

# Changing Taste by Targeting the Ion Channel TRPM5

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**Abstract:** The taste system has evolved to make nutritious foods attractive and toxic substances aversive so as to achieve a maximal health benefit for the organism. However, evolution has not kept up with changes in human diet and lifestyle, including the development of life-saving, but bitter tasting pharmaceuticals, and the over abundance of high calorie, sweet tasting, food. The recent identification of molecular components of the taste system promises to pave the way for the rational design of flavor modifiers that enhance sweetness without caloric consequences or reduce the bitterness of prescription drugs, thereby improving human health. One such molecule is the ion channel TRPM5, which is expressed in taste receptor and other chemosensory cells and is required for bitter and sweet taste sensations. Knowledge of the structure, function and tissue localization of TRPM5 provides a basis for developing pharmacological screens for small molecule taste modifiers.

**Keywords:** TRP Channel, TRPM5, taste, flavor.

## INTRODUCTION

Humans and other animals can sense at least five distinct tastes: sweet, salty, sour, and bitter and umami. Of these, sweet, salty and umami signal the presence of nutrients in the environment and are generally attractive. Bitter taste signals the presence of toxins, notably those of plant origin, while sour can signal the presence of spoiled food, and both are generally aversive. The taste system evolved to optimize our dietary choices, leading to reproductive success; however the conditions of modern life have now turned the table on this process. Over consumption of foods that are sweet or salty contributes to hypertension and obesity while we avoid bitter tasting pharmaceuticals that are life-saving. To modify taste signaling so that it works to the benefit of human health, components of taste signaling provide attractive targets.

Taste receptor cells are modified epithelial cells, clustered in groups of 50-100 cells on the tongue and palette epithelium. Subsets of cells are responsive to each of the canonical tastes, generating electrical responses and releasing transmitter onto afferent nerve fibers [1]. For bitter, sweet and umami tastes, this process is initiated by apically located taste receptors that signal through a G protein-dependent phospholipase C (PLC) based second messenger signaling cascade [2-4]. The essential role of this cascade is supported by the observation that mice with a targeted deletion of the G protein gustducin or the enzyme PLC $\beta$ 2 gene are largely insensitive to bitter, sweet and umami tastants [5, 6]. The downstream target of this cascade is likely to be the ion channel TRPM5, which is specifically expressed in taste cells [7] and is essential for bitter and sweet taste responses [6] (but see also [8]). TRPM5, which

is expressed only in taste cells and a small number of other cell types, provides an attractive target by which to modify bitter, sweet and umami taste.

## DISCOVERY AND STRUCTURE OF THE TRPM5 GENE

The transient receptor ion channels comprise a family of 28 membrane proteins that play remarkably diverse roles in cellular physiology. Several of the channels, including TRPM5, function in sensory systems as the downstream targets of G-protein coupled sensory receptors [9, 10]. TRPM5 was first identified not based on its function in taste, but rather in an effort to find genes associated Beckwith-Wiedemann syndrome (BWS). These studies while ultimately failing to link TRPM5 with BWS, defined the basic structure of the gene [11, 12]. The human TRPM5 gene encodes a protein of 1165 amino acids, on 24 exons on chromosome 11 [11] and the orthologous mouse gene encodes a protein of 1158 amino acids [12]. TRPM5 is structurally most closely related to the ion channel TRPM4, which plays a role in the immune system [13] and it is more distantly related to the cold and menthol activated TRPM8 channel [14, 15]. Like other TRP channels, TRPM5 is thought to contain 6 transmembrane domains and to assemble as a tetramer [9, 10].

## TRPM5 IS A KEY COMPONENT OF TASTE TRANSDUCTION

A major advance came with the discovery that the TRPM5 gene is largely restricted in expression to bitter, sweet and umami responsive taste receptor cells and is required for detection of these tastes in mice [6, 7]. Bitter is mediated by a small family of G-protein-coupled receptors (T1Rs), which are co-expressed in a subset of taste cells, allowing animals to detect, but not discriminate among, a range of bitter substances [16]. Sweet and umami are each mediated by a heterodimeric receptor (T2Rs) that consists of a unique subunit (T2R1 and T2R2) and a common subunit

