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TRPM5 and Taste Transduction

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Abstract TRPM5 is a cation channel that it is essential for transduction of bitter, sweet and umami tastes. Signaling of these tastes involves the activation of G protein-coupled receptors that stimulate phospholipase C (PLC) β2, leading to the breakdown of phosphatidylinositol bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol trisphosphate (IP_3), and release of Ca^{2+} from intracellular stores. TRPM5 forms a nonselective cation channel that is directly activated by Ca^{2+} and it is likely to be the downstream target of this signaling cascade. Therefore, study of TRPM5 promises to provide insight into fundamental mechanisms of taste transduction. This review highlights recent work on the mechanisms of activation of the TRPM5 channel. The mouse TRPM5 gene encodes a protein of 1,158 amino acids that is proposed to have six transmembrane domains and to function as a tetramer. TRPM5 is structurally most closely related to the Ca^{2+}-activated channel TRPM4 and it is more distantly related to the cold-activated channel TRPM8. In patch clamp recordings, TRPM5 channels are activated by micromolar concentrations of Ca^{2+} and are permeable to monovalent but not divalent cations. TRPM5 channel activity is strongly regulated by voltage, phosphoinositides and temperature, and is blocked by acid pH. Study of TRPM4 and TRPM8, which show similar modes of regulation, has yielded insights into possible structural domains of TRPM5. Understanding the structural basis for TRPM5 function will ultimately allow the design of pharmaceuticals to enhance or interfere with taste sensations.

Keywords Transient receptor potential - $PI(4,5)P_2$ - Taste - Bitter - Sweet

1
Gene and Protein Structure of TRPM5

TRPM5 was first identified in an effort to find genes associated with the tumor-producing condition known as Beckwith–Wiedemann syndrome (BWS) and, although failing to link TRPM5 with BWS, these initial studies defined the basic structure of the gene (Enklaar et al. 2000; Prawitt et al. 2000). The human TRPM5 gene comprises 24 exons on chromosome 11 and it contains an open reading frame of 3,495 bp, which predicts a protein of 1,165 amino acids (Prawitt et al. 2000). The orthologous mouse gene is located on the syntenic distal end of chromosome 7, and it contains an open reading frame that predicts a protein of 1,158 amino acids (Enklaar et al. 2000). TRPM5 shows highest homology to TRPM4 (40% identity at the amino acid level) and it is more distantly related to other TRPM channels, such as the cold and menthol receptor TRPM8 (McKemy et al. 2002; Peier et al. 2002). Like other transient receptor potential (TRP) channels, TRPM5 is thought to contain six transmembrane domains and to assemble as a tetramer (Montell et al. 2002; Clapham 2003).

2
Expression Pattern and Biological Function of TRPM5

A major advance in understanding the physiological significance of TRPM5 came with the discovery that its expression is largely restricted to taste receptor cells (Perez et al. 2002; Zhang et al. 2003). There are five modalities of taste of which three—bitter, sweet and umami—are mediated by G protein-coupled receptors that bind their respective tastant (Lindemann 2001; Margolskee 2002). These receptors activate the G protein gustducin and phospholipase C (PLC) β2 (Lindemann 2001; Margolskee 2002), thereby initiating an intracellular signaling cascade that leads to an electrical response, the nature of which is not well understood (Medler and Kinnamon 2004). The ion channel TRPM5 may be the ultimate target of this cascade, transducing the biochemical changes into an electrical signal. This is supported by the observation that TRPM5 is coexpressed with receptors for all three modalities and with gustducin and PLCβ2 (Perez et al. 2002; Zhang et al. 2003; Fig. 1a). Moreover, in a striking series of experiments, the Zuker and Ryba labs showed that both PLCβ2 and TRPM5 are essential for normal bitter, sweet and umami taste in mice (Zhang et al. 2003). Both behavioral studies and nerve recording show that mice lacking either gene are dramatically less sensitive to these three types of tastes, but retain their ability to detect sour and salty. TRPM5 is also expressed in the small intestine and stomach, where it may play a role in postingestive chemosensation (Perez et al. 2002).

