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Review

Functional diversification of taste cells in vertebrates

Ichiro Matsumoto[a,*], Makoto Ohmoto[a], Keiko Abe[b]

[a] Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA
[b] Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

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ABSTRACT

Tastes are senses resulting from the activation of taste cells distributed in oral epithelia. Sweet, umami, bitter, sour, and salty tastes are called the five "basic" tastes, but why five, and why these five? In this review, we dissect the peripheral gustatory system in vertebrates from molecular and cellular perspectives. Recent behavioral and molecular genetic studies have revealed the nature of functional taste receptors and cells and show that different taste qualities are accounted for by the activation of different subsets of taste cells. Based on this concept, the diversity of basic tastes should be defined by the diversity of taste cells in taste buds, which varies among species.

Contents

1. Introduction

We often use the phrase "five basic tastes" to express representative taste qualities. But, why are there five and not four or six? Interestingly, we knew only four taste qualities more than 100 years ago [1]. The concept of the fifth taste, "umami," from Japanese *umai* or "savory," was introduced to Western culture only recently—until that point we could "taste" savory but had no word to express this fifth taste quality. This historical fact implies that there may be yet other taste qualities that we simply do not yet know how to express.

"Tastes" are senses evoked by chemicals detected by taste cells in taste buds, which are distributed in the epithelia of the anterior digestive tract, such as the oral cavity and pharynx. Each taste bud contains various taste cells that differ in terms of morphology, function, and molecular characteristics. Based on their morphological and electrophysiological features, most taste cells are classified into three groups: type I (or type C in electrophysiological classification), type II (or type A), and type III (or type B) [2–4]. Gene expression patterns have provided further detailed classification of taste cells, especially for differences among type II (A) cells. Accompanied by the discoveries of molecules necessary for taste cell functions, we can now identify many taste cells from their function. Here we

Abbreviations: GPCR, G protein-coupled receptor; PLC-β2, phospholipase C-β2; TRPM5, transient receptor potential M5; ENaC, epithelial sodium channel.

* Corresponding author. Tel.: +1 267 519 4778.
E-mail addresses: imatsumoto@monell.org, ichiro.matsumoto1@gmail.com (I. Matsumoto).

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review a diversity of taste cells, which brings into question the meaning of "basic" taste.

2. GPCRs in taste cells

Many researchers have assumed that, by analogy with other sensory systems such as vision and olfaction, G protein-coupled receptors (GPCRs) are involved in taste reception. Two families of GPCRs have been identified as taste receptors, the Tas1r [5–11] and Tas2r [12–14] families, which combine in different ways to generate sweet, umami, and bitter taste reception. Based on biochemical characterization combined with molecular genetic analyses, we now know that the Tas1r1/Tas1r3 heterooligomer forms the umami receptor, the Tas1r2/Tas1r3 heterooligomer forms the sweet receptor, and the respective Tas2Rs form various bitter receptors [10,15–19].

2.1. Tas1r-expressing taste cells and taste attraction

The Tas1r (also known as T1R) gene family comprises three genes: *Tas1r1*, *2*, and *3*. In rodents, Tas1r-expressing cells fall into three classes: *Tas1r1*/*Tas1r3*-expressing umami taste cells, *Tas1r2*/*Tas1r3*-expressing sweet taste cells, and *Tas1r3*-expressing cells (Fig. 1) [10], which presumably respond to sweet taste. Rodents prefer taste substances that humans perceive as sweet and umami. Fish species have single *Tas1r1* and *Tas1r3* gene orthologs and several types of *Tas1r2* genes in their genome [20,21]. Due to the expansion of *Tas1r2* genes, the expression patterns of Tas1r proteins in fish taste buds are diverse compared to those in rodents [20]. However, their facial nerves containing gustatory neurons did not respond to any taste substances that humans perceive as sweet [22]. Consistently, cultured cells expressing any combination of Tas1r proteins from zebrafish and medaka fish do not respond to "sweet" substances but are activated by L-amino acids in the same way as mammalian *Tas1r1*/*Tas1r3*-expressing umami taste cells [22]. And the zebrafish prefers L-amino acid-conjugated foods to placebo [22].

Interestingly, the *Tas1r2* gene in feline species that do not prefer sugars is a pseudogene in their genome [23], and the chicken genome lacks the *Tas1r2* gene entirely [21]. Together with the fact that fish have multiple *Tas1r2* genes, it is intriguingly evident that *Tas1r2* genes are far more divergent than are *Tas1r1* and *Tas1r3* genes. Tas1r-mediated taste-attraction behaviors may be due originally to L-amino acids, and sweet taste may be a newly acquired taste in some mammalian species through the evolution of *Tas1r2* gene.

