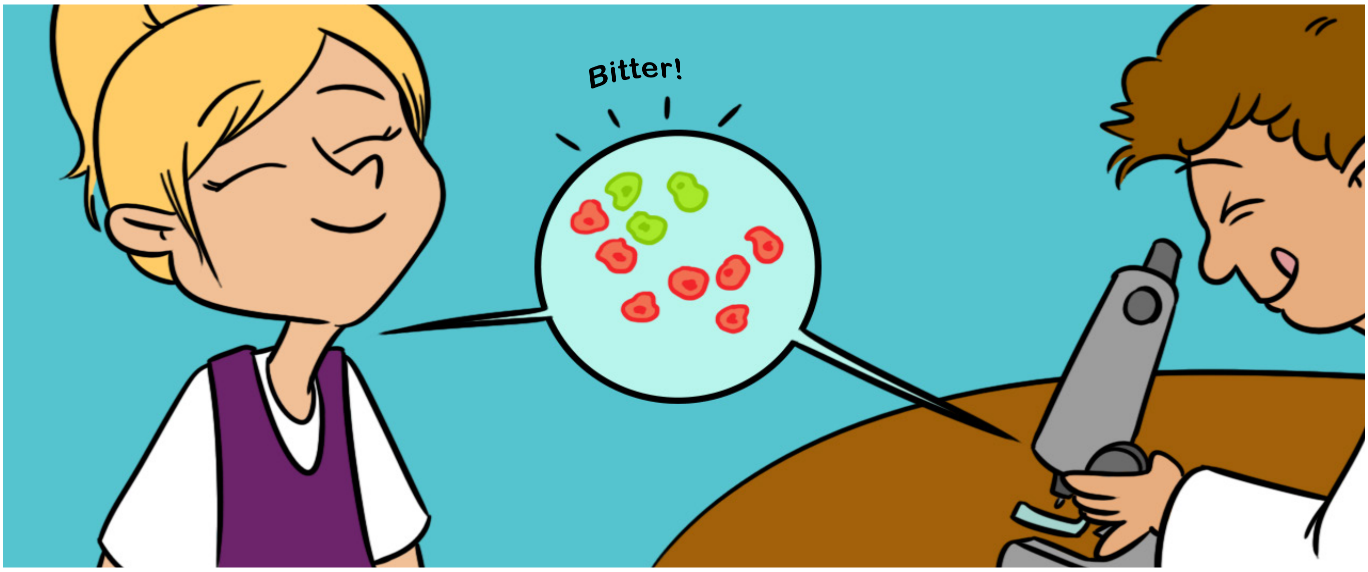
HEALTH
Published: 14 June 2018
doi:10.3389/frym.2018.00028



CAN A BITTER TASTE BE DETECTED OUTSIDE THE TONGUE?

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Bitter, sweet, sour, salty, and savory tastes can be sensed by the tongue through their related taste receptors. The taste of bitter is very important in nature. It protects us from eating harmful things, which usually taste bitter. In this research, we looked for cells that have bitter taste receptors. To make them visible, we labeled them with a green fluorescent protein. These green cells were found on the tongue, as expected, but they were also found in other places that are easily exposed to harmful things, such as the airway, the gut, and the urethra. Our work also showed that the cells expressing bitter receptors could have the ability to activate the immune system. We cannot actually taste bitter anywhere apart from the tongue, but bitter taste receptors in other parts of the body may function in a different way.

HOW CAN WE SENSE DIFFERENT TASTES?

When food enters the mouth, small molecules of the food can be sensed by the tongue. We know that different foods have different tastes. We can sense five different tastes—sweet, bitter, sour, salty, and savory. We taste these five flavors differently because the tongue has five different kinds of receptors that can distinguish between these five tastes.

