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Genetics and Bitter Taste Responses to Goitrin, a Plant Toxin Found in Vegetables

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Abstract

The perceived bitterness of cruciferous vegetables such as broccoli varies from person to person, but the functional underpinnings of this variation are not known. Some evidence suggests that it arises, in part, from variation in ability to perceive goitrin (5-vinyloxazolidine-2-thione), a potent antithyroid compound found naturally in crucifers. Individuals vary in ability to perceive synthetic compounds similar to goitrin, such as 6-propyl-2-thiouracil (PROP) and phenylthiocarbamide (PTC), as the result of mutations in the *TAS2R38* gene, which encodes a bitter taste receptor. This suggests that taste responses to goitrin itself may be mediated by *TAS2R38*. To test this hypothesis, we examined the relationships between genetic variation in *TAS2R38*, functional variation in the encoded receptor, and threshold taste responses to goitrin, PROP, and PTC in 50 subjects. We found that threshold responses to goitrin were associated with responses to both PROP ($P = 8.9 \times 10^{-4}$; $r_s = 0.46$) and PTC ($P = 7.5 \times 10^{-4}$; $r_s = 0.46$). However, functional assays revealed that goitrin elicits a weaker response from the sensitive (PAV) allele of TAS2R38 (EC_{50} = 65.0 μM) than do either PROP (EC_{50} = 2.1 μM) or PTC (EC_{50} = 1.1 μM) and no response at all from the insensitive (AVI) allele. Furthermore, goitrin responses were significantly associated with mutations in *TAS2R38* ($P = 9.3 \times 10^{-3}$), but the same mutations accounted for a smaller proportion of variance in goitrin response ($r^2 = 0.16$) than for PROP ($r^2 = 0.50$) and PTC ($r^2 = 0.57$). These findings suggest that mutations in *TAS2R38* play a role in shaping goitrin perception, but the majority of variance must be explained by other factors.

Key words: allele, goiter, goitrogen, phytotoxin, TAS2R38, 5-vinyloxazolidine-2-thione

Introduction

Virtually all plants use chemical defenses to deter herbivores (Ames et al. 1990a, 1990b; Coley and Barone 1996). The plant family Brassicaceae, which includes cruciferous vegetables such as cabbage, brussels sprouts, kale, and turnips, utilizes a system made up of 2 main components: glucosinolates and myrosinase (Figure 1A) (Bones and Rossiter 1996). In the healthy plant, these are compartmentalized to prevent reaction. However, when the plant's tissues are damaged (e.g., by chewing), the compartments break down and the glucosinolates and myrosinase react, producing a burst of noxious secondary products that has been likened to a "bomb" (Figure 1A) (Kissen et al. 2009).

One of the most abundant products of glucosinolate–myrosinase reactions is goitrin (5-vinyloxazolidine-2-thione), which results from the hydrolysis of 2-hydroxy-3-butenyl glucosinolate (progoitrin) (Mithen 2006). Goitrin is a potent inhibitor of thyroid peroxidase, which plays a central role in the organification of iodine (Gaitan 1990). Thus, consumption of goitrin interferes with thyroid hormone (TH) synthesis. The quantities of goitrin found in food plants are generally not sufficient to cause thyroid dysfunction in healthy populations. However, exposure is a risk factor for goiter and related pathologies in iodine-deficient populations, where TH production is already impaired (Vanderpas 2006).

