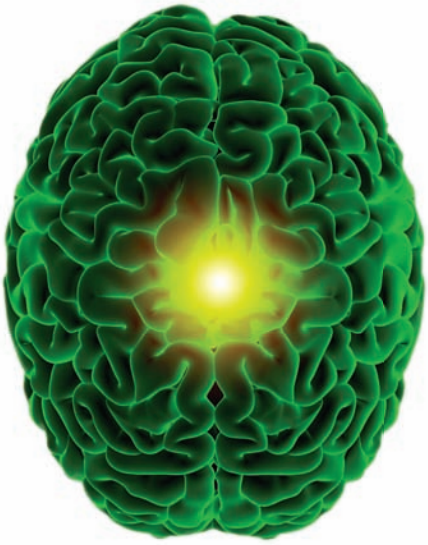
Taste, Aroma and the Brain



Emerging chemosensory research and applications for healthier, more effective flavors

"You don't taste with your mouth or your nose; you taste with your brain," said Mark Friedman, associate director of Monell Chemical Senses Center (Monell Center), addressing attendees of the recent joint Society of Flavor Chemists (SFC) and Chemical Sources Association (CSA) meeting in Philadelphia. Monell Center's Marcia Pelchat added, "The interesting thing about flavor in the brain is that the whole is often more than the sum of its parts."

The Three Chemical Senses of Flavor

Flavors are a mix of sensations, Friedman said, consisting of three chemical senses: taste, smell and what is sometimes described as chemosthesis.

Taste: Commonly and mistakenly believed to be interchangeable with "flavor," taste comprises six basic senses that are detected in the mouth: salt, sweet, sour, bitter, umami and possibly calcium.[a] Each of these, of course, represents in part a desire for particular nutrients—salt taste, for example, is really a taste for sodium.

Smell: Anyone who has suffered flavor loss due to a cold is well aware that flavor is more than just taste. In fact, aroma—experienced orthonasally and retronasally—arguably plays the most significant role in flavor, particularly in subtle variations among similar flavor types. Humans possess at least 300 different receptors in the olfactory epithelium. These receptors "mediate the variety of aromas that you can experience," Friedman noted. Yet a mystery remains. How can people detect thousands of different aromas with just 300 receptors? Whatever the answer, Friedman told the audience, the sense of smell remains a remarkably provocative sensation "because it is connected to the part of the brain that is linked to emotion and memory."

Chemosthesis: Flavor's third chemical sense is known by a number of seemingly inadequate descriptors such as mouthfeel**,** chemical feel or chemosensory irritation. Monell Center's researchers have settled on "chemosthesis."

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> —Mark Friedman

Chemosthesis is distinct from mouthfeel in that it does not encompass concepts such as astringency, which, as Friedman noted, is not a chemical reaction. Astringents merely reduce or suppress the lubricating proteins in saliva; it creates a sense of touch. Thus, astringency and other strictly mouthfeel sensations fall under the tactile senses. Chemosthesis, Friedman clarified, is "a skin sense that mediates warmth, itching, stinging, burning—the same sense that makes your eyes water when you smell ammonia or a hot pepper, or you taste champagne and experience the tingle, which isn't the bubbles but rather the carbonic acid."

Working in concert, taste, smell and chemosthesis comprise flavor, the mechanisms and implications of which are the focus of Monell Center's research.

Taste Buds and Receptors in the Oral Cavity

Taste, aroma and chemosthesis may ultimately register as flavor in the brain, but the taste buds seem to play a highly complex role. "If you want to know how the taste buds work, you have to look at the whole bud," explained John Teeter, Monell Center, during his presentation.

Like much of the science of aroma, flavor researchers' understanding of the physiology of taste buds remains incomplete, and in some cases there are strong disagreements among scientists regarding how data should be interpreted. Or, as Teeter put it, the current understanding should be taken "with a grain of salt."

The end organs for taste are the taste buds, he continued, which are housed primarily in the fungiform, foliate and circumvallate papillae on the tongue and, to a lesser extent, in the soft palate on the roof of the mouth and the throat. These buds are bundles of taste cells that interact with taste ligands, noted Alexander Bachmanov, a researcher at the Monell Center.

Teeter explained, "These tiny epithelial structures, or packages of cells, house all of the molecular machinery that's necessary to recognize the chemicals, to transduce information about the nature and concentration of those compounds into electrical signals in those cells, and then to pass that information along to the taste nerve endings." This information is sent to the brain where the sensation of taste and flavor arises.

Find photos from the event on **Page 8.**

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[a] While the ability to taste calcium has been established in mice via the work of Monell Center's Michael Tordoff, there is some question as to whether the same may be true of humans.

Taste buds' remarkably complex structures may engage in significant processing before taste information gets passed on to the brain. These dense bundles comprise 50–100 cells of varying morphological and functional types. It is precisely this structure that makes it very difficult for researchers to tell what each individual cell is doing.