Receptors are proteins found on the upper surface of cells. Taste receptors are found on the upper surface of special cells called taste cells. Many taste cells group together to form an onion-like structure known as a taste bud. Thousands of taste buds are found in nipple-like structures (called papillae) on the upper surface of the tongue. When sweet, bitter, sour, salty, or savory substances reach the surface of taste buds, they are recognized by their own respective taste receptors. Taste receptors give a signal to the taste cells, and the taste cells pass this signal through nerves to the brain. This combination of signals allows us to experience different tastes from different foods [1].

WHY IS THE BITTER TASTE SO INTERESTING TO US?

Our sense of taste enables us to enjoy the food we eat. But we usually do not like the bitter taste, and neither does the rest of the animal kingdom. Most animals reject things with a bitter taste, because toxic substances usually taste bitter. This natural rejection of bitter tastes has developed in animals from fish to humans, to prevent us from eating harmful foods. These days, we know that not all bitter-tasting things are harmful. Some bitter-tasting things can be even good for our health, such as green tea, cacao (the seeds used to make chocolate), and some drugs used to cure diseases.

A lot of things in nature taste bitter. Therefore, it is not surprising that many different kinds of bitter taste receptors exist. There are 25 kinds of bitter taste receptors in humans, compared with 35 in mice. The ability of some bitter taste receptors to recognize bitter substances differs. Some of these receptors can recognize various types of bitter substances. Others can only recognize a few specific bitter substances [2].

Researchers are interested in learning more about the function of bitter taste receptors. Which bitter substances can be recognized by individual bitter taste receptors? Do the actions of the bitter taste receptors play a role in our health?

IS THE TONGUE THE ONLY PLACE WE CAN FIND BITTER TASTE RECEPTORS?

As we have mentioned, our ability to sense a bitter taste is a protection against harmful things. Can other parts of the body, besides the tongue, also sense bitter substances?

We wanted to look for bitter taste receptors throughout the body. But bitter taste receptors are specific proteins that are hard to detect and visualize. So, we decided to look for cells that have bitter taste receptors on them, because cells are easier to see under the microscope. The mouse bitter taste receptor family has a short name, "Tas2r." We are interested in Tas2r143, Tas2r135, and Tas2r126, which are different members of the Tas2r family of mouse bitter taste receptors.

To visualize these bitter taste receptors, we made something called a reporter mouse. A reporter mouse is an animal model used to detect proteins of interest. As shown in Figure 1, we introduced a green fluorescent protein (GFP) into the cells of these mice. The cells will only glow green if they have the bitter taste receptors that we are looking for. As a result, any green fluorescence tells us that the cells have Tas2r143, Tas2r135, or Tas2r126 on their surfaces.

The green fluorescence is easily detected by a special kind of microscope that uses fluorescence to generate an image. As expected, we saw green cells in the taste buds of these mice. We also analyzed other organs in the

