Gut enzymes in sweet taste cells may point way to better-tasting non-caloric sweeteners

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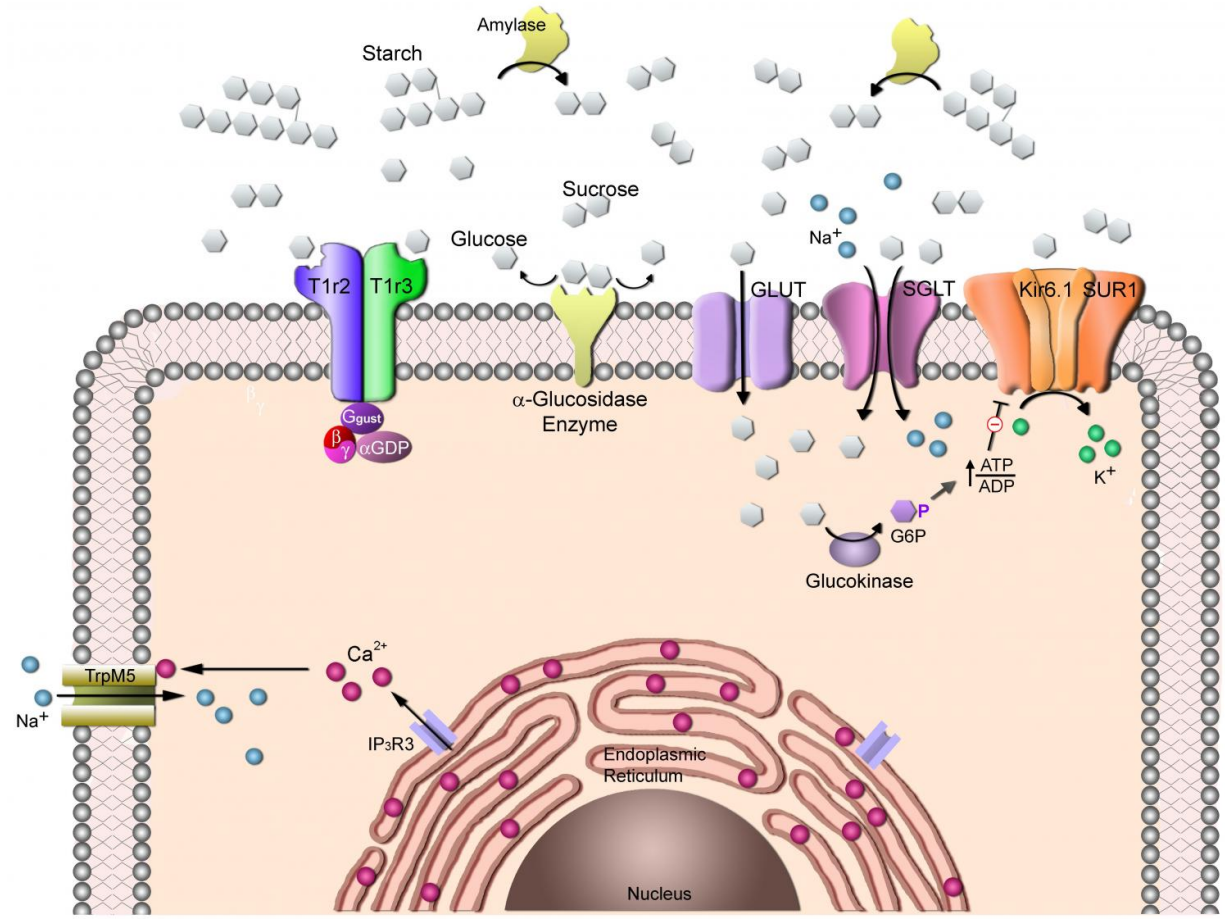


Two independent pathways enable taste cells to sense sweet-tasting compounds. The T1R pathway detects both caloric (eg, glucose, sucrose) and non-caloric (eg, saccharin, sucralose) sweet molecules. The T1R-independent 'secondary' pathway senses simple caloric sugars such as glucose and fructose. Disaccharide enzymes in the sweet taste cells break down complex dietary sugars and starch by-

