

Magnifying Taste

Compounds that enhance the sweet and salty flavors of foods could combat obesity and heart disease

By Melinda Wenner

Humans are hardwired to love the sweet, savory and salty foods that provide the energy, protein and electrolytes we need. In an age of mass-produced products laden with sugar and salt, however, our taste proclivities can readily bring on obesity, heart disease and type 2 diabetes—all among society's biggest health problems.

But what if a handful of tiny compounds could fool our brains into eating differently? That is the idea behind the new science of flavor modulation. Scientists who have unlocked the long-standing mystery of taste biology are developing inexpensive yet potent compounds that make foods taste sweeter, saltier and more savory (heartier) than they really are. By adding tiny amounts of these modulators to traditional foods, manufacturers could reduce the amount of sugar, salt and monosodium glutamate (MSG) needed to satisfy, resulting in healthier products.

San Diego-based Senomyx is at the forefront of this new technology, and large companies are responding. Nestlé started incorporating Senomyx's savory flavor modulators in its bouillon products last year. Coca-Cola and Cadbury aim to begin using Senomyx's compounds early in 2009.

Senomyx is also designing bitterness blockers to make less palatable foods taste better, which could broaden the world's sources of nutrients. For example, companies could use soy protein more widely, potentially feeding more people, if they could mask its bitter aftertaste. Such blockers could also make medicines taste better,

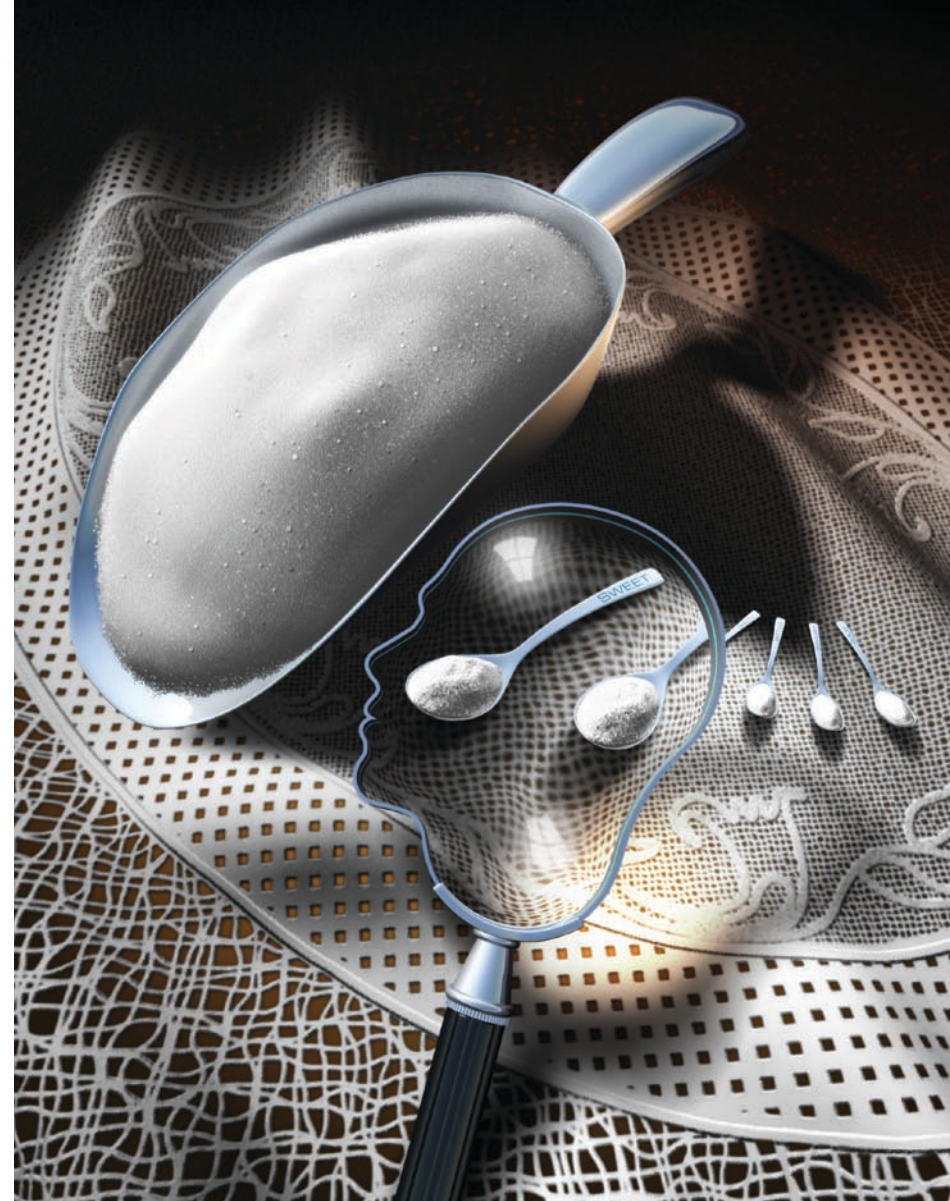
which would encourage people to take them.

