Review Article

Taste receptors in the upper airway

Jenna R. Freund a, Robert J. Lee a,b,*

a Department of Otorhinolaryngology-Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
b Department of Physiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Received 6 February 2018; accepted 26 February 2018
Available online 16 March 2018

Abstract  Taste receptors were named for their originally-identified expression on the tongue and role in the sensation of taste (gustation). They are now known to be involved in many chemosensory processes outside the tongue. Expression of the receptors for bitter, sweet, and umami was recently identified in many organs, including the brain, airway, gastrointestinal tract, and reproductive systems. We do not yet know the full roles of these receptors in all of these tissues, nor do we know all of the endogenous ligands that activate them. However, taste receptors are emerging as potentially important therapeutic targets. Moreover, they may mediate some off target effects of drugs, as many medications in common clinical use are known to be bitter. The focus of this review is on recent basic and clinical data describing the expression of bitter (T2R) and sweet (T1R) receptors in the airway and their activation by secreted bacterial compounds. These receptors play important roles in innate immune nitric oxide production and antimicrobial peptide secretion, and may be useful targets for stimulating immune responses in the upper respiratory tract via topical therapies. Moreover, genetic variation in these receptors may play a role in the differential susceptibility of patients to certain types of respiratory infections as well as to differential outcomes in patients with chronic rhinosinusitis (CRS). CRS is a syndrome of chronic upper respiratory infection and inflammation and has a significant detrimental impact on patient quality of life. CRS treatment accounts for approximately 20% of adult antibiotic prescriptions and is thus a large driver of the public health crisis of antibiotic resistance. Taste receptors represent a novel class of therapeutic target to potentially stimulate endogenous immune responses and treat CRS patients without conventional antibiotics.

Keywords  Chronic rhinosinusitis; Gustation; Nasal disease; Respiratory infection; Nitric oxide; Antimicrobial peptide; Innate immunity; Cilia

* Corresponding author. Hospital of the University of Pennsylvania, 5 Ravdin Building, Suite A, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail address: rjl@penmedicine.upenn.edu (R.J. Lee).
Peer review under responsibility of Chinese Medical Association.

https://doi.org/10.1016/j.wjorl.2018.02.004
2095-8811/© 2018 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Taste receptors were first described as sensory receptors located on the tongue, where they are expressed in taste cells of taste buds. However, bitter and sweet G protein-coupled taste receptors have recently been identified in other tissues ranging from the lungs and gut to the brain.1–3 The purpose of these seemingly misplaced, so-called “extra-oral” taste receptors was at first baffling, but it is now known that taste is only part of the responsibility of these receptors. Bitter and sweet receptors serve more general chemosensory roles in many tissues, making them potential therapeutic targets or possibly important mediators of off-target drug effects.4 Particularly as many medications in clinical use taste bitter.5,6 G protein-coupled receptor (GPCR) taste receptors have been found in a large variety of extra-oral tissues, including but not limited to the airway, brain, lungs, testes, and colon.1,8 These extra-oral taste receptors do not mediate “taste” per se as they are not linked to neuronal perceptive pathways, but they still serve as local chemoreceptors in the body. The known distribution of bitter and sweet taste receptors varies between organs, with some thought to express only bitter or only sweet receptors, while others express both (Fig. 1). The upper airway (nose and sinuses) has both bitter and sweet receptors in several different cell types that have multiple local effects on innate immunity.

We are only beginning to understand the diverse roles of these receptors. For example, sweet taste receptors in the pancreas and intestine may regulate insulin secretion,9–12 and glucose transporter expression,13–15 respectively, in response to glucose levels. Bitter taste receptors in the male reproductive system are important for fertility,16 though the mechanism behind this is unknown. In the airway, both bitter and sweet receptors play a role in the front line of innate defense, alerting cells to harmful pathogens and activating immune responses to remedy the situation, described in more detail below. Because taste receptors have a wide range of genetic polymorphisms that alter receptor functionality and contribute to the complex individual variations in taste preferences,19 their role in immunity suggests that taste receptor genetics may play a role in susceptibility to respiratory or other infections. This hypothesis has been supported by recent clinical data also described below.