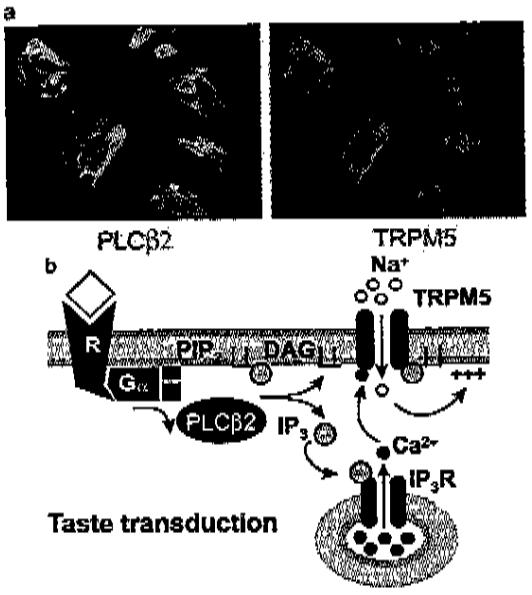

Fig. 1a, b TRPM5 is a component of taste transduction. a Immunoreactivity for taste signaling components in taste buds of the mouse circumvallate papillae, showing colocalization of TRPM5 with PLCβ2 (from Perez et al. 2002, with permission). b A model for taste transduction. Binding of taste stimuli to G protein-coupled taste receptors (*R*) leads to dissociation of the heterotrimeric G protein. βγ subunits of the G protein activate PLCβ2, which in turn hydrolyzes phosphatidylinositol bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol trisphosphate (IP_3). IP_3 activates IP_3 receptors, which release Ca^{2+} from intracellular stores. Intracellular Ca^{2+} opens TRPM5 channels, leading to an influx of Na^+ and depolarization of the cell. Note that TRPM5 is not permeable to Ca^{2+} and, therefore, there is no positive feedback loop. (From Liu and Liman 2003, with permission)

3
Ion Channel Properties

3.1
Activation by Ca^{2+}

A key to understanding the contribution of TRPM5 to taste and other physiological processes is to identify the mechanisms by which TRPM5 channels are activated. Fortunately the TRPM5 protein is well-trafficked to the plasma membrane when expressed in heterologous cell types (Liu et al. 2005), making it possible to study its functional properties with patch-clamp recording. 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

G_q-coupled receptors that activate PLC (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003; Zhang et al. 2003). PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate $PI(4,5)P_2$ into diacylglycerol (DAG) and inositol trisphosphate (IP_3), and IP_3 causes release of Ca^{2+} from intracellular stores and presumably one or more of these small molecules activates TRPM5. Of these, only Ca^{2+} is able to directly gate TRPM5 channels (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003; see Fig. 2a). Moreover, activation of TRPM5 by G_q-coupled receptors is abolished when intracellular Ca^{2+} is strongly buffered (Liu and Liman 2003; Prawitt et al. 2003) or when IP_3 receptors are inhibited with heparin (Hofmann et al. 2003). Overall, these data support a model for activation of TRPM5 shown in Fig. 1b. In this model, taste receptors (or other G protein-coupled receptors) signal through PLCβ2 to release Ca^{2+} from intracellular stores, which rapidly activates TRPM5 channels (Liu and Liman 2003). This is consistent with physiological data from taste cells and results from targeted deletion of taste transduction molecules (Akabas et al. 1988; Hwang et al. 1990; Bernhardt et al. 1996; Wong et al. 1996; Ogura et al. 1997; Huang et al. 1999; Ogura et al. 2002; Zhang et al. 2003).

