Taste Receptors: Regulators of Sinonasal Innate Immunity

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Taste receptors in the oral cavity guide our preferences for foods, preventing toxic ingestions and encouraging proper nutrient consumption. More recently, expression of taste receptors has been demonstrated in other locations throughout the body, including the airway, gastrointestinal tract, pancreas, and brain. The extent and specific roles of extraoral taste receptors are largely unknown, but a growing body of evidence suggests that taste receptors in the airway serve a critical role in sensing bacteria and regulating innate immunity. This review will focus on the function of bitter and sweet taste receptors in the human airway, with particular emphasis on T2R38, a bitter taste receptor found in sinonasal ciliated cells, and the bitter and sweet receptors found on specialized sinonasal solitary chemosensory cells. The importance of these novel taste receptor-immune circuits in the human airway and their clinical relevance in airway disease will also be reviewed.

INTRODUCTION

The airway is constantly defending itself against microbes, and the sinonasal cavity serves as the first line of immune defense.1–3 In most individuals, the respiratory epithelial innate immunity effectively utilizes mucociliary clearance (MCC) to trap and clear inhaled debris and microbes. This innate defense mechanism is essentially made of two components: 1) mucus secretions and 2) beating cilia, which propel the mucus out of the airways. There are multiple antimicrobial factors tonically and dynamically secreted in the mucus to ward off infection4,5 (Fig. 1). One consequence of inadequate sinonasal defense is chronic rhinosinusitis (CRS), a multifactorial disease involving impaired MCC, stasis of sinonasal secretions, and persistent infection and inflammation in the airway.4,6,7 Chronic rhinosinusitis effects more than 16 million Americans annually,8 contributing to an enormous economic burden and negative impact on quality of life,9–13 and generates 20% of the antibiotics prescribed to adults.14 These statistics suggest that CRS is likely an important contributor to the ongoing crisis of antibiotic resistance, emphasizing the need for alternative therapeutic strategies for managing this disease. Stimulating the endogenous host immune system to clear infection could serve as one alternative to antibiotic therapies, but this strategy requires a firm understanding of the molecular mechanisms involved. Recent research has demonstrated a connection between sinonasal immunity and bitter and sweet taste receptors, suggesting that these receptors could be innovative targets for treating CRS and other respiratory infections.

Bitter and Sweet Taste Receptors in Immunity

The immune system has been described as an additional sensory modality because it is able to perceive the presence of pathogens.15 Ironically, recent studies have actually demonstrated that bitter and sweet taste receptors, known as T2Rs and T1Rs respectively, directly participate in the immune system. T2Rs and T1Rs are G-protein-coupled receptors that were first identified and named for their role in type 2 taste receptor cells of the tongue.16–18 T2Rs detect ingested bitter compounds such as toxic plant alkaloids, and the T1Rs detect sugars such as glucose and sucrose.19,20 Taste receptors are also present beyond the tongue in a variety of organs, including the urethra, bladder, testes, gastrointestinal tract, pancreas, thyroid, brain, and airway.21–23

One hypothesis for extraoral bitter taste receptors that was offered to explain their extensive distribution in the body was that they bind bitter products secreted by pathogenetic bacteria or fungi. This theory was supported by early mouse studies of nasal solitary chemosensory cells (SCCs), which express both T2R bitter and T1R sweet receptors.24–33 It was later demonstrated that SCCs in the mouse nose respond to the quorum-sensing molecules, called acyl-homoserine lactones (AHLs), which are secreted by gram-negative bacteria such as the common respiratory pathogen Pseudomonas aeruginosa.31,34,35 Interestingly, the T2Rs (bitter) have a multitude of

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naturally occurring polymorphisms that lead to the individual taste preferences for various foods, specifically bitter foods such as green leafy vegetables and beverages such as beer, scotch, and coffee. There is also significant genetic variation in the T1Rs that correlates with sweet taste preferences in humans. The consequences of genetic variation in the T2Rs and T1Rs could explain differences in individuals’ immune responses and pathogen clearance. It is possible that taste receptor polymorphisms explain some of the genetic basis of respiratory infections. This review will discuss recent studies demonstrating that T2Rs recognize bacterial products, and that genetic variation in one of the T2Rs correlates with sinonasal infection, CRS, and surgical outcomes. The role of T1Rs in regulating sinonasal innate immunity will be discussed, although their clinical significance in airway disease has not yet been fully appreciated.