Brief overview of taste receptors

Taste receptors on the tongue alert the brain to the presence of different nutrients, toxins, and other chemicals that contribute to the overall flavor of ingested materials. Flavor is a complex sensation of taste, smell (olfaction), mouth feel (texture), and sometimes pain, as in the case of spicy foods containing capsaicin or allylisothiocyantes that activate pain-sensitive neurons. However, the human tongue can only detect five canonical basic tastes: sweet, bitter, salty, sour, and umami, which is the taste of savory amino acids like L-glutamate.20 Other tastes may also be detected by the tongue, such as metallic taste21 or the taste of fat,22–24 though these have been controversial and hard to study, as high metal salt concentrations can cross-
mediate sensation of bitter, sweet, and umami tastes.\textsuperscript{30} Homodimers may also act as glucose 10,\textsuperscript{35,36} or calcium/G protein-coupled receptors (GPCRs). Ion channels are responsible for salty and sour tastes, mediated by the epithelial sodium channel (ENaC) and acid-sensing ion channel (ASIC) proteins that detect Na\textsuperscript{+} and H\textsuperscript{+} ions, respectively.\textsuperscript{8,29} GPCRs mediate sensation of bitter, sweet, and umami tastes.\textsuperscript{30} GPCRs are transmembrane proteins that change conformation when activated by an extracellular ligand, setting off an intracellular signal cascade.\textsuperscript{1,3,8,31,32} There are two main families of taste receptors for the 5 basic tastes in vertebrates: ion channels and G protein-coupled receptors (GPCRs). Ion channels are responsible for salty and sour tastes, mediated by the epithelial sodium channel (ENaC) and acid-sensing ion channel (ASIC) proteins that detect Na\textsuperscript{+} and H\textsuperscript{+} ions, respectively.\textsuperscript{8,29} GPCRs mediate sensation of bitter, sweet, and umami tastes.\textsuperscript{30} GPCRs are transmembrane proteins that change conformation when activated by an extracellular ligand, setting off an intracellular signal cascade.\textsuperscript{1,3,8,31,32}

There are two main classes of taste receptors for the 5 basic tastes in vertebrates: ion channels and G protein-coupled receptors (GPCRs).\textsuperscript{1,3,8,31,32} There are two main families of taste receptors: taste family type 1 (T1R) and taste family type 2 (T2R) receptors.\textsuperscript{1,3,8,31,32} The T1R family contains three isoforms, T1R1, T1R2, and T1R3. Sweet is detected by activation of a receptor comprising a heterodimer of T1R2 and T1R3 (T1R2/3), while umami is detected by activation of a receptor composed of T1R1 and T1R3. Some type II taste cells have been reported to express only T1R3 without T1R1 or T1R2\textsuperscript{1,3,44}, and T1R3 homodimers may also act as glucose\textsuperscript{35,36} or calcium/magnesium receptors.\textsuperscript{21} Bitter taste is mediated by T2R receptors (T2Rs).\textsuperscript{1,3,8}

Humans have 25 different functional T2R isoforms, which may heterodimerize to form even more variants. Bitter taste is thus unique in that many different receptors contribute to bitter recognition, which fits with the hypothesized role of bitter taste being protective against a wide variety of harmful plant poisons,\textsuperscript{57} including toxic alkaloids like strychnine.\textsuperscript{36,39} On the tongue, bitter (T2R), sweet (T1R2/3), and umami (T1R1/3) receptors are expressed in distinct cells of the taste bud, called type 2 cells. Each taste cell can detect one type of taste, and coupling of that cell to differentafferent gustatory neurons dictates how the response is perceived by the brain.\textsuperscript{40} By contrast, bitter and sweet receptors are co-expressed together in many extraoral chemosensory cell types, including intestinal tuft cells that regulate anti-parasitic immunity\textsuperscript{41,42} and solitary chemosensory cells in the mouse and human airway.\textsuperscript{2,3,43–46}

These taste receptors vary in number and functionality between species, shaped by evolutionary pressures.\textsuperscript{37,38,47} For example, cats, which are obligate carnivores, do not naturally eat significant amounts of sweet sugars and, over the course of evolution, have lost their functional TAS1R2 gene for T1R2 and thus the ability to taste sweet.\textsuperscript{37} By contrast, herbivores typically have expanded numbers of T2R isoforms to protect against ingestion of toxic plants.\textsuperscript{37} Gene deletions, pseudogenizations, and duplications underlie these species-to-species differences. However, even within the same species, taste receptor function varies from individual to individual due to genetic polymorphisms. While only a few of these polymorphisms have well-documented phenotypic effects, hundreds of T2R polymorphisms and several T1R polymorphisms have been noted in humans.\textsuperscript{19,48} The most well-known and well-characterized example is the bitter receptor isoform T2R38.

The TAS2R38 gene encoding T2R38 has two common polymorphisms, one encoding a functional receptor and one encoding a nonfunctional receptor.\textsuperscript{49} 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.\textsuperscript{49} Loss of the valine at the third position in the AVI variant prevents receptor activation.\textsuperscript{50–52} These polymorphisms are distributed in a nearly Mendelian ratio in Caucasian populations. Homozygous AVI/AVI individuals (~30% frequency in Caucasian populations) are “non-tasters” for the T2R38-specific agonists phenylthiocarbamide (PTC; also known as phenylthioureia or PTU) and 6-propyl-2-thiouracil (PROP).\textsuperscript{49} PAH/PV individuals (~20% frequency in Caucasian populations) are termed “super tasters” for these agonists because they perceive them as intensely bitter, while AVI/PAH heterozygotes have varying intermediate levels of taste.\textsuperscript{49,53} There are also several rarer haplotypes in other populations, such as the non-functional AAI polymorphism more common in those of African descent.\textsuperscript{49} Because T2R38 contributes to detection of isothiocyanate compounds in leafy green vegetables like Brussels sprouts, these polymorphisms can impact individual taste preferences.

