

A Taste of Things to Come?



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Tongue taste receptors inform us about food content and safety. A family of approximately 30 bitter G protein-coupled type 2 taste receptors (TAS2R) has been identified in mammals¹ and may have evolved for avoidance of plant toxins. Upon TAS2R activation, intracellular calcium is released, opening transient receptor potential channel M5 and causing an action potential, triggering taste sensation.^{2,3} T2R38, coded for on chromosome 7q, is involved in perception of bitter phenylthiocarbamide (PTC).⁴

However, taste receptors in mammals are not confined to the tongue, but are far more widely expressed: in airway and gastrointestinal epithelia, thyroid, pancreas, and brain.⁵ Their functions are largely unknown. These extraoral receptors include bitter and sweet taste receptors in the airway, and a number of studies suggest that these receptors may be important in sensing bacteria and regulating innate immunity.

In sinonasal cilia, the T2R38 bitter taste receptor detects gram-negative bacterial quorum-sensing molecules, acyl-homoserine lactones, necessary for the formation of biofilms. Activation of T2R38 stimulates nitric oxide production, increasing ciliary beating and directly killing bacteria.⁶ T2R38 polymorphisms, which alter function, appear involved in susceptibility to upper respiratory tract infections and chronic rhinosinusitis (CRS).⁷ In a population of patients with CRS with active infection or inflammation, a relationship between T2R38 phenotype and *in vitro* biofilm formation was sought. Patients' phenotypic (functional) expression of the bitter taste receptor T2R38 was evaluated with PTC. There was an inverse linear association between *in vitro* biofilm formation and rating of PTC taste intensity ($P = .019$). This association was driven by nonpolypoid patients with CRS ($P = .0026$).⁸

A small Australian study assessed the influence of bitter taste receptor genotype on the presence of culturable bacteria in the sinuses. Middle meatal nasal swabs were sent for microbiological evaluation at the time of surgery. Mucosal biopsies were taken and sent for bitter taste receptor genotype analysis. Sequencing of 3 polymorphisms in the TAS2R38 gene was performed to identify genotypes as supertasters (PAV/PAV), nontasters

(AVI/AVI), or heterozygotes (PAV/AVI). A nontaster genotype was predictive of colonization by pathogens.⁹

Variations in the T2R38 genotype may explain differences in clinical severity in cystic fibrosis in F508 homozygous patients, where individuals with 2 functional T2R38 alleles (PAV/PAV) had significantly lower 22-item Sino-Nasal Outcome Test scores.¹⁰ Genomewide association studies have shown a TAS2R38 coding single nucleotide polymorphism rs10246939 (I296V) to be associated with CRS, which has recently been confirmed in 2 series of Canadian patients with CRS.¹¹

Some solitary chemosensory cells in the sinonasal mucosa contain other bitter (T2Rs) and sweet (T1R2+3) receptors that control antimicrobial peptide secretion.

Bitter taste receptors detect secreted bacterial products. *In vitro* activation of a subset of T2Rs activated a calcium wave that propagated through gap junctions to the surrounding respiratory epithelial cells and stimulated antimicrobial peptide release.¹²

Sweet taste receptor (T1R2/3) activation suppressed this T2R-mediated antimicrobial peptide secretion, suggesting a braking mechanism, present in health, which can be removed when bacteria deplete glucose in nasal secretions.¹² Patients with CRS have elevated glucose concentrations in their nasal secretions as do patients with hyperglycemia. This increased glucose in respiratory secretions could chronically activate T1R2/3 and suppress T2R-mediated innate defense. If confirmed, this calls into question the use of glucose in nasal douching solutions.

However, the opposite situation, hyperreactivity of the bitter taste receptor mechanism, could also be relevant in CRS with nasal polyps (CRSwNP). A recent study¹³ suggests that patients with CRSwNP with increased bacterial killing after stimulation with low levels of denatonium (a bitter receptor stimulant) undergo significantly more functional endoscopic sinus surgeries and have worse 6-month post-functional endoscopic sinus surgery 22-item Sino-Nasal Outcome Test scores.

In this issue of the journal, the authors responsible for much of the current work on taste receptors in CRS have examined their hypothesis that in CRS insensitivity to bitter tastes and hypersensitivity to sweet ones is more common than in the normal population. Patients with CRS without nasal polyps (CRSsNP) were significantly more likely to be less sensitive to denatonium, a broad T2R agonist, and those with CRSsNP and CRSwNP were more sensitive to sucrose, a T1R2/3 agonist.¹⁴ There was no difference between patients with CRS and controls in their salt sensitivity. This differential finding between polypoid and nonpolypoid CRS is consistent with the observation in the Adappa et al⁸ study that the association between *in vitro* biofilm formation and PTC taste intensity ratings occurred in patients with nonpolypoid CRS. The authors conclude that an inexpensive taste test that could indicate

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Conflicts of interest: G. K. Scadding has received consultancy fees from Mylan-MEDA, Danone, and ALK and has received lecture fees from Mylan-MEDA and ALK.

Received for publication September 14, 2017; accepted for publication September 18, 2017.

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J Allergy Clin Immunol Pract 2018;6:1081-2.
2213-2198

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<https://doi.org/10.1016/j.jaip.2017.09.006>

impaired innate immunity might be clinically useful. It might be of value to investigate whether those individuals who cannot tolerate intranasal azelastine because of its bitter taste are underrepresented in CRS cohorts.

Taste receptors may have further import: TAS2R bitter taste receptors are also found on human lower airway smooth muscle (ASM) where agonists such as denatonium evoked increased intracellular calcium ($[Ca^{2+}]_i$), which would be expected to evoke contraction. Paradoxically, bitter tastants caused relaxation of isolated ASM and dilation of airways 3-fold greater than that of β -adrenergic receptor agonists. This was associated with a localized $[Ca^{2+}]_i$ response at the cell membrane, which opens large-conductance Ca^{2+} -activated K^+ (BK_{Ca}) channels, leading to ASM membrane hyperpolarization. Inhaled bitter tastants decreased airway obstruction in a mouse model of asthma.¹⁵

Future research on airways taste receptors could further elucidate the pathogenesis of CRS and other airway problems and possibly suggest new therapeutic targets, but must be undertaken in very well-characterized patient groups for maximum benefit.

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