

Taste and Nutrition

2. Effects of genetic disposition and environmental factors on taste perception

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Taste preferences and aversions determine what we eat and drink and thus considerably impact our health. Following the previous contribution about the physiological basis of taste¹, we now discuss the effects of genetic variability and of environmental factors on taste perception and nutrition. The article to follow will describe the development of preferences and aversions.

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Introduction

Like color of eyes and hair, or blood group, the ability to taste is one of our individual characteristic traits that together shape our appearance or phenotype. In essence, our genes and environmental factors define the phenotype. For example, identical twins who are genetically identical differ in numerous phenotypical features if they grew up in different environments. Also non-identical twins differ in numerous phenotypical properties simply because of their different genotypes even if they grew up in the same family and were thus exposed to the same environment. Thus, the combination of genetic disposition and environmental influences creates, in the population, phenotypical variabilities in traits of different extents that include differences in taste perception among which differences in sensitivity can be easily diagnosed.

In the present article we will first discuss how the genome determines our perception of taste. In the second part of the contribution we will describe how environmental factors influence taste perception.

Taste perception and genetic variability

Genetic basis for the bitterness of thioureas

In the beginning of the 1930s Dr. Arthur L. Fox, researcher at *Du Pont de Nemours*, a leading chemical com-

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Summary

Taste receptor genes, particularly those for bitterness, are subject to extensive genetic variation which generates receptor variants with altered functions ranging from slightly diminished responsiveness to complete lack of function. This causes perceptual differences in the population that are confined to taste sensitivity. Even if it is disputed, the perceptual differences or the responsible genes have been associated with dietary parameters identifying taste as a critical determinant for nutrition and health. The taste system is vice versa under the influence of external factors which can transiently adapt taste to physiological requirements or disturb perception.

Keywords: Taste perception, genetic variability, taste receptors, environmental factors

pany, incidentally discovered the first 'taste blindness', i. e., the inability to taste a particular chemical substance (see ref. [1] for an overview). When weighing out phenylthiocarbamide (PTC), a synthetic thiourea derivative, one of Fox's colleagues complained about the bitter taste evoked by small particles that polluted the air in the laboratory whereas Fox himself did not perceive the bitter taste. The difference is explained by the fact that the threshold concentration of this substance, i. e., the lowest noticeable concentration, is more

than 100fold higher in insensitive subjects like Fox than in sensitive subjects like Fox's colleague (♦ Figure 1). Similar differences in taste sensitivity were later discovered also for other synthetic thiourea compounds including propylthiouracil (PROP).

Interestingly, the ability to taste PTC and PROP is independent of gender, age, or ethnical group. Instead, it is genetically inherited in a way similar to that of the ABO blood groups [1].

