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Taste Receptors in Innate Immunity

Robert J. Lee and

Department of Otorhinolaryngology, Perelman School of Medicine, University of Pennsylvania, Ravdin Building, 5th floor, Philadelphia, PA 19104

Noam A. Cohen

Department of Otorhinolaryngology, Perelman School of Medicine, University of Pennsylvania, Ravdin Building, 5th floor, Philadelphia, PA 19104. Philadelphia Veterans Affairs Medical Center Surgical Services, 3900 Woodland Ave. Philadelphia, PA 19104

Noam A. Cohen: noam.cohen@uphs.upenn.edu

Abstract

Taste receptors were first identified on the tongue, where they initiate a signaling pathway that communicates information to the brain about the nutrient content or potential toxicity of ingested foods. However, recent research has shown that taste receptors are also expressed in a myriad of other tissues, from the airway and gastrointestinal epithelia to the pancreas and brain. The functions of many of these extraoral taste receptors remain unknown, but emerging evidence suggests that bitter and sweet taste receptors in the airway are important sentinels of innate immunity. This review discusses taste receptor signaling, focusing on the G-protein coupled–receptors that detect bitter, sweet, and savory tastes, followed by an overview of extraoral taste receptors and in-depth discussion of studies demonstrating the roles of taste receptors in airway innate immunity. Future research on extraoral taste receptors has significant potential for identification of novel immune mechanisms and insights into host-pathogen interactions.

Keywords

Airway physiology; Chronic rhinosinusitis; Epithelial biology; Host-pathogen interactions; Respiratory infection; Interkingdom signaling

Introduction

It has been previously proposed that the immune system is the mammalian “sixth sense” [1–3]. While our senses of sight, smell, hearing, touch, and taste allow us to consciously perceive our external environment, our immune system similarly detects the presence of potentially dangerous foreign chemicals and organisms, albeit internally and often subconsciously. Looking at the immune system from this viewpoint, it is perhaps not surprising but nonetheless very exciting that recent studies have demonstrated that several mechanisms of mammalian innate immunity utilize components of sensory signal

Correspondence to: Noam A. Cohen, noam.cohen@uphs.upenn.edu.

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transduction. Chemosensory G-protein-coupled receptors (GPCRs) that were originally identified as “taste” receptors have now been found in many tissues outside the tongue (Table 1), and bitter and sweet taste GPCRs have recently been found to be sentinels of defence against infection in the airway, where they function as a novel arm of innate immunity, as described in more detail below. Emerging evidence [4] also supports the hypothesis that taste receptors serve similar immune roles in at least some of the other tissues in which they are expressed. Because these chemosensory receptors are likely involved in many biological processes beyond taste, it is important that researchers in other fields understand the physiology and cell biology of chemosensory receptors. Thus, the focus of this review is on taste receptor signalling mechanisms, extra-oral taste receptors, and the recently identified roles of taste receptors in the regulation of airway epithelial innate immunity.

The Biology of Taste and Taste Receptors

Overview of Taste Signaling

Taste GPCRs were first identified in the type II taste cells of the tongue. These receptors signal information to the brain regarding the nutritive value and/or potential toxicity of ingested foods and beverages [5,6]. Our sensory perception of foods and beverages is called flavor [7], which is a complex sensation made up of taste, smell, and texture, also called “mouth feel.” Flavor can also include pain, as in the case of capsaicin- or CO₂-mediated activation of nociceptor neurons during ingestion of foods containing chili peppers or carbonated beverages [8,9], respectively. However, there are only five well-defined types of tastes that are detected by the sensory cells of the taste buds of the tongue [10]. These are sweet, salty, sour, bitter, and savory (also known as umami, which is the taste of savory amino acids such as glutamate). Sweet, salty, and umami tastes reveal the presence of sugars, sodium chloride, and amino acids, respectively. These are generally perceived as beneficial nutrients, and they result in a pleasing taste. In contrast, sour and bitter tastes are often perceived as unpleasant; they signal the presence of potentially harmful chemicals. Sour taste can alert the body to the presence of spoiled foods by detecting lactic acid products from bacterial fermentation, while bitter can signal the presence of toxic plant alkaloids such as strychnine [11].

There is thought to be only one major type of receptor type for sweet (T1R2/3 [12,11,13–15]), salty (the epithelial sodium channel or ENaC [16–20]), savory (T1R1/3 [21,22,14,23,24]), and sour (acid-sensing ion channels or ASICs [25,26,20,27]). Bitter sensation is unique in that there are multiple G-protein coupled receptor (GPCR) isoforms tuned to a wide-array of different bitter compounds. These are known as T2R receptors [28,6,29–31] (Fig. 1a), and humans have at least 25 different functional T2R isoforms [15,32]. T2R bitter taste receptors are found in taste bud cells known as type II cells, sometimes also called receptor cells [33,34]. Type II cells also contain a second family of taste GPCRs, known as T1R receptors. The T1R family contains only 3 isoforms, T1R1, T1R2, and T1R3; (Fig. 1b–c), which oligomerize to make up the receptors for umami (T1R1 + T1R3) and sweet (T1R2 + T1R3). However, it is important to note that an alternative T1R3 homo-oligomeric form of a sweet taste receptor has also been recently proposed to

exist in pancreatic beta cells [35–38] and adipocytes [39]. Additionally, some type II taste cells have been observed to express only T1R3 without T1R1 or T1R2 [32,40], and T1R3 homo-oligomers have been proposed to affect calcium and magnesium taste [41]. Thus, the true range of oligomerization states of T1Rs and the resulting functional consequences are not yet fully clear. Biochemical studies of T1R and T2R oligomerization have relied on heterologous expression systems, including HEK293 cells, often utilizing tagged-versions of the receptors [42,43]. *In vivo* biochemistry has so far been hampered in particular by low levels of protein expression and poor antibody specificity [44]. It still remains to be determined if and/or how the *in vivo* oligomerization of T1Rs and T2Rs changes their pharmacological profiles or otherwise alters their physiological responses.

Within type II taste cells, T1R and T2R signaling is thought to occur through identical intracellular pathways (Fig. 2) [33,45]. Stimulation of these receptors activates intracellular calcium signals that cause the type II cells to release ATP [46,47] to activate purinergic receptors on presynaptic cells and afferent sensory fibers [11,45,48]. While these bitter, sweet, and umami GPCRs share common intracellular signaling pathways, the differential transmission of these three taste sensations occurs, at least in part, at a cellular level. The majority of type II taste cells respond to only one type of taste: bitter, sweet, or umami [49–51,34], depending on their expression of T2Rs, T1R2+T1R3, or T1R1+T1R3, respectively. Each taste bud contains multiple type II cells that are differentially coded for bitter, sweet, or umami sensation. However, we still do not yet fully understand how these three tastes are discriminated, as some type II cells have been found to express multiple types of receptors and respond to multiple types of tastes [49–51].