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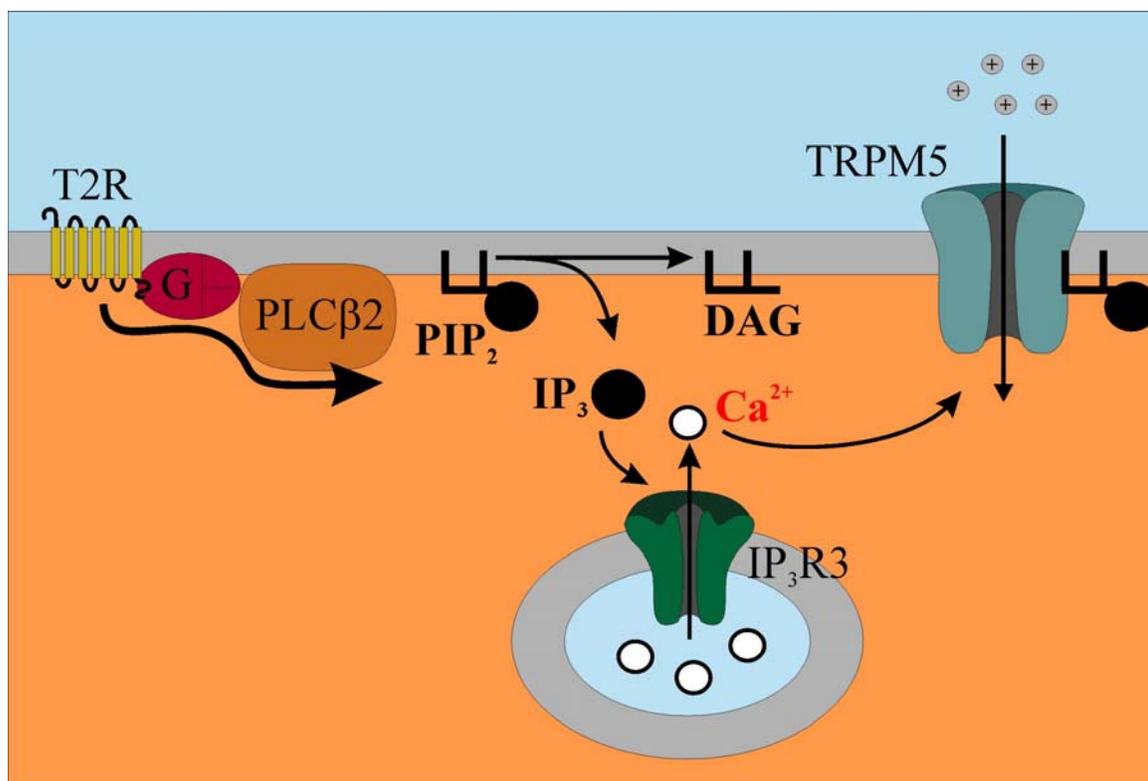
(T2R3). Individual taste receptor cells express either the T2R1/T2R3 or T2R2/T2R3 heterodimer, allowing the organism to differentiate among sweet and umami (but note that umami is not consciously perceived). TRPM5, along with the G protein gustducin and the enzyme PLC $\beta$ 2, is expressed by all three subsets of taste cells, but not by cells that mediate sour or salty [3, 17]. Evidence from many types of studies indicates that in these cells, receptor signaling activates PLC $\beta$ 2, leading to ultimately to the opening of the TRPM5 ion channel [6, 18] (Fig. 1).

#### TRPM5 IS ACTIVATED BY ELEVATION OF INTRACELLULAR $\text{Ca}^{2+}$ , DOWNSTREAM OF $\text{IP}_3$ IN HETEROLOGOUS AND NATIVE CELLS

The expression pattern of TRPM5 suggests that the channel is activated downstream of a PLC-mediated signaling cascade. Consistent with this interpretation, TRPM5 currents can be gated in heterologous cell types by stimulation of Gq-coupled receptors that activate PLC [6, 19-21]. PLC hydrolyzes PI (4, 5)  $\text{P}_2$  into DAG and  $\text{IP}_3$ , and  $\text{IP}_3$  causes release of  $\text{Ca}^{2+}$  from intracellular stores. Of these,  $\text{Ca}^{2+}$  appears to be the messenger that gates TRPM5. Direct support for this conclusion comes from studies in which single TRPM5 channels in excised patches can be shown to open in response to cytoplasmic  $\text{Ca}^{2+}$ , but not to  $\text{IP}_3$  or diacylglycerol (DAG). Under these conditions, the  $\text{EC}_{50}$  for activation of TRPM5 by intracellular  $\text{Ca}^{2+}$  is 20 - 30  $\mu\text{M}$  [20, 22]. In whole cell patch clamp recording, TRPM5 currents can be activated by extracellular application of a  $\text{Ca}^{2+}$  ionophore [20], through ultraviolet (UV) uncaging of  $\text{Ca}^{2+}$  [18, 22] or by intracellular dialysis of  $\text{Ca}^{2+}$  [19-21].

