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Why do we like sweet taste: A bitter tale?

Gary K. Beauchamp[1]

Gary K. Beauchamp: beauchamp@monell.org

[1]Monell Chemical Senses Center 3500 Market Street Philadelphia, PA 19104

Abstract

Sweet is widely considered to be one of a small number of basic or primary taste qualities. Liking for sweet tasting substances is innate, although postnatal experiences can shape responses. The power of sweet taste to induce consumption and to motivate behavior is profound, suggesting the importance of this sense for many species. Most investigators presume that the ability to identify sweet molecules through the sense of taste evolved to allow organisms to detect sources of readily available glucose from plants. Perhaps the best evidence supporting this presumption are recent discoveries in comparative biology demonstrating that species in the order Carnivora that do not consume plants also do not perceive sweet taste due to the pseudogenization of a component of the primary sweet taste receptor. However, arguing against this idea is the observation that the sweetness of a plant, or the amount of easily metabolizable sugars contained in the plant, provides little quantitative indication of the plant's energy or broadly conceived food value. Here it is suggested that the perceptual ratio of sweet taste to bitter taste (a signal for toxicity) may be a better gauge of a plant's broadly conceived food value than sweetness alone and that it is this ratio that helps guide selection or rejection of a potential plant food.

Keywords

sweet; energy; glucose; bitter; toxicity

1. Introduction

The major role for the conscious sensation of taste is to aid in deciding whether a potential food is beneficial and may be consumed or whether it is dangerous and should be rejected. Thus, it is generally believed that the sense of taste evolved to insure animals choose food appropriate for body needs. Historically it has been thought that human taste sensations can be divided into four (or now five) primary or "basic" qualities: bitter, sour, salty, sweet, with umami or savory being a recent addition. Precisely what constitutes a basic taste has been vigorously debated. Here, I adhere to the more traditional view that basic tastes are those

Corresponding Author: Gary K. Beauchamp, beauchamp@monell.org.

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that are primarily characterized by perceptual salience and uniqueness. For this reason I do not include, for example, fat or calcium although there is no doubt that they interact with the taste system and are important nutritionally. For alternative views on definitions and even the existence of basic tastes see [1] Booth, 1991; [2] Halpern, 1997; [3] Erickson, 2000 and [4] Faurion, 2008, among others.

Traditionally, human sensations are used to describe the main five taste qualities. Although there are many studies showing that the mechanisms underlying perception of particular taste qualities are similar in human and nonhuman animals [5], applying terms for human sensations to nonhuman animals should be used with caution. Nevertheless, in this essay I will use human descriptors for taste qualities even when discussing non-human animals.

Sugars (e.g. glucose, sucrose, fructose, maltose lactose) induce the hedonically positive and strongly motivating sensory quality of sweetness. They also serve as sources of glucose, the obligate metabolic fuel for the brain [6]. Most investigators assume that these two functions for sugars are related although they may be anatomically and physiologically separable [7]. In short, it is believed that sweet taste evolved as a way to detect sources of glucose. One purpose of this essay is to critically evaluate this assumption. In direct contrast to sweet, aversive bitter taste is generally thought to indicate the presence of toxins in food but it has been speculated that it may also signal positive “medicines” under certain circumstances [8]. Although there is an overall positive correlation between the toxicity of a compound and its bitterness [9], the relationship is far from perfect.

2. Sweet taste and power

In his now classic book on the intersection of sugar and anthropology, *Sweetness and Power,* Sidney Mintz [10] analyzed the powerful role that the availability of cheap pure sweetener, primarily sucrose, had on western culture. His book emphasized the importance this pure white powder had on human social systems, beginning approximately 500 years ago. He speculated that every human culture has a word for “sweet,” attesting to the centrality of this concept in human nature. To Mintz, sugar and power reinforced one another but note that he titled his book sweetness and power, not sugar and power, perhaps implying that it is the sensory attribute of sugar that truly exerts the power.