Only in 2003, the gene for the bitter receptor TAS2R38 has been identified

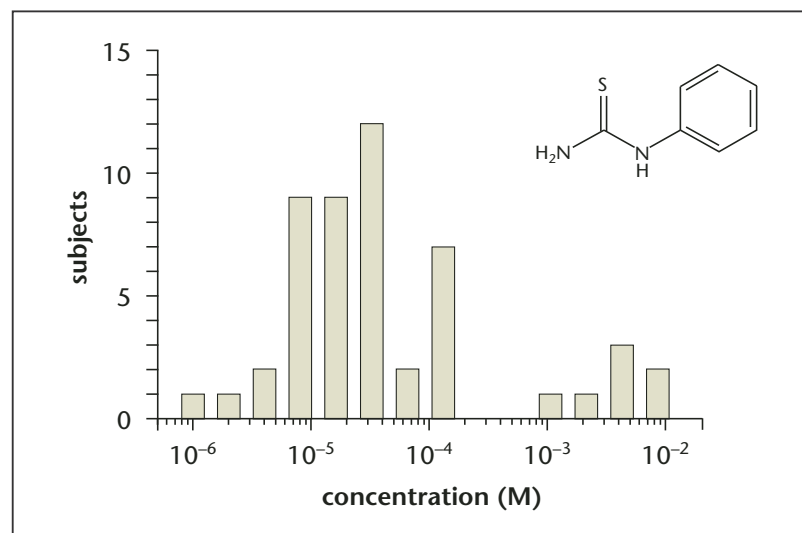


Fig. 1: **Distribution of the perceptual thresholds (lowest recognizable tastant concentrations) for PTC in a group of human subjects.** The bimodal distribution of the peaks at $3.2 \cdot 10^{-5}$ M and $4.1 \cdot 10^{-3}$ M is clearly evident [33].
PTC = phenylthiocarbamide, a synthetic thiourea derivative

as the determining factor for the bitterness of PTC [2]. The TAS2R38 gene occurs in two major variants that differ in the sequence of their nucleotide building blocks at three positions. Such genetic differences are referred to as single nucleotide polymorphisms (SNPs). The two gene variants give rise to two TAS2R38 receptor variants that also differ in three positions in the sequence of their amino acid building blocks. The affected positions of the polypeptide chain show either a proline or an alanine residue or an alanine or valine residue or a valine or isoleucine residue. Therefore, the receptor variants are designated as TAS2R38-PAV or TAS2R38-AVI. Researchers quickly discovered that in appropriate test assays the receptor variant TAS2R38-PAV responded strongly to minute concentrations of PTC, PROP and other thioureas, whereas the TAS2R38-AVI variant was completely insensitive to these compounds [3] (◆ Figure 2).

In total agreement with these findings, it was also found that subjects who inherited from both father and mother the inactive TAS2R38 variant, or in other words, who exhibit the TAS2R38-AVI/TAS2R38-AVI genotype, do not perceive the bitterness of thioureas. These subjects

have been termed PTC non-tasters. Subjects with the genotype TAS2R38-PAV/TAS2R38-PAV are on the other hand sensitive PTC tasters. Heterozygotes with the TAS2R38-PAV/TAS2R38-AVI genotype are also able to perceive the bitterness of thiourea compounds [3]. It is obvious that the frequency distribution of the TAS2R38 gene variants determines the fraction of subjects in a population who can taste PTC and other thioureas. In Western Europe, the proportion of PTC tasters is about 70% whereas it has 30% non-tasters.

Further research revealed that TAS2R38-PAV carriers are not only sensitive to synthetic thiourea derivatives but also for similar natural compounds such as goitrin, a mustard oil glycoside found in various cruciferous plants, or sinigrin, a bitter principle of cauliflower. Indeed, TAS2R38-PAV carriers described various vegetable plants containing mustard oil glycosides to be more bitter compared with TAS2R38-AVI carriers. However, both groups did not differ in their bitterness ratings for vegetable plants that contained other bitter substances but no mustard oil glycosides [4].

Since bitterness is a major factor for food preferences, these findings pro-

pose that genetically determined differences in bitter perception are relevant for diet. Numerous association studies linked various traits to PTC/PROP taster status or TAS2R38 genotype. However, these associations have often been disputed because of methodological differences, small study cohorts, and insufficient robustness of the traits under study (for an overview see ref. [5]). Despite these uncertainties, effects of PTC/PROP taster status or TAS2R38 genotypes on food preferences and vegetable intake have been reported [6]. In particular, this applies to mustard oil containing cruciferous vegetables such as cress, cabbage, turnip, broccoli and horseradish [4].

Variability in other TAS2R genes

Like TAS2R38, the other human bitter receptor genes exhibit SNPs as well (◆ Figure 3). On average, TAS2R genes contain four SNPs which often change the encoded amino acid sequences. This in turn could generate functional differences among the TAS2R variants [7]. Since SNPs in the TAS2R genes prematurely terminate the synthesis of the receptors' polypeptide chain in three cases, and since many SNPs affect regions of the TAS2Rs that are critical for agonist-binding, activation or signaling (◆ Figure 2), we can predict that additional cases of full or partial 'taste blindness' for other bitter substances occur and will be discovered in the future. In addition, copy number variation has been demonstrated for the TAS2R43 and TAS2R45 genes [8] meaning that subjects can have two, one or no copy of these genes.

