Nutritional Implications of Genetic Taste Variation: The Role of PROP Sensitivity and Other Taste Phenotypes

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Abstract

Genetic sensitivity to the bitter taste of phenylthiocarbamide and 6-n-propylthiouracil (PROP) is a well-studied human trait. It has been hypothesized that this phenotype is a marker for individual differences in taste perception that influence food preferences and dietary behavior with subsequent links to body weight and chronic disease risk. Steady progress has been made over the past several decades in defining the involvement of this phenotype and its underlying gene, TAS2R38, in this complex behavioral pathway. However, more work needs to be done to fully determine its overall nutritional and health significance. The primary goal of this review is to assess our current understanding of the role of the PROP bitter taste phenotype in food selection and body weight in both children and adults. A brief history of the field is included and controversies surrounding the use of different PROP screening methods are addressed. The contribution of other receptors (both bitter and nonbitter) to human taste variation is also discussed.

Contents

INTRODUCTION

The chemical senses (taste, smell, and chemical irritation) are the nutritional gatekeepers of the body, determining which foods should be ingested and which should be rejected. For example, the sweet taste and pleasant aroma of strawberries signals the presence of a carbohydrate source of energy, whereas the foul odor of spoiled meat guards against the accidental ingestion of contaminated food. The ability to distinguish nutritious from harmful foods was a critical survival skill of early humans faced with the task of selecting their food from a wide variety of natural sources. The modern consumer is not faced with these same life-threatening choices. Nevertheless, taste remains a powerful determinant of food selection and is ranked first by consumers as their top reason for choosing a food (49).

Bitter taste plays a dual role in human nutrition as both a warning signal and an attractant. Strong bitter taste is closely associated with the presence of toxins and is universally rejected. However, moderate bitter taste is appealing and expected in a variety of foods including beer, wine, and many cheeses. A large number of structurally diverse compounds impart bitter taste to foods. These include amino acids and peptides; polyphenols, such as tannins, catechins, and anthocyanins (from grapes, tea, and berries); isoflavones derived from soy; and glucosinolates from cruciferous vegetables (23). Humans are exquisitely sensitive to bitterness and can detect bitter compounds at concentrations several orders of magnitude lower than the other basic tastes. Nevertheless, the existence of large individual differences in bitterness perception is a well-known human characteristic. A striking example of this variation is the inherited ability to taste the bitter synthetic compounds phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). In 1931, A.L. Fox accidentally discovered this trait while synthesizing non-nutritive sweeteners in his laboratory. Some PTC powder escaped into the air, prompting complaints from his colleagues about bitter taste on their lips. Fox perceived nothing. Subsequent testing revealed that PTC was tasteless to ~30% of individuals and moderate-to-intensely bitter to the majority of individuals (43). This discovery spurred hundreds of studies around the globe to

determine the population genetics of this trait and its mode of inheritance. Wooding (120) provides a fascinating historical account of this discovery.

In 1950, Boyd (11) reported that PTC was chemically similar to *l*-5-vinyl-2-thiooxazolidone, a naturally occurring substance that was known to cause goiter in livestock and humans. This discovery was a turning point in the investigation of PTC because it suggested that this trait might have arisen through natural selection as protection against the overconsumption of dietary goitrogens. Subsequent work suggested that PTC tasting influenced general food preferences, not just the avoidance of goitrogen-containing plant foods (41, 47). Fischer and colleagues (42) also noted that PTC tasters tended to be ectomorphs (manifesting a thin and angular body type), whereas nontasters tended to be endomorphs (manifesting generous body proportions). The early recognition that tasters and nontasters manifest different body shapes served as the springboard for the current interest in this topic. Taken together, these original findings suggested that this trait had broader implications for human health and nutrition than simply guiding the momentary decision to select one food over another.

In the ensuing decades, a growing literature has addressed the role of this phenotype in contemporary patterns of food selection, dietary behavior, and weight status. However, a striking feature of this literature is the large number of conflicting findings, which make the overall gains in this field difficult to appreciate. Two factors strongly contribute to this disparity. First, the lack of standardized screening methods for PTC/PROP taste sensitivity makes valid, across-study comparisons difficult to assess. This is especially relevant for interpreting negative findings that could arise from a true null effect or merely the failure to detect genuine differences when they do exist. Second, most studies assessing the relationship between PROP and food behaviors ignore the myriad of factors that are known determinants of human food selection, including attitudes about health and nutrition, cognitive controls on eating, and personal traits such as food neophobia (the fear of new foods). On balance, studies considering these mediating variables have had more favorable outcomes.

The primary focus of this review is on genetic variation in taste sensitivity to PTC/PROP and its implications for food choice and body weight. The contribution of other receptors (both bitter and nonbitter) to human taste variation is also considered, although data remain scarce in several of these areas. The goals of this review are to evaluate the current literature in light of the weakness identified above, identify current gaps in knowledge, and suggest critical areas for future investigation.

Glucosinolates: sulfur-rich compounds from Brassica vegetables that are hydrolyzed by myrosinase enzymes to isothiocyantes

CHARACTERISTICS OF PTC/PROP TASTING

It was originally believed that PROP/PTC was transmitted as a simple Mendelian recessive trait. However, findings emerged that were at odds with this inheritance pattern (i.e., nontaster parents producing taster children), suggesting that this model was incomplete (16). Although the exact mode of transmission of PTC remains uncertain, it has features intermediate between a simple and a complex trait (22).

Taste blindness to PROP/PTC has been found in virtually all populations around the globe. However, the frequency of nontaster individuals within a population varies markedly by race and ethnicity. The estimated frequency of nontaster individuals among Caucasians is ~30%. Estimated frequencies of nontasters are generally lower (~10%–20%) in populations studied in China, Japan, and sub-Saharan Africa, but can exceed 50% in some subgroups studied in India (56). The reason(s) for this worldwide diversity is unclear.

Taste sensitivity to PROP/PTC is a stable and reliable trait with high test-retest reliability ($r = 0.75$–0.85) (58, 68, 127). However, gender, and to a lesser extent, age, can influence the expression of the phenotype. The percentage of nontasters does not differ by gender in young children (48, 67, 85, 117). However,

Supertasters: persons experiencing extreme bitterness from PTC and PROP

when tested at or near puberty, comparatively more males are nontasters and more females are tasters (50, 118), and this dichotomy persists into adulthood. Thus, it seems likely that sexual maturation plays some role in PROP taste sensitivity, but the nature of this involvement is poorly understood. One report suggested that PROP/PTC sensitivity decreased precipitously with increasing age (32). However, most other studies agree that sensitivity to PROP/PTC declines slowly across decades of adult life (48, 117).