Ca^{2+} signals can be generated from a number of different sources and they can vary in magnitude and temporal properties (Hille 2001). For example, release of Ca^{2+} through ryanodine receptors generates a rapid elevation of local Ca^{2+} ("spark") that can reach levels as high as 20–30 μM, a concentration that is able to activate closely opposed plasma membrane Ca^{2+}-activated K^+ channels (Wellman and Nelson 2003). On the other hand, global changes in Ca^{2+} concentration rarely exceed one micromolar and can last for many seconds (Hille 2001). In understanding how TRPM5 channels are gated under physiological conditions, two questions must be answered: (1) Are the channels localized in close proximity to a Ca^{2+} source? (2) How sensitive to Ca^{2+} is the gating of the channels? The second question will be dealt with in Sect. 3.1.1. In answer to the first question, we know that TRPM5 channels are distributed across the entire plasma membrane of taste cells (Perez et al. 2002; Fig. 1a). This is in striking contrast to the distribution of the pheromone-transduction channel TRPC2, which is localized to sensory microvilli of vomeronasal sensory neurons (Liman et al. 1999). The IP_3 receptor and PLCβ2 show a similarly diffuse expression pattern in taste cells (Clapp et al. 2001) and therefore it is conceivable that the three molecules are localized in a signaling complex, like that which organizes signaling components of fly phototransduction (Montell et al. 2002).

3.1.1 Sensitivity to Activation by Intracellular Ca^{2+}

Determination of the Ca^{2+} sensitivity of TRPM5, and of the related channel TRPM4, has been more difficult than might be expected and there is a great deal of variation in the values for half-activation of the channels by Ca^{2+}

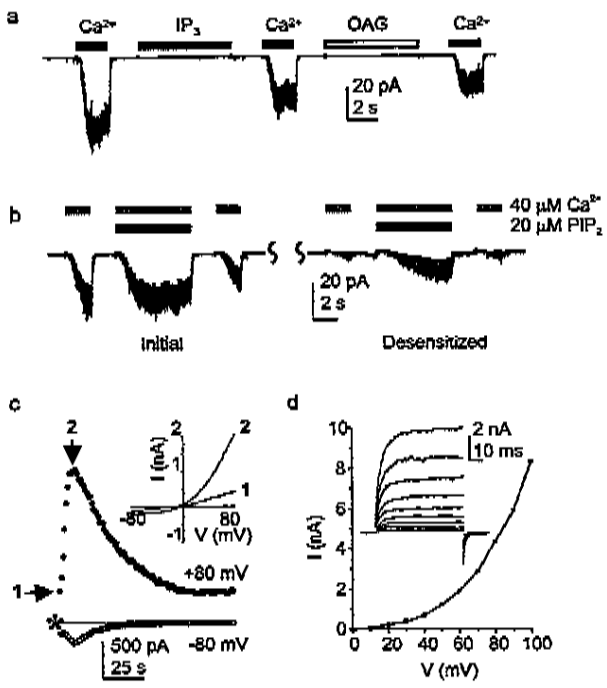

Fig. 2a–d Functional properties of TRPM5. a Activation by 40 μM Ca^{2+} of an inward current in a patch excised from a TRPM5-transfected CHO-K1 cell (V_m = −80 mV). Neither 10 μM IP_3 nor 100 μM 1-oleoyl-2 acetyl-*sn* glycerol (OAG) elicited a current in the same patch. b PIP_2 partially restores TRPM5 channel activity following desensitization. The illustration shows responses to 40 μM Ca^{2+} in the presence and absence of 20 μM PIP_2 before and after desensitization. Desensitization was induced by a 30-s exposure to 40 μM Ca^{2+} (V_m = −80 mV). c Electrophysiological properties of TRPM5 expressed in HEK-293 M1 cells. Whole-cell recording mode, 40 μM Ca^{2+} in the pipette, elicited a large rectifying current. Recording began shortly after break in to the whole-cell mode. *Inset* shows the current in response to a ramp depolarization (1 V/s). d Currents in response to a family of step depolarizations and the resulting I–V relationship for the peak current at each voltage. Steps are to 0–100 mV from a holding potential of −80 mV with repolarization to −50 mV. Note the prominent relaxation of the current upon depolarization, consistent with voltage-dependent gating of the channels. (From Liu and Liman 2003, with permission)