In nature, the vast majority of stimulus molecules that are sweet are small molecular weight sugars found primarily in plants. These sugars (e.g. fructose, sucrose, glucose, and maltose) provide sources of glucose, a key source of energy in most organisms, and thus play a significant role in nutrition. In addition, the sweet sugar lactose found in many species’ milk, can also be metabolized to provide glucose energy. Based in part on these observations, most researchers have concluded that the evolutionary basis for the strong attraction that many animals have to sweet sugars is a consequence of their need for a way to identify readily available sources of metabolic fuel, in particular, glucose.

Mintz is certainly correct that there is a close relationship between sweetness and power in that sweet stimuli have a remarkably strong motivating power as parents often discover with a jolt as they raise young children. Indeed, the liking for sweetness is perhaps the most

dramatic example known of an innate liking for a relatively simple stimulus. The best evidence for this conclusion comes from human behavioral studies that have demonstrated, using a variety of techniques, that newborn and premature human infants respond positively to sweet tasting molecules on their first presentation [11].

Sweet substances are not just liked; they also may act as analgesics. Pain reduction in the presence of sweet tastes has been demonstrated in rodents and humans [12–14]. Indeed, sweet tastes are sometimes used in very young infants during minor pain-inducing procedures such as heal pricks to obtain blood and have even been used to reduce pain and stress during circumcisions. Mechanisms are thought to involve release of endogenous opioids. Interestingly and perhaps indicative of the important role sweet taste plays in food selection and utilization are findings that leptin and endocabbinoids modulate sweet taste function at the receptor level [15–16, but see 17]. This modulatory effect of endocabbinoids may thereby play a significant role in regulating energy balance through their ability to alter taste perception.

3. Sweet taste receptors

Assuming that sweet taste represents a single perceptual quality for humans, and likely for many other species, this does not necessarily imply that there is a single physiological detection mechanism underlying the percept of sweetness, although many have assumed this. The search for this mechanism or mechanisms has been a central goal of many taste investigators over the past century. As briefly outlined in Table 1, there has been a lively debate over whether there is a single receptor entity responsible for transducing sugars and other sweeteners or whether there are multiple receptor mechanisms. The discovery of the small T1R family of g-protein coupled receptors in 1999 [18] and the realization in 2001 that a dimer of two of them – T1R2 plus T1R3 – is a sweet taste receptor represented a major advance in the field [5, 18–25]. The puzzle of how such varied structures as simple sugars, molecules such as saccharine, aspartame and even proteins such as monellin and thaumatin all taste sweet was clarified by the findings that different sweet tasting molecules could interact with different sites in the T1R2 + T1R3 dimer [26]. Moreover the observation that a single chemical, lactisole, inhibits perception of virtually all sweet tasting molecules for humans [27–28] gave strong support to the proposition that sweet taste was due to the activation of a single receptor.

But apparently it is not so simple. Damak and colleagues [36] reported that mice, with the by-then canonical sweet receptor dimer T1R2 + T1R3 disabled by gene editing technology, showed a largely intact response to glucose and sorbitol and a diminished response to other sweet sugars while being sweet blind to non-sugar sweeteners (but see Zhao et al., 2003 [37]). This striking difference in response to non-sugar sweeteners compared to some sugars led to the hypothesis that there was an additional peripheral mechanism for detecting sweet taste and to the discovery that sugar transporters in the sweet taste cell (the same cell that expressed the receptor dimer) could detect glucose and some other nutritive sugars [35]. Work on this mechanism is ongoing to determine, among other things, the functional consequences of activating these transporters. It remains a puzzle as to how the sweet inhibiting molecule lactisole [28] could disable this second mechanism. Perhaps lactisole

disrupts the sweet taste cell itself in addition to its effects on the T1R2 + T1R3 heterodimer. Whatever the resolution to this puzzle, it appears that, as is the case for many areas of biology, multiple interacting mechanisms, some even redundant, likely underlie detection of sweet sugars.