"There really is an outside and an inside," said Teeter, "and the outside is a very small piece of the cell membrane that faces the outside world and is exposed to whatever you're putting in your mouth." The rest of the cell bundle normally doesn't see the stimulus, which means it can't be well understood by, say, studying a dissociated taste bud laid bare in a dish. Another layer of complexity, said Teeter, especially in conducting physiological experiments within a taste bud, is that these cells are being continuously replaced every 10–12 days throughout one's life. And each one of those cell types is present at different developmental stages at any given time, which may mean different functional properties.

Meanwhile, there are a number of substrates present within taste buds, which facilitate lateral interactions or processing among the cells. In other words, Teeter noted, a signal in one may be immediately passed to an adjacent cell. "We know that some of the cells in the taste buds are electrically coupled in groups of two or three … There are nerve peptides being released by taste cells that have receptors on other taste cells. They 'talk amongst themselves.'" Here, adenosine triphosphate (ATP) acts as a neurotransmitter.

Taste cells: The functional organization of a taste bud comprises type 1, 2 and 3 cells. About 50% of these are type 1 cells, which some argue are the target for salty taste; Teeter remains unconvinced. Type 2 cells, meanwhile, account for about 25% of the taste bud. These comprise T1R receptor cells responsible for sweet and umami and T2R receptor cells responsible for bitter. (See **Taste receptors** below.) These are expressed on nonoverlapping sets of type 2 cells. Thus, there are sweet cells, umami cells and bitter cells. Yet, Teeter explained, this is not a one-to-one system. Sweet tastants do not simply direct to sweet receptor cells to create a sweet impression in the brain. Sweet receptor cells respond best to sweet, but not *only* to sweet. And the reason these cells react to more than a single stimuli is that there is, in Teeter's words, "drizzle" from the ATP. Finally, type 3 cells are "intermediate cells" that account for about 15-20% of the taste bud. These have been implicated in sour taste and, in some cases, salt. The latter observation is contentious.

Taste receptors: Tastants are derived from food during consumption, which then branch to one of the two major types of taste receptors—G protein-coupled taste receptors (GPCR; divided into the T1R and T2R families) or ion channels. A GPCR acts as a receptor on the taste bud on one end. Its other end feeds into the G protein to which it is attached, or "coupled." The interaction of a taste ligand with a receptor results in a dissociation with a G protein, and, according to Bachmanov, a "cascade of intercellular events which eventually excites cells and sends

About Monell Center

Monell Center (Philadelphia) is dedicated to basic research into taste and smell: how these senses work, their basic functions, and what role they play in humans and their life and health. This work covers how humans perceive chemicals such as tastants, aromas and irritants and how they form liking and preference for these different stimuli. Monell Center's research enters the worlds of neuroscience and molecular biology and beyond, which facilitate insights into how receptors on the tongue or nose or skin react to stimuli and how one goes from a chemical having contact with a cellular receptor to an event in the nervous system to information processing in the brain.

Founded in 1968, Monell Center was originally part of the University of Pennsylvania, though it now operates as an independent research institute. The organization's ~150 staff engage in cross-disciplinary research in about 80,000 square feet of facilities.

The organization's researchers study nutrition and appetite as a function of taste and smell and analyze how the chemical senses affect human food choices and what role those food choices play in conditions such as hypertension, obesity and diabetes.

Monell Center's more novel studies involve perceptions of body odor and their effects on fragrance development (**see Page 49**), how a mother's reasons for drinking affect her children's perceptions of the smell of alcohol, and even how the body odors of men and women are interpreted by both heterosexual and homosexual men and women. (Hint: the preferences align exactly as one might imagine.)

Significantly, the organization is the only US government-funded organization looking into diseases of taste and smell and their effects. Because of the connections between taste and smell, most of these cases involve a problem in relation to smell such as blockages, polyps or brain injuries that essentially sever the olfactory nerves. Monell Center's funding derives from the National Institutes of Health, National Science Foundation, US Department of Agriculture, US Department of the Interior, US Department of Defense and Defense Advanced Research Projects Agency, Pennsylvania Department of Agriculture, the Monell Foundation, and about 55 corporate sponsors from the flavor, fragrance, food and beverage world.

Most compelling is that no Monell Center research is kept proprietary, though sponsors do have certain first rights of refusal for new technologies or applications.

signals to the brain." On the other hand, easily soluble materials such as salts and acids penetrate and excite cells via ion channels. Teeter noted, however, that salt and sour receptors have not been clearly identified to date.

T1Rs are responsible for sweet and umami sensations, while T2Rs are responsible for bitter impressions. On the human tongue, these GPCRs are expressed in compelling patterns:

- ***T1R family:*** T1R3 only; T1R1 + T1R3; and T1R2 + T1R3; T1R1 and T1R2 are not co-expressed.
- ***T2R family:*** Multiple T2Rs are co-expressed in the same taste receptor cells.

According to Bachmanov, the fact that T1R1 + T1R3 and T1R2 + T1R3 are expressed in different taste cells means that the same receptor can elicit different taste qualities, such as sweet and umami. And, because different T2Rs are expressed in the same taste cells, it can be concluded that different receptors can have the same taste quality, such as bitter.