By tricking our taste buds, Senomyx could save food makers a heaping teaspoon of money, allowing them to replace volumes of sugar, salt and other ingredients with minute quantities of cheap compounds. More important, taste modulators could revolutionize our health, making what tastes good to us actually *be* good for us.

The Taste Bud, Newly Understood

The quest for flavor modulators began in 1996, when Charles Zuker, a biology professor at the University of California, San Diego, realized that the prevailing literature on taste biology was potentially wrong. Humans sense five taste qualities: sweet, salty, bitter, sour and savory (also called umami, which roughly translates from Japanese into "delicious flavor"). Most children had been taught that the tongue is partitioned into regions that each detect one type of flavor. But work at the time showed that taste buds across the tongue and mouth contain small groups of cells that enable each bud to detect every flavor. Zuker agreed but could not swallow the corollary that every taste cell in a taste bud can distinguish among the five flavors.

To Zuker, it did not make evolutionary sense for one cell to be responsible for detecting the presence of something good, like sugar, and something bad, like poison (bitter). Many sensory cells can differentiate among opposing stimuli, but each of our sensory domains also includes cells whose primary job is to respond to one type of stimulus, such as skin cells that



only respond to a certain temperature range. Zuker could not come to grips with the notion that a single taste cell "could evoke diametrically opposed behaviors—like attraction and aversion, or life and death," he recalls. Instead, he thought, a taste bud would be home to sweet cells, salt cells, bitter cells, and so on.

If taste cells were this specific, they would also be easier to tinker with—which could have big implications for the food industry. Zuker reasoned that taste cells would have specific sensors, or receptors, on their outer membrane. A salt receptor would lock onto a salt molecule but not a sweet or bitter molecule. But he had no evidence for his theory.

As a first step, Zuker had to isolate the actual taste receptors, which no one had ever done. He and his U.C.S.D. colleagues removed taste cells from the tongues of laboratory mice and compared the genes that were expressed (that is, gave rise to proteins) in each cell. Ultimately, the researchers found genes that coded for two pro-

teins that had not been discovered before. Zuker could tell by their structures that the two proteins sat on the cell surface and probably functioned as receptors, and he named them T1R1 and T1R2.

But when Zuker tried to understand what the two proteins did, he hit a wall. Neither functioned by itself as a complete taste receptor. Zuker remembered that mice vary in their preferences for sweet foods—some barely like them at all. Previous studies had shown that such apathetic mice have a genetic defect. Zuker studied these mice and, sure enough, came across another new receptor candidate. And the gene for this protein, T1R3, was indeed the gene that differed among nonsweet-loving mice and normal mice. When he introduced a functional copy of the related gene into the taste cells of the defective mice, it triggered a love for sugar.

With a few more experiments, Zuker and his colleagues revealed the structure and function of the sweet and savory taste receptors. Each kind of receptor contained two parts. The sweet one consisted of T1R2 and T1R3; the savory comprised T1R1 and T1R3. Soon afterward, Zuker identified the bitter receptor units, too—all 25 of them—as well as the receptor responsible for detecting sour. In every case, each taste cell contained the receptors for just one taste.