Bartoshuk and colleagues (7) first recognized the existence of a small subgroup of tasters called "supertasters" who perceive extreme bitterness from PTC/PROP. Approximately 25% of individuals from a given sample are supertasters. Supertasting is typically more common among women than men for reasons that remain obscure. Since supertasters also perceive greater intensity from many other oral sensations (see below), correct identification of this subgroup would be important for linking this phenotype with dietary behavior.

PROP/PTC AS A GENERAL MARKER FOR ORAL SENSATIONS: THE ROLE OF SUPERTASTING

There is considerable anatomical evidence that individuals who differ in taste sensitivity to PROP/PTC also differ in the density of fungiform taste papillae on the anterior surface of tongue (7, 38, 108, 123). Nontasters have the lowest density of fungiform papillae, whereas supertasters have the highest density. Moreover, lingual tactile acuity is strongly positively correlated with taster status (38), with supertasters having greater sensitivity to touch on the tongue (123). In rodents, the fungiform papillae are richly innervated by taste (chorda tympani) fibers and surrounded by trigeminal fibers (119). A similar configuration is thought to exist in humans (113). The trigeminal nerve responds to noxious stimuli (chemical irritation, thermal heating and cooling) as well as tactile sensations arising from the thickness and viscosity of food in the mouth (76). Presumably, individuals with more functional taste anatomy including greater somatosensory input would have greater ability to discriminate taste, pungency, and texture. These features could explain why supertasters perceive greater intensity from a range of oral stimulation including other basic tastes (such as sweetness), hotness from chili pepper, and the mouthfeel of liquid fats.

METHODOLOGICAL CONSIDERATIONS IN PTC/PROP SCREENING

The lack of standardized methods for screening and classifying individuals by PROP/PTC taste sensitivity has been a leading contributor to the lack of consensus in this field. An in-depth discussion of psychophysical methods is beyond the scope of this text, and readers are referred to several comprehensive reviews on this topic (4, 5). A brief review of common screening methods and their uses and abuses follows.

Screening methods fall into two general classes: threshold determinations that assess the ability of an individual to discriminate low concentrations of a stimulus, and suprathreshold methods that utilize rating scales to assess taste intensity at higher concentrations. Threshold measures are reliable and have a long history of use in the field (58). However, a drawback of the threshold technique is that it is not predictive of taste intensity for PROP/PTC at higher concentrations (4). Individuals who are poor discriminators at threshold (nontasters) may perceive higher concentrations of PROP/PTC to be as intense as those designated as tasters. Thus, thresholds effectively separate tasters from nontasters but do not reliably distinguish medium tasters from supertasters.

Suprathreshold screening methods can involve the presentation of multiple samples to track taste intensity over concentrations or the use a single solution as a point-estimate of taste intensity (7, 104). Impregnated filter papers have also been used (7, 127). Some methods standardize the PROP ratings by comparing

them to another stimulus that does not vary with PROP status. Sodium chloride solutions and audible tones have commonly been used as external standards (6, 104). To complicate matters further, different rating scales have also been used that vary in their sensitivity (4). Once the taste ratings have been collected, different criteria have been used for classifying subjects into groups. These criteria include calculation of the slope of the concentration-intensity function for PROP (relative to a standard, if used), the use of numerical cut-off scores, or sorting based on Mendelian frequencies of taster and nontaster alleles in the population (7, 25, 127). Three issues have been especially problematic.

First, it is well known that standard visual-analog or category scales ("zero" or "very weak" → "very strong") constrict the ratings of individuals who perceive PROP/PTC as intensely bitter (4). This ceiling effect tends to obscure medium and supertaster groups, leading to an overestimation of supertasters in the sample (see, e.g., 32). The labeled magnitude scale (LMS) gives subjects more freedom to express their perceptions (52). The label descriptors are arranged in semilog intervals along the length of the scale, ranging from "barely detectable" to "strongest imaginable oral sensation." A recent innovation of the LMS is the general labeled magnitude scale (gLMS), which expands the top anchor of the scale to include all sensations, including the strongest sound, pain, or light (5). The rationale for this change is that supertasters may have an altered frame of reference for oral stimuli—routinely rating them higher than the other taster groups. Benchmarking the top of the scale with all types of sensations removes this inherent bias. Although there has been a great deal of discussion in the field as to the optimum scale, both the LMS and gLMS have been used successfully to identify taster groups (4, 5, 104) and to detect group differences in a variety of outcome variables including taste perceptions, liking ratings, reported food preferences, and body weight (20, 110, 115, 125).

Second, the use of PROP-impregnated filter papers is popular and lends itself well to population-based studies. However, the technique of soaking filter papers in a supersaturated solution to capture the precipitate on the paper (7, 32) does not control the stimulus concentration across papers. Zhao et al. (127) developed a reliable filter paper method that utilizes a lower PROP concentration and provides consistent delivery of the taste stimulus across papers.

Third, dividing subjects into taster groups based on a hypothetical model of Mendelian phenotypic frequencies (i.e., 25% nontasters: 50% medium tasters: 25% supertasters) (25) is arbitrary. As reviewed above, it is rare for populations to adhere to strict Mendelian proportions in this trait. Also, in a mixed-gender sample, proportionately more females will be supertasters and correspondingly more males will be nontasters. Thus, the phenotypic frequency of taster groups strongly depends on the gender and ethnic makeup of the population under study. In some circumstances, however, PROP ratings are better utilized as a continuous variable (e.g., correlation or regression analysis), and hence it is not necessary to sort individuals into discrete groups.

Several reliable methods for testing adults have been published (5, 104, 127) and validated (97). A subset of these methods (104, 127) is reliable for testing children as young as 8 years of age (50). The screening technique developed by Keller and colleagues (67, 68) showed high test-retest reliability in preschool children after one-year follow-up ($r = 0.92$; $p < 0.001$) (67).

Labeled magnitude scale (LMS): a semi-logarithmic scale with label descriptors used in sensory testing

gLMS: a variation of the LMS that generalizes responses across sensory modalities (e.g., taste, light, sound)

TAS2R38: encodes a bitter taste receptor controlling sensitivity to PTC and PROP

BITTER-TASTE GENES AND THEIR RECEPTORS

Humans possess 25 functional bitter receptor genes that are located in clusters on chromosomes 5p, 7q, and 12p. These genes comprise the TAS2R family of bitter taste genes ("TAS" referring to a taste receptor gene and "2" denoting a bitter taste gene) (15). TAS2R38, the gene that controls PTC taste sensitivity, is localized to chromosome 7q (70). Three single-nucleotide polymorphisms at this locus result in amino acid substitutions at positions A49P, A262V, and V296I, giving rise to the major haplotypes PAV (the taster variant) and AVI (the

TAS2R16: encodes a receptor that recognizes α-glucopyranosides and is involved in alcohol consumption

TAS2R43 and TAS2R44: polymorphisms at these locations are associated with perception of saccharin and acesulfame-K

nontaster variant). PROP-sensitive individuals possess one or two dominant alleles (PAV/PAV or PAV/AVI), whereas insensitive individuals are recessive for the trait (AVI/AVI) (12, 70). The occurrence of other variants is rare (AAV and PVI) or is limited to specific populations (AAI in sub-Saharan Africans) (121). The heritability of this trait is high (0.60) (57).

