The Bitter and Sweet Tastes of Infection: Taste Receptors Regulate Nasal Immune Defenses

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The upper respiratory tract (nose and sinuses) is at the front line of immune defense. You inhale countless bacterial and fungal spores and viruses with every single breath. When upper respiratory defenses fail, this can lead to chronic rhinosinusitis (CRS), a syndrome of unrelenting sinus infection and inflammation affecting >35 million people in the US alone. Chronic bacterial infections and biofilm formation cause difficult-to-treat CRS requiring prolonged courses of antibiotics and anti-inflammatory steroids. Upper respiratory infections can also seed lung infections and cause life-threatening complications. CRS accounts for 20% of adult antibiotic prescriptions, contributing to the crisis of antibiotic resistance, called “arguably the greatest risk…to human health” by the World Economic Forum. Finding alternative therapies for CRS would help reduce antibiotic use.

A new way to treat CRS might be by targeting special cells in the nose called “solitary chemosensory cells” (SCCs). SCCs are named because they are dispersed throughout the nose, with 1 SCC approximately every 100 cells. SCCs serve an important immune sensory function. SCCs use the same bitter taste receptors that your tongue uses to detect bitter foods, but SCCs instead use these receptors to detect chemicals produced by bacteria. SCCs then signal to surrounding nasal cells to release small proteins called defensins that kill bacteria and other pathogens. Drugs that activating SCCs could stimulate defensin release to kill pathogens without antibiotics.

However, we found that sweet taste receptors in these SCCs inhibit the bitter receptors. Sweet taste receptors in SCCs are activated by levels of glucose, the same sugar in your blood, also contained in nasal mucus. We believe that sweet taste receptors keep the bitter receptors in check during healthy times to prevent the nose from completely killing off the normal nasal microbiome of “good” bacteria. During infection, when bacteria multiply and consume the nasal mucus glucose, SCCs can then be activated by bitter bacterial molecules.

Our recent research showed that these SCCs also express sweet taste receptors that are also activated by bacterial products. Using cells isolated from residual surgical tissue taken from CRS patients and grown in the lab, we found that the sweet taste receptors in SCCs are activated by certain D stereoisomer amino acids (D-amino acids). While almost all proteins are built from L-amino acids, bacteria secrete certain D-amino acids to communicate. Some D-amino acids taste sweet by activating the sweet taste receptor. We hypothesized that, if bacteria secrete sweet D-amino acids, this might impair how well they are sensed by nasal SCCs.

We isolated and grew both *Staphylococcus aureus* and *Staphylococcus epidermidis* bacteria from the sinuses of CRS patients and found that they produce at least two sweet D-amino acids, D-Phenylalanine and D-Leucine, which inhibited bitter-receptor activated defensin release from primary human nasal cells by activating SCC sweet taste receptors. When we infected primary human nasal cells with methicillin-resistant *Staphylococcus aureus* (MRSA) in the absence of D-amino acids, bitter compounds stimulated the cells to secrete defensins and kill the bacteria. However, in the presence of D-amino acids, defensin secretion was impaired and ~50% of the human cells died.

It is unclear if these sweet D-amino acids suppress airway defenses to prevent airway cells from killing good commensal bacteria or pathogenic bacteria use this to evade detection. The relationship between *Staphylococcus* and humans is complicated. Both *Staphylococcus aureus* and *Staphylococcus epidermidis* can be commensal bacteria, meaning they can often be found in healthy noses. However, *Staphylococcus aureus* causes infections under the right circumstances, making it an “opportunistic pathogen.”

These sweet D-amino acids may also be involved in bacterial competition. The D-amino acids secreted by *Staphylococcus* bacteria, as well as growth media from cultures of respiratory isolates of *Staphylococcus*, inhibited the growth of *Pseudomonas aeruginosa*, another opportunistic nasal pathogen, suggesting *Staphylococcus* might secrete D-amino acids to prevent *Pseudomonas* from competing with them. *Pseudomonas* grown from patient sinuses did not produce these same D-amino acids.

The immune system has been referred to as our “sixth sense,” because it detects invading microbes similarly to how our senses allow us to perceive our external environment. We now know our immune system can use the same taste receptors used by our tongue, but we still need to understand how to leverage them therapeutically. Our study suggests that sweet-receptor inhibitors, such as the compound lactisole isolated from coffee beans and used in some food products, may be useful to block activation of sweet receptors by bacterial D-amino acids to allow SCC defenses to function. This may help reduce bacterial growth and chronic infections in CRS.

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