such, in this review. Nonetheless, it is important to recognize that stimulation of these receptors within the oral cavity is just the beginning phase of a complex interrelation between taste-related chemicals, digestion, and gastric function.

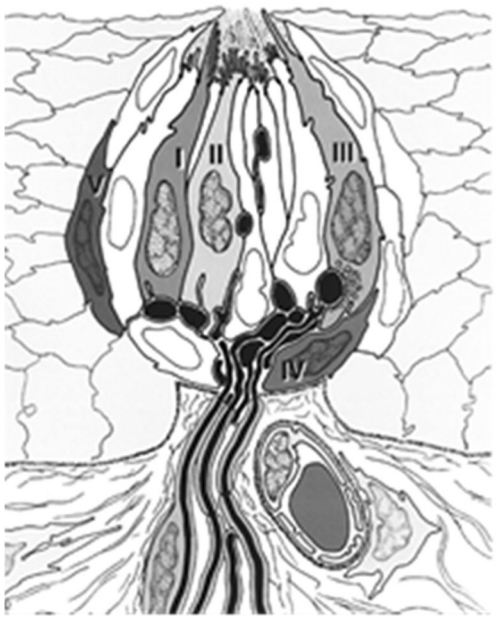

Fig. 1 Schematic longitudinal section of mammalian taste bud. Type I, II, and III cells form the sensory epithelium of the bud, with different types of microvillae extending within the taste pit, some of which may reach the taste pore. Type IV and V cells are basal and marginal cells, respectively. Synapses are most apparent at the base of Type III cells. The connecting taste nerves are myelinated. From [11]. Copyright © 2015 Richard L. Doty

In humans, taste buds are embedded in lingual papillae most prominent on the anterior, lateral, and posterior surfaces of the tongue. Although papillae vary in size and form, they can be categorized into three major types that harbor taste buds, i.e., circumvallate (rounded), foliate (fold-like), and fungiform (mushroom-like), and one type that does not (filiform or thread-like) (Fig. 3). The fungiform papillae, which average about a half millimeter in diameter, are most dense along the tip and sides of the tongue and vary in number among individuals. The foliate papillae are made up of distinct ridges along the lateral margin of the tongue adjacent to the lower third molars. The large circumvallate papillae, located across the posterior "chevron" of the tongue, range in number from 6 to 10, and contain over half of the taste buds in the oral cavity. Von Ebner's glands are located within the trenches that surround the foliate and circumvallate papillae. These glands aid in removing material from the trenches and secrete lipase, an enzyme that hydrolyzes triglycerides to glycerol and free fatty acids. These glands also secrete amylase, which hydrolyzes starch into sugars for digestion [14, 15]. Presumably von Ebner gland secretions share the functions of other salivary glands, including solubilizing tastants and lubricating, repairing, and maintaining the integrity of the oral epithelium [14, 15].

A notable feature of the taste perception is redundancy in the system, with several sets of paired nerves innervating the taste buds, depending upon their location. The taste buds of the anterior tongue are innervated by the chorda tympani nerve,

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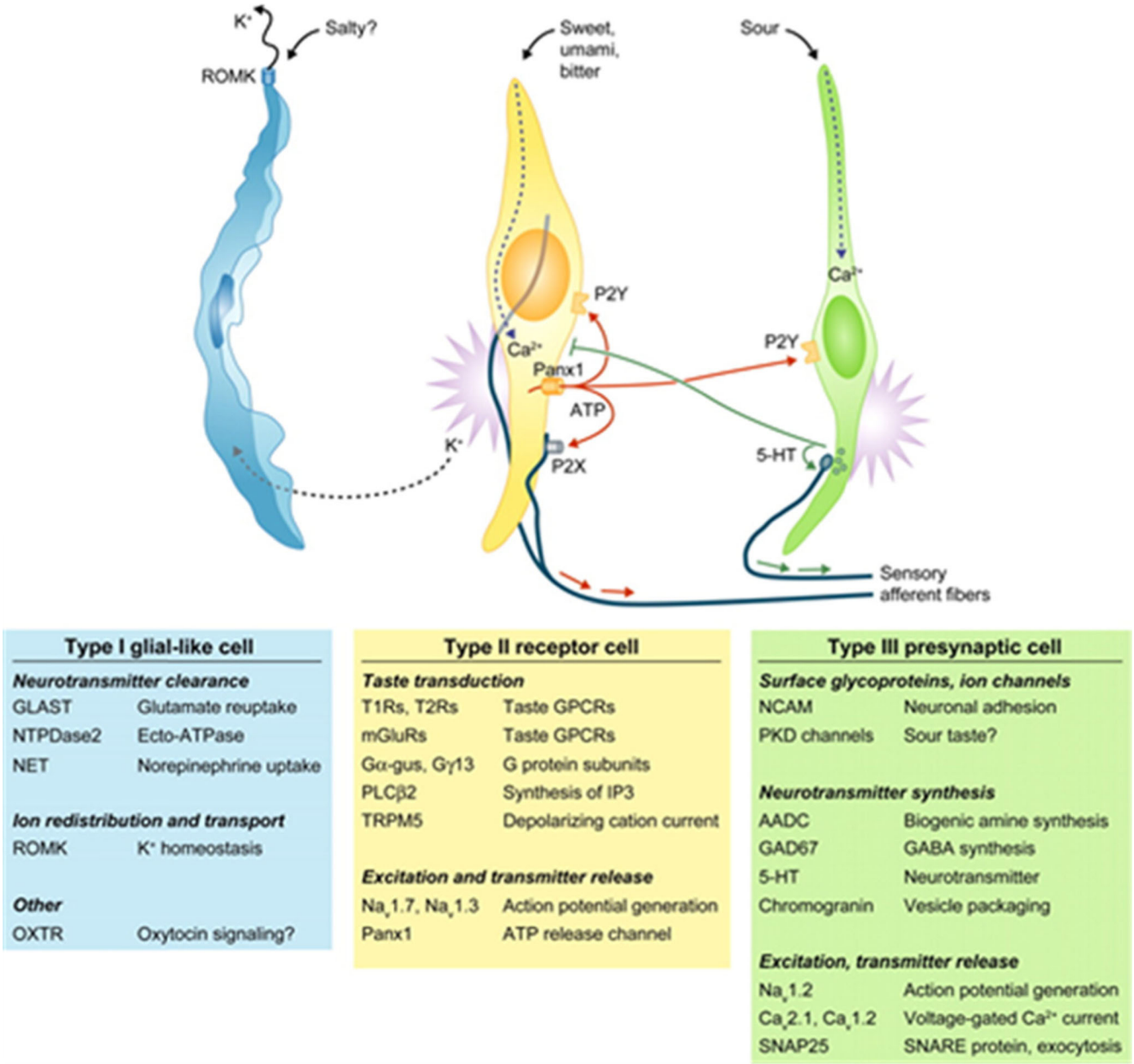

Fig. 2 Features of type I, II and III taste cells, including gene expression patterns and functional interactions. Type I cells (*blue*) degrade or absorb neurotransmitters and may clear extracellular K^+ following action potentials (shown as purple bursts) in type II (*yellow*) and type III (*green*) cells. Salt taste function may be transduced by some type I cells. Sweet, bitter, and *umami* taste stimuli activate type II cells, inducing release of ATP through pannexin1 (Panx1) hemichannels. ATP functions as a neurotransmitter in taste buds, and binds to ATP receptors (P2X, P2Y) on sensory nerve fibers and on taste receptor cells. Type III cells, in turn, release serotonin (5-HT), which inhibits receptor cells. Sour tasting stimuli (and carbonation) directly activate type III cells. Only type III cells form ultrastructurally identifiable synapses with nerves. Reprinted with permission from Chaudhari and Roper [18] Copyright © 2010, The Rockefeller University Press

whereas those on the soft palate are innervated by the superficial petrosal nerve, both of which branch off the facial nerve (CN VII). The buds on the posterior tongue are supplied by the glossopharyngeal nerve (CN IX), whereas those in the tongue root and esophagus are supplied by the vagus nerve (CN X). Although each side of the tongue is believed to be separately innervated, there may be some overlap at the tip of the tongue.

Like olfactory receptor cells, taste bud receptor cells and supporting cells are replaced periodically from stem cells located near the base of the bud within the stratum germinativum [16]. Some taste bud cells turn over after 10–11 days [16], while others are believed to be more long lived.