4. Consensus: Sweet taste exists to detect sources of digestible carbohydrate calories

Based on the considerations noted above as well as other factors, the majority view is that sweet taste exists to identify energy-rich (or more precisely, glucose-available) foods in plants. For example, almost 70 years ago, Frings [38] noted that "… any animal which in nature will take fruits would probably accept sweetened things" (p.133). Since that time, variants on this theme have been expressed by many authors but real experimental evidence for this conclusion is elusive, and even what kind of evidence might be put forward to test this hypothesis is hard to identify.

A comparative approach may provide the best evidence that sweet taste perception functions primarily to detect plant-based simple sugars. It is remarkable that insects and vertebrate lineages seem to have analogous systems to recognize nutritive simple sugars and to motivate their ingestion [39]. That a specific dedicated sensory process devoted to detecting glucose-rich molecules in plants evolved independently in these lineages speaks to the centrality of the problem to be solved and is consistent with the powerful role sweetness appears to play in food choice.

Our own work in the area of comparative taste has focused more finely on species within the order Carnivora. Many years ago we reported [40] that domestic cats appeared indifferent to a large variety of sweeteners when given acceptance tests analogous to those that demonstrate great avidity in rodents and many other species of vertebrates and invertebrates. These data were consistent with some earlier more limited studies by Carpenter [41] (but disagreed with conclusions reached by Bartoshuk et al. [42]). We argued that our data supported the proposition that as an obligate carnivore, cats would have no need to identify plant-based sweeteners and since other substances that cats eat would not contain sweeteners (with the possible exception of "sweet" amino acids), perhaps cats were blind to sweet taste. This behavioral work also revealed that zoo-housed wild cats (lions, tigers, leopards and jaguars) also showed no interests in carbohydrate sweeteners [40].

Following the discovery that the T1R2 + T1R3 dimer forms a sweet taste receptor, we investigated the structure and function of the T1R2 and T1R3 receptor components in cats, both wild and domestic. We discovered [43] that T1R2 had accumulated deleterious mutations making it a psuedogene and thereby rendering the receptor dimer non-functional. This explained the cat's indifference to carbohydrate sweeteners (see also Wang et al. [44] for indications of other changes in glucose metabolism coincident with obligate carnivory). We suggested that during the evolution of an all-meat diet, selective pressures that maintained the functionality of the sweet receptor were relaxed and random disabling mutations became fixed. It remains a puzzle as to why the alternate sweet taste receptor mechanisms identified by Yee et al. [35] are apparently not operating in adult cats to mediate

preferential behavior in response to simple sugars, although it is possible that cats lack all sweet taste cells and/or that kittens might manifest a behavioral response to glucose and perhaps some other nutritive sweeteners. It would be interesting to test these hypotheses, particularly in view of the wide-spread assumption that lactose in milk of many species serves to motivate consumption. If nursing kittens cannot taste sweetness, this proves that detecting the sweetness of milk in not necessary to motivate ingestion. The viability of genetically engineered mice that have a non-functional T1R2-T1R3 dimer also supports this inference.

The conclusion that sweet taste function was lost in cats in association to their lack of need to detect sweet sugars in plants has been strongly supported by more recent work with a range of species in the Carnivora family. Some of these species, like cats, are obligate carnivores (e.g. spotted hyena, banded linsang, sea lion) whereas others are more omnivorous (e.g. dog, raccoon) or even herbivorous (giant panda). Through structural studies of DNA from these species and limited behavioral testing of a few of them, we found that many of the obligate carnivores have lost function of T1R2, just as have the cats [45]. Strikingly, this loss happened independently; that is, in different species disabling mutations occurred at different loci within the gene. This is consistent with the hypothesis that the taste loss followed rather than preceded development of obligate meat eating. We argue that this widespread loss of sweet taste function provides evidence that sweet taste serves to detect the presence of sugars in plants and when this is no longer necessary, it is dispensed with.