It is important to note that the focus of this review is on T1R sweet and T2R bitter taste GPCRs, which have been implicated in innate immunity as described below. However, other GPCRs are expressed on taste cells of the tongue. Most notable are the free fatty acid receptor 1 (FFA1; also known as GPR40) and GPR120, which detects omega-3 fatty acids [52,53]. These may even constitute a sixth taste sensation, the taste of fats, which have previously been thought to be mainly detected through texture. Fat preference may also involve the glycoprotein CD36 (also known as fatty acid translocase or FAT) [54–62]. However, the function of these proteins in human fat taste and fat preference is not yet fully understood and remains an active area of research. Any roles for these fatty acid receptors or other taste cell GPCRs in innate immunity have not been identified.

Extraoral Taste Receptors: Identification and Potential Roles in Immunity

Recent studies have determined that the expression of T2R bitter and T1R sweet taste GPCRs extends far beyond the tongue (reviewed in [63,11,64,65,45,66]). These receptors have been found in organs as diverse as the brain, pancreas, bladder, and testes, and they have been termed “extraoral” taste receptors. A representative list of known extraoral taste GPCR expression and some of the known roles of these receptors are shown in Table 1. Research has elucidated several of the downstream signaling pathways of extraoral T2Rs and T1Rs, but for the most part their physiological roles remain to be determined. We also lack information about the identities of physiological ligands for most of these receptors in other tissues. Oral T2Rs detect poisonous ingested chemicals like toxic plant products, and

oral T1Rs detect sugar in nutrient-rich foods [67,15,28,11,68]; however, it is unclear what agonists might activate extraoral receptors in tissues that do not come into direct contact with ingested food. Nonetheless, because many compounds used as medications are known to have a bitter taste [68], one important implication of the discovery of extra-oral T2R bitter receptors is that extraoral T2Rs may be a mechanism underlying some off-target drug effects [64], reinforcing the need to better understand the role these receptors play in human biology.

In the case of T2R bitter receptors, we and other researchers have hypothesized that at least some extra-oral T2Rs may detect bitter components of or products secreted by pathogenic bacteria or fungi. The initial evidence for this comes from studies of solitary chemosensory cells (SCCs) in the mouse nose, which express both T2R and T1R receptors [69–78]. The Finger lab at the University of Colorado showed in 2010 that these SCCs exhibit intracellular calcium signals in response to acyl-homoserine lactones (AHLs) [73], which are quorum-sensing molecules secreted by gram-negative bacteria such as the airway pathogen *Pseudomonas aeruginosa* [79,80]. As many lactones are known to be bitter [81], this result suggested AHLs activate one or more extraoral T2R receptors, which has now been experimentally confirmed [82,83] and will be described in greater detail below. It is highly likely that there are other bitter or sweet products secreted by pathogenic microorganisms that are detected by extra-oral T2Rs or T1Rs, respectively.

A role for T2Rs in innate immunity is particularly intriguing, as T2Rs have a uniquely high density of naturally occurring genetic variants [84]. This variation contributes to the complex individual taste preferences for bitter foods such as green leafy vegetables [85] as well as beverages such as coffee [86], scotch [87], and beer [87]. We hypothesize that if T2Rs are important in innate or adaptive immunity, the genetic variation that causes differences in T2R receptor function governing taste preferences may cause variation in how cells from different individuals detect and respond to infection. In other words, susceptibility to or protection against infections might result from genetic variations in T2Rs that cause reduced or enhanced receptor function, respectively. It has long been thought that genetic components underlie susceptibility to certain types of infections [88], particularly respiratory infections [89–91]. As we will discuss below, recent evidence has now validated this hypothesis by demonstrating that T2Rs do indeed recognize bacterial products and that genetic variation in at least one human T2R isoform can alter susceptibility to bacterial infection.

Role of Bitter and Sweet Taste Receptors in Upper Respiratory Innate Immunity

Overview Airway Epithelial Innate Immunity

The upper respiratory tract consists of the nose and sinuses, termed the sinonasal cavity. In addition to warming and humidifying inspired air, the sinonasal cavity is also the front line of defense of the respiratory tract [92–98]. Host-pathogen interactions occur with every breath containing aerosolized fungal spores, bacteria, and virus particles [95]. However, in most individuals, the upper and lower airways remain free of pathological bacterial. This is

largely due to the multiple first-line innate immune mechanisms that work in concert to defend the sinonasal epithelium (Fig. 3). The primary physical defense is the process of mucociliary clearance [99–102,92,93,103,104]. The airway surface is lined by a mucus gel made up of cross-linked glycosylated mucin macromolecules produced by airway secretory cells; the carbohydrate side-chains of the mucins create “sticky” binding sites that trap airway pathogens and particulates in the mucus [93,92,104,99,105]. The spatially and temporally coordinated beating of ciliated epithelial cells then transports the debris- and pathogen-laden mucus from the upper and lower respiratory passages toward the throat, where the mucous/pathogens/debris mixture is cleared by swallowing or expectoration [93,92,104,99]. Mucociliary clearance is complemented by the secretion of antimicrobial compounds including proteins such as lysozyme, lactoferrin, cathelicidins, and defensins [106], as well as the generation of reactive oxygen and nitrogen species (ROS/RNS) that can have direct antibacterial, anti-fungal, and antiviral effects [107,108]. Nitric oxide (NO) is thought to be a particularly important RNS defense mechanism in the sinuses. High levels of nitric oxide synthase (NOS), the enzyme that generate NO radicals from arginine, are expressed in the sinonasal epithelium [109,110]. NO and its reactive derivatives have direct bactericidal effects [107,108], and it is thought that NO produced by the sinuses diffuses through the mucous and is important for preventing infection. Altered NO levels have been linked to chronic rhinosinusitis and other airway diseases [111–115]. Finally, when the above innate defenses are not enough, epithelial cells can also secrete cytokines and chemokines that can recruit dedicated immune cells and activate inflammatory pathways [106].

When these upper respiratory innate defenses fail, infection can result. Chronic rhinosinusitis (CRS) is a disease of chronic infection and inflammation of the nose and sinuses [92,93], frequently requiring prolonged medical therapy and severely decreasing quality of life [92,93]. In fact, CRS patients report worse quality-of-life scores for physical pain and social functioning than those suffering from chronic obstructive pulmonary disease (COPD), congestive heart failure, or angina [116,117]. In addition to severely reducing quality of life, sinus and nasal infections can “seed” lower airway infections and/or exacerbate existing lower airway diseases [118], making these infections an important public health burden. Elucidating innate airway epithelial defense mechanisms and identifying novel therapeutic targets is particularly important in light of the rising prevalence of antibiotic resistant bacteria in patients with upper airway infections and CRS [98,119–123]. Interestingly, as we will describe below, many innate defense pathways in the sinonasal cavity are regulated by taste GPCRs.