Bitter taste receptors in airway ciliated cells

In the airway, T2R bitter receptors were first discovered on the ciliated cells lining the bronchia\textsuperscript{64} and sinonasal epithelium.\textsuperscript{65–67} Ciliated cells are integral to airway defense (Fig. 2). A thin layer of mucus secreted by airway secretory goblet cells and submucosal glands traps inhaled pathogens and particulates. The coordinated and rapid (~8–12 Hz) beating of motile cilia then drives transport of this mucus and trapped pathogens out of the airway to the oropharynx, where it is cleared by expectoration or swallowing.\textsuperscript{68–71} It was previously thought that motile cilia (9 + 2 microtubule structure) have only mechanical functions, as in moving airway mucus and in setting left–right asymmetry in the developing embryo,\textsuperscript{72} unlike primary cilia (9 + 0 microtubule structure, e.g. in the kidney or in neurons), which function in signal transduction.\textsuperscript{73} The expression of
chemosensory "taste" receptors in motile cilia showed that, like primary cilia, motile cilia can also play a role in cell chemosensation.

We found several T2R isoforms, T2R4, T2R16, T2R14, and T2R38, in sinonasal ciliated cells. Stimulation of these receptors by known bitter compounds activates calcium-dependent nitric oxide (NO) production that increases phosphorylation of ciliary proteins through protein kinase G (PKG). This increases ciliary beat frequency to facilitate the movement mucus out of the airway by increasing mucociliary transport rates. The generated NO also diffuses into the airway surface liquid, where it can directly kill bacteria as well as possibly damage viral or fungal pathogens.

We found that the T2R38 isoform in airway cilia is activated by acyl-homoserine lactone quorum-sensing molecules secreted by gram-negative bacteria like Pseudomonas aeruginosa. This suggests that cilia T2Rs contribute to immune detection of bacterial invaders similarly to classic immune pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), that are also expressed in the airways. PRRs detect conserved bacterial, viral, and/or fungal products known as pathogen-associated molecular patterns (PAMPs), such as viral nucleic acids or bacterial surface glycoproteins. Activation of TLRs up-regulates mRNA for proteins involved in sustained antimicrobial responses, like the defensin family of antimicrobial peptides. These TLR responses typically occur over the course of hours. However, the NO responses activated by T2Rs are much faster, occurring within seconds. Thus, we hypothesize that T2Rs represent a fast arm of innate immunity, while other PRRs activate complementary longer-term responses.

Clinical data suggest these rapid T2R responses may be important in chronic rhinosinusitis (CRS), a syndrome of chronic upper respiratory inflammation and/or infection. CRS leads to substantial decreases in patient quality of life, creates >$8 billion in direct healthcare costs in the US alone, and can seed lower respiratory infections and exacerbate lung diseases. While multiple etiologies contribute to CRS pathogenesis, a common CRS hallmark is defective mucociliary clearance, possibly through alterations of basal or opportunistic respiratory pathogen Pseudomonas aeruginosa. This suggests that cilia T2Rs contribute to immune detection of bacterial invaders similarly to classic immune pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), that are also expressed in the airways.
stimulated ciliary beat frequency. We found that sinonasal ciliated cells from patients homozygous for the AVI polymorphism in the TAS2R38 gene resulting in a nonfunctional T2R38 receptor (described above) have decreased NO and ciliary beat frequency responses to bacterial AHLs in vitro. Clinical studies subsequently revealed that TAS2R38 AVI homozygous patients are more susceptible to gram-negative bacterial infection, have a higher prevalence of biofilm-forming sinonasal bacteria, and are at greater risk for CRS requiring functional endoscopic sinus surgery (FESS). AVI/AVI patients may have worse outcomes after FESS for CRS without nasal polyps compared with patients homozygous for the functional (PAV) allele of TAS2R38.

The full picture of T2R38’s role in sinonasal immunity in different patient populations is still being elucidated. While one subsequent study found no correlation of TAS2R38 genotype with CRS in Italian patients, this population had different clinical characteristics (e.g. more recalcitrant disease and stronger Th2 inflammatory phenotype) than other studies. A more recent study supported a correlation between TAS2R38 AVI or PAV status and CRS severity in Poland. An Australian study concluded that AVI/AVI TAS2R38 genotype is predictive of the presence of culture-positive bacteria in CRS patients. Moreover, others have reported that T2R10 and T2R14 also respond to some bacterial AHLs when expressed in HEK293 cells, and yet other studies have suggested that T2R38 is important for immune cell detection of AHLs. A genome-wide association study demonstrated that polymorphisms in at least two TAS2R genes, TAS2R38 and TAS2R13, correlate with CRS.

Multiple T2Rs likely serve an immune sentinel role in the upper airway and beyond, and it is likely that certain T2Rs can detect other bacterial products beyond AHLs. Future work on determining the full range of T2Rs endogenously expressed by airway cells may reveal useful therapeutic compounds to target these receptors to stimulate endogenous innate immune responses in the absence of antibiotics. Larger scale clinical studies will likewise reveal the contribution of the genetics of these receptors to outcomes and disease risk in different CRS patient populations. Another intriguing implication of these data are that oral taste tests targeting certain T2R receptors may be useful for predicting susceptibility to certain infections, an idea already supported by preliminary studies.