Taste receptors

More than 2000 genes are expressed in primate taste bud tissue [17], while fewer than 50 genes encode mammalian

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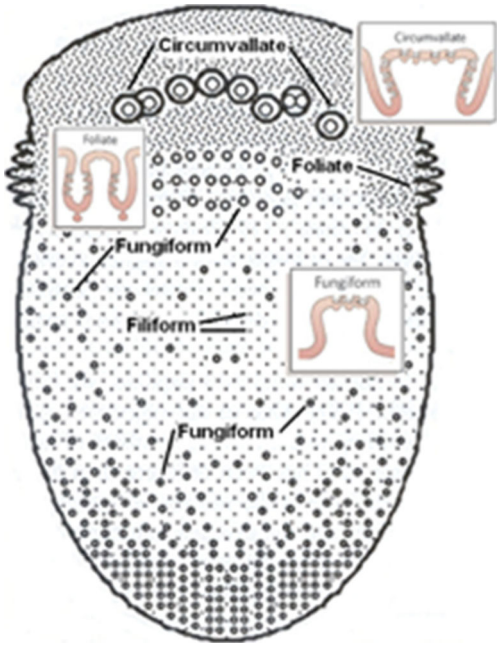

Fig. 3 Schematic representation of the tongue demonstrating the relative distribution of the four main classes of papillae. Note that the fungiform papillae can vary considerable in size, and that they are typically most dense on the anterior and lateral regions of the tongue. Copyright © 2006 Richard L. Doty

taste receptor proteins. As noted in Fig. 2, type I cells are involved in detecting salt perception. Like neuroglia, these cells also serve secretory and phagocytotic functions, including neurotransmitter redistribution and ion clearance [18]. As described in more detail in the following section, Na^+ ions directly gate specialized membrane channels for entry into cells. Type II cells contain G protein-coupled receptor (GPCR) that detect sweet-tasting stimuli, as well as a family of approximately 30 GPCRs responsible for bitter taste perception. Although different bitter receptors can be located on the plasma membrane of a single cell, bitter taste receptors have not been detected in receptor cells that express sweet or *umami* taste receptors. Type III cells appear to be specialized for detecting sour taste stimuli, in some cases via inward proton currents that flow through transient receptor potential (TRP) receptor channels PKD2LA and PKD1L3 [19]. Null mice that lack a functional gene for expressing this receptor cannot detect sour, but retain sweet, bitter, and salty taste perception [20].

Two distinct models have been proposed to describe information coding of mammalian gustatory stimuli. One model is the labeled line mode. This model predicts that individual taste receptor cells respond to only one taste quality. This taste quality information is then transmitted to the gustatory cortex of the brain via the medulla and thalamus [21]. In the labeled line model, a particular neuron signals a specific primary taste quality.

The second model for taste coding is the across-fiber model, which proposes that individual taste receptor cells respond to different taste qualities. Taste quality information is then transmitted to the brain by fibers that have broadly overlapping response ranges [22]. In the across-fiber model, the code for a specific taste quality is determined by the pattern of activity across all the afferent nerve fibers, rather than by the activity of a single afferent fiber [23].

Taste receptors that mediate bitter, sweet, and umami taste sensations

Stimulation of taste receptors for bitter, sweet, and *umami* stimuli occurs when ligands bind to the extracellular domain of taste receptors located on microvilli of taste receptor cells. These plasma membrane taste receptors span the membrane seven times. This binding leads to a conformational change in the receptor, and subsequent activation of G proteins and their effectors that include phospholipase C and adenylate cyclase. Activation of these pathways then lead to the formation of second messenger such as cyclic AMP, or inositol 1,4, 5-trisphosphate (IP_3), and diacylglycerol (DAG) [24].

More specifically, sweet, *umami,* and bitter taste stimuli activate one of two different families of heteromeric GPCRs [24–29]; type 1 (T1R1) and type 2 (T1R2). T1R1 receptors belong to class C GPCRs, and function as obligatory heteromers composed of two different subunits. These receptors have extended extracellular N termini that form a globular ligand-binding domain with a characteristic Venus flytrap motif [18, 30]. However, to produce a fully functional *umami* or sweet taste receptor, members of an additional GPCR receptor family (T1R3) must be expressed and co-assembled with either T1R1 or T1R2 subunits [31, 32]. Thus, dimeric sweet and *umami* receptors contain one common subunit (T1R3) and one stimulus-specific subunit (T1R1 or T1R2). Taste receptors that share T1R3 subunits activate G protein $G\alpha_{14}$ as well as other G_α subunits for activation of signal transduction pathways that release calcium into the cytosol [16].

Bitter taste perception is mediated by a small family of nearly 30 GPCRs that are members of the T1R2 gene family [25]. These seven transmembrane domain receptors are characterized by short extracellular N termini. Most (but not all) T1R2 receptors are narrowly tuned to bitter taste, and respond to only one, or a few structurally related, bitter taste stimuli [33, 34]. In the oral cavity, individual bitter taste receptor cells express subsets of 4 to 11 different T1R2 proteins [35].

The pathway for GPCR taste transduction for savory (*umami*), bitter, and sweet taste stimuli (where stimuli are non-caloric sweeteners such as saccharin) is thought to occur by activation of beta and gamma subunits of heterotrimeric G proteins [36, 37]. These two subunits then activate the effector phospholipase C-β2 [38]. Phospholipase C-β2 in turn catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to the second messengers IP_3 and DAG. The inositol

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sugar IP_3 then binds to, and opens type III IP_3 receptor channels on endoplasmic reticulum membranes that release stored calcium into the cytosol [39, 40]. The rapid elevation of cytosolic calcium then activates plasma membrane transient receptor potential cation channel, subfamily M, member 5 (TRPM5) [41, 42]. The TRPM5 channel is selectively expressed in cells that also respond to sweet and bitter taste stimuli [41]. The opening of TRPM5 channels activates a depolarizing cation current by mediating an influx of cations [43]. TRPM5 channel activity is thought to raise cytosolic sodium levels, which in turn activate plasma membrane voltage-gated Na^+ channels [44], which lead to membrane depolarization, and the subsequent release of ATP through gap junction pannexin-1 hemichannels [44]. The released ATP would then bind to, and activate, purinergic receptors on afferent nerve fibers in the oral cavity for transduction of the signal to the CNS [44].

In addition to hydrolyzing PIP_2 to IP_3 and DAG, most bitter, sweet (with carbohydrates as sweet taste stimuli), and savory taste stimuli depolarize taste receptor cells by modulating adenylate cyclase activity via the G protein α-gustducin [45]. Sweet taste stimuli such as sucrose and related carbohydrates increase cytosolic cyclic AMP (cAMP) levels by activating the enzyme adenylate cyclase via α-gustducin. Increases in cytosolic cAMP then activate protein kinase A, which would in turn phosphorylates, and closes basolateral potassium channels. The closure of potassium channels then inhibits the efflux of positively charged potassium ions so that membrane depolarization could occur [18].

In receptor cells that detect bitter taste, α-gustducin is released from its beta and gamma subunits, and binds to cAMP phosphodiesterase. This activated phosphodiesterase then hydrolyzes cytosolic cAMP to adenosine monophosphate. Lowered levels of cyclic AMP would in turn decrease protein kinase A activity. Decreased protein kinase A activity would then decrease the phosphorylation of target proteins. In particular, inactive protein kinase A would preserve functionally active (unphosphorylated) phospholipase Cβ2 activity that is required to generate adequate calcium for depolarizing bitter taste receptor cells via IP_3 [46]. On the other hand, elevated cAMP levels would activate protein kinase A, and phosphorylate and inhibit PLCβ2 enzymatic activity [44, 46]. In these bitter taste receptor cells, the primary function of α-gustducin may be to maintain low cytosolic cAMP levels, which in turn would inhibit protein kinase A, an important cyclic AMP-dependent protein kinase. However, a possible role for α-gustducin in modulating chronic adaptation to bitter taste stimuli (and phosphorylation of PLC-β2) remains unclear.

Signals transmitted from type II receptor cells to sensory afferents apparently use unconventional synaptic mechanisms, since they do not involve synaptic vesicles [11].

Taste receptors that mediate salty and sour taste sensations

As noted earlier, salt and sour taste perceptions are thought to be mediated by receptor channels in the plasma membranes of type I and III taste receptor cells, respectively. The membrane receptor that responds to acid (sour) stimuli is not yet identified. However, nonselective cation channels formed by polycystic kidney disease 2-like 1 (PKD2L1) and polycystic kidney disease 2-like 3 (PKD1L3) subunits have been proposed as candidate sour taste receptors [47, 48]. This heteromeric channel responds to extracellular pH rather than changes in cytoplasmic pH [47]. Nonetheless, taste receptor cells for sour taste are characterized by the expression of PKD2L1, a transient receptor potential channel that may function to detect low pH [47, 48].

Similar to the receptors for sour taste, receptors for salt taste stimuli have not been elucidated at the molecular level. The primary mechanism for salt taste transduction likely involves the passage of sodium ions through a specific channel in the plasma membrane of receptor cells [49]. Salt taste is thought to be mediated by an amiloride-sensitive epithelial sodium channel, ENaC [49–52]. Amiloride is a potassium-sparing diuretic compound that blocks Na^+ channels in kidney cells [49]. However, high concentrations of salt in the oral cavity may activate both sour and bitter taste receptor cells [53]. If true, salty compounds could activate three different classes of taste receptor cells. These classes include the sodium-selective ENaC pathway at non-aversive salt levels, and the recruitment of the sour and bitter taste-sensing pathways for detecting aversive, high salt levels in foods [53].

Long-chain *cis* unsaturated fatty acids such as linoleic acid may also stimulate a chemosensory response in the oral cavity [54]. Fatty acid taste may be mediated by oral somatosensory cues, and/or by receptor-mediated transduction, or by nonspecific transport across the plasma membrane followed by activation of intracellular signaling pathways [55]. Animal studies have suggested a variety of proposed mechanisms to explain the initial stages of oral fatty acid perception [56–61]. For example, fat taste may occur by interactions with cluster of differentiation-36 (CD36) protein [61, 62]. CD36 is a scavenger receptor that mediates lipid trafficking in a variety of cell types [63] with an affinity in the nanomolar range [64]. Fatty acid binding is thought to occur at or near a positively charged lysine residue located in a hydrophobic pocket on the extracellular surface of this membrane protein [65] (see Fig. 4). CD36 mediates cell signaling by transiently increasing intracellular calcium levels [66].