**Bitter Taste Receptors in Upper Airway Ciliated Epithelial Cells**

A study in 2009 demonstrated that T2R taste receptors were expressed by human bronchial epithelial cells, and binding of bitter agonists to these T2Rs stimulated a calcium-mediated increase in ciliary beating. It was also determined that these T2Rs were localized to the motile cilia lining the epithelium, suggesting that motile cilia might serve as chemosensory organelles, in addition to being responsible for mucociliary clearance. The authors of the study hypothesized that T2Rs in bronchial cilia are a way to sense and clear noxious inhaled substances. It was later demonstrated that there was expression of T2Rs in the human upper airway in nasal and paranasal sinus epithelium. Lee et al. were the first to discover a physiologic function for one specific taste receptor isoform, T2R38, which they demonstrated was localized to upper airway motile cilia. When ciliated epithelial cells were stimulated with known agonists of T2R38, such as phenylthiocarbamide (PTC), they exhibited low-level calcium responses that activated nitric oxide (NO) synthase (NOS) and led to robust intracellular NO production. This signaling pathway included two of the important components of the well-established taste signal transduction cascade, namely phospholipase C isoform β2 (PLCβ2) and the transient receptor potential cation channel subfamily M member 5 (TRPM5) ion channel. Nitric oxide and its derivatives are damaging to bacterial membranes, enzymes, and DNA; thus, production of NO by airway epithelial cells serves an important role in defense against infection. Nitric oxide also increases ciliary beat frequency through activation of guanylyl cyclase and protein kinase G, which phosphorylate ciliary proteins. In primary human sinonasal epithelial cultures, the NO produced through activation of T2R38 diffuses into the airway surface liquid (ASL), where it is directly bactericidal to *P. aeruginosa*; and as stated above, it serves as a second messenger for increasing ciliary beating—and thus for accelerating mucociliary clearance.

The identification of physiologic ligands that activate T2R38 is an additional piece of evidence in support of the role of T2R38 in airway immunity. Two major *P. aeruginosa* AHLs, N-butyryl-L-homoserine lactone (C4HSL) and N-3-oxo-dodecanoyl-L-homoserine lactone (C12HSL), were identified as agonists of T2R38. Through studies...
with purified AHLs and conditioned medium from wild type *P. aeruginosa*, as well as a strain mutated for the enzymes that synthesize AHLs, it was demonstrated that T2R38 detects physiological concentrations of AHLs, which results in activation of calcium-dependent NO production. Many gram-negative species secrete AHLs; therefore, T2R38 likely functions in airway ciliated cells as a sentinel receptor for detecting invading gram-negative bacteria and triggering a critical defensive bactericidal response. The T2R38 innate immune pathway in sinonasal ciliated epithelial cells is detailed in Figure 3.

**T2R38 Genetics and Airway Disease**

The degree of T2R38 activity in humans is dependent on a number of well-studied polymorphisms in *TAS2R38*. Two specific polymorphisms are common in the Caucasian population: one encodes a functional T2R38 and the other a nonfunctional T2R38 in the context of tasting PTC. These polymorphisms result in differences in the amino acids at position 49, 262, and 296, with the functional T2R38 containing proline (P), alanine (A), and valine (V) residues—and the nonfunctional T2R38 containing alanine (A), valine (V), and isoleucine (I) at these positions, respectively. Homozygous PAV/PAV individuals (20% frequency in Caucasians) are considered supertasters and perceive T2R38-specific agonists such as PTC and 6-propyl-2-thiouracil as intensely bitter. Homozygous AVI/AVI individuals (30% frequency in Caucasians) are non-tasters for T2R38-specific agonists. Heterozygote PAV/AVI individuals have varying levels of taste that correlate with the relative expression levels of the PAV and AVI alleles.