The T2R38 Bitter Taste Receptor in Human Upper Airway Cilia Detects Bacterial Quorum-Sensing Molecules and Stimulates Nitric Oxide (NO) Production

In addition to being the “engines” driving mucociliary clearance, airway ciliated cells have also long been known to function in immune detection through the expression of Toll-like receptors (TLRs [97,98,124,125]). TLRs recognize conserved structures called pathogen-associated molecular patterns (PAMPs), including lipoteichoic acid (LTA; recognized by TLR2) from gram-positive bacteria, lipopolysaccharide (LPS; recognized by TLR4) from gram-negative bacteria, and bacterial flagellin (recognized by TLR5) [97,98]. In 2009, the

Welsh Lab at the University of Iowa published the observation that human bronchial epithelial cells also express T2R bitter taste receptors that activate calcium responses to increase ciliary beating [126], proposing that this process is a response that exists to clear noxious chemicals. Interestingly, these bronchial T2Rs were found to be localized within the motile cilia themselves [126], demonstrating that motile cilia are “sensory organelles.” This finding was highly novel, as traditionally there are two distinct classifications of animal cell cilia. *Primary* or *sensory* cilia are expressed on nearly every cell type in the body with one single primary cilia per cell, containing a 9+0 microtubule structure and functioning in diverse sensory roles [127–129]. *Motile* cilia, however, are expressed only in specialized epithelial cells and exhibit a 9+2 microtubule structure, occurring at 100–300 per cell [130]. Motile cilia had long been thought to be solely responsible for mechanical transport of fluid/mucus, as in the airway epithelial (Fig. 2) and during development of embryonic left-right asymmetry in vertebrates [131]. However, the identification of chemosensory taste receptors within motile cilia suggested that they, like primary cilia, also serve a sensory role.

We examined the expression of bitter taste receptors in motile cilia of the upper respiratory tract to determine if they, too, express T2R receptors and whether these receptors might detect bacterial products and play a role in innate immunity. We found that human sinonasal ciliated epithelial cells express the bitter taste receptor T2R38, which was indeed localized to the motile cilia [82]. T2R38 function was studied in human tissue explants as well as air-liquid interface (ALI) cultures of primary sinonasal cells. ALI cultures are a state-of-the-art respiratory cell culture model that mimics a polarized respiratory epithelium with well-differentiated ciliated cells [132–136]. When ciliated epithelial cells were stimulated with T2R38-specific agonists, such as phenylthiocarbamide (PTC), they exhibited low-level calcium responses that activated NOS to drive robust intracellular NO production [82]. This signaling pathway depended on two important components of the canonical taste signal transduction cascade, TRPM5 [137,11,138,139] and phospholipase C isoform $\beta 2$ (PLC $\beta 2$) [11] (Fig. 2), as shown by pharmacological inhibition [82].

High levels of NOS are expressed in the cilia and microvilli of the sinonasal epithelium [109,110], and NO production is thought to be an important airway defense mechanism [111,140,141]. NO released by the airway epithelium is believed to be able to rapidly diffuse inside bacteria, where its reactive derivative S-nitrosothiols and peroxynitrites can damage DNA or membrane lipids and inactivate enzymes containing sulfhydryl, thiol groups, or metal cofactors [107,108]. We found that the NO produced during T2R38 activation acted in two ways. First was as a second messenger to increase mucociliary clearance through guanylyl cyclase and PKG activation, which increases ciliary beating [130]. Secondly, the NO also diffused into the airway surface liquid (ASL) and had direct bactericidal effects against *P. aeruginosa* [82]. In this study, we also identified the two major *P. aeruginosa* AHLs, N-butyryl-L-homoserine lactone (C4HSL) and N-3-oxo-dodecanoyl-L-homoserine lactone (C12HSL) [80] as T2R38 agonists [82]. Using a Wt *P. aeruginosa* strain (PAO1) as well as a strain mutated for the enzymes that synthesize AHLs (strain PAO-JP2; *lasI*, *rhlI*; [142]), we demonstrated that T2R38 detects physiological concentrations of AHLs to activate calcium-dependent NO-production, suggesting that T2R38 functions in airway ciliated cells as a sentinel receptor to detect bacteria and regulate innate immune responses.

Because many types of gram-negative bacteria secrete AHLs [143], this is likely a general innate immune mechanism against many pathogenic gram-negative bacteria. A diagram of T2R38 function in sinonasal ciliated epithelial cells is shown in Fig. 4.

While there is no clear T2R38 homologue between humans and mice, mice do express T2R receptors capable of responding to PTC [144–151,72]. We found that mouse nasal ciliated epithelial cells likewise respond to PTC or AHL stimulation with a calcium-dependent NO response that increases mucociliary clearance [83]. The use of TRPM5^{-/-} and PLCβ2^{-/-} knockout mouse cultures supported the requirement for these two signal transduction components. Interestingly, the airway epithelial T2R38 response was completely intact in mice knocked-out for the Gα protein Gα-gustducin [83], an essential component of taste signaling in the type II taste cells of the tongue [152–154,14,155,11,29]. While taste-receptor signaling has been previously observed to be partially intact in the absence of Gα-gustducin [156,21,155,157,14], to our knowledge, this finding that a T2R-receptor-linked signaling pathway is completely independent of Gα-gustducin is unique [83]. Additional research is needed to more clearly determine the signal transduction mechanisms of T2R38 and any other T2Rs that are localized to airway cilia.

To determine if T2R38 may be a marker for bacterial infection, we examined the effects of common human polymorphisms in the *TAS2R38* gene, which encodes T2R38, on airway innate immune responses. *TAS2R38* is one of the most well-studied *TAS2R* genes [158–162]. *TAS2R38* has 2 common polymorphisms in Caucasian populations, one encoding a functional receptor and one encoding a nonfunctional receptor. The differences in the resulting proteins are at amino acid positions 49, 262, and 296. The functional T2R38 receptor contains proline (P), alanine (A), and valine (V) residues while the nonfunctional T2R38 contains alanine (A), valine (V), and isoleucine (I) at these positions, respectively [158]. It has been suggested that the loss of the valine at the third position in the AVI variant prevents receptor activation [163–165]. Homozygous AVI/AVI individuals (~30% frequency in Caucasian populations) are “non-tasters” for the T2R38-specific agonists PTC (also known as phenylthiourea or PTU) and 6-propyl-2-thiouracil (PROP) [158]. PAV/PAV individuals (~20% frequency in Caucasian populations [158]) are termed “super tasters” for these agonists, while AVI/PAV heterozygotes have varying intermediate levels of taste [166,158].

