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Extrasensory perception: Odorant and taste receptors beyond the nose and mouth

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ABSTRACT

G protein-coupled receptors (GPCRs) represent the largest family of transmembrane receptors and are prime therapeutic targets. The odorant and taste receptors account for over half of the GPCR repertoire, yet they are generally excluded from large-scale, drug candidate analyses. Accumulating molecular evidence indicates that the odorant and taste receptors are widely expressed throughout the body and functional beyond the oronasal cavity — with roles including nutrient sensing, autophagy, muscle regeneration, regulation of gut motility, protective airway reflexes, bronchodilation, and respiratory disease. Given this expanding array of actions, the restricted perception of these GPCRs as mere mediators of smell and taste is outdated. Moreover, delineation of the precise actions of odorant and taste GPCRs continues to be hampered by the relative paucity of selective and specific experimental tools, as well as the lack of defined receptor pharmacology. In this review, we summarize the evidence for expression and function of odorant and taste receptors in tissues beyond the nose and mouth, and we highlight their broad potential in physiology and pathophysiology.

Contents

Abbreviations: 16HBE cells, human bronchial epithelial cells; 3T3-L1 cells, mouse embryonic fibroblast (undifferentiated preadipocyte) cells; 7TM, seven transmembrane; ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1 (*ABCB1*); AC3, adenylyl cyclase type III (*ADYC3*); ASM, airway smooth muscle; BKCa, potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (*KCNMA1*); BMSCs, bone marrow stromal cells; Caco-2 cells, human epithelial colorectal adenocarcinoma cells; cAMP, cyclic adenosine monophosphate; CCK, cholecystokinin; CNG, cyclic nucleotide-gated channel; DU145 cells, human prostate cancer cells; ELISA, enzyme-linked immunosorbent assay; EST, expressed sequence tag; FFA, free fatty acid; $G\alpha_{t3}$, G protein, alpha transducing 3 (*GNAT3*) or gustducin; $G\alpha_{olf}$, G protein, alpha activating activity polypeptide, olfactory type (*GNAL*); GIV3727, T2R competitive antagonist (4-(2,2,3-trimethylcyclopentyl) butanoic acid); GLP-1, glucagon-like peptide-1; GLUT2, solute carrier family 2 (facilitated glucose transporter), member 2 (*SLC2A2*); GPCR, G protein-coupled receptor; GRK, G protein-coupled receptor kinase; H9C2 cells, rat cardiac myoblast cells; HCT116 cells, human colon carcinoma cells; HeLa cells, human cervical cancer cells; Hu-Tu 80 cells, human duodenum adenocarcinoma cells; HuCCT1 cells, human bile duct carcinoma cells; IHC, immunohistochemistry; IP_3R3, inositol 1,4,5-trisphosphate receptor, type 3; ISH, in situ hybridization; MIN6 cells, mouse insulinoma-derived pancreatic β-cells; N38 cells, embryonic mouse hypothalamic cell line N38; NB, northern blot; NCI-H716 cells, human enteroendocrine cells; OR, odorant (or olfactory) receptor; OSN, olfactory sensory neuron; PASMCs, pulmonary artery smooth muscle cells; RGS proteins, regulators of G protein signaling proteins; RT-PCR, reverse transcription-polymerase chain reaction; PepT1, solute carrier family 15 (oligopeptide transporter), member 1 (*Slc15a1*); PKA, cyclic AMP-dependent protein kinase A; PLCβ2, phospholipase C, beta 2; SGLT1, sodium/glucose co-transporter 1; siRNA, small interfering RNA; SNP, single nucleotide polymorphism; STC-1 cells, mouse intestine enteroendocrine cell line; T1R, taste receptor type 1; *TAS1*, taste receptor type 1 gene; T2R, taste receptor type 2; *TAS2*, taste receptor type 2 gene; Tg, transgenic (or gene-targeted mice) mice; TRPM5, transient receptor potential cation channel, subfamily M, member 5; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; VSMCs, vascular smooth muscle cells; WB, western blot.

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1. Introduction

G protein-coupled receptors (GPCRs) are seven transmembrane-spanning proteins that represent the largest receptor superfamily in the human genome (Lagerstrom & Schioth, 2008). GPCRs recognize and bind an array of sensory inputs and ligands, including photons, ions, bioamines, lipids, carbohydrates, peptides and proteins, as well as a diverse range of volatile compounds. Ligand-induced activation of GPCRs converts extracellular stimuli into intracellular signals, mediating diverse cellular and physiological responses, including the senses of smell, taste, and vision. Not surprisingly, mutations and modifications of GPCRs, G proteins and their regulatory partners are linked to dysfunction and disease (Drews, 2000; Hopkins & Groom, 2002; Wettschureck & Offermanns, 2005; Overington et al., 2006), and the importance of these receptors is reflected in the fact that 40% of drugs on the market target GPCRs.

The pioneering work of Buck and Axel identified that the sense of smell was mediated by a large family of GPCRs located in the olfactory epithelium (Buck & Axel, 1991). Indeed, with the sequencing of mammalian genomes, it is now clear that there are around 900 odorant GPCRs in humans (including pseudogenes) and ~1500 in rodents — these are by far the most prevalent subgroup of GPCRs in the vertebrate genomes (representing 3–5% of all encoded genes). In humans, there are 390 *bona fide* protein-coding odorant receptor genes (Olender et al., 2008), comprising the majority of the *Rhodopsin*/family A GPCRs. The dramatic expansion of the olfactory receptor gene family since the mammalian radiation, resulting from multiple gene duplications from a common primordial ancestor gene, points to the importance of odor discrimination in evolution and survival (Dryer, 2000).