The TAS2R38 receptor recognizes PTC and PROP, but not other bitter compounds that lack the thiourea moiety. However, PTC binds more strongly than PROP, which suggests that PTC may be an optimum stimulus for this receptor (12). Additionally, the two compounds are not perceptually identical to humans. Threshold sensitivity for PTC is lower than it is for PROP, and the perceptual range for PTC is wider than for PROP. These features suggest that sensitivity to PROP may be controlled in part by other genes or nongenetic factors (12). Linkage analysis has also revealed the presence of a second locus on chromosome 5p associated with the perception of PROP (98). Despite these subtleties, polymorphisms at the TAS2R38 locus account for 60%–85% of the phenotypic variation in this trait (70, 106).

Considerable progress has been made in identifying the specific ligands for the other bitter receptors. For example, in cell-based assays, TAS2R16 recognizes α-glucopyranosides including amygdalin, which is found in apricot pits and bitter almonds, and salicin, a compound extracted from willow bark, which is chemically similar to aspirin (13). TAS2R43 and TAS2R44, which share almost complete homology in amino acid sequence, are activated by the non-nutritive sweeteners saccharin and acesulfame-K, which share structural similarity, as well as aloin and aristolochic acid, derived from the aloe plant (96). Meyerhof (86) provides a comprehensive review of bitter-taste-receptor interactions.

Until recently, TAS2R38 was considered the only bitter taste gene that exhibits prominent phenotypic variation in humans. Consequently, all of the research on genetic variation in bitter taste was focused on this trait. However, recent studies demonstrate substantial variation in TAS2R43 and TAS2R44, both of which exist in several allelic forms (96). Compelling evidence suggests that both genes are responsible for the perception of the bitter side-taste of saccharin. Individuals with at least one sensitive allele for both genes have a low bitter threshold for saccharin, whereas those who are homozygous for the insensitive allele of both genes have a high threshold for the bitterness of saccharin. Interestingly, sensitivity to the bitterness of PTC is unrelated to genetic variation in either TAS2R43 or TAS2R44 (96).

The aforementioned findings imply that assessment of polymorphisms at the TAS2R38 locus alone may not be sufficient to capture the full perceptual diversity of human bitter taste experience. Taking into account the entire repertoire of bitter taste genes, Drayna (22) estimates that 100 different protein-coding haplotypes exist that could contribute to differences in bitter taste perception across individuals. This may be particularly relevant for establishing links between taste genes and nutrition since foods exist as complex mixtures of bitter components that could interact in unique ways to influence food acceptance.

THE GOITROGEN-AVOIDANCE HYPOTHESIS: THEN AND NOW

PROP and PTC contain the thiocyanate moiety (N-C = S), which is responsible for their bitter taste. Isothiocyanates are the breakdown products of glucosinolates that are widely distributed in plants, particularly those of the family Brassicaceae. These include cruciferous vegetables such as broccoli, cabbage, cauliflower, and brussels sprouts (*Brassica oleracea*), Chinese cabbage and turnips (*B. rapa)*, mustard greens (*B. juncea*), and radishes (*Raphanus sativus*) (39). Isothiocyanates interfere with the uptake of iodine by the thyroid gland, leading to goiter, and cretinism in its extreme form. Although iodine deficiency is the primary cause of this disease, goitrogens in the food supply can play a contributing role, particularly when dietary iodine is marginal. In areas of the world where the iodine content of the soil is low (so-called

goiter belts) and the glucosinolate content of the diet is high, goitrogen overload can occur (17). According to the goitrogen-avoidance hypothesis, PTC tasters would be better protected against the overconsumption of dietary goitrogens and less likely to suffer from their toxic effects than would nontasters. Indeed, Shepard (103) demonstrated that a large percentage of athyroidic cretins in a clinical population in the United States were PTC nontasters. Also, while studying isolated communities in the Andes Mountains of Ecuador, where goiter was endemic, Greene (53) observed that nontasters had more severe neurological deficits than did tasters.

Presumably, if avoidance of dietary goitrogens were critical to survival fitness, then selective pressure would maintain the taster allele at a high frequency; the nontaster allele would no longer be conserved. This does not seem to be the case for PTC, given the high frequency of nontaster alleles in human populations worldwide. Rather, this trait may be maintained by balancing selection, where both positive and negative selective pressures act to maintain both alleles at high frequency (120). Wooding et al. (121) have proposed that the nontaster allele codes for a variant of the TAS2R38 receptor that responds to another toxic bitter phytochemical not yet identified. If this phytochemical occurred in indigenous plants in specific geographic locations, this could explain the wide diversity in nontaster alleles across different human populations worldwide.

This trait would appear to have little relevance to modern consumers since iodinization of salt is universally practiced in industrialized countries, and the incidence of dietary iodine deficiency is rare. Nevertheless, this trait could have important nutritional implications for reasons unrelated to goitrogen toxicity. Glucosinolates are known to exhibit potent anticancer properties by inhibiting the activation of carcinogens by cytochrome P-450 (phase 1) enzymes and by inducing phase 2 detoxifying enzymes (40). Diets high in fruits and vegetables, especially cruciferous and dark-green leafy vegetables, have been consistently associated with lower incidences of cancer (87). However, despite decades of nutritional recommendations strongly encouraging greater consumption of fruits and vegetables, intakes remain low (54). Bitter taste is the primary reason why consumers avoid these foods (23). In addition, the food industry routinely debitters foods using selective breeding practices and chemical modification, thereby reducing or eliminating the very compounds that provide the benefits. Thus, the greater sensitivity to bitterness that once protected humans from toxins could be undermining the adoption of more healthful food choices by today's consumers. On the other hand, Mattes (83) has argued that taste genetics has a negligible influence on everyday eating because consumers simply modify their foods with salt, fat, sugar, and other ingredients to reduce bitterness and enhance palatability. Additional study of this phenotype will eventually determine its overall importance to human nutrition and health.