We found that the AHL-induced antibacterial responses of human sinonasal epithelial cells correlate with these genetic polymorphisms. Epithelial cells derived from PAV/PAV “supertaster” individuals exhibited markedly enhanced NO production, mucociliary clearance, and bacterial killing compared with AVI/PAV heterozygote or AVI/AVI “non-taster” cells [82]. Furthermore, preliminary clinical data suggested that PAV/PAV T2R38 “supertasters” are less susceptible to gram-negative sinonasal infection than PAV/AVI or AVI/AVI patients who have lower levels of T2R38 function[82]. Now, further clinical studies have demonstrated that T2R38 supertasters are less susceptible to CRS [167–169]. Prospective clinical studies of T2R38 genotype and CRS/infection susceptibility, including patient outcomes, are currently ongoing. However, these data have already established the T2R38 pathway as a potential therapeutic target to promote innate immune responses in patients with upper respiratory infections. However, there is a large subset of patients that

would be sub-optimally responsive to treatment with T2R38 agonists (ie, PAV/AVI and AVI/AVI individuals). It is thus still necessary to further define the T2R38-mediated signaling pathway in airway epithelial cells as well as identify other T2Rs that activate similar innate immune responses. Additionally, more research is needed to determine whether AVI/AVI individuals are more susceptible to infections in other tissues where taste receptors are expressed and may contribute to innate immunity, including the lungs or gut epithelium.

Solitary Chemosensory Cells (SCCs) Use Both T2R Bitter and T1R Sweet Taste Receptors to Regulate Upper Respiratory Innate Immunity Through Antimicrobial Peptide Secretion

Beyond the T2R bitter taste receptors in ciliated epithelial cells, the upper airway also contains dedicated chemosensory cells, known as solitary chemosensory cells (SCCs), which express both bitter and sweet taste receptors [77,78,170,74,73,72,171,69,76,172,70,75]. The term “solitary chemosensory cell” was first used to describe the chemosensory epithelial cells found in fish [173–175], which exhibit an elongated morphology with heavy neuronal innervation. Morphologically similar cells were later discovered in the upper respiratory tracts of the alligators [176] and mammals, including mice, rats, and humans [76,69,171,72,177,74,73,71,75]. These cells have been classified as SCCs based on their elongated morphology as well as their expression of chemosensory signal transduction components, including T2R bitter and T1R sweet “taste” receptors [69–71,172,72,177,73–75,178,76,77], as will be described below.

Immunofluorescence, in situ hybridization, and imaging of TRPM5-GFP-labeled and gustducin-GFP-labeled mouse airways have demonstrated that mouse nasal SCCs express important components of the canonical taste signaling pathway that are known to be important for taste receptor signaling in the cells of the tongue, including Gα-gustducin, PLCβ2, and TRPM5 [69,72,74,174,73]. When mouse nasal SCCs are stimulated with bitter compounds such as denatonium benzoate or with bacterial AHL quorum sensing molecules, they exhibit intracellular calcium responses that cause ACh release to activate trigeminal afferent nerves that are peptidergic nociceptors [73,72,69], resulting in breath-holding [73] and inflammatory responses [78]. The breath-holding response, which presumably exists to limit further inhalation of toxic compounds, is similar to what is observed with nasal application of capsaicin, which directly activates the TRPV1 ion channel localized to airway trigeminal nociceptor neurons [73]. These trigeminal nociceptors can also release several types of neuropeptides into the local airway environment, including vasoactive intestinal peptide (VIP), substance P, and calcitonin gene related peptide (CGRP) [179–183]. It is thus very possible that SCC activation *in vivo* also results in local responses such as enhanced ciliary beating [99] or fluid secretion from submucosal exocrine glands [184–187]. However, any ability of SCC-activation to regulate these processes *in vivo* remains to be experimentally confirmed.

SCCs have only recently been identified in humans [76,75,77]. In addition to T2R38, which we showed is expressed in ciliated cells [82], other researchers using reverse-transcription (rt)-PCR initially demonstrated expression of T2R4, T2R14, and T2R46 in preparations from the inferior and middle turbinates, septum, and uncinate process of the human

sinonasal cavity [76]. SCC-like cells, expressing the bitter receptor T2R4, the umami receptor component T1R1, and the sweet receptor component T1R2, were initially found in the human vomeronasal duct [75]. More recently, we used immunofluorescence microscopy to identify T2R47- and T1R2/3-expressing SCC-like cells in ALI cultures derived from cells isolated from surgical specimens obtained from a variety of sinoasal anatomical regions [77]. It remains to be determined whether there are differences in SCC numbers or distribution throughout the sinonasal cavity, but it appears that SCCs can be isolated and cultured from many different regions of the sinonasal cavity.

We studied SCC physiology in ALI cultures from humans and mice as well as human sinonasal explants [77]. ALI cultures have been previously been shown to contain ciliated, goblet, and basal cells [132–136], and we now know that human and mouse ALIs also contain SCCs, as described below. When human sinonasal ALIs or inferior turbinate tissue explants were stimulated with denatonium benzoate, a bitter agonist that was previously used to stimulate mouse nasal SCCs [69,72,74,73], an intracellular calcium response was observed that originated from discrete cells. This calcium response initiated a calcium wave that spread to the surrounding cells through carbenoxolone-sensitive and 18 α -glycyrhethinic acid-sensitive gap junctions [77]. Initiation of the calcium signal required components of the canonical taste signaling pathway including α -gustducin, PLC β 2, the inositol 1,4,5-trisphosphate (IP $_3$) receptor, and TRPM5, as demonstrated by both pharmacology in human cultures as well as using cultures from knock-out mice [77]. Injection of the human denatonium-responsive cells with a fluorescent dye revealed a morphology identical to SCCs [77]. Subsequent immunofluorescence microscopy revealed the co-expression of T2R47 and T1R2 in ALI cultures in cells with a similar non-ciliated SCC-like morphology. The pharmacological profile of the bitter agonists that induced human SCC responses (denatonium benzoate, absinthin, parthenolide, and amarogentin; [188]) suggested a role for T2R isoforms T2R10, and T2R46, and T2R47 (also known as T2R30) [77]. Interestingly, human SCC responses were activated by neither T2R38-specific agonists nor *P. aeruginosa* AHLs, as previously shown for mice SCCs [69,72,177,78,74,73]. This may reflect a species-specific difference, with T2R38-expressing ciliated epithelial cells mediating the primary response to AHLs in humans rather than SCCs. It is yet unknown which, if any, bacterial or fungal products activate T2Rs in human nasal SCCs, though the strong antimicrobial response evoked by their stimulation (discussed below) strongly suggests that they are activated in response to infection. Microbes secrete numerous products in addition to AHLs, including exotoxins, metabolic products, and other quorum-sensing molecules, such as autoinducer 2 (AI-2 [189]) and various autoinducer peptides [190,191]. Further identification of T2R isoforms expressed in SCCs as well as screening of these T2Rs with bacterial and fungal compounds and/or conditioned-media will likely elucidate more bitter products secreted by airway pathogens.