The mammalian gustatory system is generally categorized into five basic taste qualities: sweet, umami, bitter, salty and sour, which together enable the assessment of nutritional value of food constituents. In the past two decades, the molecular mediators of sweet, umami and bitter tastes have been identified as families of GPCRs (referred to collectively as taste receptor type 1, T1R and taste receptor type 2, T2R).[1] The T1R family has 3 members within the *Glutamate*/family C GPCR group that form sweet and umami receptors, whereas the T2R family consists of 25 highly divergent GPCRs that mediate bitter taste. In addition, there is evidence that another taste quality related to lipid sensing is mediated via the free fatty acid (FFA) GPCR family.

Contemporaneously with the initial discovery of the GPCR mediators of olfaction and gustation, reports began to appear in the literature of odorant and taste receptor expression in tissues beyond the nose and mouth. These have predominantly been descriptive studies, for the most part relying on RT-PCR and microarray data without demonstrating either protein expression or function. However, they raised the intriguing possibility that these so-called 'chemosensory' GPCRs may subsume additional functions in multiple tissues. More recently, the field has advanced at pace with publications appearing on the function of odorant and taste receptors in the brain, skeletal muscle, the gastrointestinal tract and in the airways. These studies reinforce the idea that there remains novel and important biology to be discovered for these receptor families, with broader potential ramifications beyond the fragrance and food industries (Huang, 2005; Lagerstrom & Schioth, 2008).

In this review, we summarize the prevailing evidence for the expression of odorant and taste GPCRs in cells and tissues beyond the nose and mouth. We then highlight the putative function for these receptors in diverse physiological settings, ranging from nutrient sensing, autophagy, muscle regeneration, and regulation of gut motility to protective airway reflexes, bronchodilation and respiratory dysfunction and disease. We identify limitations in the field and discuss the currently available molecular and pharmacological toolkit for further investigation of these GPCRs in the nonchemosensory settings. Finally, we speculate on the widespread nature of the phenomenon and offer insights/predictions into the potential therapeutic utility for these GPCRs.

2. Odorant and taste GPCRs

2.1. The 'chemosensory' receptors comprise the largest GPCR families

The capacity to sense and respond to chemicals and factors in the surrounding environment is essential for life — for example, chemotaxis in simple organisms, such as the slime mold *Dictyostelium*; chemosensation in the worm *Caenorhabditis elegans*; and complex olfaction and taste in insects, fish, amphibians, reptiles, birds and mammals. These complex chemosensory systems enable the detection and discrimination of molecules of immense diversity, and provide the fundamental means to locate nutritious food and suitable mating partners and to avoid predators or ingesting toxic substances. In vertebrates, it is the olfactory and gustatory systems that facilitate the sensing of chemicals in the extracellular environment via large families of seven-transmembrane receptors.

There are six multigene families that are generally considered as 'chemosensory' GPCRs in the vertebrate genome: odorant receptor (OR), taste receptor types 1 and 2 (T1R and T2R), trace amine-associated receptor (TAAR) and vomeronasal receptor types 1 and 2 (V1R and V2R). The TAAR, V1R and V1R families encode pheromone GPCRs and are beyond the scope of this review (see Dulac & Axel, 1995; Herrada & Dulac, 1997; Liberles & Buck, 2006). However, the umbrella term 'chemosensory' can be misleading (and we will avoid using it) as the fundamental role of any GPCR/receptor is to sense chemicals in the extracellular environment. The term also evokes the narrow connotation for the function of the odorant/taste receptor families purely in the sensation of taste and smell, which is increasingly unlikely. In this review, we provide a more expansive conceptualization of the odorant and taste receptor genes, consistent with their broader functions in mammalian biology.

Accounting for more than half of the vertebrate GPCR repertoire, odorant and taste GPCRs represent two of the most heterogeneous and diverse of receptor families. These highly variable families arose from repeated random gene duplications of an ancestral gene or gene cluster, followed by adaptive and neutral mutations (Lancet & Ben-Arie, 1993; Dryer, 2000). This expansion explains the large differences in odorant and taste receptor repertoire between species, as well as the copy-number variation in these receptor genes within species (Nei et al., 2008). The genetic variation in these receptors also correlates with differences in human odor and taste perception/discrimination (Sandell & Breslin, 2006; Keller et al., 2007). In fact, odorant and taste receptor genes are among the most rapidly evolving and positively selected genes that are identified in comparative genomic analyses (Clark et al., 2003; Nielsen et al., 2005; Kosiol et al., 2008). This is undoubtedly a reflection on the need for organisms to respond and adapt to a variable chemical environment, but it provides an additional layer of intrigue when one considers the expression and function of these odorant and taste GPCRs beyond the classical cephalic sensory systems.

Although a comprehensive review of olfaction and taste is beyond the scope of this work, many excellent reviews can be found elsewhere (for olfaction/odorant receptors see (Mombaerts, 2004a; Nei et al., 2008; Spehr & Munger, 2009; Su et al., 2009; Touhara & Vosshall, 2009) and for taste (Chandrashekar et al., 2006; Bachmanov & Beauchamp, 2007; Yarmolinsky et al., 2009; Behrens & Meyerhof, 2011; Finger & Kinnamon, 2011)).

2.2. Odorant receptors and signaling

2.2.1. Odorant receptor genes

The OR family was originally identified based on sequence homology and the presence of conserved motifs within 7TM-spanning domains

[1] The receptor and gene nomenclature in this review where possible follows the guidelines set out by BPS/NC-IUPHAR (Alexander et al., 2011), except for the odorant GPCRs, which follow the HUGO and Mouse Genome Database (MGD) gene nomenclature (Eppig et al., 2012; HUGO Gene Nomenclature Committee (HGNC), 2013).