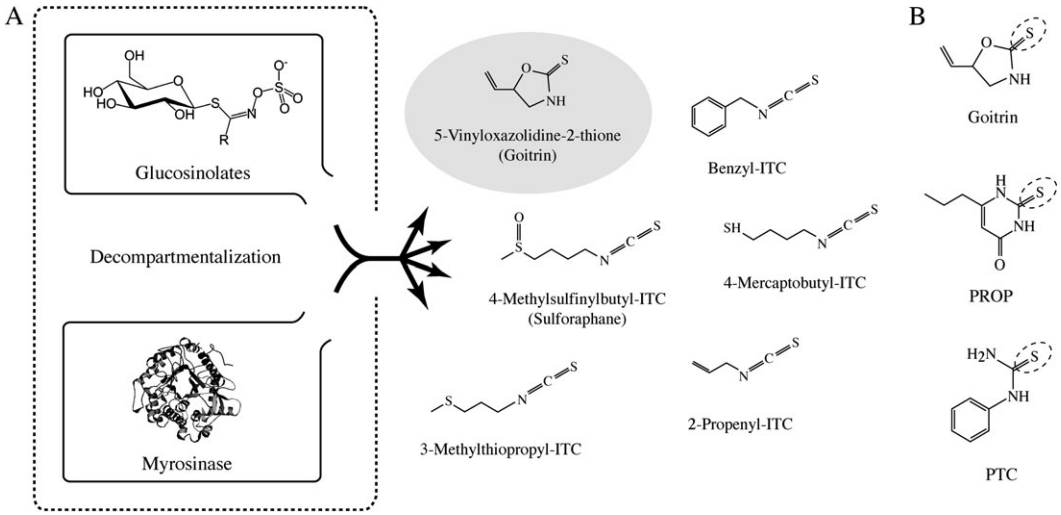

Figure 1 Glucosinolate–myrosinase reactions and chemical structures. **(A)** Glucosinolates and myrosinase are segregated in plant tissues, which prevents reaction. When they mix they react, producing a variety of noxious products. The products produced depend on the range of glucosinolates found in the plant, which varies among plant species and varieties. Most are isothiocyanates, nitriles, and thiocyanates. 5-vinyloxazolidine-2-thione, goitrin, is shaded. **(B)** Chemical structures of goitrin, PROP, and PTC. The N-C=S moiety thought to be important in conferring dualistic bitter taste is circled.

Goitrin is structurally similar to the synthetic compounds 6-propyl-2-thiouracil (PROP) and phenylthiocarbamide (PTC) (Figure 1B), which are well known for their striking taste properties. While some people find them intensely bitter, others find them nearly tasteless. In addition, it has been known since the 1950s that goitrin shares some of these characteristics. It is now known that much of the variation in perception of PROP and PTC is due to mutations in the *TAS2R38* gene, which encodes a bitter taste receptor (Chandrashekar et al. 2000; Bufe et al. 2002; Kim et al. 2003). Furthermore, both ability to perceive PROP and PTC and mutations in *TAS2R38* are associated with taste responses to vegetables containing goitrin (Sandell and Breslin 2006). These observations suggest that taste responses to goitrin itself might vary as the result of mutations in *TAS2R38*. To investigate this possibility, we examined subjects' taste responses to goitrin, their similarities to those of PROP and PTC, and their associations with functional variation in *TAS2R38*.

Materials and methods

Subjects

Fifty unrelated Caucasian subjects were recruited for phenotyping and genetic analysis under a protocol approved by the Institutional Review Board at the University of Texas Southwestern Medical Center. Subjects agreeing to participate through informed consent were prescreened via self-report to avoid inclusion of individuals with overt taste pathologies or other obvious health problems. Each subject participated in the entire course of the study, which required 4 taste tests and genotyping.

Taste thresholds

Taste responses to goitrin (Alfa Aesar L02639), PTC (Sigma Aldrich P7629), and PROP (Sigma Aldrich P3755), along with a chemically unrelated compound, salicin (a β-glycoside) (Sigma Aldrich S0625), were characterized using the method of Harris and Kalmus (1949), which estimates the lowest concentration at which a particular compound can be perceived, or threshold. This is accomplished by testing the ability of subjects to distinguish control solutions from solutions of a tastant, which are presented at increasing concentrations until they are correctly identified. This method has been used extensively in studies of PTC, PROP, and many other compounds (Guo and Reed 2001; Drayna 2005). In our study, we applied it to all 50 subjects, using aqueous solutions of goitrin, PTC, PROP, and salicin as tastants and plain water as a control. Each compound was tested at a starting concentration of 1 μM, which was doubled at each step of the test to a maximum of 8192 μM. Subjects visited the laboratory on 4 separate days, taking a different test on each visit.

Genetic variation in TAS2R38

In the course of each subject's first visit for taste testing, a blood sample was drawn to provide DNA, which was extracted and stored by the Human Genetics Clinical Laboratory core facility at the University of Texas Southwestern Medical Center.

