UCSD and NIH researchers isolate candidates for genetic basis of human taste

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UCSD AND NIH RESEARCHERS ISOLATE CANDIDATES FOR GENETIC BASIS OF HUMAN TASTE

A collaborative effort between Howard Hughes Medical Institute researchers at the University of California, San Diego and scientists at the National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH), have identified the genes likely responsible for the mammalian sense of taste.

In the Feb. 19 issue of the scientific journal Cell, the researchers describe genes that encode two novel proteins expressed in cells specifically geared to the sense of taste. The proteins, members of a new group of "G protein" receptors, were singled out as a result of their unique expression in taste buds of the tongue and palate epithelium.

The isolation of the candidate taste receptor genes provides the groundwork necessary for manipulating the perception of taste and devising methods to stimulate or block taste cell function. The identification also sets the stage for a comprehensive physiological investigation of how the sense of taste is "wired" from the mouth to the brain.

"The identity of the receptor molecules for the different sensory modalities, like vision, olfaction and taste, represents the Holy Grail of the sensory field," said UCSD Professor Charles Zuker, principal co-author of the report. "These receptor molecules provide the unique specificity and selectivity of each sensory system. The color receptors in our retinas allow us to see in color and the olfactory receptors in our nose endow us with great olfactory discrimination. In the case of taste, they are what make sweet cells respond to sweet substances, bitter cells to bitter compounds, and so on."

"These two molecules have the hallmarks we expect of taste receptors," said co- investigator Nicholas Ryba of NIDCR. "They may be the key to unlocking our understanding of how we detect taste, which is unclear at the moment. We must now demonstrate that functionally they can do the job."

By using biochemical and biological assays to identify high potency agonists and antagonists of taste receptor function, scientists could one day be able to rationally manipulate taste receptors, thereby conceivably "eliminating" bitter and sour tastes from important products, such as children's medicine.

"This paper is an exciting and important contribution to our understanding of the neurobiology of taste," said Dr. Lubert Stryer, Professor of Neurobiology at Stanford University and author of the most widely used college biochemistry textbook. "Dr. Zuker's and Ryba's group have isolated the genes for two transmembrane proteins that may well be the first taste receptors. They are specifically localized in a subset of taste neurons in the tongue, and nowhere else, and are positioned in just the right place in these cells. These candidate taste receptors

resemble the receptors that mediate sensory processes such as vision and olfaction. This work has opened new vistas in taste research."

The sense of taste is one of the most powerful sensory systems in the animal kingdom. Taste perception gives mammals the ability for basic food appraisal and valuable discrimination power. Sweet receptors allow us to recognize high caloric food, while bitter receptors can stimulate an aversion to noxious substances.

The mechanism of taste in mammals begins with the taste buds on the tongue. Sweet receptors are mostly found on the tip of the tongue; sour receptors on the sides; salty on the tip and frontal sides; and bitter on the back of the tongue (Taste buds respond to a fifth taste, umami, which is a reaction to the common food additive monosodium glutamate).

"We began a systematic search for the molecular basis of taste several years ago and it is very gratifying to find receptors that seem to be involved in this process," said Dr. Mark Hoon of the NIDCR, first author of this study.

Each taste bud contains roughly 50 to 150 taste receptor cells that act like tiny taste interpretation machines. Proteins on the surface of these cells bind to substances, recognize them and switch the cells "on" by prompting them into an active state. The cells then transmit information to nerve cells that relay the data to the taste centers of the cortex through synapses in the brain stem and thalamus.

Although researchers had made progress documenting the sense mechanisms of signal transduction and information processing in photoreceptors, and olfactory neurons, little is known about the molecular basis of taste perception. Scientists had described the nature of the basic taste modalities and the overall function of the taste receptor cells, but a mystery remained of the identification of the specific genes encoding taste receptors.

In the paper published in Cell, Hoon and the research team address the hypothesis that such receptors likely would be found in tissue and cells that are specific to the mechanism of taste.

The research team used specialized DNA screening techniques to scan for candidate receptors in taste buds of rats and mice. The strategy succeeded in isolating two novel receptors, TR1 and TR2. TR1 and TR2 belong to the G protein-coupled receptors, a "superfamily" of receptors that have a common mechanism of action, but differ greatly in structure.

The new proteins are distantly related to the candidate mammalian receptors for pheromones, another family of sensory receptors.

"The identification of candidate mammalian taste receptors makes it possible to understand how the different taste cells differ from each other (for example what makes a sweet cell a sweet cell, etc.) and how taste information is encoded so that the brain can interpret and respond to the presentation of taste stimuli on our tongue," said Zuker, a professor of biology and neurosciences at UCSD. "We may be able to mark the different cells and use the marks as a map of the pathway to the brain. Pharmacologically it could be used to identify-using biochemical

and biological assays-high potency for agonists and antagonists of taste function."

Using biological screening techniques, millions of molecules could be evaluated to find out which substances bind to which specific taste receptor. A molecule that binds and activates a bitter receptor, Zuker and Ryba say, is ultimately likely to be perceived by our sense of taste as bitter.

"If it binds the sweet receptor it means that we will perceive it as sweet," Zuker added. "It doesn't matter if it looks like a sweet molecule or behaves like a sweet molecule, but if it binds and activates the sweet receptor, it will be sweet. That is what the sense of taste is all about."

The discovery could one day hold implications for engineering foods to specific taste qualities. While today the food industry rests on qualitative tasting tests for much of their taste assays, the availability of taste receptor genes opens the door to rational food design.

In addition to Drs. Zuker, Ryba and Hoon, the research team for the study included Dr. Elliot Adler and Hirgen Lindemeier, Howard Hughes Medical Institute researchers at UCSD. The National Institute on Deafness and Other Communication Disorders of the National Institutes of Health partly supported the research.

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