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TASTE

More than meets the mouth

Certain things taste differently to different people. Why is this, and does this affect our choice of food?

BY MICHAEL EISENSTEIN

Nearly 80 years after DuPont chemists stumbled across evidence of genetic variation in perception of the bitter-tasting compound phenylthiocarbamide (PTC), Danielle Reed's team at the Monell Chemical Senses Center in Philadelphia, Pennsylvania, made a similarly serendipitous discovery.

Reed was approached by a lab technician worried she made a mistake with a experimental quinine preparation. "She said, 'I think I made the solutions wrong — here, taste this,'" recalls Reed, who then tasted the bitter compound. "I'm like, 'ugh, it seems fine to me.' But she said, 'It tastes like water to me.'"

This strange observation eventually led to the discovery of a genetic locus that affects our tongue's ability to detect bitterness in quinine — a big step on the road to understanding how people differ from one another in terms of taste, and how these differences shape what we like to eat.

A BITTER TASTE

Bitter is one of the five primary tastes — along with sweet, sour, salty and the savoury umami — that compose the gustatory system. Of these, bitter is perhaps the best characterized in terms of the influence of genetic variability on taste.

In humans, the cells responsible for bitter taste perception express 25 receptors (T2Rs) that vary in the chemicals they recognize but which appear to perform a common role in preventing people from eating toxic compounds. Accordingly, some scientists are convinced that humans evolved taste to detect harmful substances. "A newborn baby is born loving sweet and hating bitter — no experience required," says Linda Bartoshuk, director of human research at the Center for Smell and Taste at the University of Florida.

Insensitive variants have been identified for several bitter receptor genes and are common in the general population. For example, mutations in T2R38 render individuals incapable of tasting PTC or the related compound 6-n-propylthiouracil (PROP).

Such limited sensitivity can be an asset as many nutritious vegetables, including broccoli and sprouts, also produce bitter tasting glucosinolates. These compounds include goitrin, a thyroid toxin in large doses but which may protect against cancer in lower doses.

There are obvious nutritional advantages in mitigating the urge to avoid sprouts, and the adaptive value of this reduced sensitivity allele is evident in its global distribution alongside the more common sensitive version. "The ratio of the alleles varies depending on where you go," says Paul Breslin, a taste perception researcher at Monell, "but you see that both have been maintained in almost every population you look at anywhere on Earth."

Yet efforts to firmly link individual genetic variations with altered food preferences have not been easy. Several studies have revealed geographic or ethnic differences in the distribution of taste receptor variants that may have arisen from selective pressures (see Of beans and genes, page S13), but their effects on diet — and association with overall health — are controversial. "I'm a PTC non-taster: I can't taste goitrin in vegetables very well. But I think this has very little to do with how much broccoli I choose to eat on a daily basis," says Reed.

Attempts to establish similar correlations between disease and taste have proven equally problematic. For example, there is no clear link between sensitivity to sweet tastes and predisposition to obesity, diabetes or other diseases related to excess consumption of sugars.

Some of the strongest connections identified relate to alcohol preference. In one study, Bartoshuk partnered with Yale University geneticist Ken Kidd to examine how bitter taste shapes alcohol perception within a cohort of students. "There was a clear relationship between sensitivity and whether ethanol is perceived as bitter and harsh or slightly sweet," says Kidd. "Among those who were homozygous for the high-sensitivity [bitterness allele], nobody drank very much." Other studies at Monell have hinted at a parallel role for sweetness receptor variation, where sensitivity to, and preference for, sweet tastes is seemingly correlated with alcohol consumption. However, Kidd and others point out that this variability

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must be considered alongside the numerous other brain and metabolic factors involved in drinking alcohol.

Collectively, these data raise a question: given the front-line role of taste perception in food consumption, and the clear advantages of quickly recognizing good and bad food sources, why is it so hard to associate genetic differences in taste function with dietary behaviour?

NAME THAT TASTE

A large part of this problem arises from challenges in experimentally linking the highly subjective experience of taste with biological mechanisms. But gaps also remain in our understanding of the basic machinery of taste perception. This past spring, Charles Zuker's team at Columbia University, New York, validated the involvement of epithelial sodium channel ENaC as a component of sodium chloride salt perception in mice. Other salt receptors remain at large. "People describe potassium chloride as being kind of brackish tasting, maybe kind of metallic, like a dirty salt solution. It's clearly salty," says Breslin. "That can't be through an ENaC, because those channels pass potassium ions very poorly."

Furthermore, even though researchers have known the cells responsible for sour taste since 2006, a definitive receptor has yet to be identified. This is partly because of the complex nature of oral response to acid, where taste effects overlap with somatosensory sensations, a category of perceptual information that encompasses non-taste qualities such as temperature, texture or spiciness.