More recently, the apparent converse of this loss has been reported in birds. When the bird and the reptile lineage split, T1R2 was lost in all birds. Thus one might predict that if the T1R2 + T1R3 dimer is necessary for sweet taste perception, birds as a class should be sweet blind (for more detail on avian sweet taste, see Rowland et al. [46]). But there exist birds that seem to choose and relish almost pure sugar in the form of nectar, with the hummingbirds being the most familiar example. How do they detect it? It seems that they have repurposed the amino acid receptor (a related dimer consisting of T1R1 + T1R3) to detect sugars, thereby availing themselves of a new ecological niche that is closed to non-sweet-detecting birds [47–48]. Again, this provides strong circumstantial evidence that sweet receptors and sweet perception exist to detect plant-based sugars that provide a source of glucose for energy.

In summary, these comparative data provide strong evidence that there is a close association between plant-based diets, consumption of sugars, and sweet taste function. When species move into an ecological niche where plants are no longer part of their diet, sweet taste mechanisms are no longer maintained by selection and by the fixing of random mutations, receptor function is lost. Perhaps even more strikingly, alternate receptors can be modified through selection to detect sweeteners and thereby open new dietary niches.

5. Why are sugars sweet and why are they liked?

Based on the consensus that sweetness is highly palatable among species that consume plants and that sweet molecules do in fact provide glucose-based energy, it would seem that the question that serves as the title for this essay is fully answered. But there is a contrarian

view possible, as briefly suggested in a commentary by Beauchamp & Cowart in Dobbing [49] and subsequently more extensively argued by Ramirez [50]. These investigators noted that the degree of sweetness actually provides little information about the amount of available energy in a food. Indeed, it might make as much or more sense to have a basic "starch" or "fat" taste as it does to have a sweet taste. Recently there are strong indications that both starch and fat may interact with taste receptors and indeed, rodents at least may perceive a basic starch taste [51–53]. Nevertheless, at least as concerns humans, very few would argue that either starch taste or fat taste has the same perceptual salience as sweet taste.

Ramirez [50] argued that sugars are the least essential of all nutrients. He observed that fruits, the most ubiquitous source of sweet taste in nature, are relatively low in energy. Indeed, the most energy-rich fruits are the less sweet ones; their metabolic fuel comes from fat. Fruits are also low in protein, so sweetness is unlikely to be a signal for protein. Although he assumed that sugar levels are not correlated with other nutrients, it is possible that they may be associated with the presence of certain vitamins and minerals. But in any case, Ramirez concluded that degree of sweetness does not provide quantitative information about glucose energy content. More broadly, sweetness may act as a signal for the ripeness of fruit and thus for the presence of easily metabolizable sugars. Although this could help explain the attractiveness of sweet taste for fruit-eating animals, it fails to account for the wide spread presence of sweet taste perception and avidity in the vast array of plant-eating species that do not depend on a fruit-based diet.

In the end, Ramirez noted that sugars are the most abundant class of solutes in plants, which make them easier to detect by taste receptors (an argument that Dethier [29] might dispute). They also provide a very rapid source of glucose, unlike the case for fats, protein and resistant starches [54]. Thus, he concluded that the primary function of sweet preference and liking resides in the *cue value* of sweetness. By analogy, brightly colored potential prey species provide a cue to the predator that this prey is to be avoided but not necessarily quantitative information about how dangerous consumption of that particular prey might be. This of course has led to mimicry to provide protection without the need to make or sequester poisons.

Could mimicry also exist for sweet taste? There are compounds in nature that taste sweet but do not provide a glucose source. Examples include sweet (to some primates and perhaps other species) proteins such as monellin, thaumatin, brazzein and lysozyme [55–56]. Whether these proteins were specifically selected to mimic the sweetness of nutritive sugars is not known. However, the possibility that brazzein has evolved as way for plants to induce African primates to consume the fruit and thereby disperse the seeds, has been suggested [57–58]. Similarly, it has been suggested that the sweetness of steviol glycosides, which can accumulate up to 25% of the dry matter in the plant leaf, may function in part to attract humans facilitating the spread of these rare plants [59]. However, Wintjens et al. [55] are skeptical, suggesting that the sweetness of many of these proteins is a serendipitous occurrence. For example, major functions of thaumatin-like proteins involve modulation of host-pathogen interactions, stress tolerance and cell signaling [60; see also Ceunen & Geuns [59] for a comprehensive discussion of the possible functions for the sweet compounds in

Stevia species). These sweet molecules may therefore have functions other than imparting sweetness. Additional studies of this topic would be very interesting.