Surprisingly, it was noted that denatonium-induced calcium responses in ALI cultures were blocked in a dose-dependent fashion by apical sugars such as glucose and sucrose [77]. This inhibition was mimicked by a non-metabolizable artificial sweetener, sucralose, a potent T1R2/3 agonist [22,15,14]. The glucose or sucralose inhibition was reversed by the T1R2/3 antagonists lactisole [12,192,193] and amiloride [194], but not by inhibitors of glucose

transporters such as phloretin and phlorizin [77]. The data were supported by studies using T1R3 knockout mice, which lack functional T1R2/3 receptors [195,196]; ALI cultures derived from Wt mice exhibited sugar-mediated inhibition of T2R SCC Ca^{2+} responses that were abolished in cultures derived from T1R3 knockout mice [77]. Together, the immunocytochemical and physiological data confirm that sinonasal SCCs express both bitter and sweet taste receptors, which function in antagonistic physiological roles. The physiological and clinical significance of this finding will be discussed below.

Unlike T2R38, the SCC T2R stimulation did not activate nitric oxide production, nor did it activate cytokine secretion [77]. Instead, stimulation of SCC T2Rs activated robust secretion of antimicrobial peptides, including β -defensins 1 and 2. The defensin secretion required propagation of the calcium signal to the surrounding epithelial cells [77]. The secretion of these β -defensins appeared to occur directly from the surrounding ciliated and non ciliated epithelial cells, based on immunofluorescence localization of β -defensins in ALI cultures and the loss of the immunofluorescence signal after stimulation with the bitter T2R agonist denatonium. The antimicrobial secretions were found to have activity against a spectrum of both gram-positive (*Staphylococcus epidermis* and methicillin-resistant *Staphylococcus aureus*) as well as gram-negative (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) bacteria [77]. The antimicrobial peptide secretion observed during SCC T2R stimulation was immediate; the majority occurred within 5 minutes. In contrast, enhanced antimicrobial peptide secretion in response to stimulation of TLRs were observed to take up to 12 hours [77]. It has long been known that TLRs in epithelial cells up-regulate mRNA for antimicrobial peptides such as defensins [97,98]. Based on these observations, the TLR- and T2R-mediated defensin responses are distinguished by very different time scales, with T2Rs mediating a more rapid/immediate release of already-synthesized antimicrobial peptides. Thus, while TLRs are important for sustained responses through enhanced antimicrobial production, T2Rs are important for regulating rapid antimicrobial responses through more immediate antimicrobial release.

Calcium imaging and quantification of β -defensin release from human sinonasal explants suggests that ALI cultures accurately reflected the *in vivo* responses of the epithelial cells. Furthermore, the SCC/T2R-mediated epithelial antimicrobial peptide secretion is unique to the human upper airway; cultures derived from human bronchial tissue samples did not exhibit similar localized SCC-mediated calcium signals or antimicrobial peptide secretion [77]. Rather, the bronchial epithelial cell responses to bitter agonist were more global, as previously reported by others [126], likely reflecting the role of ciliated cells, rather than SCCs, as the primary sites of expression of T2Rs in the lower airway. Additionally, while many components of T2R-initiated calcium signaling appeared to be similar in human and mouse nasal ALI cultures, stimulation of mouse nasal SCCs yielded a calcium wave, it did not result in release of antimicrobial peptides.

As described above, in the mouse, denatonium-responsive T2R signaling *in vivo* is linked to activation of trigeminal neurons and breath holding responses [69,171,72,74,174,73] and activation of inflammation [78]. The data obtained so far suggest that human sinonasal SCCs and denatonium-responsive T2Rs are linked to more local responses regulating innate immunity. It cannot yet be ruled out that a similar trigeminally-mediated response exists in

humans and mice, thought the data so far suggest that the localized SCC immune response via release of antimicrobial peptides is not present in the mouse and thus illustrate a major difference between human and mouse SCCs. The role of SCCs trigeminal activation in humans awaits further investigation. Experiments in ALI cultures, which lack neuronal innervation, cannot be used to determine whether SCCs activate trigeminal neurons in the human upper airway. Further *in vivo* experiments are required to determine if this is the case, but performing such experiments in human subjects may prove difficult. It is possible that clinically-relevant *in vivo* studies of SCCs and their regulation of local immune pathways will require the identification and use of an animal model that can better recapitulate the human sinonasal physiology, potentially the rabbit [197], sheep [198], or pig [199]. However, if human SCCs do activate trigeminal nerves, they may likewise trigger the release of neuropeptides such as substance P or VIP. Such neurotransmitters could trigger airway submucosal gland secretion [200,201,186], increases secretory or ciliary beating responses from airway epithelial cells themselves [99], and/or inflammation [78].

Perhaps the most surprising revelation about human SCC physiology was the inhibition of T2R bitter receptor responses during T1R2/3 sweet receptor stimulation. As mentioned above, T1R2/3 sweet receptor activation by physiologically-relevant concentrations of glucose or by artificial sweeteners inhibited both T2R-activated calcium signaling as well as antimicrobial peptide secretion in both ALIs as well as tissue explants [77]. Interestingly, the concentrations of glucose normally found in the ASL (~ 0.5 mM), which appears to be sufficient to activate T1R2/3 expressed in human nasal SCCs, are 10–100-fold lower than the concentrations required to activate T1R2/3 in *in vitro* heterologous expression systems [22] or to activate T1R2/3-dependent sweet taste [202]. However, like airway T1R sweet receptors, T1R sweet receptors expressed in pancreatic β -cells [203] and gut endocrine [204] also respond to lower sugar concentrations than oral T1R2/3. While oral T1R2/3 sweet receptors appear to be tuned to the higher concentrations of sugars found in foods, extra-oral T1R2/3s appear to be tuned to sugar concentrations that are physiologically relevant to the tissues in which they are found. Whether the differences in extra-oral and oral T1R sweet receptor sugar sensitivity are accounted for by altered post-translational modification, changes in stoichiometry, coupling to alternative signaling pathways, or expression of tissue-specific accessory subunits remains to be determined.