The *TAS2R38* gene was sequenced, in its entirety (1002 bp), in all subjects. Sequencing was performed using standard methods. In brief, polymerase chain reaction (PCR) products were generated using oligonucleotide primers based

on the human genome reference sequence, and amplification was performed using thermal cyclers. After being tested for size and mass by gel electrophoresis, PCR products were submitted to the Southwestern Medical Center's DNA Sequencing and Genotyping core facility where they were processed using ABI 3730 high-throughput DNA sequencers. Sequencing was performed on both the forward and reverse strands of the gene to avoid base calling errors.

Raw sequencing chromatogram data were analyzed using the PHRED, PHRAP, and Consed computer programs. Following automated analysis and a manual data inspection and cleanup, in-house software was used to identify single nucleotide polymorphisms (SNPs) and determine individual genotypes. Haplotypes were inferred using the PHASE computer program, which examines SNP genotypes to determine the most likely configuration of SNP alleles along a single chromosome (Stephens et al. 2001).

Phenotype–phenotype and genotype–phenotype associations

Phenotype–phenotype associations between goitrin, PROP, and PTC thresholds were analyzed using Spearman's rank correlation tests. Genotype–phenotype associations were tested using linear regression. These analyses were performed with $\log_2$-transformed phenotypes, to take into account the doubling of tastant concentrations at each step of the threshold estimation process. Genotypes were treated as ordinal variables under a codominant model such that individuals were coded as having 0, 1, or 2 copies of a particular allele. Analyses were performed for SNP genotypes as well as with respect to haplotype pairs, or diplotypes.

Functional analysis

The responses of individual alleles to taste compounds were examined using the methods of Bufe et al. (2002, 2005a, 2005b). Target alleles were amplified from genotyped DNA samples and subcloned into a construct based on the pcDNA5/FRT/TO expression vector (Invitrogen), which was composed of an N-terminal element consisting of the amino acids 1–45 of the rat somatostatin type 3 receptor, to allow cell-surface transport, and a C-terminal herpes simplex virus (HSV) glycoprotein D epitope, to allow immunocytochemical detection (Bufe et al. 2002). Dose–response analyses were performed by transiently transfecting each construct into a human embryonic kidney HEK293T cell line stably expressing the chimeric G-protein subunit $G_{\alpha 16\text{-Gust44}}$ using Lipofectamine 2000 (Invitrogen) and exposing the cells to tastants at varying concentrations. These experiments were performed with an automated fluorometric imaging plate reader (Molecular Devices) 24–32 h post transfection. Tastants were dissolved in C1 solution (130 mM NaCl, 5 mM KCl, 10 mM HEPES, 2 mM CaCl2, and 10 mM glucose, pH 7.4). Data were collected from at least 2 independent experiments carried out in duplicate and processed with SigmaPlot (SPSS). For dose–response curve calculations, the peak fluorescence responses after compound addition were normalized to background fluorescence ($\Delta F/F = (F - F_0)/F_0$) and baseline noise was subtracted.

Results

Phenotypic distributions and associations

The distributions of threshold responses to PTC and PROP in our sample were consistent with distributions reported previously (Figure 2) (Bartoshuk et al. 1994; Kim et al. 2003). The PTC distribution was defined by 2 major features. First, it spanned a broad range, with the most sensitive subjects perceiving PTC at a concentration of 1 μM, and least sensitive perceiving it at 8192 μM. Thus, the most sensitive subjects could perceive PTC at a concentration less than 1/8000 that perceptible by the least sensitive subjects. Second, the distribution was distinctly bimodal, with an antimode at ~256 μM. Roughly 85% of subjects fell in the lower mode of the distribution, with thresholds less than 256 μM (i.e., were sensitive to PTC), whereas 15% fell above the 256 μM threshold (i.e., were insensitive to PTC). These groups correspond to what are often called PTC "tasters" and "nontasters," but they also illustrate the imprecision of the terms. For instance, PTC thresholds varied more than 100-fold within our "taster" group. The distribution of PROP thresholds was similar to that of PTC (Figure 2) but differed in some respects. It had a narrower range than the PTC distribution (256-fold vs. 8192-fold) and exhibited only weak bimodality. Nonetheless, correlations between the 2 distributions were strong (Spearman's $r_s = 0.58$; $P = 7.0 \times 10^{-6}$) (Figure 3).