**Bitter and sweet taste receptors in sinonasal solitary chemosensory cells**

Solitary chemosensory cells (SCCs) are individual specialized cells in the sinonasal epithelium with an elongated morphology that express chemosensory signal transduction components, including T1R sweet and T2R bitter receptors. In mice, SCCs make up approximately 1% of the nasal surface epithelial cells, and activation of T2Rs in nasal SCCs with bitter compounds can activate trigeminal afferent nerves resulting in reflexive breath holding and neurogenic inflammation. SCCs exist in the human sinonasal cavity in the inferior and middle turbinates, septum, and uncinate process. In contrast to mice, activation of T2Rs in human SCCs results in immediate secretion of β-defensin 1 and 2 from surrounding epithelial cells (Fig. 4) in an in vitro culture model. Defensins are antimicrobial peptides effective against both gram-positive and gram-negative bacteria, and thus SCC T2R activation is likely a defensive immune response. As the T2Rs expressed in SCCs (T2R10, 46, and 47) are different from those expressed in ciliated cells (T2R4, 14, 16, and 38), it remains to be determined what pathogen products might activate SCC T2Rs.

Intriguingly, T1R2/3 sweet taste receptors are co-expressed with T2Rs in the same SCCs, and can be activated by artificial sweeteners or by physiological concentrations of glucose found in ASL from tonic epithelial glucose leak from serosal fluid. ASL glucose is ~0.5 mmol/L in healthy patients, or approximately 10-fold below resting serum values. Activation of SCC T1R2/3 by 0.5–1.0 mmol/L glucose attenuates signaling of the T2Rs within the same SCC, reducing antimicrobial peptide release.

This may be a method of preventing “false alarms” of bacterial infection. In a true instance of infection, a decrease in sugar concentrations on the airway surface due to bacterial glucose metabolism is expected. T1Rs in the airway are tuned to sugar concentrations physiologically relevant to healthy levels in the airway surface liquid. The presence of bacterial SCC T2R ligands in the ASL

---

**Fig. 4** Nasal solitary chemosensory cells (SCCs) in airway innate immunity. Bitter chemicals secreted by microbes during infection may activate T2R bitter receptors expressed in solitary chemosensory cells (SCCs), producing a calcium (Ca^{2+}) response that propagates to surrounding epithelial cells via gap junctions. This causes the surrounding cells to rapidly (within ~5 min) secrete antimicrobial peptides (AMPs), including β-defensins, which directly kills both gram-positive and gram-negative bacteria. Distinct sets of taste receptors in ciliated cells (T2Rs 4, 14, 16, 38) and SCCs (T2Rs 10, 46, 47) respond to different bitter agonists and likely allow differential activation of these two distinct responses depending on the nature of the infecting organisms and which bitter metabolites are produced.
without a concomitant decrease in glucose may prevent rampant killing of commensal bacteria under normal conditions until a drop in airway glucose levels signals too much bacteria growth.

However, this mechanism may adversely contribute to airway disease in both CRS and diabetes. Higher concentrations of ASL glucose than normal (≥3–4 fold) are observed in patients with elevated serum glucose levels due to diabetes, as well as in CRS patients, who have decreased epithelial barrier function due to inflammation. We hypothesize that the topical use of a T1R2/3 antagonist, such the compound lactisole purified from coffee beans, could dampen the T1R response to elevated glucose and restore proper T2R immune responses in some patients.

It was also recently observed that T1R2/3 in human sinonasal SCCs can also be activated by certain bacterial D-amino acids. Some D stereo-isomer forms of amino acids (e.g. D-Phe, D-Trp, D-Leu) are known to taste sweet through activation of T1R2/3 on the tongue. Others have shown that bacteria secrete various D-amino acids that may be important for cell-to-cell communication. We found that both Staphylococcus aureus and coagulase-negative Staphylococcus (likely Staphylococcus epidermidis) cultures isolated from sinonasal cavities of CRS patients produced D-Phe and D-Leu. D-Phe and D-Leu were produced at levels sufficient to activate T1R2/3 and repress T2R-mediated SCC responses and airway epithelial defense in an in vitro culture model. It remains to be determined whether this interkingdom T1R2/3 signaling exists to allow infecting Staphylococcus to evade immune detection or if this is a mechanism for epithelial cells to recognize and not eradicate commensal Staphylococcus.

Conclusions

Host-pathogen interactions and the determination of pathogenic vs commensal bacteria are paramount to maintaining host immunity. Taste receptors may be involved in this process through detection of various bitter and sweet bacterial metabolites. However some patients are thought to be born with a hampered line of innate defense. Many studies have suggested a genetic component to human infection and infectious diseases, including CRS. As mentioned earlier, taste receptors have many common polymorphisms that can render specific receptors unable or less able to detect cognate agonists, which may include secreted pathogen metabolites, as in the case of AHL activation of T2R38. Thus, the genetics of taste receptors may play an important but previously unrecognized role in susceptibility to infection.