6. Taste mixtures may be a basis for evolution of sweet taste

Ramirez's arguments [50] raise vexing questions but they are not entirely convincing. First, there is the meaning of the evidence on glucose energy content of plants that he cited. For the most part, the plants considered are those that have gone through strong selection by humans and do not represent a sample of what was available to plant-eating organisms during a co-evolutionary process of sweet taste perception and plant chemical composition. With the exception of fruits, it is unlikely that non-cultivated plants approached the sweetness of plants currently consumed by humans that have been selected to be sweeter and less bitter than their wild ancestors [61]. Second, and more important, is that a simple cue function for sweet taste does not seem to encompass the power and ubiquity of this percept.

Perhaps the problem is that in discussing sweet taste in a vacuum – without considering how it is perceived in the "real" world – something is missing. It is likely that during evolution there were very few instances of a food that was entirely sweet (honey is one example but is likely consumed by very few vertebrates with the exception of chimpanzees and humans [62]. Indeed, taste (and flavor, here referring to the combined attributes of taste, smell and chemesthesis) mixtures were surely the rule [63], particularly as concerns the two opponent taste qualities, sweet and bitter. Most plants, both fruits and non-fruits, are mixtures of bitter compounds and sweet ones. In fruits, bitterness and sourness are reduced and sweetness is enhanced when the plant "wants" to be eaten to insure spread of seeds. But for many plants bitterness presumably serves to protect the plant and it is in the best interest of the omnivore and herbivore to minimize consumption of high levels of bitter compounds or, alternately or additionally, evolve ways of detoxifying these compounds.

It is proposed here that sweetness, as modulated by other flavor components but most prominently by bitter/toxic compounds, could be a relatively accurate measure of the broadly conceived beneficial value of a plant as food. Here beneficial value refers to the balance between amounts of energy (and other nutrients such as vitamins and minerals) and toxicity. If this suggestion has merit, it leads to consideration of what is known about flavor mixtures and particularly sweet-bitter taste mixtures. There is a substantial literature on sweet-bitter interactions in humans. In general, as is often the case for taste mixtures, bitterness and sweetness mutually suppress each other [64–65]. The suppression of bitterness by sweet and vice versa can occur at any level, from interactions between sweet and bitter molecules prior to being tasted, to interactions at the receptor protein, the receptor cell, and up to more central processes in the nervous system. In many or most cases, interactions probably occur at multiple levels simultaneously. As an example of central interactions between sweet and bitter taste, Kroeze & Bartoshuk [66] used a clever split tongue psychophysical technique to show that suppression of quinine hydrochloride bitterness by sucrose was due to interactions occurring in the brain. However, based on physiological evidence, Talavera et al. [67] suggested that quinine hydrochloride is capable of suppressing sweet neural responses in mice by inhibiting currents that are necessary for

the depolarization of taste receptor cells, suggesting a possible peripheral role for bitter suppression of sweet taste (see also [68–70]).

Thus, consider Dethier's interpretation [29] of Aristotle's view on taste (Table 1): There are two truly primary tastes, sweet and bitter. Responses to these two antagonistic qualities – preference, liking, ingestion for sweet; avoidance, dislike, rejection for bitter are largely innate [71, 39]. In the plant world, taste-active compounds eliciting these qualities coexist under many or even most circumstances. The problem the omnivorous herbivore or omnivore must successfully solve on a daily basis is whether and how much of any one plant to eat. If sweetness predominates, then the plant is safe and ingestion ensues. If bitterness predominates, the opposite occurs. Using this simple metric, the organism can determine with some accuracy the beneficial value of a novel plant-based food. One instructive example of this push-pull system occurs in the *Manduca sexta* caterpillar [72]. In this insect, some sugars suppress sensitivity to bitter compounds without the sugars themselves eliciting immediate appetitive behavior. The act of taste suppression may not necessarily be associated with the perceived taste quality.

