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How we taste sweetness: long-sought structure of human receptor mapped at last

3D structure of the tongue's sweet-sensing protein could guide future food designs.

By Elie Dolgin

The sugar in a lollipop activates a receptor in the tongue. Its 3D structure has now been revealed. Credit: Iparraguirre Recio/Getty

Sugar has long seduced the human palate — and wreaked havoc on public health. Now, researchers have taken a decisive step towards understanding how.

A team at Columbia University in New York City has, for the first time, mapped the molecular structure of the human sweet taste receptor and shown how two of the most widely consumed artificial sweeteners bind to the receptor and activate it. The discovery, reported today in *Cell*[1], offers a detailed look at how our tongues perceive sweetness, and could pave the way for more health-conscious fizzy drinks, chewing gums and other confections.

"This single receptor is responsible for our insatiable, never-ending attraction to sugar," says Columbia neuroscientist Charles Zuker, who led the study. "And now that we have this structure, perhaps we can find ways to modulate its function." For example, compounds that target the receptor could alter how natural sugars are sensed by taste buds on the tongue.

A spoonful of structure

From ripe fruit to saccharine-laden yogurt, foods containing either sugars or their substitutes turn on the sweet taste receptor, triggering a signalling cascade that the brain regards as a sign of energy-rich rewards.

Zuker and his colleagues first identified[2] the receptor in 2001, showing that it is a molecular complex made of two proteins, TAS1R2 and TAS1R3. One latches on to the

sweet molecule, and the other provides structural support.

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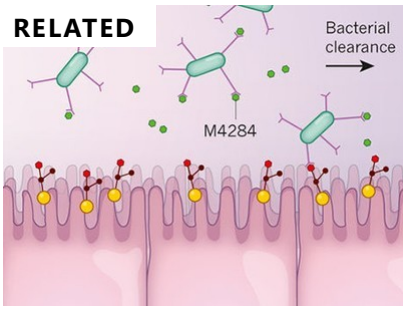

A spoonful of sugar could be the medicine

Yet, despite more than 20 years of study, the sweet receptor's precise architecture remained elusive, even as scientists deciphered the structures of other taste receptors, such as the one for bitterness.

Now Zuker's team has finally cracked the structure. The researchers stabilized the fragile protein complex in its active conformation, a crucial prerequisite step for high-resolution imaging. Using cryo-electron microscopy, they then captured atomic-level snapshots of the receptor bound to two synthetic sweeteners: sucralose (sold commercially as Splenda) and aspartame (found in NutraSweet). Both bind more tightly to the receptor than natural sugar does, helping to fix the receptor in place for the authors' structural analysis.

Sweet spot

The images revealed that the TAS1R2 subunit has a pocket that either sucralose or aspartame can occupy. Each binds to it slightly differently, however, hinting at a flexible mechanism that allows the receptor to recognize a wide range of sweet-tasting compounds. The TAS1R3 subunit, meanwhile — although not involved in binding of the sweet molecules — has a crucial supporting role by helping to assemble and stabilize the receptor complex.

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"This really begins to clarify just how this receptor works," says Kyle Palmer, a pharmacologist who co-founded and leads scientific operations at Opertech Bio, a taste-assessment company in Philadelphia, Pennsylvania.

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The structural insights could now help to explain why some people perceive sweetness more acutely than others — a topic that chemosensory scientist Loïc Briand and his colleagues at the Centre for Taste and Feeding Behaviour in Dijon, France, have explored by cataloguing naturally occurring genetic variants in the receptor[3]. "Now, with the structure, we can locate these mutations and begin to understand how they disrupt receptor function," Briand says.

The methodology could also open the door to resolving the structure of related receptors, such as that for umami, notes Bo Liu, a biochemist at Qilu University of Technology in Jinan, China.

Tricks for treats

The receptor's blueprint also equips food chemists with the tools to design no-calorie sweeteners that are safer and leave less of a cloying aftertaste on the tongue than current substitutes. (Aspartame has been described by the World Health Organization as 'possibly carcinogenic'.)

Moreover, the structure could allow researchers to engineer compounds that amplify the receptor's sensitivity to natural sweet tastes. Doing so might nudge consumers towards reduced-sugar diets without sacrificing taste — a molecular sleight of hand that could help to curb the global rise of obesity and diabetes.

"It's a very important tool that can be used to make better ingredients," says Guy Servant, head of receptor-based discovery at dsm-firmenich, a Swiss–Dutch company that develops sugar-reduction technologies. "The community has been waiting for this for a long time."

Grant DuBois, an industry veteran who is chief scientific officer at Almendra, which manufactures the sweetener stevia and is headquartered in Singapore, agrees that

"access to the structure will enable the rational design" of next-generation sweetening agents. But, he cautions, any laboratory-designed molecules will face an uphill climb amid growing demands from snack and beverage companies for ingredients that are entirely natural.

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References

1. Juen, Z. *et al. Cell* https://doi.org/10.1016/j.cell.2025.04.021 (2025).

2. Nelson, G. *et al. Cell* **106**, 381–390 (2001).

3. Belloir, C., Jeannin, M., Karolkowski, A. & Briand, L. *Nutrients* **17**, 949 (2025).

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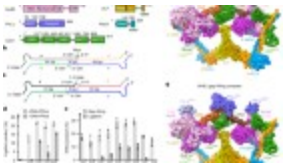

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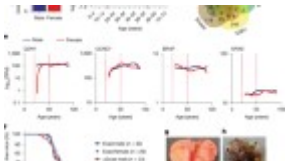

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