The GPCRs GPR40 and GPR120 may also mediate taste preferences for medium- and long-chain fats via the GTP-binding proteins $G\alpha_q/G\alpha_{11}$ [61, 67–69]. As opposed to CD36, these receptors possess a low affinity for fatty acids [70]. TRPM5 receptors may also play an important role in fatty acid transduction since inactivation of the TRPM5 gene

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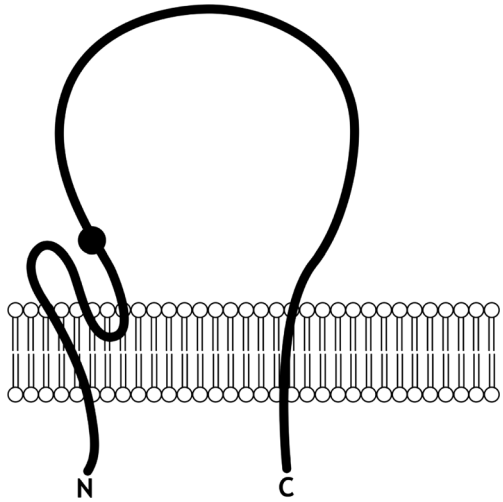

Fig. 4 Proposed structure of the CD36 receptor. This glycoprotein contains two transmembrane domains, and a hydrophobic pocket for binding fatty acids. Lysine-164 (*filled black circle*) is predicted to exhibit intermediate solvent accessibility, and localizes to the hydrophobic pocket that contains the putative binding domain for fatty acids. *N* and *C* represent the amino and carboxyl termini of CD36. Image courtesy of Eric B. Tran

abolishes preferences for fats in mice [71, 72]. Finally, some evidence suggests that fatty acid perception in the oral cavity may occur by membrane diffusion, and possibly activate fat-sensing cells by an unknown mechanism [73, 74].

Central taste pathways

Sensory fibers conduct afferent signals from the taste buds to the nucleus tractus solitarius (NTS) of the brainstem via cranial nerves VII, IX, and X in an ordered caudal/rostral fashion [75]. The NTS contains morphologically distinct regions associated with gustation, visceral afferent activity, and a combination of somatic motor and visceromotor activity [76]. Based on electrophysiological studies, a number of the afferent fibers entering into the NTS can be categorized into sweet-, sour-, bitter-, and salty-best categories. Interestingly, based on neurophysiological criteria, some cells respond solely to water, suggesting that water might be considered an independent taste modality [77].

Information from the NTS is carried within the medial lemniscus to the ventroposteromedial (VPMpc) nucleus of the thalamus [78]. It is then sent to the rostral insula, adjacent frontal operculum, and surrounding regions—structures commonly considered as the primary taste cortex [79, 80]. As with the afferent neurons, some cells within these structures respond best to sweet-, sour-, bitter-, salty and *umami* taste stimuli. Others respond to touch and smell [70, 81]. These structures are directly and reciprocally connected with frontal, temporal, and parietal cortical structures (e.g., auditory cortex, superior temporal sulcus, opercular cortex, orbitofrontal cortex) and indirectly connected with the hypothalamus, hippocampus, and striatum [82]. Links to the amygdala, basal ganglia, and entorhinal cortex are also present [79, 80]. A number of these brain regions are multimodal, most notably the orbitofrontal cortex, and serve to not only aid in interpreting the nature and meaning of taste sensations via cognitive and memory circuits, but also in developing hedonic and integrative associations that underlie flavor sensations [83].

Non-taste nerves that contribute to the gestalt of flavor

The five primary taste qualities do not explain the full range of human oral sensation. Taste receptors may be responsive to the taste of fats. Trigeminal nerve (CN V) receptors greatly add to the flavor of some foods. Small C-fiber function mediates sensations that include those related to capsaicin (hot-spicy sensation), piperine (gives rise to pungency of black pepper), and zingerone (vanillylacetone, perception of ginger) [84], as well as somatosensory sensations such as those induced by menthol (cooling sensation). Clearly, the temperature and tactile features of foodstuffs (e.g., grittiness, texture, smoothness) are critical in determining food selection and intake. Moreover, taste function and oral intake may also be affected by small fiber neuropathies that influence flavor sensation. Such findings reiterate the concept that flavor is a complex oral sensation affected by a variety of sensory systems reflecting the overlap of information arising from multiple cranial nerves.

Psychophysical tests of taste function

Evaluation of taste function is challenging, in light of the multiple neural innervations of taste buds and individual differences in the number and distribution of receptors within the oral cavity. Ideally, a number of tongue regions, including ones on the soft palate, posterior tongue, and tongue root, should be individually tested. Although whole-mouth testing by oral rinsing is useful for assessing overall taste function, this proceedure may not be sensitive to damage to single taste nerves. In addition, hedonic (pleasantness) responses can be identified during whole-mouth taste tests but do not provide detailed information that evaluation of different areas of the tongue that may support evaluation of hedonic responses [85].

Clinical tests for gustatory function

In this section, the major types of clinical tests for gustatory function are described. Since this topic is complex, various approaches for clinical taste testing are described elsewhere [86, 87]. Suffice it to say, liquid tastants can be presented to

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subjects via (a) a container\from which whole-mouth "sipping & spitting," or in some cases, swallowing, can occur; (b) medicine droppers, syringes, pumps, or micropipettes that allow for presentation of stimuli to localized regions of the tongue; (c) Q-tips or paint brushes dipped in taste solutions; and (d) small disks or strips made of filter paper or pullulan-methylcellulose films that incorporate taste stimuli [87]. Electrogustometry has been used clinically for taste testing, since it correlates with a number of chemical taste tests. However, electrical stimuli rarely produce the classic taste sensations of sweet, sour, bitter, and salty [88].

Although filter paper disks or filter paper strips, have been standardized and been made commercially available in Germany and Japan, they have limitations [89]. For example, stimuli imbedded in dry filter paper disks may not release properly in patients whose salivary output is compromised. Dissolvable disks made from pullulan-based polymers, which confine the stimulus to the region of interest, may prove more useful, as described later in this review [90].

Threshold tests

Taste thresholds can be determined using various concentrations of tastants, usually in fractional log dilutions. It is important for the investigator to distinguish between detection and recognition thresholds. Detection thresholds reflect the presence of a sensation, whereas recognition thresholds require the experience of an actual taste quality (e.g., sweet). Detection thresholds are typically lower than recognition thresholds, so instructions and operational procedures must be standardized to take this into account. Importantly, forced-choice procedures (e.g., where a comparison must be made with a blank or a series of blanks in a counterbalanced order) are most commonly employed, since non-forced-choice procedures may confound the patient's response (i.e., tendency to respond in uncertain circumstances) with the actual sensitivity of the system [91]. Factors such as the temperature of the water must be taken into consideration when evaluating taste threshold sensitivity [92].

Because threshold testing is time consuming, clinical threshold testing has focused on three procedures: the single series ascending method of limits (AML), staircase (tracking) procedures, and sorting procedures. In the typical AML procedure, a below-threshold stimulus is presented and subsequent trials are systematically increased in concentration until a sensation (detection threshold) or taste quality (recognition threshold) is reliably perceived. In modern procedures, such as that codified by the ASTM [93], forced-choice responses are required at each concentration [94]. Staircase procedures, which are more reliable that the AML procedure, start at a below-threshold concentration and once detection occurs, the next lower stimulus is presented. If missed, the next higher concentration is presented. In the adaptation of the two-down, one up staircase procedure, two correct responses are required before the next lower stimulus concentration is presented [95]. If a miss occurs on either of the two successive trials, then the next higher stimulus is presented. Following such an algorithm, a series of staircase "reversals" occurs, a number of which are averaged to provide the threshold estimate.

The classic taste sorting procedure is exemplified by a method developed by Harris and Kalmus [96–98]. In this procedure, a subject is provided, on a given trial, with eight cups, half containing a given concentration of the taste stimulus in water and the other half water alone. The task is to sort the cups into sets of four, with the four containing the taste stimulus into one of the sets. When correct sorting occurs, the next lower concentration is presented. This procedure is continued until the lowest concentration in which such sorting is not possible is reached. Although this approach is time consuming, it provides reliable recognition threshold estimates.

An example of published norms for a whole-mouth taste threshold test employing NaCl is presented in Table 1. In this test, three stimulus drops are successively presented from 60-ml medicine droppers to the anterior tongue, one being the taste stimulus and the other two being distilled water blanks. The drops are alternated between the left and right sides of the tongue. The patient is initially presented with a suprathreshold example of the target stimulus "to acquaint the subject with the modality sought" [99]. A water rinse is interspersed between each 3-drop trial. As described by Henkin et al. [100], "when responses changed from consistently correct to incorrect, retests were made at and around the transition point. Threshold is defined as the lowest concentration of test substance to which the subject gave two successive correct

Table 1 Tastant concentrations employed by Henkin et al. for assessing basic taste qualities

Bottle unit	NaCl (mM/l)	Sucrose (mM/l)	HCl (mM/l)	Urea (mM/l)
1	6	6	0.5	60
2	12	12	0.8	90
3	30	30	3	120
4	60	60	6	150
5	90	90	15	300
6	150	150	30	400
7	300	300	60	500
8	500	500	90	800
9	800	800	150	1000
10	1000	1000	300	2000
11	3000	2000	400	5000
12	Saturation	Saturation	500	8000

Bottle units greater than four are considered indicative of hypogeusia or ageusia. Based on a sample size of 150 "normal" subjects. Threshold values falling at the levels indicated in red are considered abnormal. From [96]

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responses while giving two consecutive incorrect responses at the next lower concentration."