Are there any ways this proposition could be tested experimentally in vertebrates? Scott and Mark [9] proposed that perceived bitterness and toxicity (as measured by LD50 values for rats) are roughly positively correlated; thus the more bitter a compound, the more dangerous it is to consume. Perhaps a more accurate metric of overall beneficial value of a food would be a measure that includes the extent to which sweet-bitter mixtures in foods are perceived as more sweet or more bitter. How effective a bitter compound is at suppressing the sweetness (and vice versa) may be directly related to how toxic it is. It would be worth exploring this possibility.

7. Problems and questions

The hypothesis that it is the sweet/bitter ratio, not the level of sweetness itself, which is the important variable in judging the beneficial value of a plant, is surely a massive oversimplification. Obviously other taste-active materials, be they sour [73], salty, or even substances that may modify taste receptors such as fatty acids, would also need to be incorporated. So too would other sensory components of flavor, such as volatiles and chemesthetic stimuli. Indeed, for both of these there may be innately influenced negatives that should be balanced against sweetness in controlling food selection and ingestion. And, of course, learning plays a major role in what comes to be identified as food, perhaps the major role [1, 51, 74–75]. Finally, recent studies [76] demonstrating that "taste" receptors, including sweet and bitter receptors, are found in other parts of the body, including throughout the respiratory and digestive tract, raises the question of whether even their primary purpose is perception of foods. It is conceivable, if unlikely, that the profound role of sweet taste is not really conscious perception but some other nutritional function(s). Nevertheless, the ability of sweet stimuli to modulate behavior and the recognition of the presence of bitter toxic stimuli in close association throughout the plant world, suggests that their balance may be of major importance in the evolution of food palatability and may help explain the particularly powerful, ubiquitous, and even pernicious power of sweetness when, as in modern diets, it is divorced from its evolutionary partner, bitterness.

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Highlights

- Many species find sweet tasting substances innately attractive, highly motivating.
- Sweet taste perception is thought to function for detection of readily available carbohydrates.
- Sweetness can be a relatively poor indicator of readily available energy.
- Sweet substances and bitter substances interact to mutually suppress each other.
- Ratio of sweet to bitter may be an indicator of overall food value.

Table 1

Proposed number of receptors for sweet taste over time; a selected historical survey.

Author(s)/Date	**Proposed number of sweet receptors**	***Comments***
Aristotle (interpreted by [29] Dethier 1978 and [30] McBurney & Gent 1978)	1	*That there is a single quality can be interpreted to imply a single "receptor"*
Shallenberger & Acree 1967 [31]	1	*AH-B molecular conformation interacts with "…the receptor site…" for sweet compounds*
Bartoshuk 1987 [32] (see also Walters 1997 [33]; Halpern 1997 [2]; Erickson 2000 [3]; [4] Faurion 2008)	multiple	*Based on physiological and psychophysical evidence*
[34] Breslin et al. 1994	1	*Psychophysical evidence – includes nutritive sugars sucrose, fructose and glucose only*
Hoon et al. 1999 [18]; Bachmanov et al. 2001 [19]; Kitagawa et al. 2001 [20]; Max et al. 2001 [21]; Montmayeur et al. 2001 [22]; Nelson et al. 2001 [23]; Sainz et al. 2001 [24]; Bachmanov & Beauchamp, 2007 [5]; Hayes, 2007 [25]	1	*Discovery of the T1R family of 3 g- protein coupled receptors. Sweet taste = T1R2 + T1R3*
Yee et al. 2011 [35]	multiple	*Taste cell glucose sensors and K_{ATP} may detect nutritive sugars in addition to T1R2 + T1R3*