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Review

The Role of Taste Receptors in Airway Innate Immune Defense

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Abstract: Bitter (T2R) and sweet (T1R) taste receptors are expressed in the upper airway, where they play key roles in antimicrobial innate immune defense. Bitter bacterial products are detected by taste receptors on ciliated cells and solitary chemosensory cells, resulting in downstream nitric oxide and antimicrobial peptide release, respectively. Genetic polymorphisms in taste receptors contribute to variations in T1R and T2R functionality, and phenotypic differences correlate with disease status and disease severity in chronic rhinosinusitis (CRS). Correspondingly, there are also subjective bitter and sweet taste differences between patients with CRS and individuals without CRS across a number of compounds. The ability to capture these differences with a simple and inexpensive taste test provides a potentially useful diagnostic tool, while bitter compounds themselves could potentially serve as therapeutic agents. The present review examines the physiology of airway taste receptors and the recent literature elucidating the role taste receptors play in rhinologic disease.

Keywords: taste receptors; solitary chemosensory cell; taste test; T2R; T1R

1. Introduction

Taste receptors are typically associated with oral sensory perception as an adaptive mechanism for detecting energy rich foods as well as poisons and other unpalatable compounds. Bitter taste receptors are a specific subset of taste receptors that classically respond to toxins, chemicals, and other aversive products that can be detrimental to organismal health. However, recent research has identified taste receptors in many other anatomic compartments of the body with a variety of functions extending far beyond the canonical sensory capacity of the tongue [1–6]. Taste receptors have been found in the brain, pancreas, testicles, bladder, and gastrointestinal tract [1–4,7]. This review will examine the role of bitter and sweet taste receptors that are expressed in the airway, and the important roles that these taste receptors play in innate immune defense [8,9].

2. Taste Receptor Physiology

Bitter and sweet taste receptors, unlike the ion-sensitive salt and sour taste receptors, are G-protein coupled receptors (GPCRs) [10,11]. The sweet taste receptor (T1R) family responds to sugars, including sucrose, glucose, and fructose, and T1Rs are classified as a part of taste receptor family 1 subtype 2 and 3 (TAS1R2/TAS1R3) [5,12,13]. A wider variety of bitter taste receptors exist in taste receptor family 2 (T2Rs), and these diverse receptors respond to an assortment of bitter compounds [14], including sesquiterpene lactones, strychnine, and denatonium [15]. Each bitter taste receptor can

respond to a multitude of chemically similar compounds, and each compound can stimulate more than one taste receptor. Humans have at least 25 T2R subtypes, reflecting a broad perceptual range [12,16]. There is also a high degree of genetic diversity in T2Rs. On a phenotypic level, this results in differing sensitivity to specific bitter compounds among individuals, both on the tongue and in the airway. This diversity partially explains variation in taste preferences between groups and within groups [17,18]. For example, certain individuals find some bitter foods, such as coffee, to be aversive, while others are less sensitive.

The mechanisms involved in taste receptor activation are relatively conserved and follow similar pathways in the tongue and airway. However, while the expression of taste receptors in the sinonasal epithelium is ubiquitous on disparate cell types, including ciliated cells and solitary chemosensory cells, in the tongue taste receptor expression is confined to type II cells within the taste buds. Furthermore, while some bitter taste receptors in the airway are upstream of a nervous signaling cascade, others act in a cell-autonomous fashion only [8,19,20]. When a ligand binds to a taste GPCR, there is activation of phospholipase C isoform β2 (PLCB2), which triggers downstream inositol 1,4,5-trisphosphate (IP3) production. The IP3 receptor on the endoplasmic reticulum releases calcium in response to this increase in IP3 [21]. Simultaneously, there is also an activation of phosphodiesterases (PDEs) that attenuate cyclic adenosine monophosphate (cAMP) levels and protein kinase A (PKA) activity. As PKA is an inhibitor of an IP3 receptor isoform, removal of this inhibition causes further release of calcium from the endoplasmic reticulum [22]. Calcium ultimately activates the non-selective cation channel, TRPM5, that causes cellular depolarization, activates voltage-gated sodium (Na^+) channels, and ultimately results in an action potential that causes ATP release through CALHM1, a large pore channel [5,22–25]. In the tongue, this ATP activates receptors on taste cells and sensory fibers that transmit sensations to the central nervous system [5,25,26].

