Influence of genetic variation on flavour perception and food choices

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Abstract

In 1932, Blakeslee and Fox published detailed reports on the inability of some people to taste phenylthiocarbamide (PTC), calling this heritable trait 'tasteblindness'. In 2003, the molecular mechanism underlying this trait was finally elucidated. Over the last 15 years, molecular genetics and modern psychophysics have made it clear that this heritable dimorphism is only one of many, some of which are directly relevant to the food supply. Nor are these differences restricted to taste, as other sensory modalities involved in flavour perception also show genetic variability. Here I review some mechanisms involved in systematic variation in chemosensation across individuals, and highlight a few examples that are relevant to ingestive behavior, food choice, and consumer behavior. Other complications are also discussed.

Introduction

Each year, the food industry spends millions of dollars formulating new products and reformulating existing products. For existing products, these efforts typically focus on either product improvement or margin improvement (a euphemism for cost cutting). In both cases, there is an implicit assumption that formulation influences the sensations arising from the food. That is, a classical psychophysical relationship is assumed: if I add more sucrose, my product will get sweeter. In turn, sensations are then assumed to affect the hedonic responses for the food. Finally, it has long and widely been accepted liking drives intake [1, 2], although more precisely, this relationship is heteroskedastic and disliking drives non-use [3, 4]. Whether implicitly or explicitly, extensive resources are deployed in research and development efforts under the assumption that a causal chain linking formulation to sensation to pleasure to use exists [5].

However, at each step along this chain, the relationship between pairs is clearly not perfect (i.e., the correlation is certainly less than one). Accordingly, the final relationship between formulation and use is highly attenuated. As a rough estimate, reasonable values of the individual correlations can be drawn from existing literature (e.g., [2, 6]). As shown in Figure 1, when these values are multiplied together, the potential correlation between formulation and use is between .47 and .12, suggesting total variance in use that can be explained by formulation is depressingly low, somewhere between 2 and 22%. Of course, this is not entirely surprising given the myriad other factors which influence food choices and use, including availability, cost, context, health concerns, prior experience, physiological state, personality, parental modelling, culture, etc. [7-9]. Yet despite this relatively weak relationship, the continued expenditure of substantial resources on formulation and reformulation suggest that despite all these other factors that influence use, the presumed chain outlined here must still have some influence on purchase and use, or the food industry would have abandoned this approach years ago.

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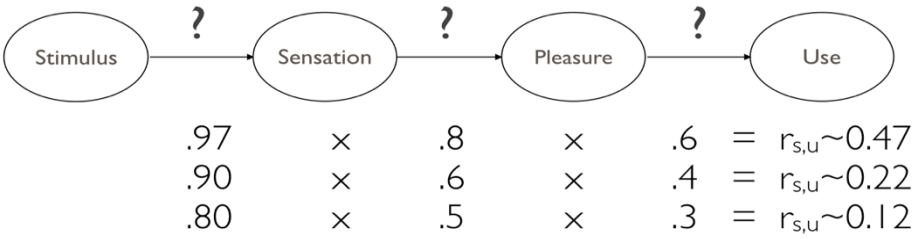

Figure 1: Putative causal chain linking stimulus to use, with estimated correlations between each step

At risk of oversimplification, for many decades, the food industry focused much of their work on formulation and reformulation toward producing foods that please the largest possible number of consumers. Acceptance tests are performed with demographi ically appropriate consumers and sample sizes [10] that allow for interferential statistics to be used, under the assumption that means estimated under controlled laboratory conditions generalize back to the broader population in the real world. Besides the issues inherent to simple measurement error (see discussion in [5]), this also leads to what I call *the paradox of the modern product development process*.

Specifically, sensory and market research studies typically use mean liking or acceptability to predict liking in some population, while decisions about what to eat are typically made at the level of the individual, and critically, individual vary. This is similar to the dilemma currently faced by the pharmaceutical industry, wherein clinical trials for new drugs are based on average responses while individuals differ in their responses to these drugs. There, one proposed solution is to use genetics to understand this variation (i.e., pharmacogenetics) towards a goal of personalized medicine [11]. Similarly, genetics can be used to systematically understand differences in chemosensation that may influence food choices and dietary behaviour [12]. That is, in addition the influence of formulation shown above, genetics also has the potential to influence the sensations from foods, with downstream implications for liking and use of various foods.