Nonetheless, T1R2/3 expression in the airway plays an important role in attenuation of antimicrobial responses. We hypothesize that, *in vivo*, sinonasal T1R2/3 sweet receptors are activated by glucose that is always present in the airway surface liquid, albeit at low levels in healthy individuals. Glucose is normally present in airway surface liquid because it tonically leaks through the epithelium via paracellular pathways. Glucose uptake via apical glucose transporters such as facilitative-diffusion GLUT transporters as well as sodium linked glucose transporters (SLGTs) keep healthy airway surface liquid glucose around 0.5 mM or less, or approximately 10-fold below fasting serum levels [205–207]. However, 0.5 mM glucose was sufficient to partially attenuate the SCC T2R antimicrobial response by approximately half [77]. We hypothesize that T1R2/3 may act as a “rheostat” to control the magnitude of the T2R response depending on the glucose concentration in the airway surface liquid. Depletion of ASL glucose concentration via bacterial glucose consumption

may signal the onset of a *bona fide* infection and play a role in the activation of T2R-mediated AMP secretion. The T1R2/3 sweet receptors in SCCs may function to desensitize SCC T2Rs to bitter compounds secreted by some bacteria during low-level colonization, but this desensitization is relieved when bacterial numbers increase enough to cause depletion of ASL glucose. A model of this proposed mechanism is shown in Fig. 5.

While intriguing, this hypothesis requires further study *in vivo*. However, if validated, it may have very novel clinical implications. As stated above, normal ASL glucose concentration from healthy individuals is approximately 0.5 mM or less [205–207,77]. However, we found that the mean glucose concentration in nasal secretions from patients with CRS were approximately 3- to 4-fold higher than healthy individuals ($P < 0.01$) [77]. As discussed above, glucose homeostasis in the ASL is the result of a balance of tonic glucose leakage through the airway epithelium as well as uptake into the airway cells via apical transporters [205–207]. Upsetting this balance can alter ASL glucose concentration, as observed in diabetic patients with elevated blood glucose levels (hyperglycemia) who have a resulting increased flux of glucose into the ASL and have elevated ASL glucose [207,208]. CRS patients have elevated ASL glucose independent of blood glucose levels. It is likely that the higher CRS glucose concentrations derive from increased leak caused by breakdown of the epithelial barrier as a consequence of chronic infection and inflammation [205], which likely varies with individual patient disease [205]. It has been demonstrated *in vitro* that pro-inflammatory mediators increase paracellular glucose flux in human bronchial cells and disrupt tight junctions in human sinonasal cells [209,210].

The higher ASL glucose concentrations in diabetic patients [205] may contribute to previous observations that diabetics are more prone to some airway infections than non-diabetics [211,205]. Recently, in a retrospective study of CRS patients, diabetics were found to be more likely to have intraoperative microbiology cultures that included gram-negative bacteria such as *P. aeruginosa* [212]. Previously, it has been speculated that keeping the ASL glucose concentrations low is important for keeping the airways sterile because it limits the nutrients available for bacteria to consume [207,205,206]. However, high ASL glucose in CRS or diabetic patients may actually facilitate airway infections by an additional mechanism of repressing T2R-mediated responses in SCCs through over-activation of T1R2/3 sweet receptors. This could predispose patients with elevated glucose levels to infection by limiting the normal SCC responses to bitter molecules produced by bacteria. Topical application of T1R2/3 antagonists like lactisole may restore the ability of sinonasal epithelial cells to mount an appropriate antimicrobial response to bitter bacterial molecules secreted during infection, and may be a useful therapy for some patients while avoiding conventional antibiotics.

It also remains to be determined if there is any correlation between susceptibility to airway infections and polymorphisms in the *TAS1R2* and *TAS1R3* genes, which encode T1R2 and T1R3. *TAS1R* polymorphisms have been identified which alter the response of T1R2/3 receptors to sugars [159,161,213]. Increased sugar sensitivity of T1R2/3 in the airway might lead to increased repression of T2R signaling in SCCs, potentially limiting antimicrobial responses. The potential role of the T1R2/3 sweet receptor polymorphisms in airway disease is strongly supported by a recent study of Canadian CRS patients and healthy individuals

showing allele frequency differences of >10% for 16 different single nucleotide polymorphisms in *TAS1R* genes [169]. Further genetic studies of *TAS1R2/3* in airway diseases are needed.

Taste receptors in other airway cell types

Airway taste receptor expression extends beyond ciliated cells and sinonasal SCCs. There are also other chemosensory cells identified in other regions of the mouse airway that await further investigation in human. In mice, tracheal chemosensory cells have been identified, which are called “brush cells” due to their apical tuft of microvilli [4,178,214–216]. Mouse tracheal brush cells express T2Rs that are activated by AHLs, including C12HSL, to stimulate ACh release that activates trigeminal-nerve-mediated breath-holding responses [4,178,214,215]. A chemosensory role for human tracheal brush cells has not yet been identified, but it is possible that human tracheal brush cells are linked to local antimicrobial responses similarly to human nasal SCCs. This requires further experimentation using human tracheal ALI cultures and tissue explants. Bronchial smooth muscle cells also express T2Rs that mediate bronchodilation [217–220]. It is unknown whether smooth muscle T2Rs respond to endogenous yet-unidentified host signaling molecules or to bitter molecules from pathogens that penetrate the epithelium. Further research is needed to identify how T2Rs in both brush cells and smooth muscle cells contribute to host-pathogen interactions as well as airway innate immunity.

Conclusions and Remaining Questions

As described above, the emerging data suggest that T2R bitter and T1R sweet taste receptors constitute a novel sentinel detection system in the upper airway epithelium. Multiple receptors are expressed in different airway cell types, including T2R38 in ciliated cells and T2R47 and T1R2/3 in SCCs. These two different cell types regulate different antibacterial defense mechanisms [77,82]. Of particular interest are the differences between nasal and bronchial taste receptor response as well as the differences between human and mouse SCCs, as described above. This suggests that taste receptors have evolved to function in highly specialized roles in different tissues as well as in different species. The ability of human SCC T2R-activated antimicrobial secretions to kill a broad range of bacteria, including antibiotic-resistant *S. aureus* [77] suggest that this antimicrobial pathway may be a promising therapeutic target. It is also possible that the airway T2Rs pathways may be involved in antifungal [221] or antiviral [222] responses as well. Importantly, at least one of these taste receptors, T2R38, appears to be part of an interkingdom “eavesdropping” system by which mammalian host cells can intercept bacterial quorum sensing communications [82]. Research into determining whether other bacterial compounds are perceived as bitter is ongoing. A better understanding of the different T2R isoforms expressed in ciliated cells and SCCs will speed identification of potential compounds that stimulate one or both of these pathways.