Recently, one of the authors (GS) has developed a taste test using edible "taste strips" composed of pullulan-hydroxypropyl methylcellulose polymers as the vehicle for administering taste stimuli [101]. Such strips, when placed on the tongue, rapidly dissolve and provide a localized taste stimulus. Thresholds using this procedure are highly reliable. In a study of 39 men and 42 women, ranging in age from 18 to 64 years, essentially equivalent values were obtained from the use of a single ascending method of limits and a staircase procedure for the bitter-tasting agent 6-*n*-propylthiouracil (PROP). The test score distribution is shown in Fig. 5. Note that a large number of "non-tasters" was detected, i.e., persons whose threshold values were larger than 800 nanomoles. If one defines abnormality as occurring at or below the fifth percentile, then concentrations that distinguish PROP tasters from PROP non-tasters would be above 219 nanomoles. The threshold values obtained using this procedure are lower than those produced by other methods, conceivably reflecting more localized and complete stimulus release from the test strip vehicle.

Since these strips have only recently been developed, the breadth of their applications is yet to be determined. These films can be prepared in various shapes and sizes, they dissolve rapidly on the tongue, and produce essentially no concurrent tactile sensations. The latter may be particularly important since they do not induce the gag reflex and once in place do not have to be retrieved. Importantly, they can reliably present hydrophobic stimuli such as capsaicin or fatty acids that are difficult to present using other means [102].

Suprathreshold tests

Suprathreshold tests assess responses of persons to stimuli that are above threshold for most individuals. Examples include tests of taste identification and the rating of intensity and pleasantness (e.g., changes across increasing stimulus concentration gradients), discrimination, and memory. In general, normative data are lacking. A fuller discussion of suprathreshold test procedures is available elsewhere [86].

Whole-mouth taste identification and attribute ratings

In a whole mouth, 10-ml samples of five concentrations each of sucrose (0.08, 0.16, 0.32, 0.64, 1.28 M); sodium chloride (0.032, 0.064, 0.128, 0.256, 0.512 M); citric acid (0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M); and caffeine (0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M) are presented in small cups in a counterbalanced order [103]. After sipping, swishing and expectorating a sample, the subject indicates whether the solution tastes sweet, sour, salty, or bitter, and rates its perceived intensity and pleasantness on rating scales. Forty stimuli are administered, i.e., 4 tastants × 5 concentrations × 2 trials.

Figure 6 illustrates the mean intensity ratings for caffeine (bitter) of subjects with and without olfactory dysfunction [104]. Note the log-linear relationship between odorant concentration and the intensity ratings, a phenomenon that occurs for other tastants, as well as the fact that smell loss has no meaningful impact on the perceived intensity of this tastant.

Clinical conditions that impact taste perception

Health can be significantly impacted by taste disturbances, as taste is intimately involved in the regulation of energy intake, water/electrolytic balance, and nutrient consumption, as well as in the rejection of potential toxins and protection from poisoning. For example, individual differences in bitter taste perception can contribute to differences in food preferences, which in turn can result in a decrease in the consumption of certain beneficial fruits and vegetables [105]. In patients following surgery and oncology care, macro- and micronutrients important for energy and nutrient intake, as well as food palatability, are critical in health maintenance and tissue repair. The psychosocial influence of taste and enjoyment from

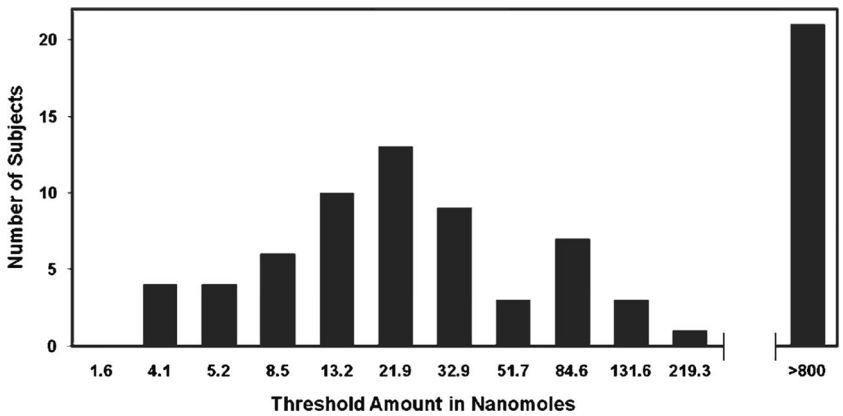

Fig. 5 Histogram of detection threshold values for PROP obtained using taste strips prepared from pullulan and hydroxypropyl methylcellulose. From [101]

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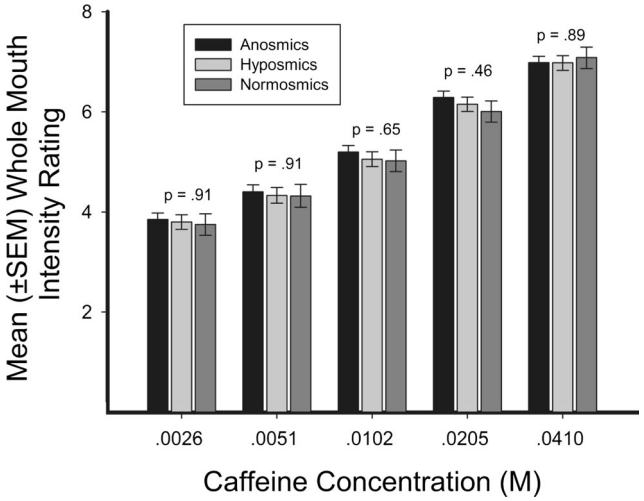

Fig. 6 Mean (±SEM) whole-mouth taste intensity ratings for five concentrations of caffeine (bitter) for subjects with three categories of smell function. *P* values are for olfactory function group main effects from ANOVAs performed on data from each stimulus concentration. From: Stinton et al. [104]. Copyright © 2010 American Psychological Association

eating is often overlooked, yet markedly impacts quality of life in persons with taste disorders [106].

The chemosensory detection of fatty acids in the oral cavity has significant implications for human health and nutrition. Fatty acid perception is important because approximately 40 % of daily caloric intake of western diets is composed of lipids, which are hydrolyzed to fatty acids and glycerol. High-fat diets contribute to the prevalence of obesity, and obesity-induced diseases such as type II diabetes, atherosclerosis, hypertension, and cancer. In addition, the ability to detect dietary fats is important for the consumption of high-caloric foods and essential fatty acids, which is important in weight maintenance and micronutrients in cancer patients. Furthermore, the palatability of high-fat foods is thought to be the primary reason for the consumption of dietary fats. *Umami* and the interest in food intake is also a key factor in weight maintenance. In oncology, interest in eating is clearly affected by mucosal, oral/oropharyngeal pain, jaw function, tongue mobility, dry mouth, and dental status, as well as by the nausea that may accompany oncology care.

A number of medical conditions can adversely influence taste function. Depending upon the condition, the alterations can consist of taste loss (ageusia), decreased taste function (hypogeusia), distorted taste sensations (dysgeusia), taste hallucinations or phantoms (phantogeusia), and increased taste sensations (hypergeusia). However, a perceived loss of taste function is most often caused by a loss of olfactory function, due to damage to the olfactory epithelium or to nasal obstruction that inhibits passage of molecules from the oral cavity into the nasal cavity via the nasopharynx. For example, individuals with a severe cold or sinus congestion often complain of taste loss. In some cases, viral damage from a URI can produce permanent loss of perceived taste function. However, these individuals are usually describing a loss of flavor, which is the sensation caused by the interaction of olfactory and gustatory stimuli. The reader is referred to an extensive reviews on this topic [107].

Disorders related to local oral and peripheral nervous system dysfunction

Hyposalivation may reduce the intensity of taste sensations due to limited dissolving of food particles, thereby reducing the number of molecules that reach the taste receptors. In addition, reduced salivary output leads to reduced clearance from the oral cavity and may lead to alterations in oral microflora that impact taste. However, there is conflicting evidence in the literature regarding saliva-related taste changes [103–111].

Oral, dental and oropharyngeal pathologies, as well as damage to cranial nerves, can affect taste function. Local factors such as oral hygiene, dental and periodontal disease, mucosal infection, tobacco use, and diet can impact taste function. Upper aerodigestive tract conditions such as sinus and nasopharyngeal disease may produce unpleasant taste sensations via the production of secretions that enter the mouth. Malignant diseases in the head and neck can induce taste changes secondary to tissue necrosis, oral bleeding, microbial colonization of the tumor surface, and/or post-surgical wounds [112]. Depending upon the treatment fields, regional radiation therapy may directly alter taste and smell receptors or associated afferent pathways [113]. Furthermore, changes in touch and temperature sensations mediated by the trigeminal nerve can also significantly impact the perceived taste of foods and beverages.