3. Bitter Taste Receptors in the Airway

Many different bitter taste receptors are expressed in the rodent and human airways [9,27–30] and in these locations, they respond to bitter bacterial products that are produced. One example of this is the lactone class of bitter compounds, which includes acyl-homoserine lactones (AHLs) that are produced by many gram-negative bacteria [31,32]. These lactones serve as biofilm "quorum-sensing molecules"; bacteria will initiate biofilm formation when a high enough concentration of AHLs is reached in a localized area. Biofilms can provide protection for bacteria from host innate immune defenses as well as antibiotics [33]. It is hypothesized that bitter taste receptors attempt to "spy" on these bacterial communications, effectively detecting AHLs before a sufficient concentration is reached for biofilm formation [8]. The bitter taste receptors themselves elicit innate immune responses that can eradicate bacteria before pathogenic levels are achieved.

This highlights a critical component of upper airway immunity: recognition of foreign bacteria, viruses, fungi, or toxins, followed by prompt reduction in pathogenic biomass. Toll-like receptors (TLRs) respond to pathogen-associated molecular patterns (PAMPs), which include foreign cellular components. However, TLR signaling is gradual, taking up to 12 h to exert an immune response through changes in expression of genes that play a role in innate immunity [34]. Conversely, bitter taste receptors can detect bacterial products, such as AHLs, and elicit downstream increases in immune defenses in a much more expedient fashion (seconds to minutes).

3.1. Bitter Taste Receptors on Ciliated Cells

Bitter taste receptors on ciliated cells respond to bacterial compounds and elicit a potent downstream response of nitric oxide (NO) production [35,36] (Figure 1). Nitric oxide diffuses quickly into bacteria, where it participates in destruction of cellular components [9,37]. Some bacteria, such as *Pseudomonas aeruginosa*, are highly sensitive to NO, while others are more resistant [38]. In addition to this antimicrobial activity, NO also activates protein kinase G (PKG) and guanylyl cyclase to directly speed up ciliary beat frequency (CBF), increasing mucociliary clearance [39]. Rapid ciliary beating

can clear bacteria and mucus to the nasopharynx or oropharynx, where they can be eliminated by swallowing. Additionally, released innate immune products are spread out across the airway surface by ciliary beating [40]. These compounds—including lactoferrin, lysozyme, and defensins—act in concert with NO and other reactive oxygen species to create a potent antimicrobial response [41].

T2R38 is a bitter taste receptor located on ciliated cells in humans, and it responds to at least three AHLs produced by *P. aeruginosa*: *N*-butyryl-L-homoserine lactone, *N*-hexanoyl-L-homoserine lactone and *N*-3-oxo-dodecanoyl-L-homoserine lactone [9]. In addition to its response to bacterial compounds, T2R38 reacts in a similar fashion to the compounds phenylthiocarbamide (PTC) and propylthiouracil (PROP) [42]. In response to PTC stimulation, sinonasal epithelial cells expressing a functional T2R38 receptor demonstrate a substantial increase in NO production. Importantly, the TRPM5 channel and PLCβ2 are necessary for this NO response, and these are two canonical components of taste signaling. Interestingly, the taste G-protein gustducin does not appear to be involved [9]. The resultant NO production following PTC stimulation is sufficient for a highly bactericidal response.

Just as the genetic variation in T2Rs can cause differences in taste preferences on the tongue, receptor variation in the airway also appears to play a key role in the ability to mount a respiratory defense in response to bitter compounds. The genetic locus for T2R38, *TAS2R38*, has common polymorphisms that can render the receptor non-functional. Individuals with a proline-alanine-valine (PAV) amino acid sequence at a key portion of the taste receptor are able to respond to T2R38 agonists, while individuals with an alanine-valine-isoleucine (AVI) sequence at this same locus possess a non-functional receptor variant [18]. Cells isolated from individuals with an AVI/AVI genotype show highly attenuated NO production in response to AHLs, PTC, or PROP stimulation, compared to cells isolated from individuals with a PAV/PAV genotype. Downstream reductions in mucociliary clearance and bacterial killing are correspondingly observed [9]. As would be expected, AVI/AVI individuals also do not taste PTC or PROP when presented with an oral taste test challenge [43].