Somewhat mysteriously, the  $\text{EC}_{50}$  for activation of TRPM5 by  $\text{Ca}^{2+}$  in whole cell recording,  $\sim 1\mu\text{M}$ , is an order of magnitude higher than it is in excised inside-out patches [21, 22] (but see also [19]). In these experiments the TRPM5 current appears as outwardly rectifying, due to some intrinsic voltage-dependent gating of the channels [19, 20, 23].

While TRPM5 has been studied extensively in heterologous cells, there has been little information on the properties of native channels. This is due in part to the complexity of the taste bud, which contains a variety of different cell types that until recently could not be visually identified. To address this question and examine the functional properties of native TRPM5 channels, Liman and colleagues [18] used genetically identified taste receptor cells from mice in which the TRPM5 promoter drives expression of GFP [24]. When crossed with mice that carry a targeted deletion of TRPM5 [8], the TRPM5-dependent current could be definitively identified. These experiments revealed that the native TRPM5 channel is a  $\text{Ca}^{2+}$ -activated nonselective cation channel, with properties similar to those of expressed channels [18]. Moreover, these studies showed that both native and expressed TRPM5 channels can be activated by elevation of  $\text{IP}_3$ , through UV uncaging, and this activation was blocked by the  $\text{Ca}^{2+}$  chelator BAPTA. Thus physiological levels of intracellular  $\text{Ca}^{2+}$ , produced by release of  $\text{Ca}^{2+}$  from  $\text{IP}_3$ -dependent stores effectively activate TRPM5. The observation that the expressed TRPM5 channel recapitulates the properties of the native channel [18] supports the use of heterologous expression of TRPM5 to understand its regulation and to identify modifiers of taste.



**Fig. (1).** Taste transduction. G-protein-coupled bitter receptors (T2R) upon binding ligand activate the G protein gustducin, which in turn activates PLC $\beta$ 2. PLC $\beta$ 2 causes a breakdown of PIP<sub>2</sub> to IP<sub>3</sub> which acts on IP<sub>3</sub> receptors to release  $\text{Ca}^{2+}$  from intracellular stores. Elevation of intracellular  $\text{Ca}^{2+}$  activates TRPM5, allowing an influx of  $\text{Na}^+$  ions which depolarize the cell.

## DESENSITIZATION

Both heterologously expressed and native TRPM5 currents rapidly desensitize after activation [18-21], a process that may play a role in sensory adaptation of taste cells. In whole cell recording mode, rundown is observed following dialysis of intracellular  $\text{Ca}^{2+}$ ; similar rundown is observed in perforated patch recording following activation by bath applied  $\text{Ca}^{2+}$  ionophore, arguing that rundown is not due to washout of signaling components [20]. In excised inside-out patches, rundown of TRPM5 currents is accompanied by both a change in the  $\text{Ca}^{2+}$  sensitivity and in the maximal magnitude of the current [18, 20]. Exogenous  $\text{PI}(4,5)\text{P}_2$  enhances both the  $\text{Ca}^{2+}$  sensitivity and magnitude of TRPM5 currents following rundown, but is ineffective prior to rundown, suggesting that loss of this signaling molecule underlies desensitization [20].  $\text{PI}(4,5)\text{P}_2$  is expected to be hydrolyzed by ubiquitous membrane bound  $\text{Ca}^{2+}$ -dependent PLCs in response to the elevated  $\text{Ca}^{2+}$  levels used to evoke TRPM5 currents in excised patches or whole cell recording [25]. Consistent with this possibility, desensitization of TRPM5 is  $\text{Ca}^{2+}$  dependent [20, 22]. Similar desensitization and recovery by  $\text{PI}(4,5)\text{P}_2$  is also observed for TRPM8 and TRPM4, and for both these channels additional data supports the conclusion that hydrolysis of  $\text{PI}(4,5)\text{P}_2$  mediates desensitization [26-29].