Zuker realized that, beyond providing insights into basic biology, his discoveries would allow scientists to design compounds that interacted only with, say, the sweet receptor or the salt receptor, affecting taste perception in specific ways. "The basic tools to begin to experimentally modulate the way the taste system operates became feasible," he says. "We thought, here perhaps we have an opportunity to help make a difference." In 1998 Zuker and some associates started a company that became Senomyx.

Flavors by the Thousands

In the past, food companies identified new flavor compounds through trial-and-error experiments, with humans tasting the results one at a time. The process was tedious; companies could test at most a few thousand compounds a year.

But using Zuker's taste-receptor structure made it possible to rapidly identify new flavor modulators. Taking a lead from the plastic arrays with many tiny receptacles that pharmaceutical companies use to screen for new drugs, Zuker devised arrays of thousands of artificial "taste cells," each receptacle containing one kind of taste receptor. He then introduced thousands of potential flavor-modulating compounds

THE ELUSIVE UMAMI

Although it was discovered a century ago, umami still struggles for acceptance as the fifth basic taste the tongue recognizes. The term is Japanese for "savory" or "deliciousness." It is typically applied to meats, cheeses, broth and other protein-heavy foods to describe their hearty nature. The sensation may be more subtle than salty or sweet, but researchers maintain it is unique and not a combination of any of the other basic tastes.

KEY CONCEPTS

Researchers have discovered tiny compounds that make foods taste sweeter, saltier and more savory than they really are, which could reduce the sugar, salt and monosodium glutamate typically added.

Several of these taste enhancers are being tested in commercial foods.

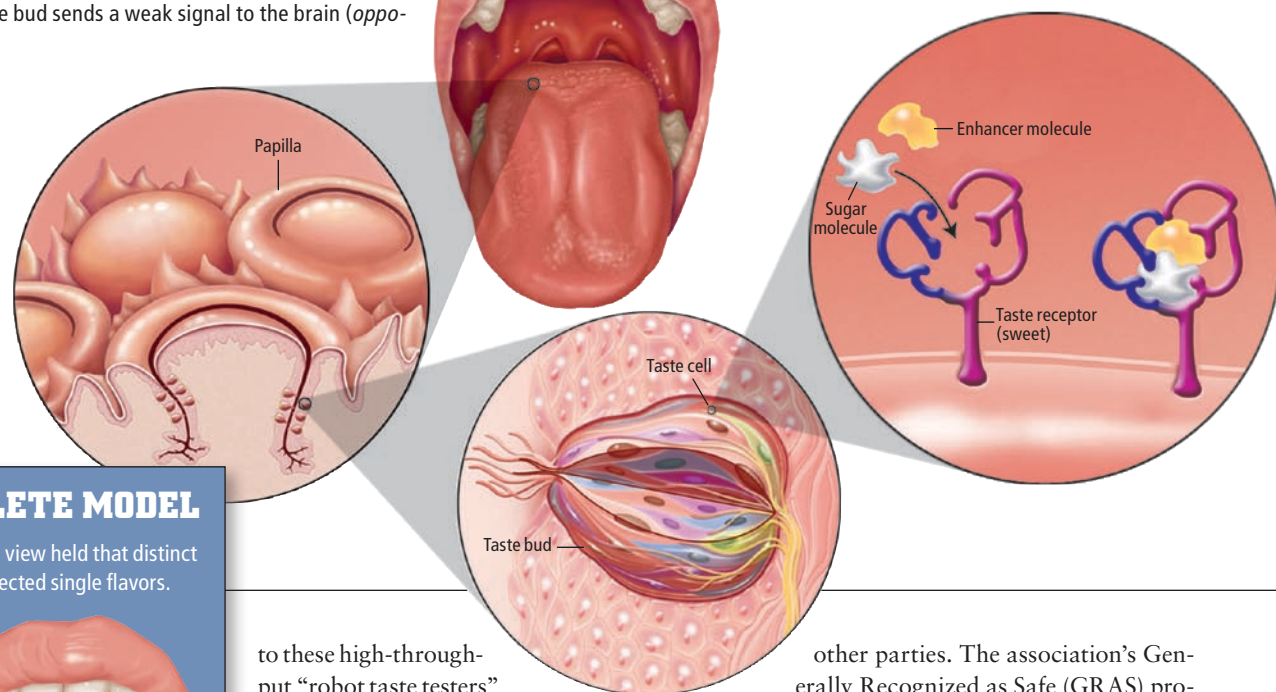
Whether people will consume fewer calories if their foods become tastier remains to be seen; people might eat lots of sweet foods for reasons that have nothing to do with taste.