It also possible that medicine has unknowingly taken advantage of extra-oral bitter taste receptors for centuries. A common Chinese proverb roughly states “a good medicine tastes bitter.” Many herbal remedies and modern medicinal compounds activate T2R receptors and taste bitter. Perhaps some of these medicines work in part by stimulating host immunity or other responses though extraoral T2Rs. Beyond the role in immunity described above, bitter and sweet taste receptors regulate cellular metabolism, absorption of nutrients in the GI tract, fertility, muscle relaxation, hormone secretion, and likely many other physiological processes. More research is necessary to uncover the roles that taste receptors play in the human body and discover how their genetic polymorphisms may affect these functions and contribute to disease.

Acknowledgments

Some of the work described in this review was supported by US National Institutes of Health grant DC013862, grant LEER1660 from the US Cystic Fibrosis Foundation, and funding from the Department of Otorhinolaryngology at the University of Pennsylvania.

References

1. Kinnamon SC. Taste receptor signalling — from tongues to lungs. Acta Physiol (Oxf). 2012;204:158–168.
2. Lee RJ, Cohen NA. Bitter taste bodyguards. Sci Am. 2016;314:38–43.
3. Lee RJ, Cohen NA. Taste receptors in innate immunity. Cell Mol Life Sci. 2015;72:217–236.
4. Clark AA, Liggett SB, Munger SD. Extraoral bitter taste receptors as mediators of off-target drug effects. FASEB J. 2012;26:4827–4831.
5. Jagupillli A, Howard R, Upadhyaya JD, Bhullar RP, Chelikani P. Bitter taste receptors: novel insights into the biochemistry and pharmacology. Int J Biochem Cell Biol. 2016;77:184–196.
6. Levit A, Nowak S, Peters M, et al. The bitter pill: clinical drugs that activate the human bitter taste receptor TAS2R14. FASEB J. 2014;28:1181–1197.
7. Mennella JA, Spector AC, Reed DR, Coldwell SE. The bad taste of medicines: overview of basic research on bitter taste. Clin Ther. 2013;35:1225–1246.
8. Li F. Taste perception: from the tongue to the testis. Mol Hum Reprod. 2013;19:349–360.
9. Kojima I, Nakagawa Y, Ohtsu Y, Medina A, Nagasawa M. Sweet taste-sensing receptors expressed in pancreatic β-cells: sweet molecules act as biased agonists. Endocrinol Metab (Seoul). 2014;29:12–19.
10. Medina A, Nakagawa Y, Ma J, et al. Expression of the glucose-sensing receptor T1R3 in pancreatic islet: changes in the expression levels in various nutritional and metabolic states. Endocr J. 2014;61:797–805.
11. Nakagawa Y, Nagasawa M, Mogami H, Lohe M, Ninomiya Y, Kojima I. Multimodal function of the sweet taste receptor expressed in pancreatic β-cells: generation of diverse patterns of intracellular signals by sweet agonists. Endocr J. 2013;60:1191–1206.
12. Kyriazis GA, Soundarapandian MM, Tyrberg B. Sweet taste-sensing receptor T1R3 in pancreatic β-cells: generation of diverse patterns of intracellular signals by sweet agonists. Endocr J. 2014;61:797–805.
13. Meyer-Gersbach AC, Wölnerhanssen B, Beglinger C. Gut taste receptors and their role in metabolism. Front Horm Res. 2014;42:123–133.
14. Kokrashvili Z, Mosinger B, Margolskee RF. Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. Am J Clin Nutr. 2009;90:8225–8255.
15. Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. Biochem Soc Trans. 2005;33:302–305.
Taste receptors in the upper airway

16. Xu J, Cao J, Iguchi N, Rietmacher D, Huang L. Functional characterization of bitter-taste receptors expressed in mammalian testis. *Mol Hum Reprod*. 2013;19:17–28.

17. Mosinger B, Redding KM, Parker MR, et al. Genetic loss or pharmacological blockade of testes-expressed taste genes causes male sterility. *Proc Natl Acad Sci U S A*. 2013;110:12319–12324.

18. Li F, Zhou M. Depletion of bitter taste transduction leads to massive spermatid loss in transgenic mice. *Mol Hum Reprod*. 2012;18:289–297.

19. Bachmanov AA, Bosak NP, Lin C, et al. Genetics of taste receptors. *Curr Pharm Des*. 2014;20:2669–2683.

20. Margolskee RF. Teaching resources. Sensory systems: taste perception. *Sci STKE*. 2005;2005:tr20.

21. Tordoff MG, Shao H, Alarcón LK, et al. Involvement of TR13 in calcium-magnesium taste. *Physiol Genomics*. 2008;34:338–348.