Bell's palsy is a relatively common cause of taste disruption [5]. In this neural disorder, sudden weakness of the muscles of one side of the face will occur in the absence of CNS, ear, or cerebellopontine disease [114]. Although generally considered idiopathic, viruses, such as herpes simplex virus-1, have been implicated in some cases [115]. A more severe form of Bell's palsy, Ramsay-Hunt syndrome, is induced by a herpes infection of the geniculate ganglion, and involves pain in the soft palate or external auditory canal.

Tumors involving the middle ear (e.g., cholesteatoma) are also known to influence taste function via their impact on the chorda tympani nerve that traverses the middle ear near the margin of the tympanic membrane [116]. Middle ear operations for otosclerosis and other diseases can similarly damage taste function. The stretching of the chorda tympani nerve has been associated with metallic taste sensation independent of taste bud stimulation.

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Central nervous system patholosis

Taste disorders occur in a number of central nervous system (CNS) diseases or disorders. Tumors that involve the CNS at the ponto-cerebellar angle can lead to changes in taste perception, as can various central lesions and cerebrovascular accidents [116]. Importantly, a number of neurological and neurodegenerative diseases are associated with taste dysfunction, including epilepsy [117], Parkinson's disease [118], Alzheimer's disease [119, 120], amyotrophic lateral sclerosis [121], myasthenia gravis [122, 123], multiple sclerosis [124, 125], and schizophrenia [126, 127].

Systemic influences and taste disorders

A number of systemic factors can influence taste function. Several paraneoplastic syndromes have been associated with altered taste perception [128]. Diabetes, in rare instances, may influence taste, as can severe anemia and leukemia [5]. Nearly two thirds of approved medications may have taste-related side effects in some individuals, although in most cases such side effects are rare (<1 %). Among those with the highest prevalence rates are antibiotics, anti-hypertensives, antidepressants, muscle relaxants, and multiple cancer chemotherapeutics [129, 130]. A classic example of a drug that has significant taste side effects is the sleep aide Lunesta® (eszopiclone). This widely used cyclopyrrolone produces bitter/metallic taste sensations in approximately two thirds of the population [131].

Oncology-related taste changes

Taste disorders are common in patients undergoing cancer therapy, ranging from 15 to 100 % of patients experiencing changes in taste [132]. Such dysfunction can significantly impact quality of life and oral intake, which have broad implications due to the potential alteration of diet, leading to compromised protein, energy, electrolyte and nutrient intake [1, 2]. A wide range of the prevalence of taste changes in oncology has been reported (56–100 %), likely due to different methods used in data collection and differences across patients and cancer therapies [1, 132]. One review found that patients treated with chemotherapy alone reported taste change in 56 %, two thirds of patients treated with regional head and neck radiotherapy alone, and by 76 % with combined chemotherapy/radiotherapy [1]. Continuing symptoms were reported in 15 %. In solid tumor chemotherapy, the most comprehensive studies have been in breast cancer patients and in a study with 1 year follow-up, dysgeusia continued in 10 % of patients [133]. Radiation therapy for treating head and neck cancers (HNCs) may cause neuroepithelial damage, and chemotherapy that causes neuropathy may also result in a taste change or loss and mucosal sensitivity [134]. To date, taste dysfunction in oncology has been primarily assessed by patient-reported outcome using various survey methods, and rarely has taste testing been conducted in cancer patients.

Taste disorders may occur following head and neck cancer surgery and dental treatment, due to nerve damage during local anesthesia or surgical manipulation [1, 2, 112, 134, 135]. Taste disorders are present in the majority of HNC cancer patients receiving RT and are reported in 75–100 % [111, 112, 136]. Following radiation therapy (RT), taste sensitivity may recover slowly within several months of resolution of mucosal damage; however, taste change may continue indefinitely.

All five primary taste qualities are affected during RT to the oral cavity [136]. Initially, sweet taste perception may be diminished, resulting in reports of increased bitter and salt taste. This alteration may then be followed by general abnormal taste and reduction in taste acuity [109, 111, 136–141]. *Umami* taste perception declines during in the third week of RT and while some may improve by the 8th week, recovery of *umami* taste may be delayed and may persist indefinitely. Loss of *umami* taste may be important in diet and oral nutritional intake because this taste quality affects interest in eating (enjoyment, pleasure) and thus may have the strongest correlation with decreases of quality of life [140]. *Umami* taste has received limited study in HNC patients, and has not been evaluated in combined therapy or with targeted chemotherapeutic agents. There are no data on free fatty acid taste loss or recovery in HNC. In addition, damage to C-fibers resulting in mucosal sensitivity may occur due to the effects of radiation, mucositis with direct taste receptor damage, or neurologic damage/neuropathy due to chemotherapy. Chemotherapy and targeted therapeutics may affect taste by direct taste receptor stimulation or direct damage or via secretion in saliva or gingival crevice fluid and taste change may persist after drug clearance due to damage to the taste buds [132, 133]. Patients frequently describe a bitter, metallic or "chemical" taste when chemotherapy is delivered.

Persistent taste loss or change in RT may be caused by damage to taste receptors [142, 143] and/or hyposalivation. Post-treatment recovery of taste is variable, in some cases improving in 2–6 months, but in others continuing indefinitely [132, 137, 138, 141, 143–147]. Parotid sparing intensity modulated radiation therapy (IMRT) has been associated with more consistent recovery in eating, which may reflect recovery in salivary secretions as well as in taste function [144]. Taste change occurs during treatment for HNC and continues in survivors of treatment, frequently with total loss of taste and slow recovery in some patients and limited recovery in others [148].

Studies of taste function, albeit limited, in solid tumor chemotherapy may provide guidance for understanding the impact of chemotherapy in HNC therapy. Breast cancer patients receiving adjuvant CT frequently report taste complaints

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[133] during chemotherapy. Thus, in one study, hypogeusia was noted in 22 % of such patients and an abnormal metallic or drug dysgeusia in 33 %. Twenty percent reported symptoms that persisted for 6 months after CT, whereas an additional 16 % continued to experience symptoms 12 months later [133]. A recent study of female breast cancer patients identified a taste change in 80 % of patients who were prescribed the microtubule inhibitor, docetaxel. The taste changes markedly affected their quality of life and leading to dietary adaptations including candy before meals, lemon flavoring, and increased sugar intake and reduced oral intake [149]. A cohort of 109 patients (breast cancer 67.9 %, gynecologic cancer 32.1 %) were assessed and taste change was reported in three quarters, with moderate to severe complaints in breast cancer patients (26.6 %) and gynecologic cancers (19.4 %) [108]. Taste change was associated with appetite loss ($r = 0.46$), fatigue ($r = 0.040$), and impact upon QOL scales ($r < 0.30$).

A recent study documented that the impact of taste function on patients is underestimated by health care workers [150]. This study in 30 HNC patients, and health care providers found that patients reported normal taste and smell as more important than anticipated by health care workers ($P = 0.013$).

There are means for preventing at least some conditioned taste aversions that occur in patients receiving chemotherapy or radiation therapy. It is well known that some patients can acquire aversions to food when these foods are eaten before the onset of therapies that induce nausea [151]. Most such aversions are directed towards less preferred and less familiar foods, as well as to major protein sources such as red meats, poultry, fish, and eggs [152]. The initial demonstration that aversions could develop to foods eaten before drug treatments that produce nausea and vomiting employed pediatric patients and a novel ice cream flavor as the target food [153]. Subsequent work demonstrated that the development of such aversions can be mitigated by presenting a novel food stimulus prior to the onset of the drug therapy [154]. In essence, novel foods have the potential to act as a "scapegoat" in blocking the development of such aversions to foods in the normal diet.

Gustatory changes in transplant patients

Taste changes are common in hematopoietic stem cell transplantation (SCT) [119]. Patient reports at day 90–100 post allogeneic SCT included reduced taste sensitivity, and increased change in sour and bitter taste, rather than salt and sweet taste. Taste changes were more common in women, and change in food preparation was reported by some [155]. Sensitivity to sour and bitter taste recovered more rapidly, and change in taste was found to be associated with dry mouth [156].

Taste and smell have also been examined in pediatric SCT patients [157]. By using salt, sweet, sour, and bitter stimuli in 10 pediatric patients, researchers found that one third of subjects reported taste alterations, and one third reported smell abnormalities at 1 month, but full recovery occurred after 2 months. Adult patients were assessed up to 6 years post-transplant, and the most common oral symptoms included dry mouth (44 %) and taste alterations (20 %) [158]. In a follow-up of adolescents post-SCT at 50 and 100 days, slow return to eating was reported, with barriers including oral pain, dry mouth, and taste affecting quality of life [159]. All patients reported taste change early post-transplant, with 30 % having a taste change present at day 100. Smell changes were reported by 30 % and dry mouth by 30 %. Other symptoms affecting eating were nausea and vomiting.

In another study [160], taste perception and salivary flow was assessed up to day 150 and 3 years post-SCT. Taste change was reported in 60.5 % and smell changes in 47.5 % of patients. Change in sweet and salt taste were noted in the patients 3 years post-SCT, but was not correlated with graft-versus-host-disease (GVHD). Taste was tested with sweet, sour, salt, and bitter solutions; sweet and bitter sensations were altered.