Indeed, other genetically determined bitter receptor variants already have been found to differ functionally. In the Paleolithic, a mutation in codon 172 generated a TAS2R16 variant, TAS2R16-172N, having moderately increased sensitivity for special bitter glycosides. Numerous plants including edible plants produce such gly-

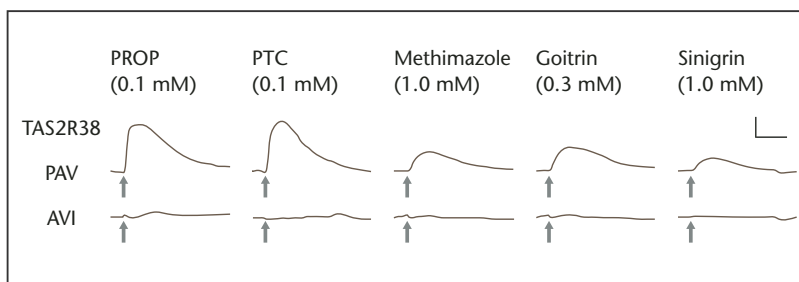


Fig. 2: Functional differences of TAS2R38 receptor variants.

Human embryonic kidney cells were equipped with either the taster (TAS2R38-PAV) or the non-taster (TAS2R38-AVI) variant of the receptor and stimulated with different bitter activators (arrows indicate the stimulus application). The monitored calcium traces show the activation of the receptors (upper row) and the lack-of activation (bottom row), respectively. Scale bar: y-axis = 2000 fluorescence units; x-axis = time (2 min.)
PROP = propylthiouracil; PTC = phenylthiocarbamide

cosides among which many are toxic such as the cyanogenic glycosides amygdalin of bitter almonds and linamarin of the worldwide major carbohydrate source manioc. The TAS2R16-172N carriers must have had an enormous selection advantage. Whereas the new sensitive TAS2R16 gene variant was rapidly fixed in the genomes of our ancestors and, with the migration of homo out of Africa, spread out over the world, the old insensitive variant only remained with moderate frequency in Central Africa. The observations propose that the new variant enabled our ancestors

to easily recognize and avoid toxic glycosides. This ability led to healthier diets, improved fitness and eventually greater reproductive success of the TAS2R16-172N carriers and with that to the world-wide distribution of the new gene variant [9]. Thus, it becomes clear that moderate genetically determined taste differences can have extensive and sustained consequences. Not at all a complete loss of function is required as in the case of TAS2R38.

Moreover, SNPs have also been found in the bitter receptor gene for TAS2R31 which mediates sensitive recognition of the bitter off-taste of saccharin and acesulfame K [8, 10] and which probably is also critical for the acceptance of these high intensity sweeteners. Still, another example for a bitter taste receptor which, due to the presence of SNPs in its gene, occurs in a functional and non-functional variant is TAS2R9. This receptor mediates the bitterness of the medical drugs

ofloxacin, procainamide, and pirenzapin. Data suggest that TAS2R9 plays a role in glucose homeostasis [11].

It is important to point out that in all of the mentioned cases, the bitterness of only selected compounds is affected, and a general "blindness" for bitter taste is not existent. It is obvious that the number of existing TAS2R genes accounts for this phenomenon. Even if several of the TAS2R genes would be non-functional, the remaining genes would allow the detection of numerous bitter compounds. The features of TAS2Rs also explain why the dimorphism for PTC tasting is so pronounced and why the K172N mutation in the TAS2R16 has such a lasting impact. Both of these TAS2Rs are the only bitter receptors for thioureas and glycosides, respectively, whereas numerous other bitter substances such as caffeine, quinine or denatonium benzoate activate several TAS2Rs. For the latter

three substances five, nine and eight receptors, respectively, exist [12] and hence, it is easily conceivable that even the complete loss of function of one or even some of these TAS2Rs may have only limited consequences on the bitter taste of caffeine, quinine or denatonium benzoate. In this respect it will be highly interesting to see how much the large genetic variability of TAS2Rs actually influences perceptual differences within the population.