22. Ozdener MH, Subramaniam S, Sundaresan S, et al. CD36- and GPR120-mediated Ca^{2+} signaling in human taste bud cells mediates differential responses to fatty acids and is altered in obese mice. *Gastroenterology*. 2014;146:995–1005.

23. Cartoni C, Yasumatsu K, Ohkuri T, et al. Taste preference for fatty acids is mediated by GPR40 and GPR120. *J Neurosci*. 2010;30:8376–8382.

24. Khan NA, Besnard P. Oro-sensory perception of dietary lipids: new insights into the fat taste transduction. *Biochim Biophys Acta*. 2009;1791:149–155.

25. Scalfani A, Zukerman S, Glendinning JJ, Margolskee RF. Fat and carbohydrate preferences in mice: the contribution of alpha-gustducin and TrpM5 taste-signaling proteins. *Am J Physiol Regul Integr Comp Physiol*. 2007;293:R1504–R1513.

26. Laugerette F, Pasilly-Degrace P, Patris B, et al. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. *J Clin Invest*. 2005;115:3177–3184.

27. Oka Y, Butnaru M, von Buchholtz L, Ryba NJ, Zuker CS. High salt recruits aversive taste pathways. *Nature*. 2012;494:472–475.

28. Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell*. 2010;142:687–698.

29. Yamamoto K, Ishimaru Y. Oral and extra-oral taste perception. *Am J Clin Nutr*. 2013;98:230–236.

30. Lee RJ, Cohen NA. Role of the bitter taste receptor T2R38 in upper respiratory infection and chronic rhinosinusitis. *Curr Opin Allergy Clin Immunol*. 2015;15:14–20.

31. Lee RJ, Cohen NA. Bitter and sweet taste receptors in the respiratory epithelium in health and disease. *J Mol Med (Berl)*. 2014;92:1235–1244.

32. Scott K. The sweet and the bitter of mammalian taste. *Curr Opin Neurobiol*. 2004;14:423–427.

33. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. Mammalian sweet taste receptors. *Cell*. 2001;106:381–390.

34. Nakagawa Y, Ohtsu Y, Nagasawa M, Shibata H, Kojima I. Glucose promotes its own metabolism by acting on the cell-surface glucose-sensing receptor T1R3. *Endocr J*. 2014;61:119–131.

35. Masubuchi Y, Nakagawa Y, Ma J, et al. A novel regulatory function of sweet taste-sensing receptor in adipogenic differentiation of 3T3-L1 cells. *PLoS One*. 2013;8:e54500.

36. Li D, Zhang J. Diet shapes the evolution of the vertebrate bitter taste receptor gene repertoire. *Mol Biol Evol*. 2014;31:303–309.

37. Lossow K, Hübner S, Roudnitzky N, et al. Comprehensive analysis of mouse bitter taste receptors reveals different molecular receptive ranges for orthologous receptors in mice and humans. *J Biol Chem*. 2016;291:15358–15377.

38. Meyerhof W, Batram C, Kühn C, et al. The molecular receptive range of human TAS2R bitter taste receptors. *Chem Senses*. 2010;35:157–170.
release and cationic fluxes in rat pancreatic islets. *Cell Signal.* 1998;10:727–733.

59. Chalmers JA, Jang JJ, Belsham DD. Glucose sensing mechanisms in hypothalamic cell models: glucose inhibition of AgRP synthesis and secretion. *Mol Cell Endocrinol.* 2014;382:262–270.

60. Dehkordi O, Rose JE, Fatemi M, et al. Neuronal expression of bitter taste receptors and downstream signaling molecules in the rat brainstem. *Brain Res.* 2012;1475:1–10.

61. Lemon CH, Margolskee RF. Contribution of the T1r3 taste receptor to the response properties of central gustatory neurons. *J Neurophysiol.* 2009;101:2459–2471.

62. Ren X, Zhou L, Terwilliger R, Newton SS, de Araujo JG. Sweet taste signaling functions as a hypothalamic glucose sensor. *Front Integr Neurosci.* 2009;3:12.

63. Martin B, Wang R, Cong WN, et al. Altered learning, memory, and social behavior in type 1 taste receptor subunit 3 knock-out mice are associated with neuronal dysfunction. *J Biol Chem.* 2017;292:11508–11530.

64. Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. *Science.* 2009;325:1131–1134.

65. Lee RJ, Xiong G, Kofonow JM, et al. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. *J Clin Invest.* 2012;122:4145–4159.

66. Knowles MR, Boucher RC. Mucus clearance as a primary innate defense mechanism for mammalian airways. *J Clin Invest.* 2002;109:571–577.

67. McMahan DB, Workman AD, Kohanski MA, et al. Protease-activated receptor 2 activates airway apical membrane chloride permeability and increases ciliary beating. *FASEB J.* 2018;32:155–167.

68. Hariri BM, Cohen NA. New insights into upper airway innate immunity. *Am J Rhinol Allergy.* 2016;30:319–323.

69. Cohen NA. Sinonasal mucociliary clearance in health and disease. *Ann Otol Rhinol Laryngol Suppl.* 2006;196:20–26.

70. Salathe M. Regulation of mammalian ciliary beating. *Annu Rev Physiol.* 2007;69:401–422.

71. Hariri BM, McMahon DB, Chen B, et al. Plant flavonoids enhance antimicrobial activity of respiratory epithelial cell secretions against *Pseudomonas aeruginosa.* *PLoS One.* 2017;12:e0185203.