—The Editors

ENHANCING TASTE

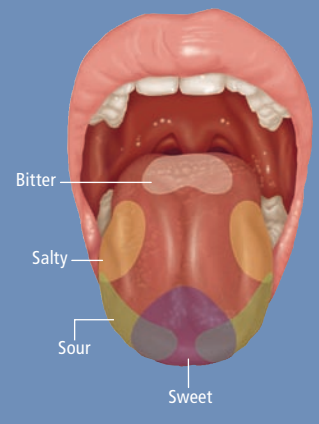
Contrary to old models (*bottom left*), the tongue does not have regions that detect one type of flavor. Instead taste buds embedded in papilla (*bumps*) across the tongue sense all flavors. Each bud contains elongated taste cells that respond to sweet, salty, sour, bitter or umami (savory). Receptors on the surface of a sweet cell, for example, bind to sugar molecules. If only a few sugars are bound, the bud sends a weak signal to the brain (*oppo-*

site page, top); if more sugars are present, more binding will cause a stronger signal of "sweet" (*middle*). Taste enhancer molecules, which do not prompt a signal on their own, strengthen the likelihood that sugar molecules and receptors will bind, intensifying the sweet sensation even when only a few sugar molecules are present (*bottom*). —M.W.



OBSELETE MODEL

Wrong: Old view held that distinct regions detected single flavors.



to these high-throughput "robot taste testers" to see which ones interacted with which cells.

Today Senomyx has a library of 500,000 synthetic and natural compounds. "We can look at hundreds and thousands of different compounds and ingredients and can find a needle in the haystack," says Mark Zoller, the company's chief scientific officer. After identifying a compound that interacts uniquely with a taste cell, employees use the screening process to further improve its physical properties. Some compounds might need to dissolve in liquids or to retain their effects when heated. Many must remain stable in products for months on end. Senomyx develops assays to test for such characteristics, and "we can actually put the new sample in a cereal flake and see how it behaves and how it tastes," says vice president Gwen Rosenberg.

The company patents promising compounds and begins safety certification by sending information to the Flavor and Extract Manufacturers Association in Washington, D.C., an organization of flavor manufacturers, ingredient suppliers and

other parties. The association's Generally Recognized as Safe (GRAS) program was established by the Food and Drug Administration in 1960 to oversee safety assessments of flavor compounds consumed in small amounts. Because the quantities are so minute, the compounds do not have to go through the more rigorous FDA safety process required for food "additives." When Senomyx submits information about a new compound, a panel of independent scientists decides, based on its chemistry, whether it will be safe to consume.

Although the process can take two years, some critics question its validity. Michael Jacobson, executive director of the Center for Science in the Public Interest in Washington, D.C., says the GRAS process "certainly is a case of the fox guarding the chicken coop." He does acknowledge that "flavorings typically have been innocuous chemicals used in small amounts" and that there is no history of safety problems.

Sweet Enhancement

Better sweeteners are at the forefront of Senomyx's work. The low-calorie sugar substitutes available today, such as aspartame, sucralose and saccharin, often have bitter aftertastes at

Few sugar molecules present; weak taste



Many sugars present; strong taste



Few sugars plus enhancers; strong taste



MORE TO EXPLORE

Taste Perception: Cracking the Code. Jane Bradbury in *PLoS Biology*, Vol. 2, No. 3, pages 0295–0297; March 16, 2004.

The Search for Sweet: Building a Better Sugar Substitute. Burkhard Bilger in *New Yorker*, page 40; May 22, 2006.