Sources of genetic variation with the potential to influence chemosensation

By some estimates, humans share about 99.9% of their genetic information. That is, given a total of ~3 billion base pairs in our DNA, on average, two randomly selected individuals will differ by about 3 million basepairs (i.e., 1 in 1000 basepairs). This variation can be broadly grouped into three categories: substitutions of individual basepairs, insertion or deletion of a string of basepairs, or structural variation. Here, I will focus on the first and third, as there is more evidence of meaningful variation in relation to flavour, with the caveat this may change in the future, as this is an active area of research.

When an individual nucleotide basepair is changed (e.g., Thymine for Cytosine), this is called a single nucleotide polymorphism, abbreviated SNP, and pronounced “snip”. Within sections of DNA known as coding regions, base pair triplets encode which specific amino acid is transcribed, so a SNP may or may not alter the resulting amino acid sequence. If the nucleotide substitution does not change which amino acid is transcribed, the SNP is termed a “synonymous SNP”, as it typically assumed that such variation does not meaningfully influence the protein structure. Conversely, a “non-synonymous SNP” results in a different amino acid being transcribed, with the potential to alter the secondary

or tertiary structure of the protein, depending in the chemical properties of the amino acid. In the case of taste or smell receptor proteins, this can affect the binding pocket, resulting in altered receptor function. Separately, SNPs also occur in so-called non-coding regions of DNA. Despite being outside the gene per se, these SNPs can also influence protein expression, as SNPs in the promoter region of a gene can influence regulatory mechanisms that control when a gene is turned on or off.

Small groups of SNPs are inherited together, meaning variation at one point in the genome may not be statistically independent from variation at another spot. Known as linkage disequilibrium (LD), this results in haplotypes, where a set of SNPs cluster within or even across genes. Critically, the existence of haplotypes can explain why robust statistical associations between SNPs and specific outcomes may still be false positives, mechanistically speaking. An example of this will be given below.

A separate source of variation with the potential to influence flavour perception comes from a type of structural variation known as a copy number variant (CNV). In a CNV, a large section of DNA, typically in excess of a kilobase (1000 basepairs), is repeated one or more times. Higher CNVs influence the level of protein that is expressed, with the downstream potential to influence flavour perception.

TAS2R polymorphisms, perception and behaviour

The best known and studied example of taste variation is the ability or inability to taste a small class of structurally similar compounds that contain a thiourea moiety [13, 14]. 'Tasteblindness' to PTC was briefly described in April 1931, followed by a more detailed formal report by Fox in 1932 [13]. Almost immediately, Snyder [15] and Blakeslee [16] each replicated Fox's initial finding, and more critically, showed that this dimorphism was heritable. In 1932, Blakeslee and Fox conducted a 'Taste Exhibit' at the American Association for the Advancement of Science meeting held in New Orleans in December 1931 and January 1932 [17], where they noted that "*Thomas Jefferson said all men are created equal, but he had not tried [phenylthiocarbamide] crystals. Taste tests show people are different. Our world is what our senses tell us. Each [of us] lives in a different world*." However, PTC is synthetic, so why would we have evolved the ability to taste it? In 1950, Boyd [18] concluded this ability must have evolved to protect us from natural anti-thyroid toxins found in plants, like 5-vinyloxazolidine-2-thione. (Interested readers should see [19] and [20] for more on early work in this area).

The ability to taste PTC and related compounds, like 6-n-propylthiouracil (PROP), is due to SNPs in the *TAS2R38* bitter receptor gene (HGCN: 9584). Three SNPs result in amino acid substitutions (Pro49Ala, Ala262Val, and Val296Ile) that alter receptor function [21, 22]. In Americans of European ancestry, the minor allele frequency of the Pro49Ala SNP is high (~.43), and the linkage disequilibrium (LD) with the other SNPs is strong, resulting in 2 common (PAV and AVI) and 4 (AAI, AAV, PAI, PVI) rare haplotypes. Diplotypes are roughly balanced between the common haplotype homozygotes (25% AVI/AVI, and 23% PAV/PAV), with proportionally more AVI/PAV heterozygotes (43%). The balance (~9%) have rare diplotypes. Of the 2 common haplotypes, the PAV variant associates with greater suprathreshold bitterness and lower (more sensitive) thresholds, while the AVI variant associates with less bitterness and higher thresholds (e.g., [23, 24]); the rare haplotypes show intermediate phenotypes [25].