During his presentation, Bachmanov presented a table summarizing taste qualities, related ligands and the receptors responsible for each quality. *Italicized* data remains undetermined.

- ***Sweet:*** sugars, amino acids, artificial sweeteners; T1R2 + T1R3
- ***Umami:*** glutamate, nucleotides; T1R1+T1R3; *mGluR metabotropic glutamate receptor*
- ***Bitter:*** quinine, caffeine, etc.; multiple T2Rs
- ***Salty:*** sodium; epithelial Na+ channel
- ***Sour:*** acid; *PKD1L3 polycystic kidney disease-like family— transient receptor potential channel family member; PKD2L1 polycystic kidney disease-like family—transient receptor potential (TRP) channel family member*
- ***Calcium:*** Ca2+; *CaSR*; *T1R*
- ***Fat:*** fatty acids; *K channels*; *CD36*; *GPR120*
- ***Carbohydrates:*** starch, unknown receptors
- ***Water:*** hypo-osmolarity, *aquaporins*

Flavor and the Brain

As Monell Center's Marcia Pelchat noted in her presentation, "The interesting thing about flavor in the brain is that the whole is often more than the sum of its parts." But certainly one of the most important parts is aroma.

People tend to say they love the "taste" of certain foods, but they almost certainly mean they love the flavor. "Arguably, the aromatic component of flavor is the most informative," Pelchat explained. Though taste qualities offer a rather limited range of sensations, it is aroma that offers the distinction amongst thousands of flavors. Wintergreen vs. spearmint, mango vs. peach, beef vs. lamb, basmati rice vs. plain rice; as Pelchat noted, these would be difficult to distinguish with one's nose pinched.

The olfactory bulb at the base of the human brain is the core of this mechanism, acting as the first stop for olfactory information. "Odorants create spacial and temporal patterns that are relatively unique to each odorant," said Pelchat, "even at the earliest stage of processing in the bulb." The olfactory bulb is connected to the pyriform cortex, which is considered the primary cortical area for olfaction. There is also a direct connection from the olfactory bulb to the orbitofrontal cortex and the hypothalamus, the latter of which is involved in feeding behavior. Meanwhile, there are a number of connections from the bulb to the limbic system, which is deeply keyed into emotions and is often called the "reptile brain" or "old smell brain" because olfaction and emotion co-evolved in this region.

Gustatory pathways in the brain: Gustatory, or sense of taste, is more closely related to the body senses of touch, sight and hearing than it is aroma. The primary

Chemical Irritation in Odors: Psychological?

While Monell Center has registered great interest in the occupational and environmental impact of odors—primarily irritation created by some chemicals—often its researchers have found that reactions to these odor materials are more a matter of belief or emotion than a matter of the sensation of the chemical itself. "There's a lot of work with regard to cognitive psychology in terms of understanding people's response to these odors that they detect in their environment," says Mark Friedman, Monell Center's associate director.

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taste cortex includes the insula and base of the frontal cortex. There are also taste projections to the orbitofrontal cortex and to the hypothalamus and amygdale with "coding for intensity similar to olfaction," according to Pelchat. The pyriform cortex receives no taste information (unimodal); that region may play a larger part in odors. Pelchat explained that the orbitofrontal cortex, ventral insula neurons and cingulate gyrus recieve both taste and smell inputs, making them multimodal. In fact, she said, the orbitofrontal cortex and ventral insula neurons may actually respond to taste, smell, visual, fat and texture stimuli.

Effects of congruent and incongruent tastes and aromas: In an experiment conducted by Monell Center in 2000, the detection threshold for orthonasally presented benzaldehyde, which is usually associated with sweet taste, was lower when subjects simultaneously held a congruent sweet taste such as saccharin in their mouths than when their mouths either held nothing or an incongruent taste such as monosodium glutamate.[1] This pattern of suppression or enhancement is mirrored in the brain.

Odorants for phantom sweet and sour effects: People often talk about odors being sweet or sour, but how do they get that way? After all, Pelchat said, those are taste qualities, not odor qualities. One hypothesis, she noted, is that these are learned associations. It has been shown that if one takes novel odors and pairs them with either sucrose or citric acid repeatedly, those odors will later be rated as being either sweet or sour. Work has shown that this association cannot be broken even by presenting the odors alone over time. If one finds an odorant that's described as being sweet, it actually acts like a sweet taste. If a formulator were to add a sweet odorant to a sour solution, the rated sourness of the solution would decrease; conversely, it would enhance the sweetness of sweet solution. This is a possible way to add sweetness to a formulation in which one doesn't want to add more sugar or high-intensity sweetener. Sweetness may instead be achieved with an odorant.

References

1. Dalton, N Doolittle, H Nagata and PA Breslin, The merging of the senses: integration of subthreshold taste and smell. *Nature Neurosci*, 3, 431-432 (2000)

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