This reduction in responsiveness observed in AVI-expressing individuals has clinical consequences. Several studies in the past five years have highlighted a potential relevance of T2R38 in chronic rhinosinusitis (CRS). Individuals who express the fully functional, PAV/PAV genotype are less likely to require surgical intervention for CRS symptoms than patients with an AVI/AVI genotype [43,44]. Additionally, levels of gram-negative infection are lower in PAV/PAV patients [43–46], confirming that the NO-dependent response of T2R38 acts as a critical defense for this class of bacteria. A hallmark of CRS is mucociliary stasis, in which bacteria are inadequately cleared. At pathogenic levels of proliferation, bacterial toxins can be destructive to cells and cilia, perpetuating the process of impaired mucociliary function [47]. It is known that sinonasal explants from patients with CRS have an attenuated response to a variety of compounds (bitter and non-bitter) that stimulate ciliary beating in control tissue [48]. Other studies, while part of an inconclusive set of literature, have shown differences in NO levels in patients with airway diseases [49]. Without the action of NO to kill bacteria and increase ciliary beating in response to AHLs, it appears that the non-functional T2R38 polymorphism has a phenotypic effect on upper airway disease [9].

Other bitter taste receptors on ciliated cells, such as T2R4 and T2R14 [50], respond to different bitter agonists, such as quinine hydrochloride. Quinine is an alkaloid derivative that is isolated from the cinchona tree, and is found in several medicinal and commercial products [51]. Recent work shows that quinine stimulates a rapid T2R-dependent NO response from ciliated cells in the airway [52]. While quinine is a more promiscuous bitter taste receptor agonist than PTC or PROP, there are common genetic variants in bitter taste receptor genes on chromosome 12 that strongly contribute to the perception of quinine taste intensity [53]. Quinine taste sensitivity has also been selected independently in some world populations, especially for low concentrations of quinine [54]. Concentrations of bitter microbial products in the airway are also at low concentrations [9], and these differences in taste perception of dilute quinine solutions may be reflective of varying responses of these bitter taste receptors in both the airway and on the tongue. Allele expression studies have shown that patients

with CRS differ from control patients at several genetic loci for taste receptors, including TAS2R14 and TAS2R49 [45].

3.2. Taste Receptors on Solitary Chemosensory Cells

Solitary chemosensory cells (SCCs) are a non-ciliated airway cell type that is relatively rare, representing approximately 1% of the total upper airway epithelial cell population [55]. These cells are immunoreactive with α-gustducin, a taste signalling component, and they share many similarities with taste bud cells [28]. Because of their rarity, they are difficult to isolate experimentally [19]. Solitary chemosensory cells express both sweet and bitter taste receptors that are capable of responding to a variety of compounds [8,20,27,56,57]. In response to bitter stimulation, these cells do not activate NO production, but instead mediate a separate cohort of responses. In mouse SCCs, the calcium response resulting from bitter taste receptor stimulation causes acetylcholine (ACh) release that has breath holding effects and also results in downstream inflammatory mediator release [8,19,20]. Both of these responses are at least partially immunomodulatory in nature: breath holding limits toxin or organism aspiration, while inflammatory mediators often participate in a larger immune signaling cascade. In the human upper airway, SCC stimulation results in the calcium-mediated release of antimicrobial peptides from adjacent ciliated cells, including β-defensin 1 (DEFB1) and β-defensin 2 (DEFB2) [29,58] (Figure 1). These defensins are potently antimicrobial and have effects on both gram-positive and gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* and *P. aeruginosa* [59]. Unlike the antimicrobial peptide release observed with TLR stimulation, which occurs over several hours as a result of changes in messenger RNA [34], bitter taste receptor stimulation causes release of pre-formed stores of antimicrobial peptides. Denatonium is a specific bitter compound that has agonist properties for bitter taste receptors on SCCs, and application of denatonium to airway epithelial cells from mouse and human cultures stimulates calcium responses that spread to adjacent cells via gap junctions [29]. Similar to the cascades observed in bitter taste receptor stimulation in ciliated cells, the calcium responses from SCC stimulation also require canonical components of taste signaling, such as TRPM5, PLCβ2, and gustducin [29].