LINKS TO FOOD ACCEPTANCE AND SELECTION

The overarching hypothesis guiding research in this field is that tasters perceive more intense bitterness, sweetness, oral irritation, and mouthfeel than do nontasters, and that these differences have opposite influences on food acceptance and selection. Tasters are hypothesized to dislike and avoid overtly bitter and strong tasting foods whereas nontasters are hypothesized to prefer and consume such foods.

The phrases "food acceptance" and "food selection" are used to describe a variety of food-related behaviors, including hedonic ratings for tasted foods, reported food preferences, self-reported intakes (from food records or frequency questionnaires), and direct observation of intake in a laboratory or seminatural setting. These measures are useful for capturing different aspects of food choice, but no single measure is ideal for predicting habitual patterns of food intake over time. This shortcoming applies broadly to studies linking taste with dietary behavior and is not unique to this literature.

Finally, many taste studies utilize laboratory solutions and model systems as surrogates of real foods and beverages. However, laboratory-modified samples lack gustatory complexity and may not provide the same sensory experiences as real foods. Thus, results obtained with laboratory solutions should be interpreted with some degree of caution.

Bitter Vegetables

Early work suggested there was an inverse relationship between the ability to taste PTC and reported preferences for glucosinolate-containing vegetables (41, 47). However, several subsequent studies provided only limited support for this hypothesis. PTC/PROP status was not associated with the dislike of cruciferous vegetables by elderly women (89) or college students (82). One study showed that the reported use of some *Brassica* vegetables but not others was negatively associated with PTC taste sensitivity (63). A study in young women reported that PROP supertasters had lower preferences for Brussels sprouts, cabbage, and spinach than did nontasters (28). However, two studies in a clinical sample of older women with newly diagnosed breast cancer reported conflicting results (25, 26). The earlier study showed that higher responsiveness to PROP was associated with lower preferences for cruciferous and other green vegetables (26). The more recent study found no meaningful differences among taster groups in either reported preferences or intake of bitter vegetables (25). Using a structural modeling approach that considers multiple variables simultaneously, Dinehart et al. (20) showed that greater sensitivity to PROP predicted lower preferences for the bitterness of Brussels sprouts, asparagus, and kale, which in turn predicted lower preferences and frequency of vegetables consumption. Age and vegetable sweetness were also positive predictors of vegetable preferences.

A number of studies examined the acceptance of bitter vegetables (among other foods) as a function of PROP taster status in children. Two studies in preschoolers showed that nontaster children gave higher liking ratings than did taster children to tasted samples of raw broccoli (9, 67). Two other studies in slightly older (5–7 years old) children assessed food preferences using an order-by-choice task and a hedonic rating task (2, 114). Taste sensitivity to PROP was not related to hedonic ratings of tasted samples of raw broccoli in either study, but in the second study, children who were less sensitive to PROP gave higher hedonic ratings to spinach than did those who were more sensitive to PROP (114). The order-by-choice task did not reveal differences in preference for bitter vegetables in either study.

Bell & Tepper (9) investigated the role of PROP status in children's selection and consumption of vegetables in a seminaturalistic setting (see **Figure 1**). When offered a choice of vegetables as a snack, nontaster children consumed more bitter vegetables (raw broccoli, cucumbers, and black olives) and more vegetables overall than did taster children. Nontaster children consumed almost one serving of vegetables during the test relative to taster children, who consumed a total of one-half serving of vegetables during the test. If these responses were repeated across meals and days, they could make an important contribution to habitual patterns of vegetable intake in children. So far, this novel finding has not been followed up with more long-term studies, but such investigations are clearly warranted. Noteworthy, however, are the results of a recent epidemiological study showing that AVI/AVI (nontaster) individuals consumed more cruciferous vegetables than those with one or two alleles of the sensitive (PAV) form (102a).

Finally, the prevailing view in the field is that the PROP phenotype serves as a general marker for bitterness perception. However, the results of a recent study challenge this point of view. Sandell & Breslin (102) showed that PROP-sensitive (PAV/PAV) individuals gave higher bitterness ratings than did PROP-insensitive (AVI/AVI) individuals to glucosinolate vegetables but not to nonglucosinolate, bitter vegetables, suggesting that PROP status was a specific

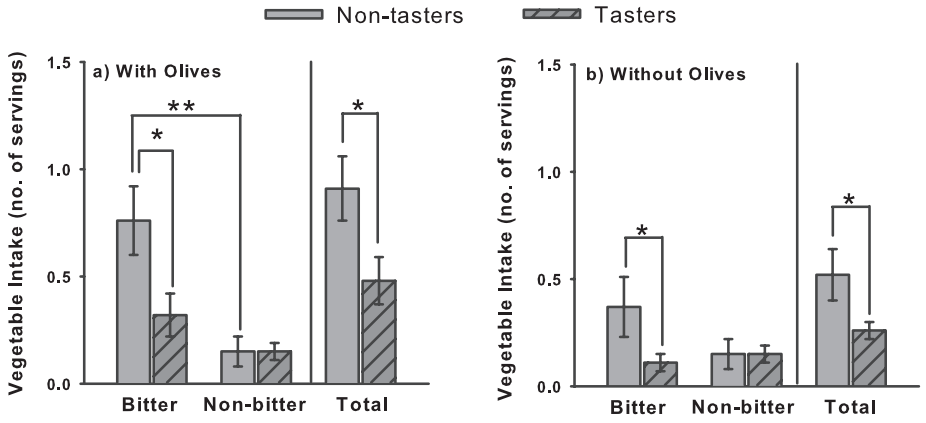

Figure 1

Mean number of vegetable servings (± SEM) consumed by nontaster and taster preschool children during a free-choice snack test. (*a*) Vegetables were grouped into bitter (black olives, cucumber, raw broccoli) and nonbitter (red peppers, carrots) categories. Nontasters consumed more bitter vegetables than nonbitter vegetables. Additionally, nontasters consumed more bitter vegetables as well as more vegetables overall than did tasters. (*b*) Black olives (which are nutritionally classified as fats) were removed, and the analysis was repeated. Nontasters consumed more bitter vegetables and more vegetables overall than did taster children. $^{*}p < 0.05$; $^{**}p < 0.01$. Reproduced with permission of American Society for Nutrition (9).

marker for the bitterness of glucosinolates. This finding agrees with the results of some experiments with laboratory solutions showing that PROP bitterness ratings are not correlated with bitterness ratings for other bitter compounds (18, 57). Future studies will need to reconcile these opposing findings, particularly as they relate to vegetable preferences.

Citrus Fruit

A few studies investigated the influence of PROP status on the acceptance of bitter citrus. A study in women showed that supertasters gave lower acceptance ratings to aqueous solutions of naringin (from grapefruit peel) as well as lower reported preferences for grapefruit juice (27). Two studies in preschoolers came to opposite conclusions yet nevertheless revealed that taster children respond to differences in taste intensity. The first study showed no difference between taster groups in liking of a 25:75 grapefruit-orange juice blend (67). However, the second study used a 50:50 grapefruit-orange juice blend and found that taster children liked the sample less than did nontaster children (105).