Alcohol consumption

Already prior to the discovery of TAS2R genes, a correlation between the ability of tasting the synthetic bitter substances PTC and PROP with high sensitivity and alcohol tasting (see [13] and references therein), alcoholism, as well as the heritability of the risk for alcoholism was investigated [13]. Later, these studies were extended to associate these findings with TAS2R38 genotypes [2]. As a direct correlation between the phar-

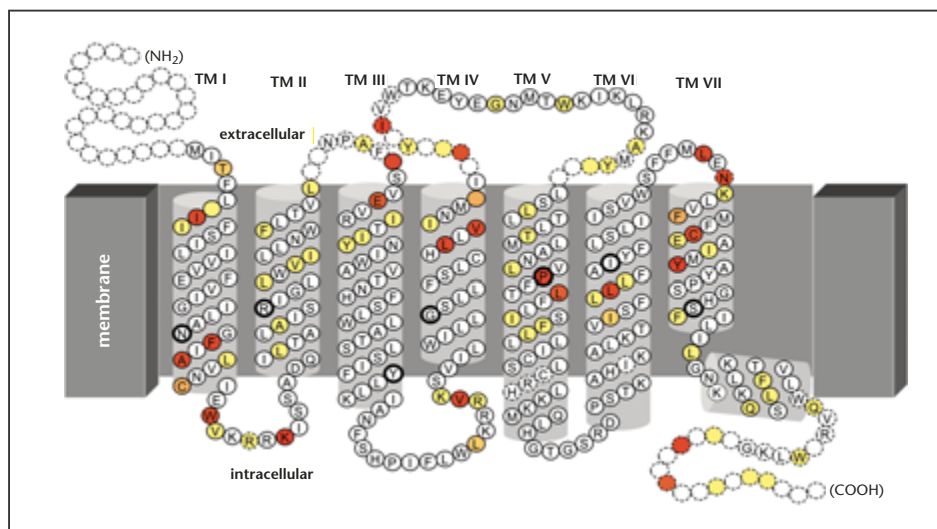


Fig. 3: TAS2R with consensus sequence and labeled positions affected by SNPs [7]. Indicated in yellow are positions affected by SNPs with a frequency of less than 5%. Graded from yellow to red are positions affected by SNPs with a frequency of 5–50%. Positions circled with a broken line indicate amino acid positions occurring only in some of the ~ 25 TAS2Rs. Positions circled with a bold line indicate the highest conserved amino acid position within each transmembrane domain (TM). Note that many of the positions affected by SNPs reside in regions important for ligand binding in TAS2Rs (extracellular loops and TM regions oriented towards the extracellular side) and regions involved in receptor activation and signal transmission (intracellular loops and TM regions oriented towards the intracellular side), respectively. SNP = single nucleotide polymorphism

macological features of TAS2R38 and ethanol is not evident, and the correlation between PROP-tasting and the risk for alcoholism has led to contradictory results published in the literature [13], more research on this topic is required. The TAS2R38 gene is not the only bitter taste receptor gene which seems to influence the risk for alcohol dependency. Also the less sensitive variant of the receptor TAS2R16 is, similar to the non-taster variant of the TAS2R38, associated with an elevated risk for alcoholism [14].

Moreover, an association between the preference for sweets and the risk for alcoholism, this time in the opposite direction, has been observed [15]. It appears conceivable that the balance between these hedonically opposite taste qualities influences the tolerance for oral alcohol perception leading to modified consummatory behavior.