Summary

As the biology of taste and flavor of food becomes better understood, the potential to evaluate diagnosis and manage changes in taste perception will improve. The impact of taste and flavor on the care of cancer patients has had limited study to date, but the available data suggests that taste change are more common than generally appreciated. Taste alterations are present during the active part of treatment, and may or may not recover, significantly impacting many survivors. New testing technology for objectively measuring taste function, along with well-validated patient-based outcome scales, will undoubtedly improve our understanding of the nature of disease- and treatment-related changes in taste function, including the natural history of altered taste and its recovery. These tools will promote testing to understand the natural history of taste change in the oncology setting, to lead to interventions for prevention, and management of taste/flavor change. In addition, study of taste in oncology may allow development of specific therapy and products that will facilitate nutritional status and general well-being with potential impact on weight maintenance, energy level, fatigue, mood, and improving the quality of life for cancer survivors.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in review of the biology and testing of taste in oncology. Dr. Epstein and Smutzer are on the advisory board of Insys Rx that is planning development of an intervention for taste change, Dr. Smutzer is supported by an FSSMF grant from Temple University, and Dr. Doty is a shareholder in Sensonics International, a manufacturer and distributor of test of taste and smell.

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References

1. Hovan AJ, Williams PM, Stevenson-Moore P, et al. (2010) A systematic review of dysgeusia induced by cancer therapies. Support Care Cancer 18:1081–1087
2. Epstein JB, Barasch A (2010) Taste disorders in cancer patients: pathogenesis, and approach to assessment and management. Oral Oncol 46:77–81
3. Chaudhari N, Landin AM, Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. Nat Neurosci 3:113–119
4. Hawkes CH (2002) Anatomy and physiology of taste sense. Smell and Taste Complaints, Butterworth Heinemann, Amsterdam, pp 123–45
5. Bromley SM, Doty RL (2015) Clinical disorders affecting taste: an update. In: Doty RL (ed) Handbook of olfaction and gustation, 3rd edn. John Wiley & Sons, Hoboken, N.J., pp. 887–910
6. Prescott J, Stevenson R (2015) Chemosensory integration and the perception of flavor. In: Doty RL (ed) Handbook of olfaction and gustation, 3rd edn. John Wiley & Sons, Hoboken, N.J., pp. 1007–1026
7. Rolls ET (2015) Neural integration of taste, smell, oral texture, and visual modalities. In: Doty RL (ed) Handbook of olfaction and gustation, 3rd edn. John Wiley & Sons, Hoboken, N.J., pp. 1027–1050
8. Sternini C, Anselmi L, Rozengurt E (2008) Enteroendocrine cells: a site of 'taste' in gastrointestinal chemosensing. Curr Opin Endocrinol Diabetes Obes 15:73–78
9. Rozengurt E, Sternini C (2007) Taste receptor signaling in the mammalian gut. Curr Opin Pharmacol 7:557–562
10. Kokrashvili Z, Mosinger B, Margolskee RF (2009) Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. Am J Clin Nutr 90:822S–825S
11. Roper SD (2014) TRPs in taste and chemesthesis. Hand Exp Pharmacol 223:827–871
12. Murray RG (1973) The ultrastructure of taste buds. In: Friedmann I (ed) The ultrastructure of sensory organs. North Holland Publishing Company, Amsterdam, pp. 1–81
13. Witt M, Reutter K (2015) Anatomy of the tongue and taste buds. In: Doty RL (ed) Handbook of olfaction and gustation, 3rd edn. John Wiley & Sons, Hoboken, N.J., pp. 637–663
14. Lebenthal E, Lee PC (1984) Alternative pathways for digestion and adsoprtion in early infancy. J Pediatr GastroenterolNutrition 3: 1–3
15. Murray RD, Kerzner B, Sloan HR, Juhling MH, Gilbert M, Ailabouni A (1986) The contribution of salivary amylase to glucose polymer hydrolysis in premature infants. Pediatr Res 20: 186–191
16. Beidler LM, Smallman RL (1965) Renewal of cells within taste buds. J Cell Biol 27:263–272
17. Hevezi P, Moyer BD, Lu M, et al. (2009) Genome-wide analysis of gene expression in primate taste buds reveals links to diverse processes. PLoS One 4:e6395
18. Chaudhari N, Roper SD (2010) The cell biology of taste. J Cell Biol 190:285–296
19. Chang RB, Waters H, Liman ER (2010) A proton current drives action potentials in genetically identified sour taste cells. Proc Natl Acad Sci U S A 107:22320–22325
20. Mennella JA, Beauchamp GK (1993) The effects of repeated exposure to garlic-flavored milk on the nursling's behavior. Pediatr Res 34:805–808
21. Frank M, Pfaffmann C (1969) Taste nerve fibers: a random distribution of sensitivities to four tastes. Science 164:1183–1185
22. Pfaffmann C (1941) Gustatory afferent impulses. J Cell Comp Physiol 17:253–258
23. Firestein SJ, Margolskee RF, Kinnamon S 1999 "Taste" Basic Neurochemistry: Molecular, Cellular and Medical Aspects (6th edition). Siegel GJ, Agranoff BW, Albers RW, et al., eds. Lippincott-Raven, Philadelphia, Chapter 48.
24. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS (2006) The receptors and cells for mammalian taste. Nature 16(444):288–294
25. Chandrashekar J, Mueller KL, Hoon MA, et al. (2000) T2Rs function as bitter taste receptors. Cell 100:703–711
26. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS (2001) Mammalian sweet taste receptors. Cell 10(106):381–390
27. Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E (2002) Human receptors for sweet and umami taste. Proc Natl Acad Sci U S A 99:4692–4696
28. Nelson G, Chandrashekar J, Hoon MA, et al. (2002) An amino-acid taste receptor. Nature 14(416):199–202
29. Zhao GQ, Zhang Y, Hoon MA, et al. (2003) The receptors for mammalian sweet and umami taste. Cell 115:255–266.
30. Li X (2009) T1R receptors mediate mammalian sweet and umami taste. Am J Clin Nutr 90:733S–737S
31. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS (2001) Mammalian sweet taste receptors. Cell 106:381–390
32. Li X, Bachmanov AA, Maehashi K, et al. (2011) Sweet taste receptor gene variation and aspartame taste in primates and other species. Chem Senses 36:453–475
33. Ji M, Su X, Su X, et al. (2014) Identification of novel compounds for human bitter taste receptors. Chem Biol Drug Des 84:63–74
34. Meyerhof W, Batram C, Kuhn C, et al. (2010) The molecular receptive ranges of human TAS2R bitter taste receptors. Chem Senses 35:157–170
35. Behrens M, Foerster S, Staehler F, Raguse JD, Meyerhof W (2007) Gustatory expression pattern of the human TAS2R bitter receptor gene family reveals a heterogenous population of bitter responsive taste receptor cells. J Neurosci 27:12630–12640
36. Ruiz-Avila L, McLaughlin SK, Wildman D, et al. (1995) Coupling of bitter receptor to phosphodiesterase through transducin in taste receptor cells. Nature 376:80–85
37. Huang L, Shanker YG, Dubauskaite J, et al. (1999) Ggamma13 colocalizes with gustducin in taste receptor cells and mediates IP3 responses to bitter denatonium. Nat Neurosci 2:1055–1062
38. Rossler P, Kroner C, Freitag J, Noe J, Breer H (1998) Identification of a phospholipase C beta subtype in rat taste cells. Europ J Cell Biol 77:253–261
39. Simon SA, de Araujo IE, Gutierrez R, Nicolelis MA (2006) The neural mechanisms of gustation: a distributed processing code. Nat Rev Neurosci 7:890–901
40. Roper SD (2007) Signal transduction and information processing in mammalian taste buds. Pflugers Arch 454:759–776
41. Perez CA, Huang L, Rong M, et al. (2002) A transient receptor potential channel expressed in taste receptor cells. Nat Neurosci 5: 1169–1176
42. Huang YJ, Maruyama Y, Dvoryanchikov G, Pereira E, Chaudhari N, Roper SD (2007) The role of pannexin 1 hemichannels in ATP release and cell-cell communication in mouse taste buds. Proc Natl Acad Sci U S A 104:6436–6441
43. Liu D, Liman ER (2003) Intracellular Ca2+ and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5. Proc Natl Acad Sci U S A 100:15160–15165
44. Kinnamon S (2012) Taste receptor signaling – from tongues to lungs. Acta Physiol 204:158–168
45. Takami S, Getchell TV, McLaughlin SK, Margolskee RF, Getchell ML (1994) Human taste cells express the G-protein alpha-gustducin and neuron-specific enolase. Molecular Brain Res 22: 193–203