Alcohol

The hypothesis that greater taste sensitivity to PROP influences the oral sensation of alcohol and serves as a deterrent to the consumption of alcohol has received some attention. Several studies have shown that tasters perceive more bitterness from beer (62) as well as more irritation from ethyl alcohol (36) and red wine (92). In another investigation, PROP status was a negative predictor of the oral sensation of alcohol and alcohol consumption (34). In that same study, polymorphisms at the TAS2R38 locus predicted alcohol intake but not the oral sensation of alcohol. A subsequent study by the same laboratory in college students showed that PROP bitterness did not predict alcohol intake directly (74). However, PROP bitterness did influence the perceived bitterness and sweetness of Scotch whiskey, which in turn influenced alcohol intake (74). It is not known if PROP status affects total energy intake via alcohol consumption or the consumption of active compounds from alcohol (e.g., catechins), both of which have long-term health consequences.

A possible link between PROP tasting and alcohol dependence and abuse has also been

suggested (91). In one study, PROP status was associated with two types of alcoholism. College students with a family history of alcoholism alone were more likely to be nontasters, whereas those with a family history of both alcoholism and depression were more likely to be supertasters (19). In another study among college students, male supertasters reported fewer problems with alcohol and less significant family history of alcoholism (33). However, these results were reversed for female supertasters.

Recent evidence suggests that another bitter taste gene, TAS2R16, may also be involved in behavioral responses to alcohol. Two studies suggest a strong relation between the frequency of a specific allele of this gene (N172) and alcohol dependence in an African American population (60, 116). In a study assessing both TAS2R38 and TAS2R16, variation in TAS2R38 was associated with alcohol consumption, whereas variation in TAS2R16 was associated with both alcohol consumption and alcohol dependence in African American high-risk families (116).

Other Bitter Foods

There is some evidence that tasters perceive more bitterness from tasted samples of dark chocolate, black coffee, and caffeine solutions (80, 111), as well as soy products and green tea (1). Supertasters also discriminated added bitterness in yogurt and cream cheese better than did nontasters (94). However, differences in perception did not influence the acceptance of these samples to an appreciable degree. Two reports in children showed that nontasters gave more favorable ratings to cheese than did taster children (2, 67).

Sweet Taste

Studies in adults have shown that PROP supertasters perceived greater intensity from sucrose solutions (45, 78) and were more likely to be sweet dislikers (77). Drewnowski et al. (30, 31, 80) did not replicate these findings, and one study (31) suggested that the differences in liking reported earlier (77) were the result of failure to account for restrained eating in the subjects. A recent study resolved this issue by demonstrating that 67% of supertasters were sweet dislikers compared with 12% of nontasters and that restrained eating and body weight did not influence the results (125).

Non-nutritive sweeteners can have bitter aftertastes that limit the acceptability of diet and reduced-sugar beverages to some individuals. Bartoshuk (3) first reported that supertasters perceived greater bitter aftertaste from saccharin solutions, but this finding was not replicated in another study investigating the perception of saccharin and acesulfame-K solutions (61). More recent studies examined the perception and liking of soft drinks formulated with non-nutritive sweeteners either singly or in blends. One study showed that supertasters perceived greater intensity across all sweeteners and blends in cola beverages (97), and another showed that supertasters perceived greater intensity of bitterness, persistence of bitter aftertaste, and sweetness in citrus soft drinks than did nontasters (128). Neither study revealed a significant influence of PROP status on acceptability of the beverages.

Overall, studies attempting to link PROP status with perception and acceptance of sweetened drinks in adults have not supported this association. Positive findings obtained with laboratory solutions might have overestimated the influence of PROP in real beverages. On the other hand, all of the studies addressing this question have had sample sizes too small to reliably address consumer acceptance. Larger, consumer-based studies are needed to adequately address this issue. Also, because polymorphisms in TAS2R43 and TAS2R44 have been associated with bitter taste threshold to saccharin (96), future studies should explore variation at these loci in relation to preferences for non-nutritive sweeteners.

In contrast to its influence in adults, PROP status has a robust influence on sweet preferences in children. However, the direction of this effect in children is opposite to what is observed in adults. Specifically, taster children

show greater preferences for sweets than do nontaster children. This phenomenon was first reported in a diet study in preschool children, which showed that taster children consumed more sweet snacks (pastries, candy, fruit drinks, and table sugar) and a higher percentage of daily energy as simple sugars than did nontaster children (68). Another study in slightly older children who were grouped by TAS2R38 polymorphisms also showed that tasters preferred higher concentrations of sucrose solutions (in laboratory taste tests) as well as cereals with higher sucrose content (by self-report) (85). Tasters were also more likely to report that carbonated beverages were one of their most preferred beverages. The reasons for this reversal in children are unclear. The authors speculated that the taster children favored sweet foods because other foods were too bitter or strong tasting to them (85). This issue deserves further study in light of current concerns about an excess of sweet carbohydrates in the diets of children. This relationship was absent in the mothers, which suggests that the influence of PROP on sweet preferences fades with increasing age, a conclusion that agrees with the adult studies reviewed above.

Pungency and Flavor

There is clear evidence that PROP sensitivity influences the perception of oral irritation from capsaicin (chili pepper) (66, 95, 108), cinnamaldehyde (from cinnamon) (95), and carbonation (94). Given these results, it is surprising that little work has investigated the role of PROP status in the acceptability of pungent foods. Deciphering this role would be especially complicated because the acceptance of chili pepper is strongly affected by cultural norms, prior experience with spicy foods, and personality traits (101). Studies conducted by Ullrich et al. (115) illustrate how one personality factor, an individual's self-described food adventurousness, can clarify the relationship between PROP status and reported food likes and dislikes. Subjects were classified in two ways, by taster status (taster or nontaster) and by high or low food adventurousness. Tasters who were more food adventurous liked a broad range of bitter and pungent foods, including chili pepper and hot sauce, cruciferous and other bitter vegetables, allium vegetables (onion, garlic, etc.), and distilled spirits. Tasters who were less food adventurous reported liking fewer of these foods. Classification by PROP status alone failed to identify these two subgroups of tasters with divergent food preferences. Also, classification by food adventurousness alone did not illuminate the food preferences of these individuals. Other personal characteristics are likely to play a clarifying role in the relationship between PROP and food preferences and should also be investigated.