The distribution of goitrin thresholds, which has not been reported previously, bore similarities to those of both PROP and PTC (Figure 2). The association between goitrin and PTC thresholds was highly significant ($P = 7.5 \times 10^{-4}$), as was the association between goitrin and PROP thresholds ($P = 8.9 \times 10^{-4}$) (Figure 3). Both of these associations were strong, with r_s values of 0.46 in each case (Figure 3). However, the goitrin distribution was somewhat more similar to the PROP distribution than it was to the PTC distribution. Like PROP, goitrin elicited a narrower range of responses than did PTC, with the most and least sensitive subjects differing just 64-fold in threshold. Goitrin thresholds also spanned roughly the same range of concentrations as PROP (64–4096 μM vs. 8–2048 μM, as opposed to the 1–8192 μM range of PTC). And, like the PROP distribution, the goitrin distribution exhibited only weak bimodality compared with that of PTC.

The distribution of salicin thresholds differed from those of the other 3 compounds in being unimodal, and with a smaller range (128–2048 μM). Salicin threshold was not associated with threshold response to any of the other compounds ($P > 0.15$ in all 3 cases).

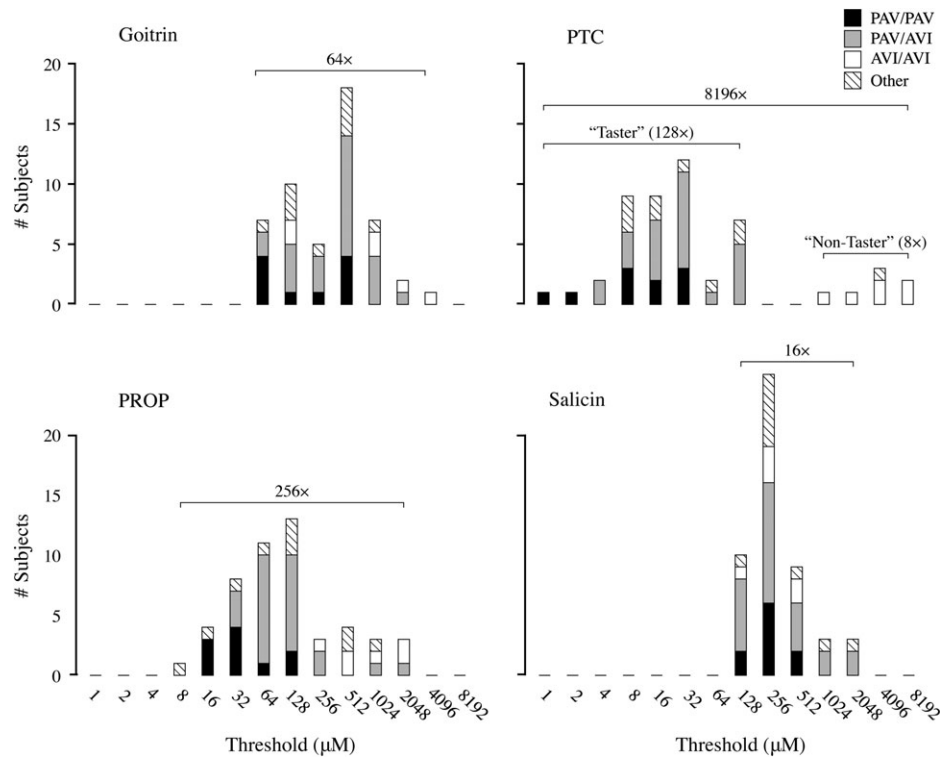

Figure 2 Distributions of goitrin, PTC, and PROP thresholds. Shading indicates diplotype with respect to the haplotypes outlined in Figure 4. Bars above each distribution indicate the magnitude of differences between the highest and lowest observed thresholds.

Genetic variation

DNA sequencing revealed 3 SNPs in our sample: G145C, T785C, and A886G (Figure 4). Each of these variants corresponds to an amino acid substitution in the encoded receptor: A49P, V262A, and I269V. All 3 have been reported previously and are found at high frequencies in human populations (Guo and Reed 2001; Kim et al. 2003; Wooding et al. 2004). In our sample, the minor allele frequencies at these positions were 0.45 (G145), 0.39 (T785), and 0.45 (A886). In a previous study, Wooding et al. (2004) reported 2 additional polymorphisms, A239G (H80R) and C820T (C274R), but neither these nor any other variants were present in our sample.