Variability in other taste receptor genes

The genes for sweet and umami receptors also exhibit pronounced genetic variability within the worlds' population with in total 30 SNPs leading to exchanges of amino acids. The TAS1R1 and TAS1R2 genes coding for the specific receptor subunits are predominantly affected, however, also the TAS1R3 gene exhibits SNPs [16]. For the umami tasting ability, a complete taste "blindness" as well as taste differences of a factor of 2-fold among individuals have been described. These differences result from polymorphisms in TAS1R1 and TAS1R3 genes with a higher contribution from SNPs in the TAS1R3 gene [17].

For the sweet taste quality, only few perceptual differences have been observed in the population. Responsible for the documented differences are polymorphisms within the promoter region of the TAS1R3 gene, which affect the level of TAS1R3

mRNA [18], most likely resulting in a different amount of receptor molecules within taste receptor cells. Also polymorphisms in the gene coding for the alpha-subunit of the regulatory protein gustducin that plays an important role for sweet taste receptor signal transmission affect sweet taste sensitivity considerably [19].

At present, no genetically determined taste "blindness" or impaired tasting abilities have been reported for the taste qualities salty and sour, perhaps indicating the fundamental importance of these taste qualities for the maintenance of cellular homeostasis [20].

Taste and environment

Via the sensory systems, we establish contact to our environment. In case of our sense of taste, which is important to analyze the quality of food items, the interaction with the environment extends beyond the pure collection of information. Apparently, the human sense of taste determines not only which chemicals are perceived, but the taste sense itself is influenced by a number of external factors.

External factors influencing taste perception

Documented cases of environmental influences on taste perception are rare compared to other sensory systems. On the one hand, this is due to the possibility of the affected persons to compensate impaired sensitivity towards single or all taste qualities by simply increasing the concentration of tastants in consumed food, on the other hand, this is due to the difficulties associated with the differentiation between pure taste information and concomitant olfactory perception [21]. Additionally, taste receptor cells are, similar to olfactory sensory cells, subjected to environmental influences exerted by

direct mechanical, chemical and thermal insults and, moreover, general taste sensitivity decreases upon ageing [22].

Together, these factors complicate an objective judgment of individual sensory capacities. Pathological changes of tasting abilities can be distinguished in: hypogeusia (reduced taste sensitivity), dysgeusia (an aberrantly changed taste perception), phantogeusia (taste perception in the absence of a taste stimulus) as well as ageusia (loss of taste).

A frequently contemplated reason for an "environmentally" caused reduction in taste sensitivity is tobacco abuse. Indeed, tobacco smoke elevates the risk for an impairment of the sense of smell and hence, flavor perception associated with olfaction. However, only strong smokers show an elevated risk for an impaired taste perception *per se* [23]. A better investigated environmental risk factor for the development of pathological taste conditions is heavy metal pollution (for an overview see [24]). For example, the frequent contact with high doses of chrome containing compounds was shown to result in generally elevated taste thresholds, whereas the development of phantogeusia was reported to be associated with cadmium, lead, and mercury containing compounds. An opposite effect is discussed for the metal zinc which has been reported to improve taste sensitivity under certain conditions [25].

Also numerous drugs bear the potential to impair the taste perception of patients (♦ Table 1). The mechanisms underlying these drug-induced taste impairments are frequently not well investigated. In general, all levels of taste perception, ranging from the flow of saliva as well as its composition, over the taste receptor cells and their signaling components, to neuronal components from the periphery to the central nervous system, can be affected [26].

In general, such drug-induced taste disturbances only occur transiently and for a limited time. For some drugs, such as the antifungal agent Terbinafine, sustained gustatory side-effects lasting days to months have been reported [27]. Also the observed frequency of such side-effects deviates largely. Whereas they occur in case of the antiarrhythmic medicine Amiodaron in 1–3 %, in case of the antiviral drug Maribavir 83 % of the users can be affected (see [28] and references therein).

Intrinsic influences on taste perception

Some observations indicate that taste perception in man fluctuates dynamically. While these fluctuations are not necessarily influenced by environmental parameters, they may contribute to a better adaptation of individuals to their environment and hence should be briefly discussed here.