72. Hariri BM, Payne SJ, Chen B, et al. In vitro effects of anthocyanidins on sinonasal epithelial nitric oxide production and bacterial physiology. *Am J Rhinol Allergy.* 2016;30:261–268.

73. 157. Hariri BM, McMahon DB, Chen B, et al. In vitro effects of plant flavonoids on sinonasal epithelial nitric oxide production and bacterial physiology. *Am J Rhinol Allergy.* 2016;30:261–268.
necessitating surgical intervention. *Int Forum Allergy Rhinol.* 2013;3:184–187.

103. Adappa ND, Farquhar D, Palmer JN, et al. TAS2R38 genotype predicts surgical outcome in nonpolyoid chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6:25–33.

104. Gallo S, Grossi S, Montrasio G, et al. TAS2R38 taste receptor gene and chronic rhinosinusitis: new data from an Italian population. *BMC Med Genet.* 2016;17:54.

105. Ozaman K, Zagor M, Szarnowska E, Krzeski A, Kantor I. The correlation of TAS2R38 gene variants with higher risk for chronic rhinosinusitis in Polish patients. *Otolaryngol Pol.* 2016;70:13–18.

106. Rom DI, Christensen JM, Alvarado R, Sacks R, Harvey RJ. The impact of bitter taste receptor genetics on culturable bacteria in chronic rhinosinusitis. *Rhinology.* 2017;55:90–94.

107. Maurer S, Wabnitz GH, Kahle NA, et al. Tasting *Pseudomonas aeruginosa* biofilms: human neutrophils express the bitter receptor T2R38 as sensor for the quorum sensing molecule N-(3-oxodecanoyl)-ω-homoserine lactone. *Front Immunol.* 2015;6:369.

108. Gaída MW, Dapunt U, Hänisch GM. Sensing developing biofilms: the bitter receptor T2R38 on myeloid cells. *Pathog Dis.* 2016;74.*

109. Muna EL, Filali-Mouhim A, Bosse Y, Boulet LP, Bossé Y, Desrosiers M. Genetic variations in taste receptors are associated with chronic rhinosinusitis: a replication study. *Int Forum Allergy Rhinol.* 2014;4:200–206.

110. Workman AD, Brooks SG, Kohanski MA, et al. Bitter and sweet taste tests are reflective of disease status in chronic rhinosinusitis. *J Allergy Clin Immunol Pract.* 2017 Oct 17. https://doi.org/10.1016/j.jaip.2017.09.014. pii: S2213-2198(17)30739-0. [Epub ahead of print].

111. Tizzano M, Gulbransen BD, Vandenbeuch A, et al. Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. *Proc Natl Acad Sci U S A.* 2010;107:3210–3215.

112. Saunders CJ, Christensen M, Finger TE, Tizzano M. Cholinergic neurotransmission links solitary chemosensory cells to nasal inflammation. *Proc Natl Acad Sci U S A.* 2011;111:6075–6080.

113. Lee RJ, Cohen NA. Sinonasal solitary chemosensory cells “taste” the upper respiratory environment to regulate innate immunity. *Am J Rhinol Allergy.* 2014;28:366–373.

114. Garnett JP, Baker EH, Baines DL. Sweet talk: insights into the nature and importance of glucose transport in lung epithelium. *Eur Respir J.* 2012;40:1269–1276.

115. Garnett JP, Braun D, McCarthy AJ, et al. Fructose transport-deficient *Staphylococcus aureus* reveals important role of epithelial glucose transporters in limiting sugar-driven bacterial growth in airway surface liquid. *Cell Mol Life Sci.* 2014;71:4665–4673.

116. Pezzuto AA, Gutiérrez J, Duschesnky KS, et al. Glucose depletion in the airway surface liquid is essential for sterility of the airways. *Plos One.* 2011;6:e16166.

117. Baker EH, Clark N, Brennan AL, et al. Hyperglycemia and cystic fibrosis alter respiratory fluid glucose concentrations estimated by breath condensate analysis. *J Appl Physiol.* 1985;2007(102):1969–1975.

118. Hatten KM, Palmer JN, Lee RJ, Adappa ND, Kennedy DW, Cohen NA. Corticosteroid use does not alter nasal mucus glucose in chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2015;152:1140–1144.

119. Jiang P, Cui M, Zhao B, et al. Lactisole interacts with the transmembrane domains of human T1R3 to inhibit sweet taste. *J Biol Chem.* 2005;280:15238–15246.

120. Bassolí A, Borgonovi C, Caremoli F, Mancuso G. The taste of D- and L-amino acids: in vitro binding assays with cloned human bitter (TAS2Rs) and sweet (TAS1R2/TAS1R3) receptors. *Food Chem.* 2014;150:27–33.