The Receptors and Cells for Mammalian Taste. Jayaram Chandrasekar, Mark A. Hoon, Nicholas J. P. Ryba and Charles S. Zuker in *Nature*, Vol. 444, pages 288–294; November 16, 2006.

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the high concentrations at which they are needed. "From a sensory point of view, they're not ideal," says Gary Beauchamp, director of the Monell Chemical Senses Center in Philadelphia. Diet sodas, for example, never taste quite as good as the real thing because the bitter aftertaste alters the brain's perception. If food companies could use less of the substitute, the bitter taste pathway would not be activated. (Coke Zero, which reportedly tastes better than Diet Coke, uses a mixture of sweeteners with less combined volume; the lower amount avoids activating the bitter receptor.)

With the ability to test so many compounds, Zuker realized Senomyx could identify molecules that did not have any flavor on their own but interacted with sweeteners and sweet receptors to enhance the perception. "We thought, my God, if we have the receptors, maybe we can find clever ways to make a little bit of sugar taste as if you have a lot," he says.

After screening 200,000 compounds, Senomyx researchers identified one that makes sucralose taste four times sweeter. The modulator recently completed the taste association's approval process and could be added to products in early 2009. The potential market is huge: an estimated 5,000 retail products currently contain sucralose. Senomyx has also found a sugar enhancer that makes sucrose, or table sugar, taste more than twice as sweet. In this way, Senomyx could cut the calories in foods yet ensure that they taste the same. And diet foods could taste even better than they do now.

Similarly, Senomyx's first savory enhancer is already in some Nestlé products. It makes foods taste heartier—a trait common to protein-rich foods such as meats and cheeses as well as snacks such as flavored potato chips—without lots of the MSG usually added to achieve this effect.

Bitter and Salty, Too

Senomyx is also developing bitter blockers that could broaden the use of soy proteins, as well as rid cocoa of its bitter aftertaste, lessening the sugar that manufacturers add to cocoa-based products. Such blockers could also aid drug companies that are trying to develop "pharmaceutical crops," such as rice and soybeans that contain oral vaccines for hepatitis B and other diseases. These crops might be grown in developing countries where access to vaccination is limited, but if the medicinal component makes them taste bad, local people will not eat them.

A blocker would make the food palatable; of course, it would have to be affordable.

Another company, Redpoint Bio in Ewing, N.J., is developing bitter blockers using a slightly different approach. Instead of hunting for compounds that affect receptors on a taste cell's surface, the firm is seeking compounds that interact with signal pathways inside such cells. One target is a common ion channel called TRPM5; Redpoint is looking for compounds that either block or activate it. The company is collaborating with Coca-Cola and with Givaudan, a Swiss flavor and fragrance company, and anticipates that foods containing its compounds will be on grocery shelves within two years.

Salt is another grail because it is linked to cardiovascular disease. This year Senomyx identified the primary receptor responsible for salt perception: a pore or channel that spans the membrane of a taste cell, allowing sodium and hydrogen ions inside. Compounds that interact with the channel could enhance the potency of salt's effect. Reducing salt intake by even a small amount "could have a significant impact on both health and quality of life," says Zuker, who has stayed at U.C.S.D. while being a scientific adviser to Senomyx. If it is so hard to change people's eating habits, he reasons, then it makes sense to change their perceptions instead. In a few years, consumers might find themselves eating foods with a fraction of the calories and salt they once had, without noticing the difference.

Whether people will actually consume fewer calories if their foods become tastier and healthier remains to be seen, however. "That's a tough question, a very controversial one," Monell's Beauchamp says. People might consume lots of sweet food for reasons that have nothing to do with taste. Monell, which has received some funding from Senomyx, is studying how food and flavor preferences differ among people; how flavor affects digestion, metabolism and appetite; and how the body controls eating behavior. Preliminary findings, for example, suggest that our flavor preferences are essentially solidified by the age of three months and that a mother's meals during pregnancy and breast-feeding influence the foods her offspring end up enjoying. But the link between flavor preferences and satiety is not yet clear, Senomyx's Rosenberg acknowledges: "Satiety is a complex issue, and more work needs to be done."

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