The respiratory defensive properties of the *TAS2R38* polymorphisms were studied by growing primary sinonasal cells from genotyped patients that were PAV/PAV (supertasters), AVI/AVI (nontasters), or PAV/AVI heterozygotes. Nitric oxide production was found to correlate with the *TAS2R38* polymorphism. Compared to cells from AVI/PAV heterozygotes or AVI/AVI nontasters, the cells from PAV/PAV supertasters had significantly enhanced NO production, mucociliary clearance, and bacterial killing in response to both PTC and AHLs. This data strongly suggested that *TAS2R38* polymorphisms alter sinonasal epithelial cells’ responsiveness to gram-negative bacteria and prompted clinical investigations.

Initial clinical studies discovered that PAV/PAV supertasters had a lower frequency of gram-negative sinonasal infection compared to PAV/AVI or AVI/AVI patients, with less-robust T2R38-dependent responses. *TAS2R38* genotype was compared in 56 patients who had undergone sinonasal surgery for CRS or for non-CRS disease and who had microbiology results of either no growth or normal respiratory flora (e.g., *Staphylococcus epidermidis*; n = 35), or positive cultures for gram-negative bacteria (n = 21) or specifically *P. aeruginosa* (n = 14). None of the
patients with the PAV/PAV genotype had gram-negative or *P. aeruginosa* growth. Furthermore, there was a significant difference in the distribution of AVI/AVI, PAV/AVI, and PAV/PAV genotypes between control patients (no growth or normal respiratory flora) and either gram-negative (*P < 0.006 by χ²*) or *P. aeruginosa* (*P < 0.029*) patients. 

The control and gram-negative/*P. aeruginosa* patients had no significant differences in the distributions of common polymorphisms of other receptors, including TAS2R19, TAS2R30 (also known as TAS2R47), or TAS2R46.

Additional clinical studies confirmed the preliminary studies of TAS2R38 genotype in sinonasal disease. 

One retrospective study was conducted using TAS2R38-genotyped sinonasal tissue samples from patients (*N* = 28) who had undergone primary functional endoscopic sinus surgery (FESS). 

The distribution of genotypes was 46% AVI/AVI nontasters, 50% PAV/AVI heterozygotes, and 3.6% PAV/PAV supertasters. This distribution was significantly different from the expected distributions of 30% AVI/AVI, 50% PAV/AVI, and 20% PAV/PAV (*P < 0.043 by χ²* analysis), indicating that PAV/PAV supertasters are less likely to need surgical intervention for CRS. Furthermore, a prospective study of TAS2R38 genotype in 70 patients undergoing primary FESS demonstrated a statistically significant difference in the frequency of AVI and PAV alleles compared with the general population. 

The distribution of diplotypes in these CRS patients were 37% AVI/AVI, 38% PAV/AVI, and 8.5% PAV/PAV compared with 29%, 51%, and 20%, respectively, in the general population of Philadelphia, PA (*P < 0.0383 by χ²* analysis). No significant differences were found in the allele distribution of other known risk factors, such as allergies, smoking exposure, asthma, diabetes, nasal polyposis, or aspirin sensitivity, demonstrating that TAS2R38 is an independent risk factor for CRS requiring FESS.

Independent confirmation of taste receptor genetics, as contributory to CRS, was presented in a study investigating two Canadian CRS populations compared with a control population using previously collected pooling-based genome-wide association data that had included single-nucleotide polymorphisms (SNPs) in taste receptors. 

The TAS2R38 I296V (*rs10246939*) SNP, thought to underlie the difference in functionality between PAV and AVI variants, was one SNP included in the analysis. The I296V SNP frequency differences were ~11% and 15% in the two CRS groups compared to the control population, confirming that this SNP is associated with CRS. 

This study also found three additional missense variants in TAS2R genes that were associated with CRS, one in TAS2R14 (*rs1015443*) and two in TAS2R49 (*rs12226919 and rs12226920*). The potential roles of T2R14 or T2R49 in sinonasal immunity have yet to be elucidated.

More recent studies have suggested that TAS2R38 genotype may predict surgical (FESS) outcomes and correlates with sinonasal quality of life in cystic fibrosis (CF) patients. 