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46. Clapp TR, Trubey KR, Vandenbeuch A, et al. (2008) Tonic activity of galpha-gustducin regulates taste cell responsivity. FEBS Lett 12(582):3783–3787
47. Ishimaru Y, Inada H, Kubota M, Zhuang H, Tominaga M, Matsunami H (2006) Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. Proc Natl Acad Sci U S A 103:12569–12574
48. LopezJimenez ND, Cavenagh MM, Sainz E, Cruz-Ithier MA, Battey JF, Sullivan SL (2006) Two members of the TRPP family of ion channels, Pkd1l3 and Pkd2l1, are co-expressed in a subset of taste receptor cells. J Neurochem 98:68–77
49. Roper SD (2015) The taste of table salt. Pflugers Arch 467:457–463
50. Heck GL, Mierson S, DeSimone JA (1984) Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. Science 223:403–405
51. Lindemann B (2001) Receptors and transduction in taste. Nature 413:219–225
52. Lin W, Finger TE, Rossier BC, Kinnamon SC (1999) Epithelial Na+ channel subunits in rat taste cells: localization and regulation by aldosterone. J Comp Neurol 15(405):406–420
53. Oka Y, Butnaru M, von BL, Ryba NJ, Zuker CS (2013) High salt recruits aversive taste pathways. Nature 494:472–475
54. Mattes RD (2011) Accumulating evidence supports a taste component for free fatty acids in humans. Physiol Behav 104:624–631
55. Tucker RM, Mattes RD, Running CA (2014) Mechanisms and effects of "fat taste" in humans. Biofactors 40:313–326
56. Kulkarni BV, Mattes RD (2014) Lingual lipase activity in the orosensory detection of fat by humans. Am J Physiol Regul Integr Comp Physiol 306:R879–R885
57. Gilbertson TA, Fontenot DT, Liu L, Zhang H, Monroe WT (1997) Fatty acid modulation of K+ channels in taste receptor cells: gustatory cues for dietary fat. Am J Physiol 272:C1203–C1210
58. Fukuwatari T, Kawada T, Tsuruta M, et al. (1997) Expression of the putative membrane fatty acid transporter (FAT) in taste buds of the circumvallate papillae in rats. FEBS Lett 414:461–464
59. Ibrahimi A, Abumrad NA (2002) Role of CD36 in membrane transport of long-chain fatty acids. Curr Opin Clin Nutr Metab Care 139-145
60. Gaillard D, Laugerette F, Darcel N, et al 2008 The gustatory pathway is involved in CD36-mediated orosensory perception of long-chain fatty acids in the mouse. FASEB J 1458-68
61. Laugerette F, Passilly-Degrace P, Patris B, et al. (2005) CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clin Invest 115:3177–3184
62. Ehehalt R, Sparla R, Kulaksiz H, Herrmann T, Fullekrug J, Stremmel W (2008) Uptake of long chain fatty acids is regulated by dynamic interaction of FAT/CD36 with cholesterol/sphingolipid enriched microdomains (lipid rafts). BMC Cell Biol 9:45
63. Cartoni C, Yasumatsu K, Ohkuri T, et al. (2010) Taste preference for fatty acids is mediated by GPR40 and GPR120. J Neurosci 30:8376–8382
64. Febbraio M, Guy E, Coburn C, et al. (2002) The impact of overexpression and deficiency of fatty acid translocase (FAT)/CD36. Mol Cell Biochem 239:193–197
65. Su X, Abumrad NA (2009) Cellular fatty acid uptake: a pathway under construction. Trends Endocrinol Metab 20:72–77
66. Martin C, Chevrot M, Poirier H, Passilly-Degrace P, Niot I, et al. (2011) CD36 as a lipid sensor. Physiol Behav 105:36–42
67. Zhou S, Tang QJ, Zhang Z, et al. (2015) Nutritional composition of three domesticated culinary-medicinal mushrooms: oudemansiella sudmusida, lentinus squarrosulus, and tremella aurantialba. Int J Med Mushrooms 17:43–49
68. Chen CS, Bench EM, Allerton TD, Schreiber AL, Arceneaux III KP, Primeaux SD (2013) Preference for linoleic acid in obesity-prone and obesity-resistant rats is attenuated by the reduction of CD36 on the tongue. Am J Physiol Regul Integr Comp Physiol 305:R1346–R1355
69. Keller KL, Liang LC, Sakimura J, et al. (2012) Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. Obesity (Silver Spring) 20:1066–1073
70. Itoh Y, Kawamata Y, Harada M, et al. (2003) Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature 13(422):173–176
71. Iwata S, Yoshida R, Ninomiya Y (2014) Taste transductions in taste receptor cells: basic tastes and moreover. Curr Pharm Des 20:2684–2692
72. Sclafani A, Zukerman S, Glendinning JI, Margolskee RF (2007) Fat and carbohydrate preferences in mice: the contribution of alpha-gustducin and Trpm5 taste-signaling proteins. Am J Physiol Regul Integr Comp Physiol 293:R1504–R1513
73. Liu P, Shah BP, Croasdell S, Gilbertson TA (2011) Transient receptor potential channel type M5 is essential for fat taste. J Neurosci 31:8634–8642
74. Hamilton JA, Kamp F (1999) How are free fatty acids transported in membranes? Is it by proteins or by free diffusion through the lipids? Diabetes 48:2255–2269
75. Scott K (2005) Taste recognition: food for thought. Neuron 48:455–464
76. Travers SP, Norgren R (1995) Organization of orosensory responses in the nucleus of the solitary tract of rat. J Neurophysiol 73:2144–2162
77. Rosen AM, Roussin AT, Di Lorenzo PM (2010) Water as an independent taste modality. Front Neurosci 4:175
78. Beckstead RM, Morse JR, Norgren R (1980) The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. J Comp Neurol 15(190):259–282
79. Pritchard TC, Hamilton RB, Morse JR, Norgren R (1986) Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. J Comp Neurol 244:213–228
80. Rolls ET, Yaxley S, Sienkiewicz ZJ (1990) Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. J Neurophysiol 64:1055–1066
81. Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S (1988) The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. J Physiol 397:1–12
82. Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10:220–242
83. Rolls ET (2000) Taste, olfactory, visual and somatosensory representations of the sensory properties of foods in the brain, and their relation to the control of food intake. In: Berthoud HR, Seeley RJ (eds) Neural and metabolic control of macronutrient intake. CRC Press, Boca Raton, pp. 247–262
84. Green BG, Hayes JE (2004) Individual differences in perception of bitterness from capsaicin, piperine and zingerone. Chem Senses 29:53–60
85. Bornstein WS (1940) Cortical representation of taste in man and monkey. II. The localization of the cortical taste area in man, a method of measuring impairment of taste in man. Yale J Biol Med 13:133–156
86. Snyder DJ, Sims CA, Bartoshuk LM (2015) Psychophysical measures of human oral sensation. In: Doty RL (ed) Handbook of olfaction and gustation. John Wiley & Sons, Hoboken, N.J., pp. 751–774
87. Hawkes CH, Doty RL (2016) Smell and taste complaints. Cambridge University Press, Cambridge