Despite PTC and PROP being synthetic compounds not found in nature or the food supply, tasteblindness is not merely an academic curiosity. As presaged by Boyd's speculation, responses to 5-vinyloxazolidine-2-thione (i.e., goitrin), show the same (but

weaker) patterns of responses as PTC and PROP for PAV homozygotes, heterozygotes and AVI homozygotes [26]. Indeed, recent work on *TAS2R38* variation and vegetable intake is highly consistent with earlier work associating PROP phenotype with vegetable intake (e.g., [27, 28]). Specifically, PAV carriers report more bitterness from vegetables [29, 30], lower liking [30], and thus less intake [31], in general agreement with the model in Figure 1. Work by Duffy et al. [31] suggests these effects are not small: AVI/AVI homozygotes (i.e., those who experience the least bitterness) reported eating vegetables much more frequently than heterozygotes or PAV homozygotes (roughly 700 versus 400 times per year). Also, these findings seem to be robust, as similar effects on intake have also been reported in Italians [32], Brazilians [33], and Finns [34].

The influence of *TAS2R38* variants on diet is not limited to vegetables, as multiple studies show an association with alcohol use. Using a quantity-frequency measure in non-dependent European-Americans, Duffy et al. found PAV homozygotes drank less than heterozygotes, who drank less than AVI homozygotes [35]. Hayes et al. replicated this for both drinking occasions and total intake [36]. In older white mostly male cancer patients, *TAS2R38* SNPs associated with drinking frequency and heavy drinking frequency, but not drinks per drinking day [37]. In Mexicans, drinker status associated with the *TAS2R38* Pro49Ala and Ala262Val SNPs [38]. In older Australians undergoing colonoscopy, intake associated with *TAS2R38* Pro49Ala SNP (although effects varied by gender and beverage type) [39]. Again, consistent with the model in Figure 1, these associations appear to be mediated via differences in bitterness [40] and liking [41].

Critically, *TAS2R38* is only one of 25 different bitter receptor genes in humans, and several others also appear to have functional polymorphisms that potentially influence ingestive behavior and food choices. For example, *TAS2R31* (formerly *TAS2R44* before being renamed; HGNC: 19113) is activated by numerous ligands including the plant derived compound aloin and the sweeteners saccharin and acesulfame potassium (aceK). SNPs in *TAS2R31* alter receptor function and associate with differences in the bitterness from saccharin and aceK [42, 43]. As would be expected, this SNP also associates with differential liking of aceK [44]; whether it also predicts differences in use of aceK or saccharin containing products is currently unknown, at least in the open literature. Separately, yet another variant, the Val96Leu SNP in *TAS2R4* (HGNC: 14911), associates with differential bitterness of the non-nutritive sweetener stevioside [45].

Finally, it should be noted that all these SNPs and haplotypes are unrelated and independent of each other. That is, the bitterness of PROP is unrelated to the bitterness of saccharin or aceK [43, 46], and the bitterness of the sweetener aceK does not predict the bitterness of stevia derived sweeteners like rebaudioside A [47]. This highlights that being sensitive to bitterness is not a monolithic trait where an individual is universally a sensitive or insensitive responder. Indeed, back in 1932, Blakeslee and Fox [17] noted “a person may be an acute taster for one kind of bitter but a poor taster for another.”

