

Taste-tester cells discover intense flavour boosters

Now that human taste receptors can be grown in the lab, expect platefuls of tasty breakthroughs

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ARE you trying to cut down on your calorie intake? The next time you add some sugar to sweeten up your coffee, rather than reaching for a second spoonful, sprinkle in a pinch of S6973 instead.

A few molecules of this experimental sweetener could double the intensity of sugar. It is one of many new taste enhancers being synthesised to improve the flavour of foods.

Unlike artificial sweeteners – the aspartame in diet drinks, for example, or sucralose – an enhancer is relatively tasteless on its own. But when paired with a natural or artificial sweetener, it works like the volume knob on a stereo, turning its potency up or down.

Taste enhancers are a new approach for the \$1.5 billion global sweetener industry, which has previously created new products by tinkering with the structure of the sugar molecule. Their development has been made possible by the creation of cellular taste-testers which, unlike their human counterparts, can cheaply screen thousands of candidate molecules to spot those that make sweet foods taste sweeter or block bitter tastes.

The idea is the brainchild of biotech firm Senomyx of San Diego, California. To create its taste

testers, the company adapted a tool that has been used by the pharmaceutical industry for over 20 years – lines of kidney cells with genetically modified DNA. Drug companies typically insert genes into these cells that coat their surfaces with receptors involved in certain diseases, to test how they respond to treatments.

Senomyx inserts genes from the surface of the human tongue instead, which cover the cells with taste receptors. The company has developed cell lines that respond to each of the five tastes: sweet, bitter, salty, sour and savoury (also known as “umami”).

Using these cellular taste-testers, Senomyx’s Mark Zoller can screen 250,000 candidate enhancers every three months. To find sweetness enhancers like S6973, he coats the base of

“Senomyx has developed cell lines that respond to each of the five tastes”

thousands of tiny wells with cells containing the human sweetness receptor. He then douses each compartment with sugar and a candidate molecule.

The sugar activates the sweet receptor in each cell, sending a signal that causes them to glow fluorescent green. Though simple, the cell-receptor models are as sensitive as the human tongue,

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Zoller says. And it is easy to spot if any of the candidate compounds increase the sugar’s potency, he says. “The sweeter the taste, the brighter the glow.”

Once a strong glow has been detected, Senomyx tweaks the structure of the molecule to further increase its potency. If the compound passes a series of safety tests, the US Food and Drug Administration stamps it

glutamate. Nestlé, which funded that research, is already using the molecules to add flavour to stock (bouillon) cubes sold in countries in the Pacific Rim, west Africa and South America.

Other compounds are being developed to make tasty food healthier and healthy foods tastier. The Campbell Soup company has hired Senomyx to create new salty-taste enhancers, which will allow it to reduce the salt content of its soups.

Meanwhile, the health food company Solae, based in St Louis, Missouri, is financing the development of “bitter blockers” to mask the unpleasant aftertaste of soy. Such blockers could also prove useful in getting children to take medicines that have strong, unpleasant tastes.

All of these developments are based on advances in our understanding of how people detect tastes. It was Charles Zuker of the University of California,



Very tasty – now imagine a low-salt pizza with all of that flavour

San Diego, who in 1998 first plucked a gene which coded for a taste receptor from a rat's tongue. When he engineered rats without this gene, he found they were unable to taste sweet things, suggesting that each receptor on the tongue is specialised for one kind of taste. Zuker's laboratory went on to isolate receptors associated with the other tastes.

But it wasn't until the Human Genome Project was completed in 2003 that the research could be applied to the human sense of taste. Zuker's team was then able to check for genetic sequences in humans that were similar to those that code for the rat taste receptors. As a result, they discovered one receptor apiece for sweet, sour, salty and savoury, and almost 30 for bitterness.

Now other researchers are using receptor-cell lines similar

to those created by Senomyx, in combination with well-understood compounds, to try to discover how the receptors work; to figure out what molecules activate them and how.

Marianna Max of Mount Sinai Medical Center in New York has been using cell lines to study how humans detect sweet tastes. She has tackled one of the biggest mysteries in taste perception: how a single sweetness receptor can recognise such a range of sweet compounds. The sweet receptor had been thought to act like a Venus fly trap, catching all sweet molecules with a simple clamping action, but Max found that it is actually lined with multiple sensors for different types of sweet molecule.

In contrast, no single receptor can detect all of the bitter molecules out there. Instead, each receptor works like an antenna tuned to recognise a certain group of molecules. Wolfgang Meyerhof

BEHIND THE TASTE SENSATIONS

It is tempting to think of cellular taste-testers as miniature tongues. But one common criticism of the technology is that it is too simplistic, and that information is lost when the complexity of the tongue is reduced to single molecules in single cells.

Biotech firm Senomyx has addressed this criticism: once one of its taster cells has identified a taste-enhancing molecule (and it is confirmed as safe), it is mixed into foods that are then tasted by human testers to ensure the flavour is genuinely enhanced.

But researchers are still divided as to how humans process tastes detected by receptors on the tongue into the complex perceptions of flavour that make, say, eating a hamburger so different from eating sirloin steak.

One theory, called the "labelled-line" model, says that each taste cell on our tongue works as a single hard-wired line to the brain. Some cells – those covered with bitter or sour receptors – tell the brain that a taste is bad. Others send a positive response indicating the presence of sugary or

savoury molecules. In this model, each receptor detects the presence of certain kinds of molecules, but the cell it is attached to determines the value of those molecules. For example, a mouse whose sweet taste cells are engineered to be covered with bitter receptors, will suddenly find bitter tastes pleasant. "In theory, you could take a light receptor from your eye and put it into a mouse's taste cell, shine a light on its tongue, and the mouse would experience a sweet taste," says Zuker.

Proponents of the competing "across-fibre" theory, such as Steven Roper of the University of Miami in Florida, argue that different cells on the tongue talk to each other before passing information to the brain.

In addition to cells dedicated to each type of taste, Roper has found evidence for a second kind of cell on the tongue which itself lacks receptors but responds when neighbouring taste cells are activated. He says these "presynaptic cells" may collect information from surrounding taste cells and process it in situ before sending it to the brain.

at the German Institute of Human Nutrition in Potsdam-Rehbruecke has been working on the 30 known bitter receptors. His research provides clues as to how the anatomy of the tongue came to be.

Sweetness is usually a sign that something is safe to eat, while bitterness is a warning that items, such as wild almonds, contain toxic chemicals. "There are many more things that can hurt us than help us," Meyerhof says. As a result, our tongue requires a larger array of detectors for toxins.

What's more, each of us has slightly different bitter receptors with varying levels of sensitivity. Some receptors carry mutations that stop them working altogether, but having many receptors that can detect a wide range of overlapping compounds provides insurance if one fails. "Nature has provided us with backup copies," says Meyerhof.

Danielle Reed and colleagues at the Monell Chemical Senses

Center in Philadelphia, Pennsylvania, have engineered cell lines with a new type of receptor. She had noticed that individual mice have different preferences for calcium. Some seemed different to its presence in water, while it would entice others to drink huge quantities. The receptor involved responds to calcium and magnesium – molecules not usually associated with taste.

"I can taste calcium chloride, but I don't have a word for it," says Reed. She believes that this response to calcium may be a sixth taste. The team hope that by understanding how calcium is detected, they can encourage people to consume more of it, by tweaking its taste.

So while the cellular taste-testers are allowing Senomyx to search for new molecules to tickle the taste buds we already know about, they may ultimately help us to discover new types of taste altogether. ●