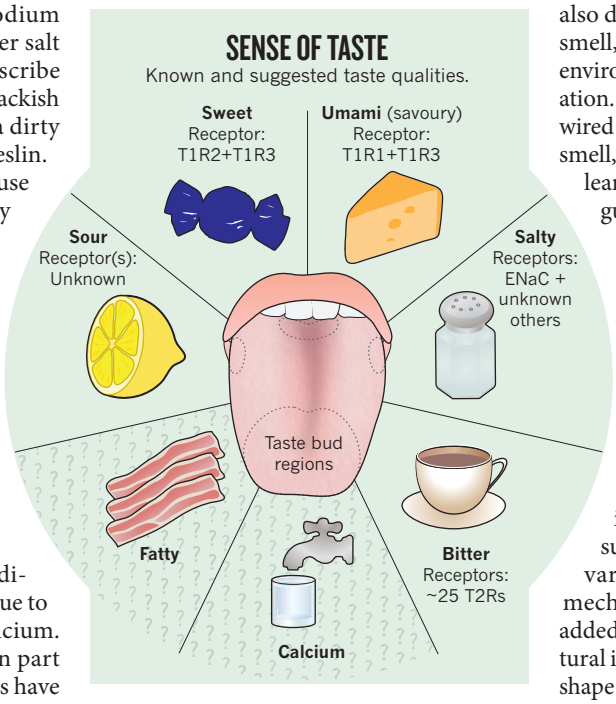
Preliminary reports also hint at additional taste qualities, enabling the tongue to recognize things like fatty acids or calcium. But there is little consensus on this, in part because no dedicated taste-quality cells have been identified and also because candidate receptors only partially account for our ability to distinguish these putative tastes. Some scientists are also sceptical because humans lack a lexicon to describe these qualities. "Just take a little canola oil and taste it — it doesn't really have a taste," says Bartoshuk. "My guess is that the real sensory input from fat is tactile — fat is gooey and oily and viscous and creamy."

Most investigators remain open to the possibility that there's more to the mouth than just the 'basic five'. A 2009 study by Zuker's team identified a protein expressed in sour cells that apparently contributes — in conjunction with somatosensory receptors — to the discrimination of a 'carbonation taste', and they are on the hunt for mechanisms that monitor other undiscovered qualities. "If you take an animal and label all the sweet, sour, bitter, salty and umami cells, there are still plenty of cells left," he says. "What we're doing now is looking for things that are uniquely found in those [other] cells."

A GUT FEELING

Taste doesn't end at the back of the tongue. Many of the same taste receptor genes expressed in taste buds are expressed throughout the digestive system and in other tissues. Preliminary investigations suggest that these non-oral receptors help regulate appetite and metabolism. "What better way to do so than having the very same receptors reporting back from the gastrointestinal tract?" asks Zuker.

There is already strong evidence that taste receptors in the mouth help steer organisms towards the nutrients that the body needs most. "If you offer malnourished kids soups that are either plain, ordinary stocks or stocks that have been fortified, they generally prefer soups that are amino acid-fortified over everything else, including very tasty high-calorie soups," says Breslin. "This is in young kids, who have no idea what's going on. This suggests that somehow there's this 'wisdom of the body'."



Evidence suggests that at least some of this activity may arise from metabolic signals triggered by taste receptor activation. "Taste cells express all sorts of different peptide hormones that are used in other areas of the body for regulating satiety or blood glucose," says Steven Munger, a neurobiologist at the University of Maryland.

Several studies in the past few years suggest that these receptors also direct the secretion of metabolic hormones in the lower digestive tract in response to sweet, bitter or umami stimuli; for example, intestinal sweetness receptor signalling may help regulate glucose absorption from the blood. Munger adds that his own investigations of genes associated with diabetes among Amish people have been confounded by these gut receptors and the ambiguity of their function. "We did see an association with variation in a particular bitter receptor and the ability of non-diabetic individuals to regulate their blood glucose," he says. However, it remains unclear whether this association arises from the effects of receptor variation on tongue-level taste preference and food selection or whether the difference lies in how the gut reacts to particular foods.

UNWIRING FLAVOUR

The biggest outstanding issue for many taste scientists is understanding how the various raw chemical sensations that transmit taste are incorporated into a more nuanced and sophisticated sense of flavour. Perception at this level also depends on signals received by sense of smell, which exhibits far greater complexity, environmental adaptability and personal variation. "You've got one sense, taste, that's hard-wired for affect," says Bartoshuk, "and another, smell, where the affect is extremely labile and learned very quickly and can also be extinguished."

Equally important is how the brain decides whether or not it likes what it senses. Alexander Bachmanov, a geneticist at Monell, cites the example of sweet-liking mice developed in his lab. "Through selective breeding, we have created mice with the same genotype for sweet taste receptors, but some are very avid consumers of sweeteners while others consume them in very modest amounts," he says, and suggests that this behaviour arises from variations in more central neurological mechanisms related to taste response. This added complexity leaves a lot of room for cultural influences and environmental factors to shape how we assign reward value to a flavour and might in turn affect the contribution of more subtle genome-level factors. As such, inherited differences in taste receptor expression or function alone are probably insufficient to explain how many of us overcome our innate aversion to bitterness and sourness to thoroughly enjoy a steaming demitasse of espresso or a bracing gin and tonic.

Nevertheless, there is evidence that genetic changes can modulate the response of this normally hard-wired sensory system. Zuker concludes that meaningful progress in untangling the neural processes behind food choice will require a solid understanding of what happens when meal meets mouth. "Before we can understand how the brain knows," he says, "we need to figure out how the tongue knows." ■

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