The Tastemakers: Semonyx Targets Taste Receptors

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Our society is awash with cheap food, high in calories and salt. Currently over two thirds of Americans are overweight, with a third considered obese. Consumer advocacy groups are lobbying food manufacturers to market healthier foods and drinks, even pushing taxes on sugary sodas.

Unfortunately, stripping the sugar, fat, and salt also strips away taste. But genomics advances could indirectly save our cookies, as molecular biology meets taste perception. Companies like San Diego-based Semonyx (http://www.senomyx.com) are using drug discovery techniques to engineer a new generation of taste enhancers that can fool our tastebuds. Senomyx targets G protein-coupled receptors for sweet, bitter, and savory tastes and ion channels for saltiness. In addition, the company is developing bitter blockers and menthol cooling agents.

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"I think there is great interest in big food and fragrance companies and entrepreneurial companies like Senomyx and Redpoint to try to find technological ways to make food healthier." said Gary Beauchamp, Ph.D., director of the Monell Chemical Senses Center. "The trouble is that if you look at the history of public health organizations telling you to eat a healthier diet, the results are not very encouraging."

Good Taste Is a Matter of Perception

Humans can taste five different tastes: sweet, sour, bitter, salty, and umami (savory). It has long been known that taste is linked to sense of smell. Research groups continue to explore the function of distinct taste receptors on the tongue and on the lining of the gut. The human sweet receptor is comprised of two proteins, T1R2 and T1R3, expressed on the surface of particular taste receptor cells. Savory taste receptors consist of T1R1 and T1R3 proteins. The selectivity of these heterodimeric receptors for sweet or savory is determined by the combination of receptor subunits. The T1R3 protein is used by both the sweet and savory taste receptors.

There are 25 receptors for bitter taste, 22 of which have known function. This plethora of bitter receptors is believed to be due to nearly all naturally occurring toxins tasting bitter. Some people are more sensitive to bitter taste because of polymorphisms in their receptor genes. There may be polymorphisms in the regulatory system for sweet perception as well. People can sense fat, but it is not yet understood how. The salt receptor is still unknown but is hypothesized to be through ion channels.

Zuker Is Sugar in German

"Rapid progress over the past five plus years has been enabled by the sequencing of the Human Genome." said Grant Dubois, Ph.D., research fellow at The Coca-Cola Company, one of the largest users of sweeteners in the world. "[To find the sequence of the gene of the human sweet receptor] people were staying up round the clock watching what was published on the NIH website," Dubois said.

The first to do this, according to Dubois, was the collaborative group of Charles Zuker, professor of Biological Sciences and Neurobiology at the University of California, San Diego (now at Columbia), and Nicholas Ryba, D.Phil., at the National Institute of Dental and Craniofacial Research (NIDCR). Their groups were the most advanced in the rodent model system. In 1999, Zuker's and Ryba's groups published work on the sweet receptor, characterizing three members of the T1R family of G protein-coupled receptors (Hoon et al., 1999). That same year, Zuker, Nobel Laureate Roger Tsien, also from UCSD, and Lubert Stryer from Stanford Medical School, founded Senomyx. Zuker's and Ryba's groups further published research on the T2R family of bitter taste receptors on the tongue and palate in 2000, findings on the shared circuitry of the sweet and umani receptor in 2003, and research on the sour receptor in 2006 (Chandrashekar et al., 2006).

The Search for Sweet at Coke

In the mid 90s at The Coca-Cola Company, Dubois was exploring low-calorie sweetness enhancement. "I knew that it didn't make sense to look for new sweeteners," Dubois recalled. "I recognized that we were never going to be able to come up with a noncaloric sweetener that tasted just like sugar." Dubois envisioned a simple small-molecule compound that would bind to the sweet receptor without activating it, causing a lower level of sugar to activate it instead.

"You've got this receptor that is shaped like a Venus fly trap," said Dubois. "When it closes on a sugar molecule, then the receptor is in its active form." With an enhancer that bound on the receptor and didn't cause it to close, but allowed it to stay closed longer after sugar was bound, his company could make a soda with half the sugar that would taste the same as a full-calorie drink. "It was a simple idea," said Dubois. "But it probably would have taken us another thousand years at the rate we were working on it, as the only way we had to test it would be by human taste."

Senomyx had the receptor actually cloned into a heterologous cell system. "With one analyst they could screen in the neighborhood of ten thousand compounds per day," Dubois recalled. The Coca-Cola Company initiated a collaboration with Senomyx in 2002, leading to

proof of concept with two sweetness enhancers cleared for use in the U.S. Dubois reports that the enhancers work as initially envisioned.

Swish and Spit Methodology

In a room at Senomyx, taste panelists selected for the sensitivity of their palates drink liquid and spit it into cups. They are evaluating candidate compounds that surface through Senomyx's high throughput screening program. "They get better at it over time," says Don Karanewsky, Ph.D., senior vice president, Discovery.

