Biochimica et Biophysica Acta 1853 (2015) 2025–2032

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Calcium signaling in taste cells☆

Kathryn F. Medler

Department of Biological Sciences, University at Buffalo, The State University of New York, Buffalo, NY 14260, USA

ARTICLE INFO

Article history:
Received 11 September 2014
Received in revised form 21 October 2014
Accepted 7 November 2014
Available online 16 November 2014

Keywords:
Taste
Calcium influx
Calcium release
Ryanodine receptors
Mitochondria
Sodium–calcium exchangers

ABSTRACT

The sense of taste is a common ability shared by all organisms and is used to detect nutrients as well as potentially harmful compounds. Thus taste is critical to survival. Despite its importance, surprisingly little is known about the mechanisms generating and regulating responses to taste stimuli. All taste responses depend on calcium signals to generate appropriate responses which are relayed to the brain. Some taste cells have conventional synapses and rely on calcium influx through voltage-gated calcium channels. Other taste cells lack these synapses and depend on calcium release to formulate an output signal through a hemichannel. Beyond establishing these characteristics, few studies have focused on understanding how these calcium signals are formed. We identified multiple calcium clearance mechanisms that regulate calcium levels in taste cells as well as a calcium influx that contributes to maintaining appropriate calcium homeostasis in these cells. Multiple factors regulate the evoked taste signals with varying roles in different cell populations. Clearly, calcium signaling is a dynamic process in taste cells and is more complex than has previously been appreciated. This article is part of a Special Issue entitled: 13th European Symposium on Calcium.

1. Introduction

There are multiple sensory systems to detect environmental stimuli. These sensory systems provide our brains with information about our surroundings that is critical for our survival. Sensory systems vary with the needs of the organism, some organisms do not detect light or sound waves while others detect electrical signals and magnetic fields. All organisms, however, possess the ability to detect chemicals in their environment. Chemosensation is used to find nutrients and conspecifics as well as to identify predators and avoid potentially harmful compounds or environmental conditions. Some organisms, including single-celled organisms have a single chemosensory system; other groups, including vertebrates, have evolved two separate systems which are comprised of olfaction and taste. Olfaction and taste function independently and jointly to inform the brain about chemicals in the environment. The olfactory system detects odorants and is used to identify potential dangers in the environment as well as being involved in many behavioral interactions, including kin recognition and mate selection. Taste is used to detect nutrients for consumption as well as potentially toxic compounds that should be avoided. The taste system is required for survival and its impairment often causes malnutrition which can lead to death [1].

The cells that detect the chemicals for taste are called taste receptor cells (TRCs) and these cells are grouped together in taste buds found in the oral cavity. Taste buds consist of 50–150 TRCs; in some organisms, taste buds are scattered across the tongue. In the channel catfish, additional taste buds are located on the outer epithelium across their entire body, essentially making the catfish a "giant tongue" [2]. This is quite unusual and for most vertebrates, taste buds are contained within the oral cavity. In mammals, taste buds are housed in specialized bumps and grooves called papillae. There are three types of papillae: circumvallate (CV), foliate (Fol) and fungiform (Fun). The CV papillae are found on the back of the tongue and are comprised of crypts that are lined with hundreds of taste buds. The Fol papillae also house hundreds of taste buds and are found on the both sides of the tongue. The Fun papillae are small protrusions that house 1–2 taste buds each and are scattered across the anterior two thirds of the tongue. Additional taste buds are located on the palate and throat, including a row of taste buds found between the hard and soft palate called the geschmacksstreifen [1,3–12].

TRCs are unique in that they have properties of both neurons and epithelial cells. Like epithelial cells, TRCs express certain keratinocyte markers and are routinely replaced throughout an organism's life, having a limited lifespan between two weeks and two months [4,13]. Like neurons, TRCs are excitable cells, fire action potentials and form synapses with gustatory neurons. TRCs extend microvilli into the oral cavity where receptors on these microvilli detect chemicals that are being released during mastication. TRCs convert this chemical stimulus into an output signal that is sent to the brain for processing via the afferent gustatory neurons. Depending on this message, the food item will either be ingested or ejected. Compared to other sensory systems, the taste system is able to detect a large number of chemically diverse stimuli that vary in size, charge, pH, and lipophilicity. In order to detect all of these different types of stimuli, the TRCs use a variety of receptors and signaling pathways. A particular TRC does not express all of these

☆ This article is part of a Special Issue entitled: 13th European Symposium on Calcium.

E-mail address: kmedler@buffalo.edu.

http://dx.doi.org/10.1016/j.bbamcr.2014.11.013
0167-4889/

signaling mechanisms and is sensitive to a subset of different taste stimuli [1,3–12]. This review is focused on the role that calcium plays in the signaling pathways that are used by taste cells to formulate a signal that is sent to the brain for processing.

2. Taste transduction

The sense of taste is comprised of five basic taste qualities that include bitter, sour, salty, sweet and umami. Bitter detects potentially toxic compounds that usually should be avoided; sour detects protons which indicate spoiled food; salty is used to identify ions that are needed to maintain ionic balance; sweet is used to detect energy rich carbohydrates and umami detects glutamate and other amino acids. Based on the general chemical nature of the different taste stimuli, we can divide them into two broad groups, ionic and chemically complex. Salty and sour is the detection of different ions and are called ionic stimuli while the other taste qualities, bitter, sweet and umami are more chemically complex. Due to their simple ionic nature and charge, salty and sour activate ionotropic receptors to cause a cell depolarization. This activates a voltage-gated calcium influx which generates an increase in intracellular calcium that subsequently initiates neurotransmitter release from a conventional chemical synapse [1,4,9,10].