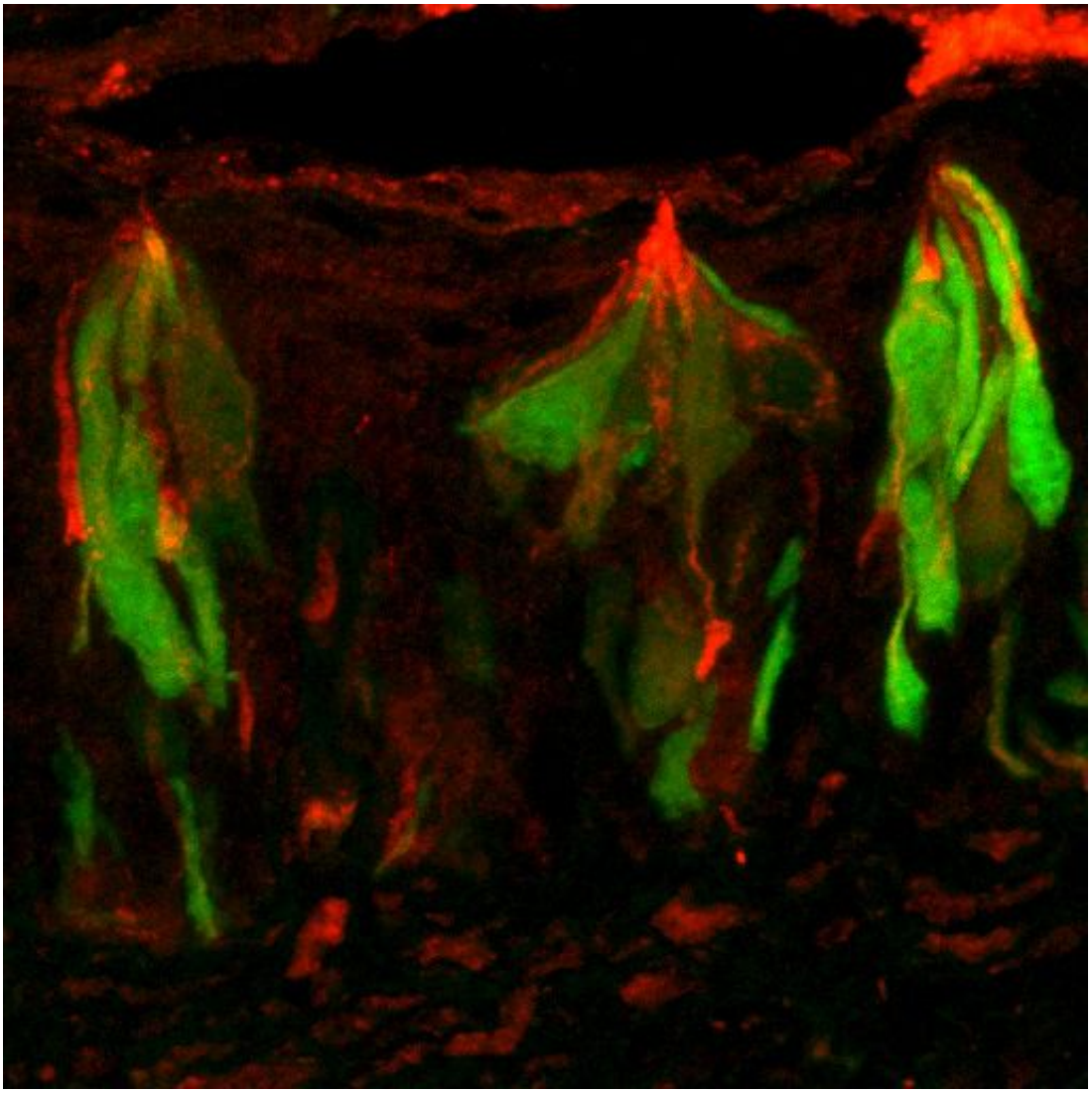
products into simple sugars that can activate both pathways. Credit: Karen Yee, Monell Center

According to new research from the Monell Center and collaborating institutions, the sweet taste cells that respond to sugars and sweeteners on the tongue also contain digestive enzymes capable of converting sucrose (table sugar) into glucose and fructose, simple sugars that can be detected by both known sweet taste pathways. The findings increase understanding of the complex cellular mechanisms underlying sweet taste detection.