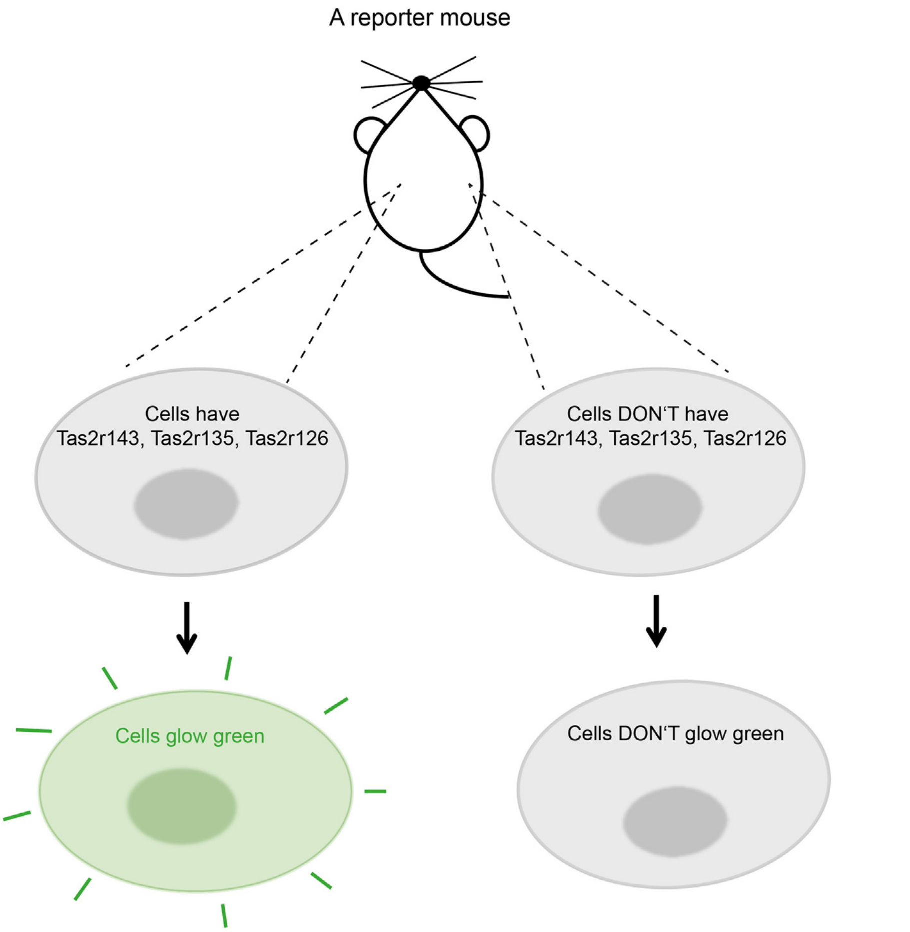

FIGURE 1

FIGURE 1

We made a reporter mouse for Tas2r143, Tas2r135, and Tas2r126. A green fluorescent protein is added into the cells of these mice. When cells in this mouse have the bitter taste receptors listed, they glow green. The other cells, without the bitter taste receptors, do not glow green.

reporter mouse. We detected green cells in the trachea, stomach, and urethra. In Figure 2, we you can see the actual pictures of the green cells from the tongue and trachea, taken using the microscope. There were only a few of these green cells in each location. They were found distributed on the surface layer, called the epithelium, of these organs. The trachea is a part of the airway. The stomach is a part of the gut. And the urethra is a part of the urine outlet. All of these body locations are easily exposed to substances from the environment, which might include some harmful things, like allergens or bacteria. The epithelium of these organs is very important. It works like a barrier to protect the body from harmful substances.

WHAT ARE THESE GREEN FLUORESCENT CELLS?

Different types of cells express special proteins, enabling them to have different biological functions. We wanted to investigate special proteins in these green cells.

To collect green fluorescent cells from an organ, we used a laboratory technique called fluorescence-activated cell sorting. This technique can tell cells apart based on their fluorescent color and actually sort the cells we are interested in (in this case, the green ones) into collection tubes. First, the organ from the mouse must be broken down into single cells by digesting it with special