Perhaps already since ancient times it has been observed, but astonishingly rarely studied, that women during pregnancy show profound changes in their taste preferences accompanied by changes in their nutritional habits. From an evolutionary perspective it makes perfect sense that the protective function of the taste system has an elevated importance particularly during the early phase of pregnancy, in order to allow proper embryonic development. Later during pregnancy, an elevated need for nutrient supply takes over to secure the supply of the rapidly growing fetus. Indeed, it has been shown that during the first trimester of pregnancy, the sensitivity for and the perceived intensity of bitter compounds is elevated (for an overview see [29]) which is easily conceivable given that numerous bitter substances are toxic. Also the hedonic rating of bitter, salty and sour test stimuli is modified during pregnancy with all three taste qualities being

judged to be less pleasant in the early phase of pregnancy and a subsequent attenuation of the aversion from the first to the third trimester [29].

It seems likely that hormonal fluctuations are responsible for the observed taste deviations. Indeed, different taste thresholds for sucrose were also reported for women during the menstrual cycle. Phases of highest sensitivity for sucrose correlated with high blood estrogen levels [30]. The fact that animal experiments revealed contrasting evidence seems to reward further research efforts in the future [31].

Human taste perception is also affected by the current nutritional status of an individual. Hormones involved in the regulation of hunger and satiety play an important role for the modulation of sensitivities at the level of the taste receptor cells, particularly in case of the sweet taste. Here, it was demonstrated that the satiety hormone leptin, which is produced by adipose tissue and secreted into the blood stream, selectively reduces the sweet taste perception (for an overview see [32]). An opposite orexigenic effect has been observed for endocannabinoids for which receptors, at least in mice, were localized on sweet taste receptor cells. As a consequence, a hungry status elevates the sweet taste sensitivity, whereas satiety leads to a reduced taste of sweet food items. Moreover, the paracrine action of the incretin hormone GLP-1 (glucagon-like peptide 1) results in a stabilization and elevation of the sweet taste sensitivity, respectively [32].

Outlook

We have presented a number of examples indicating that genetic variability in taste receptor genes can have extensive consequences. The extent, however, to which the entire

Compound class	Exemplary substance
Anesthetics	Procaine-HCl
Antibiotics	i. a. Ampicillin
Anticoagulants	Phenindione
Antidiabetics	Glipizide, Phenformin
Antifungals	Terbinafine
Anthelmintics	Niridazole
Antihistamines	Chlorpheniramine
Antihypertensives	Captopril, Nifedipine
Antiinflammatory drugs	Salicylates, Dexamethasone
Antiparkinsonians	L-DOPA
Antiprotozoal agents	Metronidazole
Antiseptics	Hexetidine, Chlorhexidine
Antithyroid agents	Methimazole, Propylthiouracil
Diuretics	Amiloride
Hypolipidemic agents	Clofibrate
Immunosuppressive agents, antiproliferative drugs	Azathioprine
Muscle relaxants	Baclofen, Chlorzemanone
Psychiatric drugs	Lithium salts, Carbamazepine
Sympathomimetic drugs	Amphetamines
Vasodilators	Nitroglycerin, Dipyridamole

Tab. 1: Drugs that can influence taste perception

taste system is concerned, remains unexplored. In particular, the impact of taste on nutrition is not well known. For this purpose, the paucity of relevant research with sufficiently large study cohorts and complex modern methodology must be overcome. In particular, a precise assessment of the study subjects for their intake of vegetables, fruits and other food or beverages containing known bitter compounds is lacking. These data must be matched with hedonic ratings of the consumed food as well as with the complete genotype of taste receptors. This is not only a scientific but also logistic challenge that can perhaps only be mastered through collaborative efforts across different research groups and institutions. ▶

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Conflict of Interests

The authors declare no conflict of interests according to the guidelines of the International Committee of Medical Journal Editors.

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