Additionally, more research is needed to examine the role of bitter and sweet taste receptors in other epithelia beyond the airway (Table 1). It is very logical to hypothesize that at least some extra-oral T1Rs and T2Rs receptors play immune roles beyond the airway. Their roles

in airway epithelial innate immunity may only represent the “tip of the iceberg” of the true scope of the importance of taste receptors to immunity. Supporting this, it was recently demonstrated that chemosensory brush cells of the rodent urethra, which express both T2R bitter and T1R1/3 umami receptors, respond to the bitter compound denatonium and the umami agonist monosodium glutamate, resulting in release ACh to activate the bladder detrusor muscle [4]. Moreover, these chemosensory cells also respond to a heat-inactivated uropathogenic *E. coli* strain, suggesting that these chemosensory cells function to detect infecting bacteria and trigger their expulsion.

It is becoming increasingly clearer that taste receptors have important roles beyond simply that of gustation. The chemosensory functions of T1Rs and T2Rs as sentinels of innate immunity may partly explain why these receptors are so widely expressed throughout the body. While variations in the genes encoding these bitter and sweet GPCRs have long been known to control human food and beverage preferences, they may be even more important to human biology than previously thought if these genes also impact susceptibility to infection. It is very probable that future studies of extra-oral taste receptors will reveal additional novel insights into immune pathways as well as interkingdom-signaling mechanisms that play key roles in host-pathogen interactions between mammalian cells and invading pathogens. Differences in chemical signals and activation of chemosensory receptors might also one day be found to play a role in how host cells differentiate between pathogenic and commensal or symbiotic bacteria.

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Non-Standard Abbreviations

ACh	acetylcholine
AHL	acyl-homoserine lactone
AMP	antimicrobial peptide
ASL	airway surface liquid
ATP	adenosine triphosphate
C4HSL	<i>N</i> -butyryl- <i>L</i> -homoserine lactone
C12HSL	<i>N</i> -3-oxo-dodecanoyl- <i>L</i> -homoserine lactone
CALHM1	calcium homeostasis modulator isoform 1
cAMP	cyclic adenosine monophosphate
CGRP	calcitonin gene-related peptide
COPD	chronic obstructive pulmonary disease
CRS	chronic rhinosinusitis

CSF	cerebrospinal fluid
ENaC	epithelial sodium channel
ER	endoplasmic reticulum
GPCR	G-protein–coupled receptor
IP₃	inositol 1,4,5-trisphosphate
IP3R3	inositol trisphosphate receptor isoform 3
NO	nitric oxide
NOS	nitric oxide synthase
PDE	phosphodiesterase
PKA	cAMP-dependent protein kinase A
PKG	cGMP-dependent protein kinase G
PLCβ2	phospholipase C isoform β 2
PROP	propylthiouracil
PTC	phenylthiocarbamide, also known as phenylthiourea
RNS	reactive nitrogen species
ROS	reactive oxygen species
SCC	solitary chemosensory cell
T1R	taste receptor family 1 protein isoform
T2R	taste receptor family 2 protein isoform
TAS1R	taste receptor family 1 gene
TAS2R	taste receptor family 2 gene
TLR	toll-like receptor
TRPM5	transient receptor potential cation channel subfamily M isoform

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Fig. 1.

G-protein coupled receptors (GPCRs) involved in bitter, sweet, and umami taste. **a** Bitter taste receptors are generally believed to be primarily composed of homo- or hetero-oligomers of isoforms of the taste receptor 2 (T2R) family [28,6,29–32]. Most T2R isoforms have been shown to co-immunoprecipitate with other T2R isoforms co-expressed in heterologous expression systems [43,42]. However, while most bitter responsive type II taste cells express multiple T2Rs, the state of T2R oligomerization *in vivo* is almost completely unknown. values for receptors do not appear to be shifted by co-expression of Additionally, the EC₅₀ different T2Rs in the same cells, as measured through calcium signaling in heterologous expression systems *in vitro* [43,42]. However, potential effects of T2R oligomerization in type II taste cell signaling *in vivo* are unknown. It remains unclear

whether each T2R oligomer signals independently or cooperatively. **b, c** Umami and sweet receptors are made up of oligomers of the taste receptor 1 (T1R) family. T1R1 and T1R3 oligomers form umami receptors [21,22,14,23], while T1R2 and T1R3 oligomers form sweet receptors [12,11,13–15]. Both T1R and T2R family members are believed to have similar structures to other 7-transmembrane domain GPCRs, but T1Rs are believed to have more extensive extracellular N-termini than do T2Rs. The N-termini of T1Rs are thought to contain multiple ligand binding sites [12,22,48,40,32].

Fig. 2.

Signal transduction pathway of bitter (T2R), sweet (T1R2/3), and umami (T1R1/3) GPCRs in type II taste cells of the tongue. As described in the text and reviewed in [11,33], ligand binding to taste GPCRs results in Ca $^{2+}$ signaling through two G-protein-coupled pathways. $G_{\beta\gamma}$ activation of phospholipase C isoform β 2 (PLC β 2) results in production of inositol 1,4,5-trisphosphate (IP $_3$), which activates the IP $_3$ receptor (IP $_3$ R), an intracellular ion channel that allows calcium (Ca $^{2+}$) release from the intracellular endoplasmic reticulum (ER) calcium stores [255]. Simultaneously, $G_{\alpha}\text{-gustducin}$ activates phosphodiesterases (PDEs), which reduce the levels of cyclic-AMP (cAMP) and decrease protein kinase A (PKA) activity [29]. PKA can phosphorylate and inhibit the activity of the type III IP $_3$ R [256,257], the major IP $_3$ R isoform found in type II taste cells [258–260], thus reduction of PKA activity can enhance IP $_3$ R3-mediated calcium signaling. Calcium activates the plasma membrane-localized cation channel TRPM5 [138,139], causing depolarization of cellular membrane potential, activation of voltage-gated sodium (Na $^{+}$) channels [261], and generation of an action potential that results in ATP release [11] through the CALHM1 ion channel [46,47] and subsequent purinergic neurotransmission of taste sensations.

Fig. 3.

Mechanisms of epithelial innate immunity in the airway. As described in the text and reviewed in [106,262], inhaled viruses, bacteria, and fungi are trapped by sticky mucus created by mucin macromolecules secreted by secretory goblet cells. Trapped pathogens are removed from the airway by mucociliary transport, which is driven by ciliary beating and is dependent upon regulation of ion and fluid transport by epithelial cells that regulates the mucus viscosity. In addition to mucociliary transport, direct pathogen killing or inactivation can occur via the secretion of antimicrobial peptides as well as the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). During longer-term exposure to pathogens, epithelial cells can also secrete cytokines to recruit dedicated immune cells and activate inflammatory pathways.