One study reported that the aroma of diacetyl (butter flavor) was more intense to supertasters, raising the possibility that PROP-related sensory differences extended to the olfactory system as well (123). It is noteworthy, however, that most flavor compounds are not pure olfactory stimuli and also stimulate nasal trigeminal fibers (21). Thus, it is unclear whether this outcome was due to olfactory flavor stimulation, nasal irritation, or both. The notion that taster status may influence the perception of foods via their aromas or flavors is an intriguing possibility that deserves further attention. Studies have already suggested this might be the case for the flavor of fluid dairy products (59) and the aroma of common foods such as cabbage, grapefruit, tea, and dark chocolate (83).

Salty and Sour Taste

The role of PROP status in the perception of sodium chloride (NaCl) remains controversial. Some studies have shown that NaCl at high concentrations is more intense to supertasters than to the other groups, although the overall magnitude of this effect appears to be small (6, 125). Studies on PROP and salt perception have primarily focused on the validity of using of NaCl as the reference standard in PROP screening. One study showed that PROP threshold was negatively associated

with hedonic ratings for salty solutions (90). Thus far, evidence suggesting that PROP status influences the perception or selection of salty foods is lacking. Only one study examined sour taste and showed that supertasters perceive more sourness in foods and beverages than do nontasters (94).

Fats

Milk provides a convenient medium for manipulating fat content, and a number of studies have been conducted using this stimulus. Most studies (35, 59, 93), but not all (24), have shown that supertasters discriminate fat content and creaminess in laboratory-manipulated, fluid dairy samples more accurately than do nontasters. Kirkmeyer & Tepper (72, 73) further showed that in comparison with nontasters, supertasters used more vocabulary that was more complex to describe creaminess in nine commercial dairy products. Perceptual modeling revealed that supertasters put more weight on flavor/texture attributes in their descriptions of the samples, whereas nontasters depended equally on flavor/texture and basic taste sensations (sweet, sour, salty). Thus, in the absence of strong perceptual cues for fat, nontasters depended more heavily on basic tastes in judging creaminess. A second study in female consumers confirmed the initial findings for creaminess but also showed that liking of the foods did not differ between nontasters and supertasters (73). This finding weakens the argument for a dietary impact of PROP on dairy food selection. However, all the products tested were full fat and were well liked. These studies need to be repeated using low-fat and reduced-fat products that are generally less acceptable than their full-fat alternatives (55). A better understanding of individual differences in creaminess perception could ultimately lead to better formulation of reduced-fat dairy products.

An earlier study by Tepper & Nurse (108) in college students showed that medium and supertasters reliably discriminated a high-fat from a low-fat salad dressing, whereas nontasters could not distinguish the two samples. Moreover, nontasters preferred the high-fat sample, whereas the other groups liked the two samples equally well (109). To date, these findings have not been replicated for other foods or by other laboratories. Another study examined fat and flavor-manipulated pudding, mashed potatoes, chocolate drink, and potato chips, but did not show the expected differences among taster groups (123). The reasons for these discrepant findings are unclear, but differences in study design might provide one explanation. Tepper & Nurse (108) used a simple manipulation of one food. In contrast, Yackinous & Guinard (123) manipulated both the fat and flavor content across several food types that might have posed a more difficult perceptual challenge to subjects.

Other findings suggest that this phenotype might have a greater influence on preferences for fats in females than males. In the preschool studies by Keller and coworkers mentioned above (67), nontaster girls gave higher acceptance ratings to full-fat milk than did taster girls, an effect not seen in boys. In that same study, maternal reports of child intake showed that nontaster girls consumed 2–3 more daily servings of discretionary fats (e.g., vegetable oils, salad dressing, and spreads) than did taster girls. Discretionary fat intake did not differ between taster and nontaster boys. A subsequent dietary study in a similar cohort of children did not replicate the finding for discretionary fats, although nontaster children of both sexes consumed a higher percentage of protein and more daily meat servings than did taster children (68). Finally, a study in college students showed that PROP-tasting females, but not males, consumed a higher rather than a lower percentage of dietary energy from fats (124). Although the results of the latter study were not in the hypothesized direction, they further illustrate the influence of this gender dichotomy on the relationship between PROP and fat selection.

At present, the precise role of PROP status in the selection of fat remains unclear. However, a few general conclusions can be drawn from the current literature. Nontasters are less discriminating of liquid fats that are typically

found in fluid dairy products and discretionary fats. Whether these differences reliably affect habitual intakes of these foods or overall fat intake remains an open question, especially in adults where few published data are available. Evidence in children provides some support for this hypothesis, although additional studies are needed to clarify current findings. An important finding to emerge from these studies was that PROP status can have different influences on taste and dietary selection of fat in males and females. This finding has subsequently provided important insights for interpreting PROP-diet and PROP-body weight relationships.

ROLE IN BODY WEIGHT VARIATION

The role of PROP status in body weight remains highly controversial. Initial studies, which were conducted exclusively in lean individuals, provided inconsistent support for this role. For example, Tepper & Nurse (109) reported a small inverse association between PROP status and body mass index (BMI) (weight[kg]/height[m^2]) in college males but not females. A study in preschool children reported an inverse relationship between PROP status and BMI percentile-for-age in boys, but the opposite effect was observed in girls (67). However, a second study in a similar cohort of children failed to replicate these findings (68). Negative findings have also been reported in studies of lean young women (64) and a mixed-gender sample of lean young adults (124).

Studies in overweight middle-aged women have provided more convincing evidence linking PROP status with body weight. Goldstein et al. (51) showed that nontaster women were heavier than supertaster women by ~6 BMI units. These results are illustrated in **Figure 2**. BMI approached the obese range (≥30 kg/m^2) for nontaster women, whereas BMI was within the healthy range (19–25 kg/m^2) for supertaster women. Additionally, percent body fatness and triceps skinfold thickness were elevated in nontaster women relative to supertaster women. Waist circumference showed a trend in the expected direction but did not differ significantly among the groups. These data suggest that PROP status was inversely associated with overall adiposity in this sample of moderately overweight women, but not with central adiposity. It would be of interest to determine if this phenotype associates with central adiposity in obese individuals, given the links between central adiposity, the metabolic syndrome, and the risk of cardiovascular disease and diabetes.