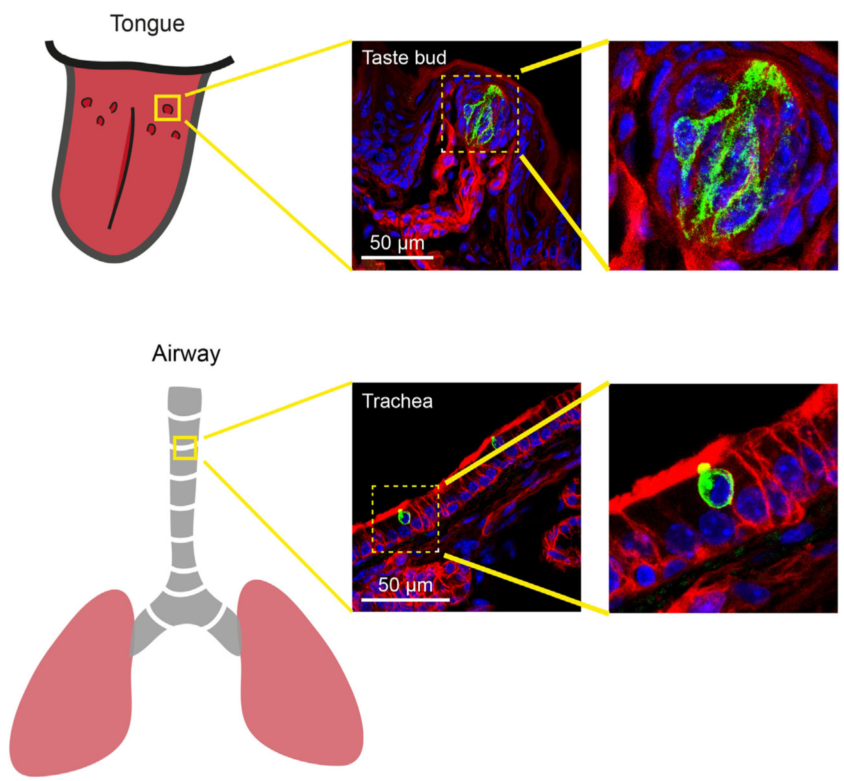

FIGURE 2

FIGURE 2

Cells with bitter taste receptors can be visualized using a microscope that can detect fluorescent cells. By using a special microscope, cells and cellular structures that have been labeled with fluorescent colors can be seen. The green color in the images on the right side of the figure shows cells expressing Tas2r143, Tas2r135, and Tas2r126. All other cells are in red. The cell nucleus is in blue. In the tongue, green cells are found among the other taste cells in the taste buds. In the airway, green cells are found among the other epithelial cells in the surface cellular layer of the trachea. White lines are scale bars: 50 μm.

proteins called enzymes. The cells are then suspended in a liquid and put into the fluorescence-activated cell sorter. This instrument can organize cells to flow in single file, so that it can analyze one cell at a time. In our case, when the instrument detects a green cell, it captures it in a drop of the liquid and deposits it into a collection tube.

We analyzed the green cells collected from the mouse trachea and stomach. As expected, the green cells had bitter taste receptors on them. We mentioned earlier in this article that we call cells with taste receptors "taste cells" when they are on the tongue. When these cells are found in places other than the tongue, we call them chemosensory cells. We use two different names for cells with the same receptors, because we think the cells have different functions. Previous studies showed that pathogens can activate chemosensory cells. Pathogens are bacteria or parasitic worms that can cause disease. The activated chemosensory cells can stimulate a protective response in the body by activating the immune system. For example, when we breathe bacteria in through the nose, chemosensory cells can sense certain molecules from the bacteria. The chemosensory cells send signals to the nervous system, so that the breathing rate is decreased. In this way, we breathe less bacteria in [3].

In our study, we found a high level of a protein called IL-25 in the green cells. IL-25 is a type of protein called a cytokine. Cytokines are released by certain cells and have an effect on other cells around them. Scientists have discovered one function of IL-25 in the intestine. When parasitic worms invade the inside space of the intestine (called the intestinal lumen), chemosensory cells in the intestine release IL-25 to activate cells of the immune system. This action starts something called the "weep and sweep" response. "Weep" means the intestinal lumen produces more fluid. "Sweep" means the intestinal lumen increases muscle contraction. In this way, the intestinal lumen can get rid of the parasites that have invaded. Since our green cells contain IL-25, we suspect that these green cells can release the IL-25 to help protect infected organs [4].

REMAINING QUESTIONS AND THINGS TO DO IN THE FUTURE

As we explained, we made the cells that have Tas2r143, Tas2r135, and Tas2r126 visible by using a GFP. We found green cells in the epithelial layer of the trachea, stomach, and urethra. These fluorescent green cells also have a high level of the cytokine IL-25. These results suggest that these cells could stimulate an immune response that might help to protect the organs from pathogens.