Fig. 4.

T2R38 bitter taste receptor regulation of airway epithelial innate immunity. Reading from left to right, acyl-homoserine lactone (AHL) molecules are secreted by gram-negative bacteria to regulate quorum sensing. These AHL molecules activate T2R38 expressed in human sinonasal cilia [82] and yet-unidentified T2Rs in mouse nasal cilia [83], which results in activation of PLCβ2, which liberates IP₃ and causes initiation of a calcium (Ca²⁺) signal that activates nitric oxide synthase (NOS)-dependent nitric oxide (NO) production. Because the NOS activation is rapid (within seconds) and Ca²⁺-dependent, it is likely that the NOS isoforms involved are of the endothelial NOS (eNOS) family [263], known to be expressed in the airway [264]. NO production has 2 distinct effects. The first is activation of cellular protein kinase G (PKG), which phosphorylates ciliary proteins [265,130] to increase ciliary beating and mucociliary transport [82,83]. NO additionally diffuses directly into the airway surface liquid, where it has direct bactericidal effects [82].

Fig. 5.

Nasal solitary chemosensory cell (SCC)- and taste receptor-dependent regulation of airway innate immunity. Reading from left to right, bitter chemicals are secreted by microbes during infection. Some of these molecules, which are yet unidentified but are distinct from AHLs, activate the T2R bitter receptors expressed in solitary chemosensory cells (SCCs), which activates a $G_{\alpha\text{gust}}$ -dependent and $\text{PLC}\beta 2$ -dependent calcium (Ca^{2+}) response that propagates to surrounding epithelial cells via gap junctions [77]. In human, but not mouse, sinonasal epithelial cells, this calcium signal causes the surrounding cells to secrete antimicrobial peptides (AMPs), including β -defensins, which directly kills both gram-positive and gram-negative bacteria. Airway surface liquid (ASL) glucose (~0.5 mM in healthy individuals [77]) normally attenuates T2R-mediated signaling through activation of T1R2/3 sweet receptors, except during times of infection, when bacteria likely decrease ASL glucose concentration by consuming and metabolizing the glucose. Reduction of ASL glucose relieves the T1R2/3-mediated inhibition of T2R signaling and AMP secretion [77]. In mice, SCC activation by bitter compounds results in acetylcholine (ACh) release and activation of trigeminal neurons [78]; it remains to be determined if this mechanism also exists in the human nasal epithelium. For purposes of simplicity and clarity, T2R receptors present in nasal ciliated cells are not shown in this figure.

Table 1

Examples of known mammalian extra-oral GPCR taste receptor expression and function. Note that this list contains extraoral taste receptors identified up to the date of this review, and it is likely that there will be further identification of taste receptors isoforms in other cell types, particularly in epithelia.

Organ/Tissue	Cell Type or Region	Taste Receptors Expressed	Physiological Role(s)	Endogenous ligand(s)	Reference(s)
airway (nose and sinuses)	ciliated epithelial cells	T2R38 bitter receptors (human)	Nitric oxide production to increase cilia beating and directly kill bacteria	Bacterial AHL quorum-sensing molecules	[83,223,82]
airway (nose and sinuses)	solitary chemosensory cells (SCCs)	Various T2R bitter receptors (mouse and human)	Antimicrobial peptide secretion (human); breath-holding and inflammation (mouse)	Unknown (human); bacterial AHL quorum-sensing molecules (mouse)	[77,76,69,171,72,177,74,73,78,70]
		T1R2/3 sweet receptor (mouse and human)	Attenuate antimicrobial secretion (human); unknown (mouse)	Airway surface liquid glucose	[77]
airway (trachea)	chemosensory brush cells	Various T2R bitter receptors (mouse)	Breath-holding mediated by Ach release and trigeminal neuron activation (mouse); unknown (human)	bacterial AHL quorum-sensing molecules (mouse)	[178,215,216, 214]
airway (bronchi)	ciliated epithelial cells	Various T2R bitter receptors (human)	Increase ciliary beat frequency and mucociliary clearance	unknown	[126,224]
	smooth muscle	Various T2R bitter receptors (human)	bronchodilation	unknown	[218,217,219, 216,225,226, 220]
auditory tube	Solitary chemosensory brush cells	T2R105, T2R108 bitter receptors (mouse)	Unknown; may release ACh and/or CGRP	unknown	[227]
		T1R1/3 umami receptor (mouse)	Unknown; may release ACh and/or CGRP	unknown	[227]
bladder	Smooth muscle	T1R2/3 sweet receptor	Bladder contraction	unknown	[228]
brain	medulla oblongata	T2R1, 4, 107, 38 bitter receptors (rat)	unknown	unknown	[229,230]
	Hippo-campus, cornu ammonis fields, dentate gyrus	T2R2/3 sweet receptor (mouse)	regulation of brain glucose homeostasis	CSF glucose concentration	[231,232]
breast	Mammary epithelial cells	T2R1,4,10,38,49 bitter taste receptors (human)	unknown	unknown	[233]
heart	cardiac myocytes	Various T2R bitter receptors (mouse)	unknown; upregulated by glucose starvation and proposed to be involved in "nutrient-sensing"	unknown	[234]
		T1R1/3 umami receptor (mouse)	unknown, likely serum glucose levels	unknown	[234]

Organ/Tissue	Cell Type or Region	Taste Receptors Expressed	Physiological Role(s)	Endogenous ligand(s)	Reference(s)
intestine	Enteroendocrine/neuroendocrine cells	Various T2R bitter receptors (mouse and human)	regulation of gastric emptying; influence on glucose homeostasis; contributing to avoidance responses of ingested toxic substances	ingested "bitter" compounds (plant alkaloids, bacterial products, etc.)	[235–238]
		T1R2/3 sweet receptor (mouse and human)	secretion of glucagon-like peptide 1, glucose- dependent insulinotropic peptide, cholecystokinin; peptide YY; regulation of glucose transporter expression	ingested sugars	[204,239–248]
pancreas	beta-cells	T1R2/3 sweet receptor (mouse and human); potentially a T1R3 homodimer	potentiation of insulin secretion	fructose	[203,249,36,35]
testes	seminiferous tubule cells; spermatids and spermatozoa	Various T2R bitter receptors (mouse and human)	unknown	unknown	[250,251]
		T1R1/3 umami receptors (mouse and human)	Regulation of sperm motility	unknown	[252–254]
urethra	chemosensory brush cells	T2R bitter receptors	ACh release to stimulate bladder smooth muscle contraction	uropathogenic <i>E. coli</i> cell components and/or secreted product(s)	[4]