2.2. Tas2r-expressing taste cells and avoidance

Tas2r (also known as *T2R* and *TRB*) gene products expressed in taste cells receive chemicals that humans perceive as bitter. The number of *Tas2r* genes varies depending on the species: 41 (including 6 pseudogenes) in mouse, 36 (11) in human, 7 (0) in zebrafish, 4 (0) in fugu fish, 8 (2) in puffer fish, and 3 (0) in chicken, although genome sequences in some species remain incomplete [21,24,25]. Orthologous *Tas2r* genes have been found between mouse and human, and species-specific expansion and loss have also been observed in *Tas2r* genes of mouse and human [26]. *zfT2R5* of zebrafish and *mfT2R1* of medaka fish seem to be orthologs of each other, and both products of both genes detect denatonium, a bitter substance [22]. Intriguingly, *Tas2r* genes in teleost fish are phylogenetically different from tetrapod *Tas2r* genes, and the fish denatonium receptors zfT2R5 and mfT2R1 are not orthologs of the mouse denatonium receptor mTas2r108 (former mouse T2R8) [27]. However, zebrafish avoid eating a diet that contains denatonium [22], suggesting that Tas2rs of some type are involved in avoidance feeding behaviors in fish as well as in mammals. Activation of *Tas2r*-expressing chemosensory cells in respiratory epithelia in mice leads to self-defensive responses by activating trigeminal and vagal neurons [28,29]. These *Tas2r*-expressing cells function as detectors of harmful chemicals and trigger self-defensive responses such as avoidance.

Frequencies and intensities of expression vary among human *Tas2r* genes [30]. However, it is possible that all *Tas2r* cells express all receptors, but at different levels. In one study, mice were genetically bred not to produce phospholipase C-β2 (PLC-β2). Because PLC-β2 is necessary for mediating sweet, umami, and bitter tastes in mammals, these mice are blind to these tastes [31]. Exogenous PLC-β2 induced by three different *Tas2r* gene promoters/enhancers restored aversive behavior to diverse "bitter" substances [17], which strongly suggests that *Tas2r*-expressing taste cells express all *Tas2r* genes [12], presumably with different expression levels. However, we cannot preclude the possibility that the three *Tas2r* genes used to rescue PLC-β2 function in this study are far more widely expressed than are other *Tas2r* genes with limited expression in a subset of *Tas2r*-expressing cells. In comparison, fish have two to four kinds of *Tas2r*-expressing taste cells [24], so which "bitter" chemicals can be distinguished may depend on the species.

2.3. Enigmatic taste cells coexpressing Tas1rs and Tas2rs

In zebrafish taste buds, a minor but significant population of taste cells expresses both *Tas1rs* and *Tas2rs* [32]. Considering that zebrafish prefers amino acids that are received by various Tas1r heterooligomers [22], the activation of taste cells coexpressing *Tas1rs* and *Tas2rs* should result in attraction behaviors. It is unclear whether zebrafish would like or dislike the substances that are detected by zfT2Rs other than zfT2R5. Interestingly, the expression of *zfT2R5* is completely segregated from that of *Tas1rs* [22], so the cells expressing *zfT2R5*, causing averse responses, are distinct from those causing attraction responses, even in zebrafish (Fig. 1). Unfortunately, we have no rational explanation for how zebrafish taste cells coexpressing *Tas1rs* and *Tas2rs* contribute to taste sensations. However, these cells derive from the same precursors in mammals [33]. These cells may be immature (*i.e.*, at the beginning of terminal differentiation); if so, it is possible that their activation, if it should occur, would not lead to any behavior.

2.4. Unidentified GPCRs

GPCRs contain seven transmembrane domains, and in many cases GPCRs can be recognized based on their structure. Insect olfactory and gustatory receptors are GPCRs [34–37]; however, unlike mammalian GPCRs, they function not as metabotrophic receptors, which use G proteins as signals, but instead function as ionotropic receptor channels, which do not need G proteins to activate olfactory and gustatory neurons [38–40]. Conversely, GPCR(s) are likely expressed in vertebrate cells that express G proteins, so studying G protein expression may help identify new categories of taste cells that express unknown GPCRs as taste receptors.

PLC-β2 and TRPM5 (transient receptor potential M5) are indispensable for mediating sweet, umami, and bitter tastes in mammals [31]. The cells expressing *PLC-β2* and *TRPM5* can be classified into two groups: *Tas1r*- and *Tas2r*-expressing cells [31]. In zebrafish, *PLC-β2* and *TRPM5* genes are also coexpressed in a subset of taste cells [41], but the total population of *Tas1r*- and *Tas2r*-expressing taste cells is only a small subset of *PLC-β2*/*TRPM5*-expressing taste cells [20]. All known zebrafish *PLC-β2*/*TRPM5*-expressing taste cells express either *Gnaia* or *Gna14*, both G protein α-subunit genes; known expression of *Tas1rs* and *Tas2rs* is confined to a subset of *Gnaia*-expressing taste cells [32]. This suggests that zebrafish *Gna14*-expressing taste cells express GPCRs other than Tas1rs