How many tastes are there?

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How many basic tastes are there? Most people list four: sweet, sour, salty and bitter. Those with a background in the chemosensory sciences usually add a fifth, umami. But why stop there? There is growing evidence that there are more—perhaps many more.

The idea that there are four basic tastes goes back at least as far as ancient Greece, so if there are more than four basic tastes why haven't they been discovered by now? There are three reasons: The first is that research on taste has been self-fulfilling. Scientists who believe there are four basic tastes conduct research on the four basic tastes! This richens the literature on the four basic tastes, and thus strengthens the impression that there are only four tastes worthy of study. It's very difficult to work (and fund) outside the box. The second reason is that there is a natural reluctance to open this box—a Pandora's Box— if things can be explained satisfactorily with the basic four (or five) tastes. Occam's razor argues that the best explanation is the one with the fewest components, and until recently, four (or five) basic tastes have seemed to do the trick.

The third reason why we have been limited to four basic tastes is that, until recently, there haven't been the tools available to identify others. However, over the last decade or so, there has been a revolution in the study of taste, which has been spearheaded by the invention of new molecular and genetic tools that allow investigation of cellular and intracellular events. These have, for the first time, revealed the identity and nature of taste receptors. They allow us to determine that a particular taste receptor exists, find where it is located, and establish what it can and cannot detect.

Monell has been at the forefront of this research, being among the first to discover the sweet taste receptor (2), paving the way for the discovery of some bitter taste receptors (1,8), and having a large industry-sponsored program to discover the salt taste receptor(s). To mix modalities and metaphors, taste science has been in the dark—or dark ages—and we are now beginning to see a new and much bigger picture. We are beginning a renaissance, with new findings leading to new ideas.

My contribution to this picture has been the discovery of taste receptors for calcium. It has been known since the 1930s that rats and birds have a "calcium appetite". That is, when deprived of calcium they will seek it out and, if necessary, work to obtain it. The more calcium they need, the more they like it and the more they ingest when it becomes available. So how do animals recognize calcium? Early work suggested that they may simply learn that a particular taste alleviates their calcium deficiency. However, in 1996, I showed that calcium-deprived rats given calcium solutions to drink for the first time in their lives recognized the calcium within a few seconds—they drank calcium faster and for longer than did replete rats tested under identical conditions (4). Not only that, the deprived rats smiled while they drank calcium (5). Such a rapid response could not be due to learning. This, and a series of related experiments (3, 5-7) established that the appetite for calcium was innate and that calcium was sensed in the oral cavity. The implication was that taste receptors for calcium must be present, although it remained possible that calcium taste was a complex mixture of bitter, sour, and salty tastes (nobody would argue that calcium is sweet).

To discover the taste receptors involved in the detection of calcium needed a genetic approach, and until very recently, the tools required have been available only for the mouse. Consequently, I screened the calcium preferences of 40 inbred strains of mice (11). Most mice avoided high concentrations of calcium but one strain—the PWK strain—showed strong preferences for them. Using this strain, I was able to combine classical breeding methods with state-of-the art genotyping (10) to identify the approximate chromosomal locations of the genes responsible for the avidity for calcium (12). This led my colleagues and I to discover two genes that influence calcium taste: *Tas1r3* and *Casr* (10,13). *Tas1r3* has previously been implicated as a receptor for sweet and umami taste (2). *Casr* has previously been implicated as a receptor for calcium in the parathyroid gland, kidney, and brain, but not in taste buds. We have begun to look for these calcium receptors in human tongue, and have several reasons to believe that we will find them (9).

So if calcium is detected on the tongue, is it a sixth basic taste? The answer to this question rests on what is meant by a "basic taste". To qualify, the existence of a receptor might be all that is required, at least from the molecular biologist's viewpoint, but this leads to a problem. We already know there are at least 25 bitter receptors, each differing slightly from the others in structure and each sensitive to different bitter compounds. Should each be considered the source of a basic taste? Should we discard the concept of "bitter" in favor of "urea" taste, "quinine" taste, "denatonium" taste…and so on, with each receptor classified by its major ligand? Probably not, because we know that each of these receptors is wired to the same nerve fibers leaving the tongue: urea, quinine, and denatonium all activate some of the same neural pathways. Presumably, there is a central core of nerve fibers activated by all compounds we consider to be bitter. It may be that the ultimate determinant of whether a basic taste exists will require identification of a unique neural substrate, probably somewhere in the cerebral cortex. At present, the only way to approach this in humans is with noninvasive imaging, and although there have been some initial attempts using fMRI to distinguish the brain regions responsible for different tastes, the technique is not sufficiently precise to be very helpful. Until we have a better understanding of the brain sites involved, the definition of "basic taste" is lodged between anatomy and philosophy.

But having opened Pandora's Box to let out calcium, can we peek inside to see what else is in there? The view is murky but, at least in my opinion, there is good evidence for fat taste receptors, and receptors for some of the amino acids. There is also strong evidence, albeit indirect, for non-sweet carbohydrate receptors, including separate tastes for starch and Polycose (a polysaccharide). Thus, the mouth can detect each of the three macronutrients in our diet and at least some of the individual types of macronutrient. There may also be distinct mechanisms for the detection of metals and/or minerals, which makes intuitive sense. We already know we have internal detectors for the homeostatic regulation of some of these cations so it seems reasonable for evolution to slip a few of them onto the tongue. The possibility of anion detectors, for example, for hydroxides or pyrophosphates, has not been investigated more than cursorily. At the moment, there are more questions than answers. However, for the first time, the questions are being asked; the answers are on the tip of the tongue.

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