reported by different groups. This may be in part due to the fact that the Ca^{2+} sensitivity of these channels is subject to modulatory influences that are not completely understood. Perhaps the most robust and reproducible way to measure intracellular Ca^{2+} sensitivity is in inside-out patches (Fig. 2a). In this mode, immediately after patch excision TRPM5 channels are activated by intracellular Ca^{2+} with an EC_{50} of 20–30 μM (Liu and Liman 2003; Ullrich et al. 2005). This value increases over time, possibly as a result of loss of $PI(4,5)P_2$ from the channels, to 80 μM (Liu and Liman 2003). Under the same conditions,

the structurally related channel TRPM4 is five times less sensitive to activation by intracellular Ca^{2+} (Ullrich et al. 2005; Zhang et al. 2005). The low sensitivity of TRPM5 channels in this recording mode argues that to be activated by physiological stimuli the channels are most likely localized in close proximity to a Ca^{2+} source.

Somewhat mysteriously, the sensitivity of TRPM5 channels to activation by Ca^{2+} in whole-cell recording mode is several orders of magnitude higher than it is in excised inside-out patches. While dose–response data are more difficult to obtain in this mode due to rundown of the current (Fig. 2c) and the need to use population data, there is nonetheless general consensus that TRPM5 can be near-maximally activated by intracellular dialysis of 1 µM Ca^{2+} (Prawitt et al. 2003; Ullrich et al. 2005; but see also Hofmann et al. 2003). This might reflect the loss of a factor that enhances the sensitivity of the channels to Ca^{2+}, as will be discussed in Sect. 4.2. In addition, it is possible that perfusion of the cells with relatively low concentrations of Ca^{2+} elicits Ca^{2+} release in the vicinity of the TRPM5 channels, which further augments their activation. The high sensitivity to Ca^{2+} of TRPM5 channels in whole-cell recoding mode could be used to argue that the channels detect global changes in Ca^{2+} (Prawitt et al. 2003), a conclusion at odds with that based on data from excised inside-out patch recording. Clearly we need to understand more about how these channels are regulated to resolve this discrepancy.

3.2 Ion Selectivity

The ease of activation of TRPM5 in heterologous expression systems has allowed careful investigation of the channel's selectivity and gating. These experiments have shown that TRPM5 channels show little discrimination among the monovalent cations Na^+, K^+, and Cs^+ and do not conduct divalent cations (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003). It is probably not a coincidence that the two Ca^{2+}-activated TRP channels are also the only two that are impermeable to Ca^{2+}. The structural basis for the differential Ca^{2+} permeability of TRP channels is not known. In a detailed set of experiments, residues in the putative pore of TRPM4 were changed to the corresponding residues in a Ca^{2+}-permeable TRP channel, TRPV6, and this conferred moderate Ca^{2+} permeability to the chimeric channel (Nilius et al. 2005a). However, the fact that these authors were not able to identify a mutant that could confer more substantial Ca^{2+} permeability suggests that multiple residues or regions of the channel contribute to this process. Nonetheless, these experiments have provided experimental evidence that the region between the fifth and sixth transmembrane domain of TRPM4, and by homology TRPM5, contains the pore of the channel (Owsianik et al. 2005).

3.3 Unitary Properties

Single TRPM5 channels show a conductance of approximately 16–25 pS (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003). Channel openings are short-lived and flickery (Liu and Liman 2003), which has precluded a detailed analysis of gating properties. This is in contrast to the long-lived openings of TRPM4 channels (bursts can last several seconds) (Launay et al. 2002; Zhang et al. 2005), and may serve as a defining feature in categorizing native channels.