A prospective study was conducted from 123 CRS patients undergoing primary FESS with preoperative and 6-month postoperative Sino-Nasal Outcome Test (SNOT-22), a validated patient-reported measure of sinonasal disease severity. 

82 of the patients in the study had nasal polyps and 41 patients were without nasal polyps. In the nonpolyp group, it was demonstrated that homozygotes for the functional receptor (PAV/PAV) had a 6-month postoperative mean SNOT-22 score improvement of 38 ± 21; whereas heterozygotes (AVI/PAV) or homozygotes for the nonfunctional receptor (AVI/AVI) had a mean improvement of 12 ± 22 (*P = 0.006*). 

This data supports the notion that the TAS2R38 genotype is the first genetic polymorphism predictive of surgical outcome for a select group of CRS (nonpolyp) patients. In a separate study of TAS2R38 genotype, SNOT-22 scores were analyzed from CF patients aged 18 to 32 years who were ΔF508 homozygous, the most common CF mutation. 

The PAV/PAV patients had significantly lower SNOT-22 scores (*N* = 49, *P < 0.05), and rhinologic symptoms (*n* = 47, *P < 0.05) were less severe in PAV/PAV patients than in patients with other TAS2R38 genotypes.

With additional studies exploring the effects of T2R38 in CRS susceptibility, quality of life, and surgical outcomes, TAS2R38 genotyping or phenotyping with a taste test could eventually guide clinical decision making. Current data have already established the T2R38 pathway as a promising therapeutic target, potentially allowing the exploitation of the native immune system’s ability to clear upper respiratory infections. 

With that in mind, further exploration of the T2R38-mediated signaling pathway and identification of other T2Rs will be important because there is a large subset of PAV/AVI and AVI/AVI individuals that would be less responsive to T2R38 agonist therapies.

**Bitter and Sweet Receptors in Upper Airway Solitary Chemosensory Cells**

The upper airway also contains solitary chemosensory cells (SCCs) which express both T2R bitter and T1R sweet taste receptors. 

These SCCs are dedicated chemosensory cells that are scattered throughout the sinonasal cavity at a density of about one in 100 cells. Nasal SCCs from mice respond to bitter compounds, such as denatonium benzoate or bacterial AHLs, using molecular transduction cascades that are similar to those utilized by oral taste receptor pathways, with key components including Gz-gustducin, PLCβ2, and TRPM5. 

When activated by bitter compounds, mouse nasal SCCs exhibit intracellular calcium responses; this result in acetylcholine release, which activates trigeminal nociceptors, causing inflammatory responses and breath-holding. 

Trigeminal nociceptors can also release different types of neuropeptides into the airway, including vasointestinal peptide and calcitonin gene-related peptide. 

These findings suggest that in vivo activation of mouse nasal SCC could cause local responses, such as fluid secretion or increased ciliary beating, but this has not yet been determined experimentally.

Years after their discovery in mice, SCCs were recognized in humans. The SCCs expressing the bitter receptor T2R47 and the sweet receptor T1R2/3 have been identified in primary cell cultures derived from human post-surgical tissues from different sinonasal
anatomical locations. Moreover, SCC-like cells found in the human vomeronasal duct were observed to express T2R4, T1R1, and T1R2. Additional studies of SCC distributions will likely reveal that this cell type is expressed throughout other areas of the human sinonasal cavity.