The company's corporate compound library contains more than 400,000 synthetic molecules and about 200,000 fractionated natural product extracts. According to Karanewsky, compounds are selected for physical properties considered "food friendly." The compounds are optimized for potency in Semonyx's proprietary cell-based receptor assays as well as for heat tolerance, stability, safety, and solubility.

Semonyx's sucralose enhancer S2383, as well as its sucrose enhancer S6973, received the Flavor and Extract Manufacturers Association (FEMA) Generally Recognized As Safe (GRAS) status. According to Karanewsky, different sweeteners require different enhancers.

The company has so far identified blockers for 18 bitter receptors. "We have found ligands or molecules that have acted on 22 out of 25 receptors," said Karanewsky. The company is also looking for cool flavor enhancers.

In addition to the Coca-Cola collaboration, Semonyx has a licensing agreement with Firmenich for its sucrose enhancer S6973 and other enhancers of sucrose, fructose, and various forms of Rebaudioside (stevia, a natural sweetener), which could net more than $34.5 million if all milestones are met. The company also is collaborating with Ajinomoto Co., Inc.; Cadbury plc; Campbell Soup Company; and Solae. Nestlé now uses a Senomyx savory flavor ingredient.

Senomyx flavor and food producer customers also have in-house programs. The company's products compete with existing food chemistry methods. The 121 employee company went public in June 2004. Semonyx is capitalized at $33 million as of September 30, 2009, but projects losses over the next two years.

The Discriminating Rodents of Redpoint Bio

Ewing, New Jersey, based Redpoint Bio (http://www.redpointbio.com) focuses on taste biology to develop drugs for diabetes that control metabolism as well as natural taste enhancers to reduce the calorie content of sweetened foods. The now 12 person company (restructured this spring) originally focused on using molecular cloning and screening techniques based on work done in the lab of company founder Robert Margolskee, M.D., Ph.D., now at Monell Chemical Senses Center. The public company currently has $7.5 million in cash.

As industry focus has shifted to finding natural ingredients, Redpoint has developed some new variations on classical pharmacology to find new compounds. "We've gone back to behavioral models of taste," said Raymond Salemme, Ph.D., Redpoint Bio CEO. But natural products are often impure and can produce off-target effects in cell-based assays that are often difficult to sort out. To complement its cell-based assays, Redpoint employs trained rodents. "It is classical Skinner box stuff," said Salemme. "You can train an animal to make a discrimination. If they make the right discrimination, they press a lever and they get a food pellet. We have computerized everything and put a sample plate under the bottom of the animal's cage, providing fairly high sample throughput. The animal sticks his tongue in a well and interrupts a laser beam. We can see how many times the animal actually licks the sample to see how much he likes it. "

According to Salemme, researchers have observed that the symptoms of diabetes frequently cease in morbidly obese people who undergo radical bariatric surgery. This is consistent with the proposed role of taste or related chemosensory signaling circuits in the gut that can provide feedback signals that control hunger and metabolism. Redpoint Bio is working on developing compounds that work on gut signaling as novel therapies for diabetes.

Redpoint Bio uses cheminformatic approaches for navigating chemical space to find new natural products with desirable taste properties. "One thing that people are interested in is finding natural high-potency sweeteners that come from a fermentation source that could be cheaper to produce than farming plants like stevia," said Salemme. However, Redpoint Bio has no current funded collaborations. "It has been a rough environment for biotech," says Salemme.

Some consumer advocates question the regulation of these new flavor ingredients. As they appear in minute quantities, they are not identified on product labeling. Potentially more controversial is the question if the tongue and brain registers something as sweet that really isn't, does the metabolism concur?

"To play with the taste perception may not be harmful" said Bedrich Mosinger, M.D., Ph.D., senior research associate, Monell Chemical Senses Center. "However, we find taste receptors on endocrine cells in the body. We currently study in detail their physiological role, but we already know that they participate in regulation of release of several hormones. Therefore, agents that affect taste may also affect hormonal balance." Who could imagine that feeding our sweet tooth could be so complicated?

"We are responding to our clients' desires and they are responding to consumers desires." said Jeannine Delwiche, Ph.D. senior scientist at flavor giant Firmenich. "The dream compound would be something that would be sweet, cheap, natural, and low calorie without side effects, and we'd like it to have the same functional properties as sucrose."

REFERENCES

Chandrashekar, J., Hoon, M.A., Ryba, N.J., and Zuker, C.S. (2006). The receptors and cells for mammalian taste. Nature *444*, 288–294.

Hoon, M.A., Adler, E., Lindemeier, J., Battey, J.F., Ryba, N.J., and Zuker, C.S. (1999). Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. Cell *96*, 541–551.

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