Odorant receptor variation, food sensations, and affective responses

Like taste receptors, odor receptors are G-protein coupled receptors (GPCRs) that bind ligands, initiating the signal cascade we eventually perceive as a sensation. And like taste receptor genes, genetic variants have the ability to alter sensation. The observation that individuals are smell blind to specific odorants is not new, as Amoore first described what he called specific anosmia a half century ago [48]. However, unlike taste, direct evidence of the influence on food liking and intake is much more sparse. The best example to date is the meat defect known as boar taint. Androstenone is a hormone

produced in the testicles of male pigs, and this steroid can be found in adipose tissue. Notably, not all humans can smell this compound, but those who do describe it as having a sweaty / urine-like character. In humans, the *OR7D4* gene contains multiple SNPs, two of which (R88W and T113M) are in very strong LD, resulting two common haplotypes: RT and WM. When the RT/RT homozygotes are compared to RT/WM heterozygotes, or the WM/WM homoyzygotes, they report more intense as well as less pleasant sensations from pure androstenone sniffed in a laboratory setting [49]. Notably, these effects also generalize to cooked meat samples spiked to contain varying levels of androstenone: the RT/RT individuals dislike the androstenone samples significantly more [50]. To date, there is no published data showing this variant influences food intake, but this seems highly likely, as can be attested to by anyone who has ever been served tainted pork. Other examples of genetic variants in odor receptors that may potentially influence food choice include β-ionone [51], guaiacol [52], and cilantro [53].

Influence of genetics on texture perception

There is some evidence that texture perception differs across people due to genetic variability, at least with respect to starch. Salivary amylase is encoded by the gene *AMY1*, and humans have between 2 and 15 copies [54]. As with other CNV (see above), this has the potential to influence the amount of protein produced. In the case of salivary amylase, those with higher copy numbers have both higher amounts of amylase and higher amylase activity [55, 56]. Because salivary amylase begins breaking down starch while it is still in the mouth, this has the potential to influence texture perception. Indeed, those with great amylase activity experience faster breakdown and greater overall changes in perceived viscosity [55]. There is no evidence that *AMY1* CNV influences food liking or intake to date, but this may change as this is an active area of research.

Further complications: perceptual interactions and false positives

Despite the model given above, it is not sufficient to know the stimulus concentration in the food and the genetic makeup of the consumer. Even if they could each be measured perfectly, that ignores the key role of interactions that occur centrally [57]. Mixture suppression describes the phenomenon that occurs when two qualitatively distinct stimuli are mixed: in a mixture, the intensity of each quality is lower than the intensity would have been had the same stimulus been given in isolation. For example, sweetness from sucrose suppresses the bitterness from caffeine; the reverse is also true, although the effect is smaller [58]. This asymmetry is consistent across studies [59, 60], meaning that sweetness reduces bitterness more than bitterness reduces sweetness. Critically, such interactions can influence liking in non-intuitive ways: bitterness is normally aversive, but adding small amounts of quinine to concentrated sucrose can actually increase pleasantness ratings, due to mixture suppression [59]. Nor are such effects limited to model systems. Grapefruit juice is both sweet and bitter. Accordingly, when *TAS2R* variants cause some individuals to experience more bitterness from grapefruit juice, they also tend to experience less sweetness, presumably due to mixture suppression; as expected, more bitterness and less sweetness lead to lower liking [36].

Additional complications come from false positives that can arise from haplotypes within and across genes. For example, multiple studies have consistently suggested the Arg299Cys SNP in *TAS2R19* (neé *TAS2R48;* HGNC: 19108) predicts the bitterness of quinine and grapefruit juice [36, 61] and liking of grapefruit juice [3, 36]. Critically however, newer data show the *TAS2R19* Arg299Cys SNP is in strong LD with *TAS2R31*

SNPs, which also predict grapefruit liking and quinine bitterness [62]. As the major bitter constituents from grapefruit juice fail to activate hT2R19 receptors in vitro, this suggests prior findings for *TAS2R19* were false positives, at least mechanistically.

Conclusions

Flavour is, ultimately, a perceptual construct that occurs within a human, so it must be studied interdisciplinarily using multiple levels of analysis. There is a causal chain from stimulus to food intake, via sensation and affect, even if we only focus on one narrow part of this chain within our own research. Biologically driven differences in perception are very common, and exist for taste, smell, and texture. This ubiquity also implies that past work with very low numbers of observers need to be interpreted cautiously. Further work is needed to better understand how flavour drives food choices.

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