In addition to expressing bitter taste receptors, SCCs also express sweet taste receptors, the T1Rs [27,29,60]. These receptors are sensitive to sweet compounds, such as glucose, in concentrations far lower than those detected orally [61]. Typically, airway surface liquid (ASL) glucose levels are maintained at a homeostatic level of approximately 0.5 mM; there is a physiologic leak and continuous reuptake of glucose from the adjacent basolateral serum that maintains this concentration [29]. At this physiologic level of glucose, T1R2 and T1R3 receptors are tonically activated. The activation of sweet taste receptors on SCCs appears to antagonize the action of bitter taste receptor cascades through activation of cAMP and phosphodiesterase which subsequently block activation of the IP3 receptor [29]. During bacterial infection, there is a reduction in ASL glucose due to increased bacterial consumption. It is hypothesized that it is this reduction in glucose that causes a reduction in sweet taste receptor activation, resulting in a corresponding increase in bitter taste receptor activity and responsivity to microbial bitter products [29]. Thus, the balance tips in favor of T2R responses and mobilization of innate immune defenses, theoretically restoring the balance towards airway microbial homeostasis and normalized glucose concentrations.

Several experiments have been conducted to support this hypothesis of antagonistic actions of bitter and sweet taste receptors. When glucose or sucrose is added to airway surface liquid of in vitro mouse cultures, calcium responses to denatonium are greatly diminished. Mice that were genetically modified to not express sweet taste receptors showed a normal SCC response to denatonium under the same conditions [29,62]. Additional experiments have shown that T1Rs can also be activated by D-amino acids produced by bacteria. Lee et al. demonstrated that at least two T1R-activating D-amino acids produced by *S. aureus* suppress SCC calcium responses, with corresponding decreases in antimicrobial peptide secretion [58]. These D-amino acids may be produced by the bacteria for protection from host innate immune responses and may allow for increased colonization and potential

opportunistic infection. Just as observed with T2Rs, there is *TAS1R* genetic variation that contributes to preferences in oral sweet taste perception [63]. Several allelic variations in *TAS1R* genes demonstrate frequency differences of greater than 10% when comparing CRS patients and control individuals [45]. Just as is the case with bitter receptors, there is genetic variation in *TAS1R* genes that manifests as individual preference in sweet taste [63]. While no single locus has yet been identified, there are allele variations among the *TAS1R* genes that show frequency differences of >10% in 16 loci between patients with CRS and controls [45].

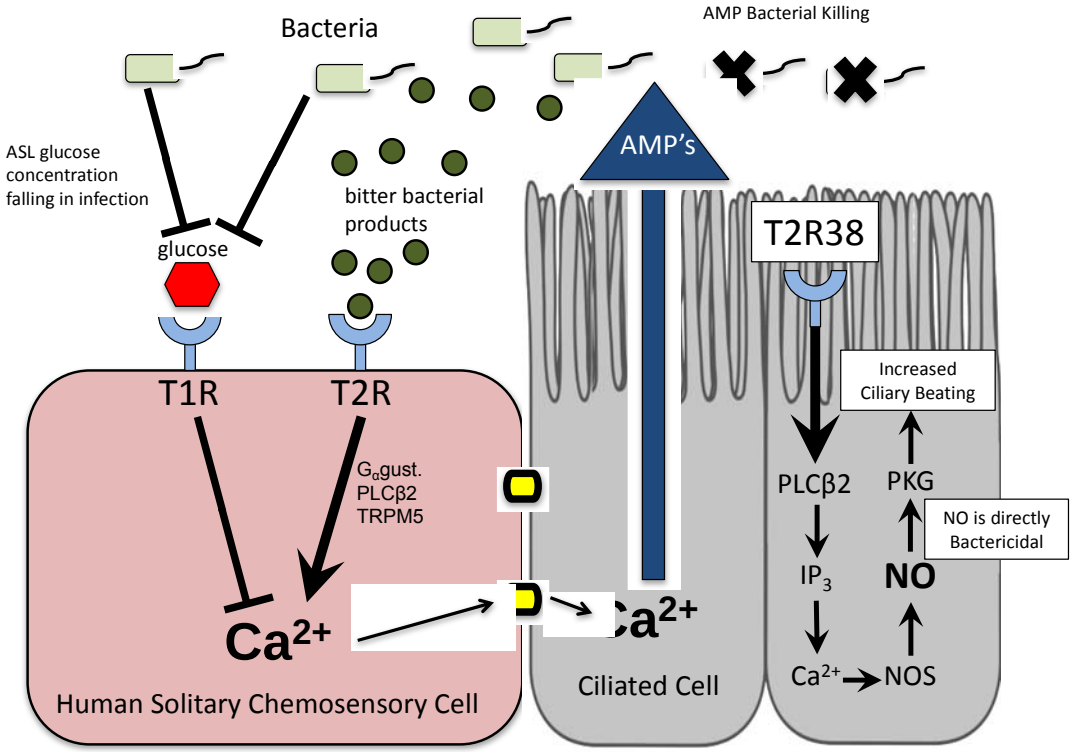

Figure 1. Bitter and sweet taste receptor-induced innate immune defenses in ciliated and solitary chemosensory cells in the human upper airway. ASL: airway surface liquid; AMP: anti-microbial peptide; NOS: nitric oxide synthase; NO: nitric oxide; PKG: protein kinase G.