"Through these insights we are better able to understand how sweet taste works, why sucrose is so appealing, and even perhaps what would be needed to make a sucrose substitute that tastes good but has no calories," said study senior author Robert F. Margolskee, MD, PhD, a molecular neurobiologist at Monell.

A sweet taste receptor called T1R2+T1R3 is the primary mechanism that enables taste cells to detect many different types of sweet compounds, including sucrose and other caloric sugars as well as non-caloric sweeteners such as saccharin and sucralose. However, mice with inactivated T1R2+T1R3 sweet receptors, called T1R3 knockout mice, still are able to sense glucose, sucrose and other caloric sugars, suggesting the existence of additional sweet receptors.

In 2011, Margolskee's team used knowledge of sugar sensors in the intestine and pancreas to identify a second class of sweet taste sensors on the tongue. These 'secondary' sensors are sensitive to simple sugars like glucose but not to sucrose (glucose + fructose) and other complex food-related sugars. Thus, the researchers still needed to explain how the T1R3 knockout mice are able to sense sucrose.



Taste cells, identified by presence of T1R (green), also contain the disaccaridase enzyme sucrase (red), which cleaves sucrose into the simple sugars glucose and fructose, which can be detected by both sugar-sensing pathways. Sucrase is preferentially localized in the apical tip of the taste cell, where it can act on sugars from ingested foods. Credit: Karen Yee, Monell Center

In the present study, published in the *Proceedings of the National Academy of Sciences*, the taste researchers once again turned to the intestines for an answer. Knowing that gut enzymes break down complex

sugars into simple sugars that can be absorbed into the bloodstream, the research team asked whether these same enzymes could also be breaking down sucrose and other complex sugars on the tongue.

"It makes sense that the tongue and gut would share similar pathways, as both detect ingested chemicals that are important for metabolic energy," said study author Karen Yee, PhD, a cellular physiologist who co-led the research with molecular biologist Sunil K. Sukumaran, PhD. Both scientists are from Monell.

Using a mouse model, the researchers found that the intestinal digestive enzymes sucrase and maltase are also expressed in sweet taste cells on the tongue. The tongue enzymes are in the ideal location to cleave complex sugars from ingested foods into glucose and fructose, which can then activate the secondary sugar sensors.

Noting that the T1R2+T1R3 sweet receptor senses a range of molecules that includes non-caloric sweeteners, the authors speculate that the second sugar sensor pathway serves as a calorie detector for metabolizable sugars. Working together, the two sweet pathways can identify sweet substances with caloric value, providing a potential explanation for why humans and other mammals respond so positively to the taste of sucrose as opposed to non-caloric sweeteners.

"Sucrose is the perfect sweet compound. As a complex sugar, it activates the 'classic' main sweet receptor, but after being broken down by sucrase in the taste cells, the released glucose also activates the second sweet pathway," said Margolskee.

The findings also have implications for the development of a new class of non-caloric sweeteners. Current non-caloric sweeteners, which only activate the T1R2+T1R3 receptor, are limited by their inability to replicate the full sweet taste of sugars. The researchers speculate this

may be because existing non-caloric sweeteners do not target the secondary sugar sensors, which may mediate the unique sweet taste of sugar.

"A lot of effort is being put into developing strategies to limit sugar consumption, which leads to diseases such as diabetes and obesity. Our study potentially enlarges the arsenal to tackle them, especially because many pharmacological agents that target the secondary sugar sensors are already available," said Sukumaran.

Moving forward, the researchers intend to explore if and how the second sugar sensor pathway contributes to sweet taste perception and perhaps regulation of sugar intake in humans.

More information: Taste cell-expressed α-glucosidase enzymes contribute to gustatory responses to disaccharides, *PNAS*, DOI: 10.1073/pnas.1520843113

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