Analysis of genotypes using PHASE identified 5 haplotypes (Figure 4). These were named according to their amino acid composition following the convention of Kim et al. (2003) such that the AVI haplotype was composed of an A at position 49, a V at position 262, and an I at position 269, and so on. These varied in frequency from 0.02 to 0.49. Two, PAV and AVI, were far more common than the others with frequencies of 0.49 and 0.39, thus comprising 88% of the sample. The remaining 3 (AAV, PAI, and PVI) were each present at a frequencies of 2–6%. These results are in agreement with previous studies. For instance, Wooding et al. (2004) found the PAV, AVI, and AAV alleles at frequencies of 0.46, 0.49, and 0.05, respectively in a comparable sample of 55 Caucasian subjects.

Genotype–phenotype associations

Consistent with previous studies, SNP-by-SNP association analyses revealed highly significant correlations between genotype and threshold response to PTC and PROP, but not salicin (Bufe et al. 2002; Kim et al. 2003; Meyerhof et al. 2010) (Figure 5). C145 (P49), C785 (A262), and G886 (V296) homozygotes had the lowest mean thresholds (i.e., greater sensitivity) to both PTC and PROP (Figure 5). Associated P values ranged from 5.0×10^{-10} (between G145C and PTC) to 8.2×10^{-4} (between A886G and PROP). The fraction of phenotypic variance accounted for by each SNP (i.e., r^2) ranged from 0.21 (between A886G and PROP) to 0.56 (between G145C and PTC). In addition, the estimated effect sizes were large, with β ranging from 1.34 (between A886G and PROP) to 3.54 (between G145C and PTC). These findings are consistent with those of Bufe et al. (2005b), who found using in vitro assays that the A49P variant has a stronger effect on TAS2R38 response to PTC and PROP than does either V262A or I296V.

Associations between *TAS2R38* genotype and goitrin response, like those between genotype and PROP and PTC responses, were highly significant, with P values ranging from 1.2×10^{-2} (for G145C) to 3.8×10^{-2} (for A886G). However, genotype accounted for a smaller proportion of phenotypic variance in goitrin threshold than in PROP and PTC thresholds (9–12% vs. 21–56%). The estimated effect sizes of these