121. Radkov AD, Moe LA. Bacterial synthesis of ω-amino acids. *Appl Microbiol Biotechnol.* 2014;98:5363–5374.

122. Rementeria A, López-Molina N, Ludwig A, et al. Genes and molecules involved in *Aspergillus fumigatus* virulence. *Rev Iberoam Micol.* 2005;22:1–23.

123. Liounnik MS, Netea MG, Holland SM. Mendelian genetics of human susceptibility to fungal infection. *Cold Spring Harb Perspect Med.* 2014;4.*

124. Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. Genetics of chronic rhinosinusitis: state of the field and directions forward. *J Allergy Clin Immunol.* 2013;131:977–993, e1–993.e5.

125. Zhang Y, Endam LM, Filali-Mouhim A, Bossé Y, Castano R, Desrosiers M. Polymorphisms in the nitric oxide synthase 1 gene are associated with severe chronic rhinosinusitis. *Am J Rhinol Allergy.* 2011;25:e49–e54.

126. Cohen NA, Wideltiz JS, Chiu AG, Palmer JN, Kennedy DW. Familial aggregation of sinonasal polyps correlates with severity of disease. *Otolaryngol Head Neck Surg.* 2006;134:601–604.

127. Behrens M, Gu M, Fan S, Huang C, Meyerhofer W. Bitter substances from plants used in traditional Chinese medicine exert biased activation of human bitter taste receptors. *Chem Biol Drug Des.* 2018;91:422–433.

128. Wauson EM, Zagajnor E, Cobb MH. Amino acid regulation of autophagy through the GPCR TAS1R1-A-TAS1R3. *Autophagy.* 2013:9;418–419.

129. Wauson EM, Zagajnor E, Lee AY, et al. The G protein-coupled taste receptor T1R1/T1R3 regulates mTORC1 and autophagy. *Mol Cell.* 2012;47:851–862.

130. Shirazi-Beechey SP, Daly K, Al-Rammahi M, Moran AW, Bravo D. Role of nutrient-sensing taste 1 receptor (T1R) family members in gastrointestinal chemosensing. *Br J Nutr.* 2014;111(suppl 1):S8–S15.

131. Reimann F, Tolhurst G, Gribble FM. G-protein-coupled receptors in intestinal chemosensation. *Cell Metab.* 2012;15:421–431.

132. Jeon TI, Lee JK, Osborne TF. Bitter taste receptor signaling induces ABCB1 through a mechanism involving CCK. *Biochem J.* 2011;438:33–37.

133. Gerspach AC, Steinert RE, Schönenberger L, Graber-Maier A, Beglinger C. The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. *Am J Physiol Endocrinol Metab.* 2011;301:E317–E325.

134. Égan JM, Margolskee RF. Taste cells of the gut and gastrointestinal chemosensation. *Mol Interv.* 2008;8:78–81.

135. Dotson CD, Zhang L, Xu H, et al. Bitter taste receptors influence glucose homeostasis. *Plos One.* 2008;3:e3974.

136. Jang HJ, Kokrashvili Z, Theodorakis MJ, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A.* 2007;104:15069–15074.

137. Margolskee RF, Dyer J, Kokrashvili Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na+/glucose cotransporter 1. *Proc Natl Acad Sci U S A.* 2007;104:15075–15080.

138. Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C, Rozengurt E. Colocalization of the alpha-subunit of gustducin with PYY and GLP-1 in L cells of human colon. *Am J Physiol Gastrointest Liver Physiol.* 2006;291:G792–G802.

139. An SS, Liggett SB. Taste and smell GPCRs in the lung: evidence for a previously unrecognized widespread chemosensory system. *Cell Signal.* 2018;41:82–88.

140. Robinet KS, Koziol-White CJ, Alokul A, An SS, Panettieri RA, Liggett SB. Bitter taste receptor function in asthmatic and nonasthmatic human airway smooth muscle cells. *Am J Respir Cell Mol Biol.* 2014;50:678–683.
141. An SS, Wang WC, Koziol-White CJ, et al. TAS2R activation promotes airway smooth muscle relaxation despite β(2)-adrenergic receptor tachyphylaxis. *Am J Physiol Lung Cell Mol Physiol*. 2012;303:L304–L311.

142. Deshpande DA, Wang WC, McIlmoyle EL, et al. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. *Nat Med*. 2010;16:1299–1304.

143. Janssen S, Laermans J, Verhulst PJ, Thijs T, Tack J, Depoortere I. Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *Proc Natl Acad Sci U S A*. 2011;108:2094–2099.

144. Antunes MB, Gudis DA, Cohen NA. Epithelium, cilia, and mucus: their importance in chronic rhinosinusitis. *Immunol Allergy Clin North Am*. 2009;29:631–643.

145. Stout SL, Wyatt TA, Adams JJ, Sisson JH. Nitric oxide-dependent cilia regulatory enzyme localization in bovine bronchial epithelial cells. *J Histochem Cytochem*. 2007;55:433–442.

Edited by Jing Li