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Review

Functional diversification of taste cells in vertebrates

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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.

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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 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 metabotropic 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

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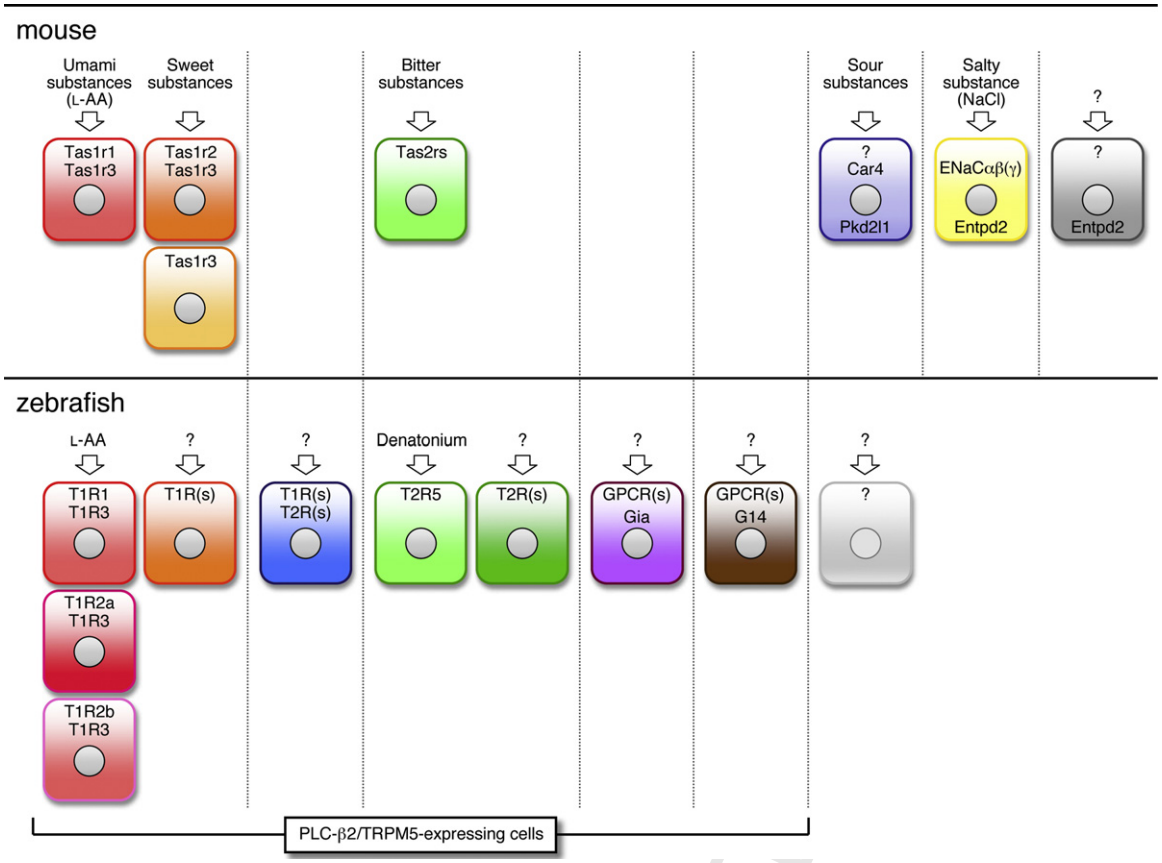

Fig. 1. Diverse array of taste cells in mouse and zebrafish. Types of taste cells are illustrated with specific molecular features such as taste receptors and (in)dispensable markers. Their ligands identified thus far are indicated. Unidentified receptors and ligands are shown by question marks. The unidentified receptors in PLC-β2/TRPM5-expressing taste cells are presumably GPCRs [32]. Pkd2l1 is not a sour receptor channel, because its knockout had little effect to sour response in gustatory neurons [70]. ENaC is indispensable for NaCl attraction [48], but it remains unclear whether it is the specific receptor. Many types of T1R(s)-expressing and T1R(s)/T2R(s)-expressing cells exist in zebrafish, depending on the expression pattern of receptor genes. Taste buds in zebrafish have many cells that do not express PLC-β2 or TRPM5, although little is known for their molecular features.

and Tas2rs as taste receptors. Presumably, so does a subset of *Gnaia*-expressing taste cells that lack *Tas1r* and *Tas2r* expression. Identification of GPCRs expressed in fish taste cells and their ligands will provide new insight into the similarities and differences of taste systems in vertebrates.