Bitter, sweet and umami stimuli activate G-protein coupled receptors (GPCRs) that initiate a common signaling pathway. Upon activation, these GPCRs activate a phospholipase C (PLC) signaling pathway which causes calcium release from stores via activation of inositol triphosphate receptors (IP_3Rs). These cells do not have conventional synapses but still communicate to gustatory nerves using neurotransmitters. The calcium release from ER stores activates a TRP channel, TRPM5. TRPM5 is a sodium selective TRP channel which causes a membrane depolarization through a sodium influx. This depolarization activates a hemichannel which opens and releases ATP onto the gustatory nerve. The identity of this hemichannel is still being debated with several candidate proteins including connexins, pannexins, and the calcium homeostasis modulator 1 (CALHM1). Regardless of its identity, the neurotransmitter ATP is released which causes a signal to be sent to the brain. Thus, calcium release from stores is sufficient for neurotransmitter release to occur in these cells [3,11,12,14–28]. For all taste stimuli, a calcium signal is required for normal taste transduction to occur.

3. Calcium signaling in taste cells

Beyond this calcium signal requirement in taste transduction, very little is known about these signals. Analyses of the calcium release and calcium influx signals found, as expected, that these signals are significantly different from each other both in their timing as well as their magnitude. An additional PLC signaling pathway was also identified in some of the taste cells that have conventional synapses and express voltage-gated calcium channels (VGCCs). These TRCs can respond to multiple taste stimuli. The taste-evoked calcium signals in these cells are still different from each other in both their kinetics and their magnitude, further supporting the conclusion that unique calcium signals are generated for different taste stimuli [29].

Further studies have demonstrated that ryanodine receptors are expressed in a sub-population of taste cells and that these receptors are contributing to the calcium release signal in about 30% of the taste cells expressing the PLC signaling pathway and hemichannels for ATP neurotransmitter release. When ryanodine receptors are present, the taste-evoked calcium signal is significantly larger, which is predicted to increase the amount of neurotransmitter that is released. Interestingly, ryanodine receptors were also expressed in some TRCs with voltage-gated channels. In this population of taste cells, the ryanodine receptors were contributing to the calcium influx signal generated by VGCCs. Further analysis found that in the TRCs with both VGCCs and the PLC signaling pathway, the ryanodine receptors were exclusively contributing to the calcium influx signal generated by VGCCs and no longer contributed to the calcium release signal generated by activating the PLC signaling pathway [30]. Data indicated that the ryanodine receptors were associating with L-type VGCCs in these cells and that there is a functional, but not physical interaction, between these proteins [31]. The mechanism underlying this selective interaction has not been identified in taste cells but this specificity may be due to the localization of these different signaling components on the endoplasmic reticulum. Further work is needed to determine the mechanism that is directing the selectivity of the ryanodine receptor function in the different taste cell populations.

4. Calcium regulation in taste cells

Since TRCs are detecting chemicals from the environment, they must be in contact with the environment, which dictates their position in the oral cavity. These cells extend microvilli into the oral cavity which makes them susceptible to damage and for this reason, TRCs are routinely replaced. In addition to their exposure to potential dangers such as bacteria, viruses, or significant temperature changes, TRCs must also be capable of dealing with a variable external environment. The environment in the oral cavity changes every time potential nutrients are being consumed. But within this context, TRCs must accurately respond to the chemicals that are introduced during consumption so it is absolutely critical that these cells maintain an appropriate intracellular ionic balance during feeding. As a result, TRCs are very actively regulating cytosolic calcium levels, even in the absence of any stimulation. TRCs can undergo a constitutive calcium influx even in the absence of stimulation but this influx is buffered by multiple mechanisms to maintain appropriate resting cytosolic calcium levels and thus allow the cell to respond appropriately when taste stimuli are presented.

5. Calcium clearance mechanisms in basal calcium regulation

While the evoked calcium signals are not particularly well-described in taste cells, even less is understood about how TRCs regulate their calcium levels. While TRCs maintain resting calcium levels around 100 nM, there is evidence that these cells can have a constitutive calcium influx in the absence of cell stimulation which they actively regulate. In the absence of external calcium, the resting calcium levels in TRCs often decrease to a resting value between 30 nM and 50 nM which suggests that TRCs may also depend on this constitutive calcium influx to maintain their normal resting calcium levels. When the external calcium concentration is increased around TRCs, their baseline calcium levels also increase [32], further supporting an active relationship between the cytosolic calcium and the external calcium environment in these cells. This constitutive calcium influx is regulated by multiple calcium clearance mechanisms, including both the mitochondria and the sodium/calcium exchanger (NCX) [32,33]. Inhibiting the mitochondria's ability to take up calcium using the protonophore, carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP) in unstimulated TRCs caused an increase in cytosolic calcium that remained elevated until the mitochondria were once again able to buffer calcium [32] (Fig. 1A). When FCCP is applied to TRCs, its acts as an uncoupler of the proton gradient in the mitochondria and disrupts ATP synthesis. In addition, it dispels the large negative potential inside the mitochondrial matrix which normally creates a strong driving force for calcium to leave the cytosol and enter the inner mitochondrial matrix. In the presence of FCCP, there is no longer a driving force on calcium to enter the mitochondria.

One of the primary functions of mitochondria is to produce ATP and support the metabolic needs of the taste cell, so it was possible that inhibiting the mitochondria's ability to make ATP was causing the observed changes in the cytosolic calcium. Since both PMCAs and SERCA pumps require ATP to function, it was possible that the mitochondria were not directly buffering cytosolic calcium but were indirectly inhibiting the calcium ATPases through ATP depletion. However, control