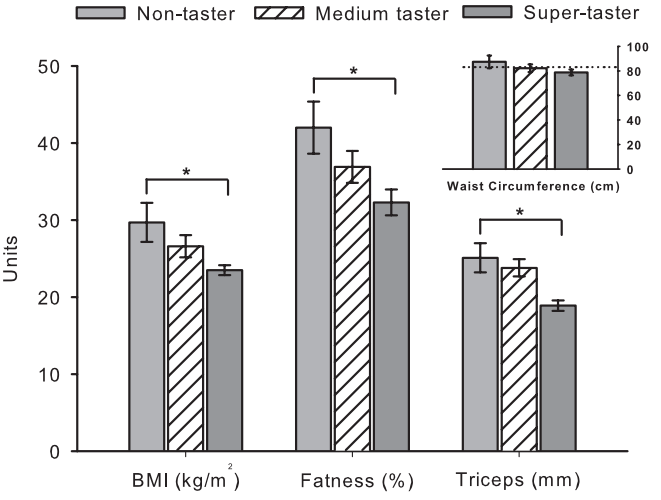

Figure 2

Mean (± SEM) adiposity measures in women classified by 6-n-propylthiouracil (PROP) taste phenotype. In comparison with supertaster women, nontaster women had significantly higher body mass index (BMI) (kg/m^2), body fatness (%), and triceps skinfold (mm). No group differences were found for waist circumference (mm) (see inset). *$p < 0.05$; **$p < 0.01$. These women were the mothers of the preadolescent children described in **Figure 3**. Reproduced with permission from NAASO, The Obesity Society (51).

Goldstein and coworkers (50) also studied the children of the women described in **Figure 2** as part of a larger investigation on the role of maternal factors in dietary intake and body weight in preadolescence. **Figure 3** shows the children's BMI percentile-for-age and reported daily energy intakes (from three-day diet records) as a function of PROP status. BMI percentile-for-age did not differ among the taster groups in this cohort of lean children. However, there was a strong inverse relationship between taster status and energy intake such that nontasters consumed

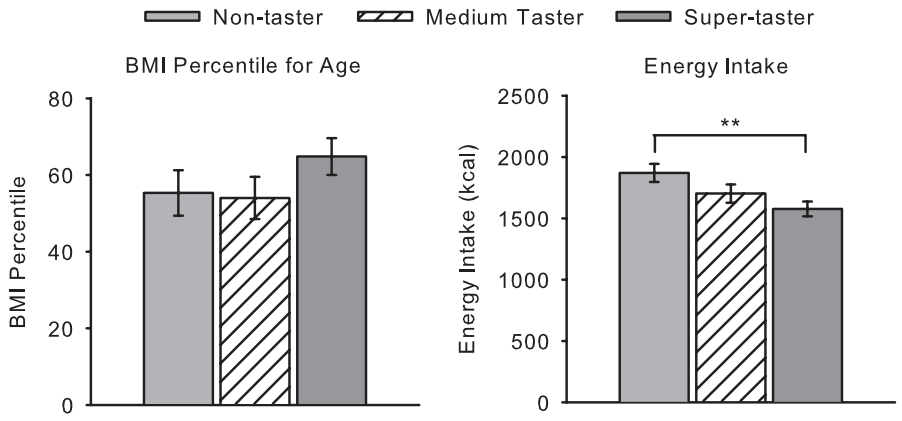

Figure 3

Mean (± SEM) body mass index (BMI) percentile-for-age and reported daily energy intake of preadolescents classified by 6-n-propylthiouracil (PROP) taster status. BMI percentile-for-age did not differ among the groups. However, reported energy intake was higher in nontaster children relative to supertaster children. **$p < 0.01$. These children were the offspring of the women described in **Figure 2**. Modified and reproduced with permission from Elsevier (50).

~300 kcal/d more energy than did supertasters. These data suggest that higher energy intake, a major precursor to weight gain, was already apparent in the nontaster children. One could speculate that if these nontaster children continued to follow this dietary pattern, they could be at risk for increased weight gain later in their lifecycle as observed in the nontaster mothers. One shortcoming of this study was that physical activity was not measured, which could have led to an overestimation of energy differences among the groups. Future studies need to control for daily energy expenditure to more accurately assess group differences in energy intake and body weight relative to PROP status.

Cognitive factors such as dietary restraint (the conscious control of eating) and disinhibition (the loss of control over eating) are considered major determinants of body weight in women (110). However, these variables have generally been overlooked in studies on PROP tasting and may be important for interpreting the relationship between PROP phenotype and body weight. In another study in middle-aged women, Tepper & Ullrich (110) found that restrained eating masked the relationship between PROP status and body weight. In the low-restraint group, the nontaster women were significantly heavier than the supertaster women. However, in the high-restraint group, no PROP-related differences in body weight were found. These findings imply that the food choices of restrained eaters may be more motivated by weight concerns than taste, thereby disrupting the relationship between PROP status and body weight. Results also showed that disinhibition was positively associated with BMI but was not related to PROP status.

The aforementioned studies have been criticized for having small sample sizes and failing to include demographic variables that are strong predictors of body weight (25). However, a third study conducted in >400 inhabitants of a genetically isolated community in Italy further confirmed the earlier findings (106). Regression analysis revealed that among females, age was a positive predictor and PROP status was a negative predictor of BMI when demographic variables and the PROP by dietary restraint interaction term were included in the model. In contrast, age was the only predictor of BMI in males. DNA analysis also revealed that polymorphisms at the TAS2R38 locus were not associated with BMI in either males or females. These data suggest that the PROP phenotype better predicts variation in body weight than

Dietary restraint: conscious control of eating to lose weight or maintain current weight

Disinhibition: loss of control over eating associated with exposure to palatable food and negative emotions

TAS2R38 genotype, and that the trait has a more salient influence on body weight in females than in males. These observations agree in part with the earlier findings of Timpson et al. (112), who reported no association between polymorphisms at the TAS2R38 locus and BMI in a large population of elderly British women. PROP phenotype was not measured by Timpson et al. (112).

Drewnowski and colleagues have consistently reported no evidence for an association between PROP status and body weight in adult men and women (32) or in female breast cancer patients (25, 26). However, these studies are at the focal point of an ongoing debate in the literature about the reliability of different PROP screening methods (4, 5, 51). Several of the methodological shortcomings identified in this review (see Methodological Considerations section above) apply to these studies. Given these outstanding questions, it is unclear whether the null effects observed in these studies are real or represent the failure to discriminate differences that truly exist.

ROLE IN CHRONIC DISEASE RISK

Only a few studies have examined associations between PROP status and disease risk, hence data addressing this issue are scarce. Three studies examined associations between PROP status and cardiovascular risk. No associations were reported between TAS2R38 polymorphisms and cardiovascular risk in the elderly women studied by Timpson et al. (112) or between PROP status and lipid profiles in the breast cancer patients studied by Drewnowski et al. (25). However, preliminary data from another study in elderly women showed that nontaster women had less desirable lipid profiles than did supertaster women (35). Finally, one study reported a modest association between greater sensitivity to PROP and a higher number of colonic polyps in older men undergoing routine screening for colon pathology (8). In a subset of the men reporting diet intake, those who tasted PROP as more bitter reported lower vegetable intakes. These provocative findings suggest that PROP status could provide a link between vegetable intake and colon cancer risk and need to be confirmed with larger, more comprehensive studies.