3. Pkd2l1-expressing cells and sour taste

A subset of taste bud cells have neuron-like features, represented by synaptic structures [2]. In mammals these cells, which are different from *Tas1r*- and *Tas2r*-expressing cells, express the *Pkd2l1* gene and detect decreases in pH in the extracellular environment [42–44]. Transgenic mice lacking *Pkd2l1*-expressing cells show no gustatory nerve responses to sour stimuli [42], suggesting that these cells are sour taste cells. They are also responsible for the "taste" of carbonation that is mediated by the Car4 [45]. The gene and protein expression profile of *Pkd2l1*-expressing sour cells is quite different from that of *Tas1r*- and *Tas2r*-expressing cells [33,46]. It is still unclear whether sour cells exist in other species such as fish.

4. Entpd2-expressing cells and sodium attraction

Entpd2-expressing cells are a distinct subset of *Tas1r*-, *Tas2r*-, and *Pkd2l1*-expressing cells [47]. Like that of the *Pkd2l1* gene, the expression of the *Entpd2* gene in fish and other tetrapod species is unclear. In mice, *Entpd2*-expressing cells comprise almost half of all taste bud cells, possibly more [33,47]. Although the function of many of *Entpd2*-expressing cells remains unidentified, a subset of these cells has been found in anterior taste buds that detect sodium ion using ENaC (epithelial sodium channel) [48]. Molecules and cells involved in salt reception other than sodium chloride have not been identified. Despite the fact that *Entpd2*-expressing cells comprise the largest cell population in taste buds, few data are available for the genes and proteins they express. Extensive effort to reveal molecular features of *Entpd2*-expressing cells is needed to characterize their physiological function(s).

5. Taste cell lineages

Taste cells belong to the epithelial cell lineage and are turned over continuously throughout an animal's life [49,50]. Therefore, in taste buds, some cells are fully differentiated and mature, and others are immature. Genetic ablations of specific cell subsets responsible for sour and sweet taste reception has revealed that *Pkd2l1*-expressing and *Tas1r2*-expressing cells are devoted to sour and sweet tastes, respectively [42]. It has also revealed that *Pkd2l1*-expressing and *Tas1r2*-expressing cells are terminally differentiated. It is presumed that other taste cells would be also terminally differentiated.

5.1. Taste stem cell

Cells expressing the *Shh* gene, which are located at the base of taste buds [51], give rise to all the types of cells described above [52]. Since *Shh*-expressing cells are postmitotic, they are thought

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to be precursors of functional taste cells. However, details of how the diverse taste cells are generated are unknown.

The cells in intestinal and olfactory epithelia are also maintained through continuous turnover, although their periods are quite different (3–4 days for epithelial cells in intestine, 30 days or longer for olfactory sensory neurons) [53–55]. The turnover rate of taste cells has long been thought to be around 10 days [49], but recent evidence suggests that it may be longer, depending on the type of cell [56]. Stem cells of intestinal epithelial cells are located at the crypts [57,58], and those of olfactory sensory neurons are distributed at the base of olfactory epithelia [59]. Therefore, it is reasonable to predict that taste stem cells are also distributed at the basal region of oral epithelia, but they have not yet been identified.