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88. Murphy C, Quinonez C, Nordin S (1995) Reliability and validity of electrogustometry and its application to young and elderly persons. Chem Senses 20:499–503
89. Hara S (1955) Interrelationship among stimulus intensity, stimulated area and reaction time in the human gustatory sensation. Bull Tokyo Med Dental Univ 2:147–157
90. Smutzer G, Lam S, Hastings L, et al. (2008) A test for measuring gustatory function. Laryngoscope 118:1411–1416
91. Doty RL, Laing DG (2003) Psychophysical measurement of olfactory function, including odorant mixture assessment. In: Doty RL (ed) Handbook of olfaction and gustation, 2nd edn. Marcel Dekker, New York, pp. 203–228
92. Hahn H, Günther H (1932) Uber die reize und die reizbedingungen des geschmackssinnes. Pflügers Arch Ges Physiol 231:48–67
93. ASTM (1997) Standard practice for determination of odor and taste thresholds by a forced-choice ascending concentration series method of limits (E679-97 & E679-04). American Society for Testing and Materials, Philadelphia
94. Jones FN (1956) A forced-choice method of limits. Am J Psychol 69:672–673
95. Kunka M, Doty RL, Settle RG (1981) An examination of intertrial interval and gender influences on sucrose detection thresholds established by a modified staircase procedure. Perception 10:35–38
96. Harris H, Kalmus H (1949) The measurement of taste sensitivity to phenylthiourea (P.T.C.). Annals of Eugenics 15:24–31
97. Barnicot NA, Harris H, Kalmus H (1951) Taste thresholds of further eighteen compounds and their correlation with P.T.C thresholds. Annals of Eugenics 16:119–128
98. Harris H, Kalmus H (1951) The distribution of taste thresholds for phenylthiourea of 384 sib pairs. Ann Eugen 16:226–230
99. Henkin RI, Solomon DH (1962) Salt-taste threshold in adrenal insufficiency in man. J Clin Endocrinol Metab 22:856–858
100. Henkin RI, Gill JR, Bartter FC (1963) Studies on taste thresholds in normal man and in patients with adrenal cortical insufficiency: the role of adrenal cortical steroids and of serum sodium concentration. J Clin Invest 42:727–735
101. Desai H, Smutzer G, Coldwell SE, Griffith JW (2011) Validation of edible taste strips for identifying PROP taste recognition thresholds. Laryngoscope 121:1177–1183
102. Tucker R, Nuessle TM, Garneau NL, Smutzer G, Mattes RD (2015) No difference in perceived intensity of linoleic acid in the oral cavity between obese and non-obese adults. Chem Senses 40:557–563
103. Soter A, Kim J, Jackman A, Tourbier I, Kaul A, Doty RL (2008) Accuracy of self-report in detecting taste dysfunction. Laryngoscope 118:611–617
104. Stinton N, Atif MA, Barkat N, Doty RL (2010) Influence of smell loss on taste function. Behav Neurosci 124:256–264
105. Sandell MA, Breslin PA (2006) Variability in a taste-receptor gene determines whether we taste toxins in food. Curr Biol 16:R792–R794
106. Ganzer H, Touger-Decker R, Byham-Gray L, Murphy BA, Epstein JB (2015) The eating experience after treatment for head and neck cancer: a review of the literature. Oral Oncol 51:634–642
107. Doty RL (2015) Handbook of olfaction and gustation, 3rd edn. John Wiley & Sons, Inc., Hoboken, N.J., pp. 1–1217
108. Mossman K, Shatzman A, Chencharick J (1982) Long-term effects of radiotherapy on taste and salivary function in man. Int J Radiat Oncol Biol Phys 8:991–997
109. Zheng WK, Inokuchi A, Yamamoto T, Komiyama S (2002) Taste dysfunction in irradiated patients with head and neck cancer. Fukuoka Igaku Zasshi 93:64–76
110. Fernando IN, Patel T, Billingham L, et al. (1995) The effect of head and neck irradiation on taste dysfunction: a prospective study. Clin Oncol (Royal College of Radiologists) 7:173–178
111. Yamashita H, Nakagawa K, Tago M, et al. (2006) Taste dysfunction in patients receiving radiotherapy. Head Neck 28:508–516
112. Comeau TB, Epstein JB, Migas C (2001) Taste and smell dysfunction in patients receiving chemotherapy: a review of current knowledge. J Support Care Cancer 9:575–580
113. Holscher T, Seibt A, Appold S, et al. (2005) Effects of radiotherapy on olfactory function. Radiother Oncol 77:157–163
114. Taverner D (1973) Medical management of idiopathic facial (Bell's) palsy. Proc R Soc Med 66:554–556
115. Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N (1996) Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 124:27–30
116. Landis BN, Beutner D, Frasnelli J, Huttenbrink KB, Hummel T (2005) Gustatory function in chronic inflammatory middle ear diseases. Laryngoscope 115:1124–1127
117. Doty RL, Tourbier I, Neff JK, et al 2015 Influences of temporal lobe epilepsy and temporal lobe resection on olfactory function. Ann Neurol, submitted
118. Doty RL, Nsoesie MT, Chung I, et al. (2015) Taste function in early stage treated and untreated Parkinson's disease. J Neurol 262:547–557
119. Sakai M, Ikeda M, Kazui H, Shigenobu K, Nishikawa T (2015) Decline of gustatory sensitivity with the progression of Alzheimer's disease. Int Psychogeriatr 1:1–7
120. Suto T, Meguro K, Nakatsuka M, et al. (2014) Disorders of "taste cognition" are associated with insular involvement in patients with Alzheimer's disease and vascular dementia: "memory of food is impaired in dementia and responsible for poor diet". Int Psychogeriatr 26:1127–1138
121. Petzold GC, Einhaupl KM, Valdueza JM (2003) Persistent bitter taste as an initial symptom of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 74:687–688
122. Leon-Sarmiento FE, Leon-Ariza DS, Doty RL (2013) Dysfunctional chemosensation in myasthenia gravis: a systematic review. J Clin Neuromuscul Dis 15:1–6
123. Kabasawa C, Shimizu Y, Suzuki S, et al. (2013) Taste disorders in myasthenia gravis: a multicenter cooperative study. Eur J Neurol 20:205–207
124. Dahlslett SB, Goektas O, Schmidt F, Harms L, Olze H, et al. (2012) Psychophysiological and electrophysiological testing of olfactory and gustatory function in patients with multiple sclerosis. Eur Arch Otorhinolaryngol 269:1163–1169
125. Doty RL, Tourbier IA, Pham DL, et al. (2015) Taste dysfunction in multiple sclerosis. Neurology, submitted
126. Ansoleaga B, Garcia-Esparcia P, Pinacho R, Haro JM, Ramos B, et al. (2015) Decrease in olfactory and taste receptor expression in the dorsolateral prefrontal cortex in chronic schizophrenia. J Psychiatr Res 60:109–116
127. Moberg PJ, Mcgue C, Kanes SJ, et al. (2007) Phenylthiocarbamide (PTC) perception in patients with schizophrenia and first-degree family members: relationship to clinical symptomatology and psychophysical olfactory performance. Schizophr Res 90:221–228
128. Panayiotou H, Small SC, Hunter JH, Culpepper RM (1995) Sweet taste (dysgeusia). The first symptom of hyponatremia in small cell carcinoma of the lung. Arch Intern Med 155:1325–1328
129. Schiffman SS, Gatlin CA (1993) Clinical physiology of taste and smell. Ann Rev Nutr 13:405–436
130. Doty RL, Shah M, Bromley SM (2008) Drug-induced taste disorders. Drug Saf 31:199–215

Author's personal copy

131. Doty RL, Treem J, Tourbier I, Mirza N (2009) A double-blind study of the influences of eszopiclone on dysgeusia and taste function. Pharmacol Biochem Behav 94:312–318
132. Ripamonti C, Fulfaro F (1998) Taste alterations in cancer patients. J Pain Symptom Manag 16:349–351
133. Jensen SB, Mouridsen HT, Bergmann OJ, Reibel J, Brunner N, Nauntofte B (2008) Oral mucosal lesions, microbial changes, and taste disturbances induced by adjuvant chemotherapy in breast cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106:217–226
134. Leitzen C, Bootz F, Herberhold S, et al. (2012) Changes in taste during IM/IMRT radiotherapy for head and neck cancer patients. Strahlentherapie. Onkologie 188:184–185
135. Landis BN, Giger R, Dulguerov P, Hugentobler M, Hummel T, et al. (2007) Gustatory function after microlaryngoscopy. Acta Otolaryngol (Stockh) 127:1086–1090
136. Yamashita H, Nakagawa K, Hosoi Y, et al. (2009) Umami taste dysfunction in patients receiving radiotherapy for head and neck cancer. Oral Oncol 45:e19–e23
137. Redda MGR, Allis S (2006) Radiotherapy-induced taste impairment. Cancer Treat Rev 32:541–547
138. Maes A, Huygh I, Weltens C, et al. (2002) De gustibus: time scale of loss and recovery of tastes caused by radiotherapy. Radiother Oncol 63:195–201
139. Mossman KL, Chencharick JD, Scheer AC, et al. (1979) Radiation-induced changes in gustatory function: comparison of effects of neutron and photon irradiation. Int J Radiat Oncol Biol Phys 5:521–528
140. Shi HB, Masuda M, Umezaki T, et al. (2004) Irradiation impairment of umami taste in patients with head and neck cancer. Auris Nasus Larynx 31:401–406
141. Halyard MY, Jatoi A, Sloan JA, et al. (2007) Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central cancer treatment group (N01C4). Int J Radiat Oncol Biol Phys 67:1318–1322
142. Nelson GM (1998) Biology of taste buds and the clinical problem of taste loss. Anat Rec 253:70–78
143. Sandow PL, Hejrat-Yazdi M, Heft MW (2006) Taste loss and recovery following radiation therapy. J Dent Res 85:608–611
144. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A (2003) Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys 57:61–70
145. Epstein JB, Emerton S, Kolbinson DA, et al. (1999) Quality of life and oral function following radiotherapy for head and neck cancer. Head Neck- 21:1–11
146. de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA (2000) Long-term quality of life of patients with head and neck cancer. Laryngoscope 110:98–106
147. Oates JE, Clark JR, Read J, et al. (2007) Prospective evaluation of quality of life and nutrition before and after treatment for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 133:533–540
148. Cooperstein E, Gilbert J, Epstein JB, et al. (2012) Vanderbilt head and neck symptom survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck 34:797–804
149. Speck RM, DeMichele A, Farrar JT, et al. (2013) Taste alteration in breast cancer patients treated with taxane chemotherapy: experience, effect, and coping strategies. Support Care Cancer 21:549–555
150. Gill SS, Frew J, Fry A, et al. (2011) Priorities for the head and neck cancer patient, their companion and members of the multidisciplinary team and decision regret. Clin Oncol (R Coll Radiol) 23:518–524
151. Bernstein IL, Webster MM (1980) Learned taste aversions in humans. Physiol Behav 25:363–366
152. Midkiff EE, Bernstein IL (1985) Targets of learned food aversions in humans. Physiol Behav 34:839–841
153. Bernstein IL, Webster MM, Bernstein ID (1982) Food aversions in children receiving chemotherapy for cancer. Cancer 50:2961–2963
154. Broberg DJ, Bernstein IL (1987) Candy as a scapegoat in the prevention of food aversions in children receiving chemotherapy. Cancer 60:2344–2347
155. Haverman TM, Raber-Durlacher JE, Rademacher WM, et al. (2014) Oral complications in hematopoietic stem cell recipients: the role of inflammation. Mediat Inflamm 2014:378281
156. Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P (2002) Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 30:785–792
157. Cohen J, Laing DG, Wilkes FJ (2012) Taste and smell function in pediatric blood and marrow transplant patients. Support Care Cancer 20:3019–3023
158. Hull KM, Kerridge I, Schifter M (2012) Long-term oral complications of allogeneic haematopoietic SCT. Bone Marrow Transplant 47:265–270
159. Rodgers C, Young A, Hockenberry M, Binder B, Symes L (2010) The meaning of adolescents' eating experiences during bone marrow transplant recovery. J Pediatr Oncol Nurs 27:65–72
160. Watters AL, Epstein JB, Agulnik M (2011) Oral complications of targeted cancer therapies: a narrative literature review. Oral Oncol 47:441–448