4 Modulation of TRPM5 Function

4.1 Voltage-Dependent Activation

Although activation of TRPM5 requires elevated Ca^{2+} levels, gating of the channel is also strongly affected by voltage (Hofmann et al. 2003; Liu and Liman 2003; Talavera et al. 2005). This is apparent in the outward rectification of TRPM5 currents in response to a voltage ramps, despite a linear current–voltage relationship (I–V) for the single channel conductance, and in the time-dependent relaxation of the current following a voltage step (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003; Talavera et al. 2005; Fig. 2c,d). Voltage-dependent activation has also been reported for TRPM8 and TRPM4 and thus may be a common feature of TRPM channels (Hofmann et al. 2003; Nilius et al. 2003; Nilius et al. 2005b; Rohacs et al. 2005). Why should channels whose primary role is to transduce sensory signals be voltage-dependent? While the answer to this question is not known, it has been hypothesized that the weak voltage dependence of these channels allows their gating to be easily modulated (Nilius et al. 2005b), a hypothesis that is supported by work on cold regulation of TRPM8, TRPV1, and TRPM5 (Voets et al. 2004; Talavera et al. 2005), decavanadate modulation of TRPM4 (Nilius et al. 2004), and $PI(4,5)P_2$ regulation of TRPM4 and TRPM8 (Rohacs et al. 2005; Zhang et al. 2005; see Sect. 4.2). At present the structural mechanism of voltage sensing of any of the TRP channels is not known. The fourth transmembrane of these channels contain several charged residues that might act as the voltage sensor, by analogy to voltage-activation of K^+ channels (Jiang et al. 2003; Nilius et al. 2005b).

4.2 Desensitization and Regulation by $PI(4,5)P_2$

A consistent observation is that TRPM5 currents rapidly desensitize after activation (Hofmann et al. 2003; Liu and Liman 2003; Prawitt et al. 2003),

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 Ca^{2+} (Fig. 2c) and similar rundown is observed in perforated patch recording following activation by bath applied Ca^{2+} ionophore, arguing that rundown is not due to washout of signaling components (Liu and Liman 2003). In excised inside-out patches, rundown of TRPM5 currents is accompanied by both a change in the Ca^{2+} sensitivity and in the maximal magnitude of the current (Liu and Liman 2003).

Recently the phosphoinositide $PI(4,5)P_2$ has emerged as an important co-factor in the activation of ion channels, and hydrolysis of $PI(4,5)P_2$ has been proposed to underlie rundown of many types of $PI(4,5)P_2$-sensitive ion channels (Suh and Hille 2005). $PI(4,5)P_2$ is likewise a cofactor for activation of TRPM5 (Liu and Liman 2003). Exogenous $PI(4,5)P_2$ enhances both the Ca^{2+} sensitivity and magnitude of TRPM5 currents following rundown, but is ineffective prior to rundown (see Fig. 2b), suggesting that loss of this signaling molecule underlies desensitization (Liu and Liman 2003). $PI(4,5)P_2$ is expected to be hydrolyzed by ubiquitous membrane bound Ca^{2+}-dependent PLCs in response to the elevated Ca^{2+} levels used to evoke TRPM5 currents in excised patches or whole-cell recording (Varnai and Balla 1998). Consistent with this possibility, desensitization of TRPM5 is Ca^{2+}-dependent (Liu and Liman 2003; Ullrich et al. 2005). Similar desensitization and recovery by $PI(4,5)P_2$ is also observed for TRPM8 and TRPM4, and for both these channels additional data support the conclusion that hydrolysis of $PI(4,5)P_2$ mediates desensitization (Liu and Qin 2005; Rohacs et al. 2005; Zhang et al. 2005; Nilius et al. 2006). A structural determinant for $PI(4,5)P_2$ modulation of TRPM8 has been identified in positively charged residues among the 25 amino acids proximal to the sixth transmembrane domain (Rohacs et al. 2005). It is not known yet whether this region also contains key structural determinants for regulation of TRPM5 by $PI(4,5)P_2$.