GENETIC VARIATION IN OTHER TASTE RECEPTORS

TAS1R Receptors

Unlike the TAS2R bitter receptor genes, the TAS1R gene family contains only three members: TAS1R1, TAS1R2, and TAS1R3. The TAS1R gene family encodes receptors for sweet taste and umami taste (exemplified by the savory taste of glutamate). Sweet taste is mediated by a dimer consisting of TAS1R2 + TAS1R3, whereas umami taste is mediated by a dimer consisting of TAS1R1 + TAS1R3 (126). Although some individuals are reported to have weak or no sensitivity to umami taste (79), neither sweet nor umami taste show a bimodal distribution of taste sensitivity typical of PTC and PROP. Nevertheless, recent evidence suggests an unusually high level of genetic diversity in TAS1R2, which codes for the sweet-specific domain of the receptor. Neither TAS1R1, the umami-specific subunit, nor TAS1R3, the common subunit that likely maintains the functional integrity of the dimer, show significant genetic variation. Multiple forms of TAS1R2 might have evolved to sense the large number of structurally divergent sweet substances (71). Linkage analysis has also identified a locus on chromosome 16p associated with sweet taste (69). Heritability estimates for the pleasantness of sucrose and use frequency of sweet foods were 40% and 50%, respectively. These are the first data to suggest that the preference for sweetness is under partial genetic control and could contribute to individual differences in dietary intake of sweet foods.

Fat Detectors

It was previously thought that fat had no "taste" of its own, and the detection of fat was

Gut chemoreception: nutrient sensing by taste cells localized to endoendocrine cells in the gut

mediated primarily by texture and flavor cues (84, 107). This view was reinforced by the lack of any evidence for a specific oral receptor for fat. However, Gilbertson et al. (46) demonstrated that direct application of *cis*-polyunsaturated fatty acids to isolated taste receptor cells of the rat inhibited delayed rectifying K+ channels. Fukuwatari et al. (44) showed that CD36, which regulates fatty acids transport across a variety of cell membranes including adipose tissue and skeletal muscle, was also localized to the surface of taste papillae in rodents. Evidence that this channel serves as a putative fat detector comes from studies demonstrating that CD36 knock-out mice fail to form a preference for linoleic acid (75). Recent psychophysical studies have also shown that humans detect long-chain fatty acids (LCFAs) in the mouth, and this detection is mediated by a variety of cues including taste (14).

There is also limited evidence for human variation in taste sensitivity to LCFA. One study stratified subjects as LCFA tasters and LCFA nontasters and showed that tasters could distinguish linoleic from oleic acid (65). Another study on PROP tasting revealed that PROP tasters reliably discriminated ice cream with added conjugated linoleic acid from control ice cream without conjugated linoleic acid (88). Since CD36 exists in several allelic forms, it is possible that variation at this locus contributes to individual differences in the perception of LCFA. Investigation of the role of PROP and CD36 in fat perception and preference could better characterize the genetic contribution to fat ingestion and shed light on potential links to obesity.

BEYOND GUSTATION—THE ROLE OF GUT CHEMORECEPTION

New findings from the emerging field of gut chemoreception demonstrate the presence of chemoreceptors localized to the endoendocrine cells of the gastrointestinal tract (99, 100). These receptors sense the chemical composition of the luminal contents and initiate endocrine and neural responses that control gastric emptying, gut motility, and hormone release. Functional receptors for glucose, glutamate, and bitter substances have been identified that utilize the same signaling elements as oral taste receptor cells (10, 37, 81). In rodent models, application of the bitter compound, denatonium benzoate, or PTC to these bitter receptors causes a potent release of cholecystokinin (CCK) from endoendocrine cells (100, 122). Moreover, intragastric infusion of denatonium or PTC has recently been shown to activate neurons in the brain stem of mice, and this activation is mediated by CCK and another regulatory peptide, PYY (57a). Thus, it is plausible that intestinal PTC/PROP receptors are involved in satiety responses to food ingestion and that genetic variation in the expression of these receptors could modify these same responses. This novel idea suggests an entirely new role for taste genes in food intake regulatory mechanisms.

CONCLUSIONS AND FUTURE DIRECTIONS

A great deal that has been learned over the past decades supports a role for PROP status as a marker for food preferences and diet selection, with ties to body weight and disease risk. Studies have already shown that gender, dietary restraint, and food neophobia mediate the relationship between PROP status and a variety of study outcomes. Additional variables may be relevant for interpreting these relationships, and efforts to identify these factors should be an ongoing goal. Variables related to food selection might include consumer motives and intentions (such as personal involvement with food) as well as cultural identity and ethnicity. The latter two factors have largely been ignored in PROP-tasting studies and deserve greater attention. For example, it would be important to know the extent to which cultural food experiences interact with PROP status to modify the acceptability of hot and spicy foods or bitter fruits and vegetables.

Obtaining a fundamental understanding of supertasting may be particularly important for moving the field forward. Presumably, the ability of supertasters to perceive greater intensity from nonbitter oral sensations is mediated by greater fungiform taste bud densities and more neural innervation. It is not known if the association between supertasting and these anatomical features is genetically determined or merely coincidental. If a genetic link were discovered (e.g., if alleles controlling taste bud density cosegregate with alleles of TAS2R38), further characterization of this link would help to resolve a longstanding puzzle in the field: Why does TAS2R38 have such broad-based effects on oral sensations outside the realm of bitter taste? Interestingly, a recent study (58a) reported that TAS2R38 polymorphisms and fungiform papillae number did not completely account for heightened responses to PROP, which suggests that another bitter receptor may be involved.

Critical questions also remain about the exact nature of the associations between the PROP phenotype and chronic disease. Thus far, only a few relationships have been examined, and a limited number of covariates have been included in these investigations. As is the case for other complex traits, large, population-based studies using more sophisticated approaches may be needed to confirm and better elucidate the role of this phenotype in human health. Since obesity is a common factor in the etiology of many chronic diseases, determining why the PROP phenotype appears to differentially influence body weight in females would contribute to our understanding of gender differences in disease development.

Finally, data are accumulating on the contribution of other taste genes to individual differences in food selection. The examination of multiple taste phenotypes is likely to provide greater insights into the complexities of human eating behavior than would a single phenotype. Advances in this area could have novel applications in clinical nutrition and weight management. For example, assessing an individual's genetic taste profile or personal taste genome could one day help nutritionists develop more personalized and effective diet strategies.

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The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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