5.2. Candidate selector genes

As is often the case with the nervous system, transcription factors govern the development and differentiation of neurons. In mammalian taste buds, seven transcription factors are known to be expressed: *Prox1* and *Nkx2-2*, which are homeobox genes; *Pou2f3* (also known as *Skn-1a*), a Pou homeodomain protein gene; *Hes1*, *Hes6*, and *Ascl1* (also known as *Mash1*), which are basic helix-loop-helix transcription factor genes; and *Sox2*, an SRY box gene [33,51,60–63]. Among them, *Sox2* expression is not confined to the taste bud: it is also expressed in the tongue epithelium, to a lesser extent [61]. Although genetic analyses have revealed that *Sox2* is involved in the differentiation of taste cells [61], it is difficult to attribute phenotype to *Sox2* function either in epithelial cells or in taste cells. Identification of types of Sox2-expressing cells in taste buds and conditional genetic analyses would clarify the contribution of *Sox2* to taste cell differentiation.

Although direct demonstration is needed, *Ascl1* seems to be expressed in sour taste cells that can be regarded as so-called type III cells [64]. *Ascl1* expression partially overlaps both *Shh* and *Prox1* expression [65]. We could hypothesize that *Prox1* and *Ascl1* may regulate the differentiation of *Shh*-expressing cells to sour taste cells. However, *Ascl1* at most contributes to sour cell differentiation partially by regulating *Ddc* [66], which is expressed in sour taste cells [67], and the absence of *Ascl1* does not eliminate the expression of other sour cell genes such as *Snap25* and *Ncam* in taste buds [66]. *Nkx2-2* expression overlaps with *Ascl1* in mouse taste buds [51]. However, we have not observed *Nkx2-2* expression in our microarray data of isolated taste buds from rat circumvallate papillae. We also have not detected its signal in *in situ* hybridization analysis (unpublished data). It is doubtful that *Nkx2-2* functions as a major factor to regulate sour taste cell differentiation, but we cannot completely rule out the possibility.

Expression of *Hes6* is confined to the basal cells [63], like that of *Shh*, but it is clearly distinct from *Ascl1* expression. As described above, basal cells are suspected to be taste stem cells. Since *Hes6*-knockout mice seem to be viable [68], this genetic strain is available for experimentation, so the function of *Hes6* and *Hes6*-expressing cells will be elucidated soon.

Hes1 functions as a transcription repressor upstream of *Ascl1* during neurogenesis [69]. However, in taste buds, Hes1 appears to suppress the differentiation of *PLC-β2*-expressing taste cells [62]. In addition to Hes1, the differentiation to *PLC-β2*-expressing taste cells is regulated by *Pou2f3* [33]. The fact that *Pou2f3* loss-of-function yielded the expansion of the sour taste cell population suggests that *Pou2f3* directs the differentiation to *PLC-β2*-expressing taste cells, and that *PLC-β2*-expressing and sour taste cell lineages derive from the same precursors [33]. However, many issues regarding taste cell lineages remain elusive, such as which signal activates the expression of *Pou2f3*, how *Pou2f3*-expressing cells generate sweet, umami, and bitter taste cells, and whether terminal selectors toward these taste cells exist.

6. Conclusion

From molecular genetic analyses of taste receptor and taste-related genes, almost half of taste cells in mice have been functionally identified. In addition, genetic ablation of sour and sweet taste cells has demonstrated that each taste cell is terminally differentiated or on the way to terminal differentiation. These data indicate that so-called "basic" tastes are evoked by activating distinct subsets of terminally differentiated taste cells. We still await genetic analyses to know whether single Tas1r3 receptors that are present in Tas1r1/Tas1r3-expressing "umami" taste cells receive sucrose. At present, however, a "basic" taste can be defined as a taste evoked by the chemicals that are received by independent differentiated taste cells. But then, why do we say "five" basic tastes? It seems obvious that mice can perceive and discriminate more than five basic tastes, because mouse taste cells can be classified into at least six: sweet, umami, bitter, sour, NaCl salty, and functionally unidentified taste cells. Dissecting the respective populations of taste cells in human taste buds will tell why we have five basic tastes, or possibly point to new "basic" tastes. Fish may have taste cells that mammals do not have and may distinguish taste different qualities evoked by the activation of Tas2r-expressing taste cells. It seems apparent that each vertebrate species has its own "basic" tastes that differ in both number and quality.

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