Human SCC physiology has been studied using both sinonasal tissue explants and air–liquid interface (ALI) cell cultures, which are a well-validated cell model containing various cell types, including basal, ciliated, and goblet cells, and SCCs. When human sinonasal ALIs or inferior turbinate explants were stimulated with the bitter agonist denatonium benzoate, saliva, and methicillin-resistant S. aureus, the majority of the AMP secretion after SCC and methicillin-resistant P. aeruginosa AMPs were bactericidal to gram-negative bacteria. The inhibition of T2R bitter receptor responses by T1R sweet receptor activation is possibly the most interesting aspect of human SCC physiology. This is of particular interest as the glucose concentration normally found in the human ASL is 0.5 mM, which appears to be sufficient for activation of T1Rs expressed in the human airway and inhibits SCC-mediated AMP secretion by approximately 50%. This concentration is 10- to 100-fold lower than concentrations required to activate T1R-dependent sweet taste in the oral cavity. At least two other extraoral sweet receptors have also been shown to respond to lower sugar concentration such as the T1Rs in pancreatic β-cells and gut endocrine cells. It is likely that the oral SCC sensitivities are tuned to the significantly higher sugar concentrations found in most foods; whereas the extraoral T1R sensitivities are calibrated to respond to the lower sugar concentrations in accordance with the physiologic demands of the tissues where they are located. Although the responsible mechanism has yet to be determined, it is possible that the differences in oral and extraoral SCC sensitivities are related to posttranslational modifications, stoichiometric differences, coupling to other signaling pathways, or the presence location-specific accessory subunits. Evidence from β-cells suggests that changes in subunit stoichiometry are important; however, similar studies have not been conducted in the airway.

Airway T1R sweet receptors may in fact be calibrated to control the degree of SCC-T2R-mediated AMP secretion in a physiologic significant manner. The T1R sweet receptors detect the concentration of glucose in the ASL, which may drop with the onset of infection. Specifically, SCC T1R sweet receptors would be activated by the normal in vivo ASL glucose concentration (~0.5 mM) of the upper airway; therefore, the activated T1Rs would inhibit intracellularly the SCC T2Rs to the bitter compounds secreted by some bacteria during low-level colonization in healthy individuals. The
in human sinonasal cells and increase the paracellular glucose flux in human bronchial cells. It is plausible that the elevated ASL glucose concentration in diabetics contributes to the observation that diabetics are more prone to airway infections than nondiabetics. One retrospective study of CRS patients showed that diabetics had a higher frequency of positive intraoperative microbiology cultures for gram-negative bacteria such as P. aeruginosa. It has been speculated that low ASL glucose promotes airway sterility by limiting the nutrients available for bacterial consumption. This proposed mechanism may be compounded by higher ASL glucose in CRS or diabetic patients, repressing T2R-mediated SCCs responses to bitter bacterial molecules through over-activation of T1R sweet receptors, as proposed above. If this were the case, topical application of sweet receptor antagonists, such as lactisole, could be novel therapies for restoring normal sinonasal immune dynamics in select patients.

Additional studies are necessary to investigate potential polymorphisms in TASIR genes that could alter T1R sweet receptor responses to sugars and impact susceptibility to infection in the airway, as has been shown in T2R38. Increased sensitivity of T1Rs in the airway might lead to increased repression of SCC T2R-mediated AMP secretion. The study discussed above investigating Canadian CRS patients and healthy individuals showed allele frequency differences of > 10% for 16 different SNPs in TASIR genes, stressing the importance of further exploration into TASIR genetics.

CONCLUSION

There is significant evidence supporting the role of T2R and T1R taste receptors as integral regulators of immediate phase innate immunity in the upper airway. A multitude of taste receptors are expressed in a variety of airway cell types and serve as immune sentinels in both mice and humans. Beyond the oral cavity and the upper airway, T2R38 is also present on the extracellular membrane of peripheral blood neutrophils, monocytes, and lymphocytes, as well as intracellularly in neutrophil vesicles, where it binds C12HSL secreted by P. aeruginosa. Furthermore, expression of T2R38 on myeloid cells has been demonstrated to be upregulated in biopsy specimens from patients with bacterial osteomyelitis, possibly as protection against developing biofilms. Chemosensory cells expressing bitter and umami taste receptors, along with other components of the taste transduction pathway, have been identified in the mammalian urethra, where they respond to stimulation by uropathogenic Escherichia coli. Activation of these chemosensory cells in the urethra trigger release of acetylcholine, which increases bladder detrusor muscle activity in rats. Identification of taste receptors as immune regulators is ironic; the immune system has been described by some as the sixth sensory modality. The human airway represents just one anatomical region where extraoral taste receptors may one day be exploited to treat infection and disease, highlighting the importance of further research in the field.
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