3.3. Bitter and Sweet Taste Testing

Based on the existing evidence that genetic variation in bitter and sweet taste receptors is correlated with disease status and disease severity, phenotypic oral taste tests may be clinically useful to assess taste receptor variation. On a broad level, individuals with insensitive bitter taste receptors or hypersensitive sweet taste receptors would be expected to be overrepresented in a cohort of individuals with CRS. Two recent papers report on taste testing results in hundreds of patients with CRS as well as propensity matched control individuals without rhinologic disease [52,64]. Patients with CRS without nasal polyps perceived denatonium, an SCC T2R agonist, as having lower subjective intensity, while patients with CRS with nasal polyps perceived quinine, a ciliated cell T2R agonists, as having lower subjective intensity as well (Table 1). All CRS patients rated sucrose, a T1R agonist, as having higher subjective intensity. There was no difference in taste sensitivity to a neutral compound, sodium chloride, between CRS and control patients [52,64]. When bitter and sweet taste ratings were aggregated into an overall "score" that took into account the opposing physiologic effects of bitter and sweet taste receptor stimulation in SCCs, there were even more highly significant differences between CRS and control subjects. Some of these subjective taste differences also appear to be reflected at the physiologic level; experiments have shown an inverse association between in vitro

biofilm formation and PTC taste intensity ratings [65]. The implications for these differences are broad. Physiologically, this may reflect a less active SCC response to bitter microbial products in the airway of CRS patients, with an additional compounding effect of an increased sensitivity to glucose. This increased glucose sensitivity would perhaps inhibit SCC T2R immunomodulatory function even with intact T2R responses, due to the relative T1R affinity. These phenotypic differences can also help explain why CRS tends to run in families, suggesting a critical genetic influence in the disease [66]. Furthermore, the stratification of patient sensitivity in ciliated and SCCs T2Rs based on CRS polyp status is additionally interesting, as this may demonstrate unique T2R contributions to different types of CRS.

Table 1. Subjective taste intensity ratings in patients with chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP), relative to control patient taste intensity ratings.

	Bitter Perception		**Sweet Perception**	**Salt Perception**
	Quinine	**Denatonium**	**Sucrose**	**NaCl**
CRSsNP	*No difference*	*Decreased*	*Increased*	*No difference*
CRSwNP	*Decreased*	*No difference*	*Increased*	*No difference*

3.4. Diagnostics and Therapeutics

Oral taste tests are inexpensive to produce and administer, and the ability to assess variations in airway taste receptor functionality could help predict impaired innate immunity or predisposition to respiratory disease. Bitter taste testing with specific agonists, such as PTC, could potentially be used to stratify surgical candidates or identify individuals who should receive more aggressive management. With optimized taste testing compound concentrations that reflect respiratory tract affinity levels, improved patient stratification for CRS and control patients could be achieved. Additionally, the utilization of multiple bitter and sweet compounds for taste testing could improve performance parameters with an overall "taste score". Beyond the diagnostic realm, bitter taste receptor agonists may have therapeutic potential as topical agents in harnessing potent innate immune defenses as an alternative to more conventional treatments, such as antibiotics. T1R antagonists, such as lactisole and amiloride, could also release the inhibition of T1Rs on antimicrobial responses [29,67].

4. Conclusions

Bitter and sweet taste receptors play important roles in the regulation of innate immune defenses in the upper respiratory tract. Bitter taste receptors mediate rapid antimicrobial nitric oxide or β-defensin responses in the presence of bacterial compounds, while sweet taste receptors attenuate these responses at higher levels of glucose. There is a high degree of genetic variation in airway taste receptors, and genetic polymorphisms can predispose people to recalcitrant CRS and create an increased susceptibility to infection. Phenotypic oral taste tests can capture some of this taste receptor variation, correlating with disease status in CRS. Further, bitter taste receptor agonists and sweet taste receptor antagonists can potentially serve as alternative therapies for respiratory disease that harness endogenous immune defenses.

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