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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

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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.

* Corresponding author. Hospital of the University of Pennsylvania, 5 Ravdin Building, Suite A, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail address: rjl@pennmedicine.upenn.edu (R.J. Lee).
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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 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.[5–7] 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,[16–18] 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 taste[21] or the taste of fat,[22–26] though these have been controversial and hard to study, as high metal salt concentrations can cross-

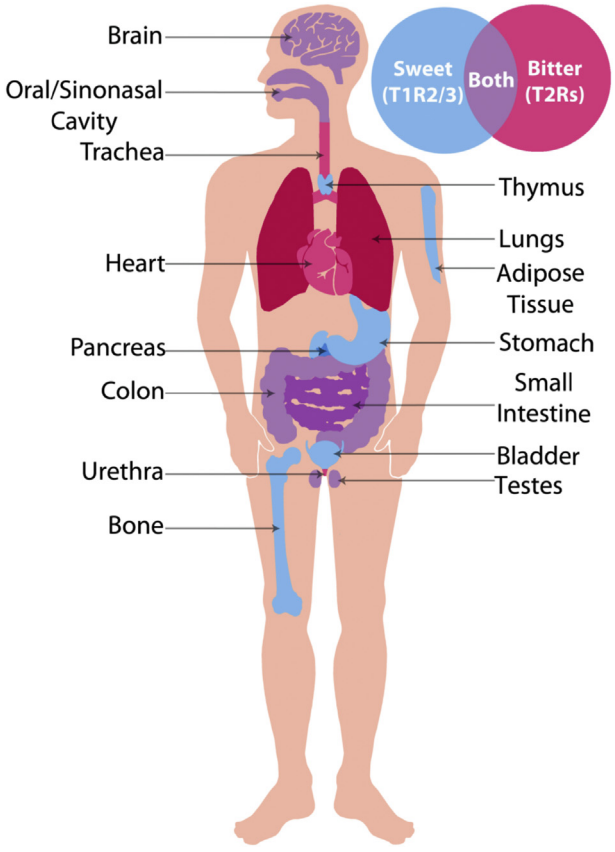

Fig. 1 "Extra-oral" expression of G protein-coupled receptors (GPCRs) involved in bitter, sweet, and umami taste. While named for their originally-identified role on the tongue, taste receptors are have been found in multiple organs and tissues outside of the oral cavity, where they play largely unknown roles in response to largely unknown ligands.[2,3] Red and blue colors indicate organs/tissues where bitter and sweet taste receptors, respectively, have been identified. Purple color indicates organs where both types of receptors have been identified. Bitter taste receptors are generally believed to be primarily composed of homo- or hetero-oligomers of isoforms of the taste receptor 2 (T2R) family. Umami and sweet receptors are made up of oligomers of the taste receptor 1 (T1R) family. T1R1 and T1R3 oligomers form umami receptors, while T1R2 and T1R3 oligomers form sweet receptors.