4.3 Temperature Modulation of TRPM5

TRPM5 is structurally related to the cold-activated channel TRPM8 and more distantly related to heat-activated TRPV channels, suggesting the possibility that its activity is also thermal-sensitive. Indeed, warm temperatures promote activation of TRPM5, similar to the effects of heat on the TRPV channels (Talavera et al. 2005). An elegant theoretical framework has been developed to explain heat and cold activation of TRP channels, which postulates that their extreme thermal sensitivity derives from their small voltage dependence (Nilius et al. 2005b). Heat acts by shifting the midpoint for voltage-dependent activation to negative voltages for TRPV1 and TRPM5 and positive voltages for TRPM8, leading to opposing thermal sensitivities of the channels (Voets et al. 2004; Talavera et al. 2005). However, unlike TRPV1, heat is not suffi-

cient to activate TRPM5, which even at warm temperatures requires elevated Ca^{2+}(Talavera et al. 2005). The thermal sensitivity of TRPM5 suggests that sensation of bitter, sweet, and umami tastes might be reduced at cold temperatures. Electrophysiological recordings from mice indeed show that sweet taste is highly sensitive to temperature, although bitter and umami are unaffected (Talavera et al. 2005). Thus, while these data support a role for TRPM5 in the thermal sensitivity of sweet taste, there are likely other factors that contribute to the thermal sensitivity of this process.

5
Pharmacology: Block by Acid pH

Blockers of TRPM5 have the potential to alter taste sensation, and therefore identification of these molecules is of great interest. Although no specific blockers have yet been reported, acid pH has been found to be a very potent and relatively specific blocker of the channel (Liu et al. 2005). TRPM5 is sensitive to pH levels below 7.0 and is completely blocked by pH 5.9. In comparison, TRPM4 is insensitive to pH levels as low as 5.4. By comparing sequence differences between TRPM4 and TRPM5, two residues were identified that account for most of the pH sensitivity of TRPM5—a Glu residue in the S3–S4 linker and a His residue in the pore region (S5–S6 linker; Liu et al. 2005). Acid pH also enhances the rate of inactivation of TRPM5 channels through its effects on these residues. It is tempting to speculate that acid block of TRPM5 may play a functional role in taste sensation, possibly decreasing responses of taste cells to activation by bitter, sweet, or umami when consumed at acid pH.

6
A Bitter-Sweet Conclusion

TRPM5 plays an essential role in the detection of bitter, sweet, and umami tastes and therefore a better understanding of its regulation will lead to insights into taste sensory transduction. The elegant molecular work of the last decade has shown that bitter, sweet, and umami tastes are mediated by distinct G protein-coupled receptors, and that these receptors activate a common downstream signaling cascade of which PLCβ2 and TRPM5 are critical components. Currently it is well established that Ca^{2+} is the primary stimulus for activating TRPM5 in heterologous cells types. Thus, the simplest model for taste sensation envisions that receptor activation promotes hydrolysis of $PI(4,5)P_2$ by PLCβ2 leading to the generation of IP_3 and release of Ca^{2+} from intracellular stores. Ca^{2+} then activates TRPM5, which conducts an inward Na^+ current and depolarizes the cell. Whether, indeed, activation of TRPM5 by Ca^{2+} underlies the electrical response of taste cells to sensory stimuli remains to be established.

The identification of a robust mechanism for activation of TRPM5 in heterologous cells has facilitated the discovery of basic features of the channel and novel regulatory mechanisms that are likely to be of physiological significance. $PI(4,5)P_2$ hydrolysis has been proposed to play an important role in desensitization of TRPM5 and may mediate sensory adaptation of taste. Thermal sensitivity of TRPM5 has been shown to contribute to the temperature dependence of sweet sensation, and acid inhibition of TRPM5 may also modulate sensory responses to taste. Finally, in the future we can look forward to structural information that will allow the design of rational chemicals to block or enhance TRPM5 function and thereby remove some of the bitterness or enhance some of the sweetness of pharmaceuticals and foods we consume.

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