## ION SELECTIVITY OF TRPM5

Both heterologously expressed and native TRPM5 channels show little discrimination among the monovalent cations  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$  and do not conduct divalent cations [18-21]. It is probably not a coincidence that the two  $\text{Ca}^{2+}$ -activated TRP channels TRPM4 and TRPM5 are also the only two that are impermeable to  $\text{Ca}^{2+}$ . The structural basis for the differential  $\text{Ca}^{2+}$  permeability of TRP channels is not known, but is likely due to subtle alterations in the linker between the 5<sup>th</sup> and 6<sup>th</sup> transmembrane domains which contains the pore of the channel [30, 31]. From a practical point of view, the  $\text{Ca}^{2+}$ -impermeability of TRPM5, and the requirement for intracellular  $\text{Ca}^{2+}$  elevation to activate the channel means that TRPM5 mediated responses cannot be measured with  $\text{Ca}^{2+}$  imaging. Instead, high throughput assays will require measurement of changes in membrane potential.

## TRPM5 MAY FUNCTION TO MEDIATE COMPLEX TASTE RESPONSES

Taste sensation may be more complex than initially assumed as in addition to the five canonical tastes, animals may perceive other taste qualities, such as fatty or metallic, and taste stimuli may interact to suppress or enhance perception. Recent evidence indicates that the TRPM5 channel itself may produce some of this complexity, as it can be blocked or activated by chemicals to which it comes into contact. A particularly beautiful example of this principle is the observation that quinine suppresses sweet taste, an observation that can be attributed to the direct and specific block of TRPM5 by this membrane permeable chemical, ( $\text{EC}(50) \approx$  approximately 1.6 mM *in vivo*) [32]. Similarly, heat, which activates TRPM5, enhances sweet taste [33]. In other examples, TRPM5 may function as the downstream element in the transduction of tastes other than bitter, sweet and umami. Metallic tastes of  $\text{FeSO}_4$  and  $\text{ZnSO}_4$  appear to be mediated by the TIR3 subunit of the sweet and umami

receptors, and TRPM5 is essential for the hedonically positive perception of these tastes in mice [34]. TRPM5 is also activated by linoleic acid [35] and has been shown to play a role in the attractive responses of mice to fat and carbohydrate [36].

## TRPM5 IS WIDELY EXPRESSED IN CHEMOSENSORY EPITHELIA

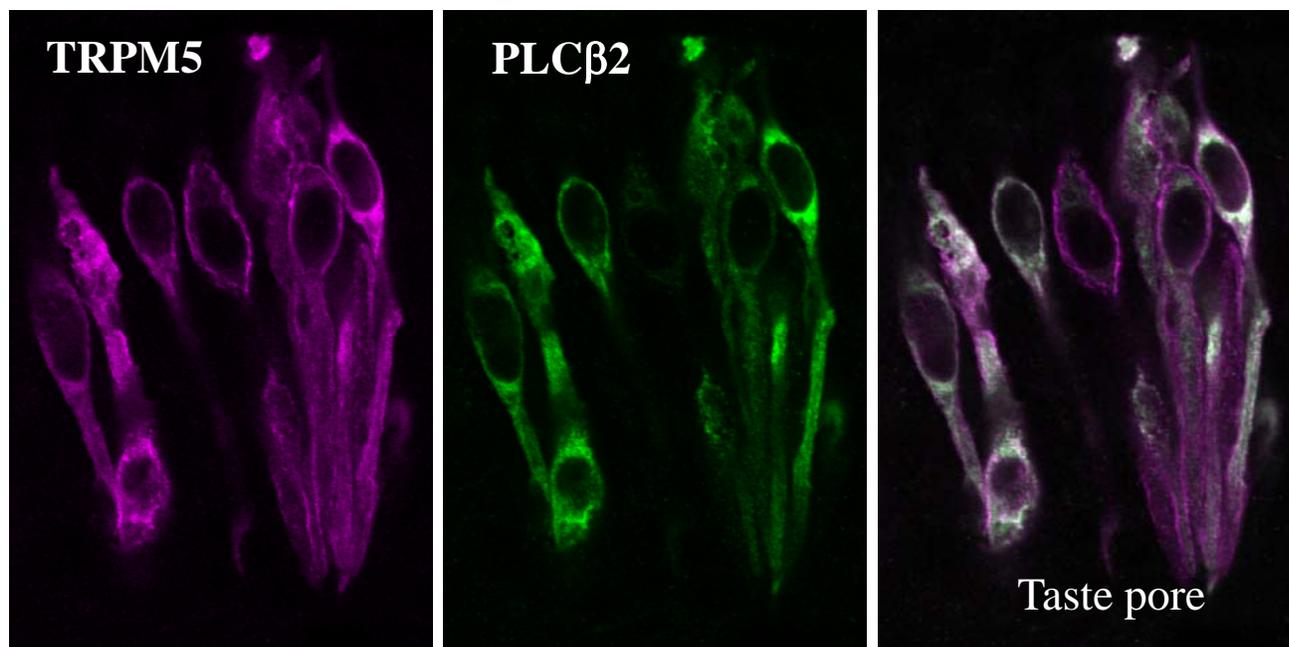
Despite initial reports that TRPM5 expression was restricted to taste cells, more recent data indicates that TRPM5 is expressed in a variety of chemosensory cells within the oral and nasal cavities and digestive tract. TRPM5 expressing cells in these tissues are generally observed as solitary microvillar cells, some of which can be seen to be innervated by nerve fibers. In the anterior nasal epithelium, TRPM5 cells co-express T2R bitter receptors and a-gustducin and may mediate trigeminal responses to odorless irritants [37]. Within the main olfactory epithelium TRPM5 cells show functional responses to elevation of intracellular calcium, but lack signaling molecules with which to communicate with the nervous system, thus their functional significance is mysterious [38, 39]. In the duodenum, small intestine and stomach, where TRPM5 is also expressed, the channel appears to mediate the release of opioid peptides in response to dietary factors and to thereby play a role in post-ingestive chemosensation [7, 40].