In Figure 3, you can see our ideas about Tas2r143, Tas2r135, and Tas2r126. We speculate that these bitter taste receptors might be able to sense some

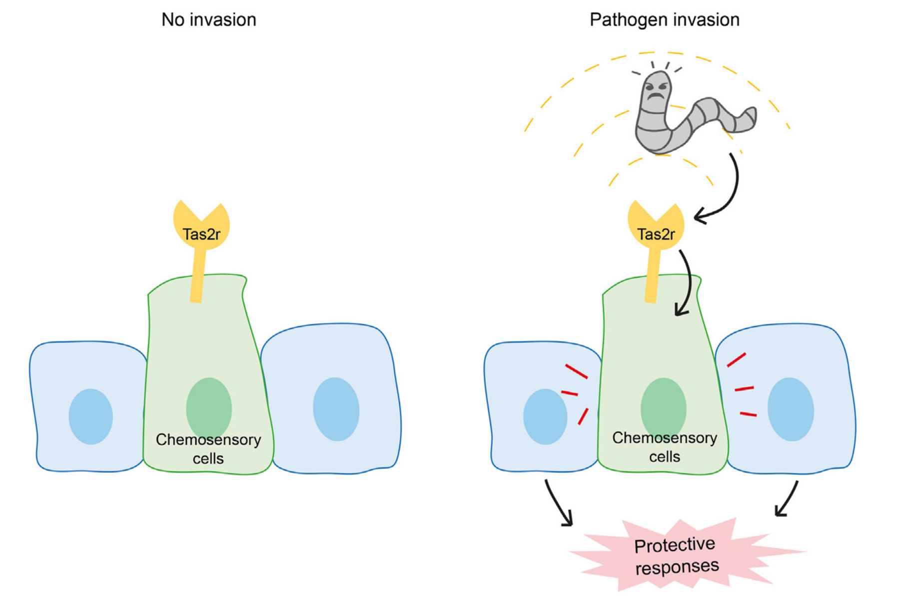

FIGURE 3

An idea about the function of Tas2r143, Tas2r135, and Tas2r126. When certain pathogens invade the body, some molecules from these pathogens could be sensed by the bitter taste receptors. Bitter taste receptors activate chemosensory cells. Chemosensory cells might then send some signals to the neighboring cells, indicated by the red lines in the right-hand figure, such as epithelial cells and cells of the immune system. These neighboring cells can start some responses to protect the body.

molecules from pathogens. Sensing these molecules could activate the chemosensory cells to release signals, such as IL-25, that sound an alarm telling the immune system that a pathogen is invading. But we do not know what kind of pathogens can activate Tas2r143, Tas2r135, and Tas2r126. This question needs to be answered by future studies.

You may remember that we said there are 35 bitter taste receptors in mice. Researchers have looked for other bitter taste receptors outside the tongue. For example, they have found Tas2r131 in the thymus, trachea, and ovary. They have found Tas2r105 in the kidney, small intestine, and testis. The function of bitter taste receptors in these organs is not very clear. There are collections of known natural molecules available. These collections are known as libraries. By using these libraries, researchers have found molecules that can be sensed by bitter taste receptors. In the future, it will be helpful to build libraries that contain pathogen molecules and harmful molecules from the environment. We can use these libraries to find out which molecules can be sensed by bitter taste receptors, and then we might also be able to figure out the way that cells and organisms respond to these molecules.

ORIGINAL SOURCE ARTICLE

Liu, S., Lu, S., Xu, R., Atzberger, A., Günther, S., Wettschureck, N., et al. 2017. Members of bitter taste receptor cluster Tas2r143/Tas2r135/Tas2r126 are expressed in the epithelium of murine airways and other non-gustatory tissues. Front. Physiol. 8:849. doi:10.3389/fphys.2017.00849

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SUBMITTED: 23 February 2018; **ACCEPTED:** 30 May 2018;
PUBLISHED ONLINE: 14 June 2018.

EDITED BY: Bergithe Eikeland Oftedal, University of Bergen, Norway

CITATION: Liu S and Atzberger AK (2018) Can a Bitter Taste Be Detected Outside the Tongue? Front. Young Minds 6:28. doi:10.3389/frym.2018.00028

CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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