## LOCALIZATION OF TRPM5: IMPLICATION FOR DRUG DESIGN

In cell biology, as in real estate, one principle rules "location, location, location." Taste receptors for bitter, sweet and umami are located on the apical surface of the taste receptor cells, where they have access to ingested foods, but the localization of TRPM5 is less clear. Immunohistochemical studies with TRPM5 specific antibodies show that the channels are distributed along the basolateral surface of the cell (Fig. 2). Moreover, based on the observation that extracellular protons potently block TRPM5 channel activity [41], but sour tastes do not interfere with bitter or sweet, one can infer that the functional TRPM5 channels are located on the basolateral surface. How then does the signal propagate from the apical surface of the cell, wherein lie the receptors, to the basolateral surface of the cell? Most likely, it is  $\text{IP}_3$ , which connects the two compartments, diffusing from the apical surface and activating the widely distributed ER  $\text{Ca}^{2+}$  stores. Indeed imaging studies of isolated taste cells, although limited in temporal and spatial resolution, show a "global"  $\text{Ca}^{2+}$  signal in response to bitter tastes indicating that  $\text{Ca}^{2+}$  is released, or diffuses throughout the cell [42-45]. Together this information suggests that to block functional activity, pharmaceuticals aimed at modifying TRPM5 channel gating may need to gain access to the basolateral surface of the taste receptor cell.

## PROSPECTS FOR DEVELOPING FLAVOR MODIFIERS THAT TARGET TRPM5

The identification of molecular components of the taste system provides an exciting set of molecules against which flavor modifiers can be directed. The ion channel TRPM5 is an attractive target in this endeavor, as it is required for sensitivity to all bitter substances while identified taste



**Fig. (2).** Distribution of TRPM5 and PLC $\beta$ 2 in the taste bud. TRPM5 and PLC $\beta$ 2 were detected with isoform specific antibodies and visualized with fluorescent secondary antibodies. Note that TRPM5 is distributed throughout the plasma membrane of the cell.

receptors mediate responses only to a subset of bitter compounds. The utility of TRPM5 as a target to reduce the rejection of bitter-tasting pharmaceuticals is highlighted by a recent study which showed that the aversiveness of many pharmaceuticals was TRPM5-dependent [46]. With efforts now underway at several companies to identify flavor modifiers, we can look forward in the near future to specific blockers of TRPM5. However, the distribution of TRPM5 within diverse cells types in the taste bud, including sweet and umami cells, and within other chemosensory systems, suggest that such blockers may have undesirable side-effects. Thus in eliminating life's bitterness, we must be careful not to lose its sweetness.

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