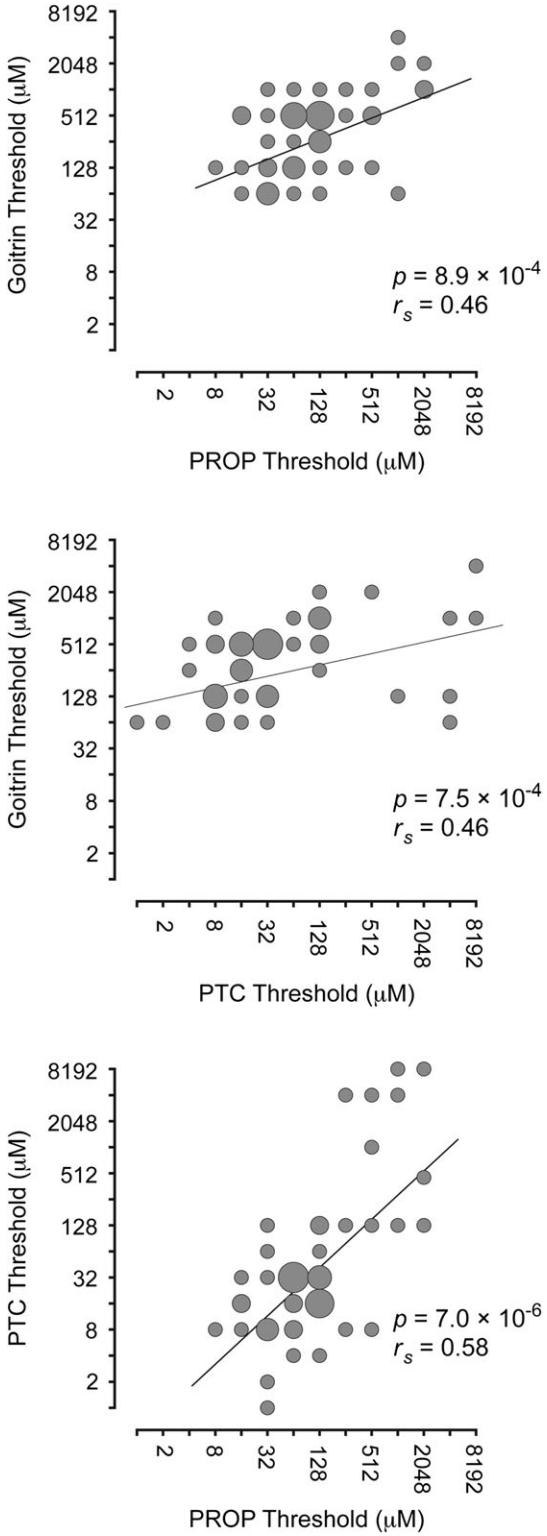

Figure 3 Correlations between goitrin, PTC, and PROP thresholds. The area of each point is proportional to the number of occurrences. r_s indicates Spearman's correlation coefficient, and *P* indicates the probability of no association. The solid line indicates the least squares regression.

A

	Nucleotide			Amino Acid				
Haplotype	145	785	886	49	262	296	Occ.	Freq.
AAV	G	C	G	A	A	V	6	0.06
AVI	G	T	A	A	V	I	39	0.39
PAI	C	C	A	P	A	I	2	0.02
PAV	C	C	G	P	A	V	49	0.49
PVI	C	C	A	P	A	I	4	0.04
							100	1.00

B

Diplotype	Occ.	Freq.
AAV/AVI	2	0.04
AVI/AVI	6	0.12
PAI/PVI	2	0.04
PAV/AAV	4	0.08
PAV/AVI	24	0.48
PAV/PAV	10	0.20
PVI/AVI	1	0.02
PVI/AVI	1	0.02
	50	1.00

Figure 4 *TAS2R38* haplotypes, diplotypes, and frequencies. **(A)** Six haplotypes were observed in our sample. The composition of each haplotype with respect to nucleotide positions 145, 785, and 886 of the *TAS2R38* gene is shown. The composition of each haplotype with respect to amino acid positions 49, 262, and 296 of the TAS2R38 protein is also shown. The number of occurrences of each haplotype indicates the total number of observations in the sample, which includes 2 haplotypes for each of the 50 subjects, for a total of 100 observations. **(B)** The number of occurrences of each observed diplotype (i.e., haplotype pairing in an individual).

SNPs were lower, as well, with β ranging from 0.67 to 0.84 (vs. 1.34 to 3.54 for PROP and PTC).

Diplotype–phenotype associations

To determine the extent to which nucleotide variants jointly predict taste response, we tested for associations between diplotypes (haplotype pairings within subjects) and threshold phenotypes. Eight diplotypes were observed in our sample, suggesting that a variety of associations might be present. However, the fact that most haplotypes were rare constrained our ability to test for such effects. For this reason, we tested for associations only in subjects with diplotypes composed of the 2 most common haplotypes, AVI and PAV, for a total of 40 subjects (6 AVI/AVI, 24 AVI/PAV, and 10 PAV/PAV).

Like the SNP-by-SNP analyses, diplotype analyses were consistent with previous studies, revealing highly significant associations between variation in *TAS2R38* and taste responses to PTC and PROP, but not salicin (Figure 6). Significance levels were high for both PROP and PTC ($P = 1.6 \times 10^{-8}$ and $P = 3.0 \times 10^{-7}$) with the PAV/PAV diplotypes having the lowest thresholds. Diplotypes accounted for 57% and 50% of variance in PTC and PROP threshold, respectively. These results are similar to those of Kim et al. (2003), who found that *TAS2R38* diplotypes account for 60–85% of variance in threshold response to PTC, depending on the

	SNP	Amino Acid	Goitrin	PTC	PROP	Salicin
p	G145C	A49P	1.2×10^{-2}	5.0×10^{-10}	5.7×10^{-10}	0.64
	T785C	V262A	2.0×10^{-2}	1.4×10^{-7}	4.3×10^{-5}	0.85
	A886G	I269V	3.8×10^{-2}	2.7×10^{-6}	8.2×10^{-4}	0.96
r^2	G145C	A49P	0.12	0.56	0.55	4.1×10^{-3}
	T785C	V262A	0.11	0.44	0.30	7.5×10^{-4}
	A886G	I269V	0.09	0.37	0.21	6.1×10^{-5}
β	G145C	A49P	0.84	3.54	2.29	0.12
	T785C	V262A	0.79	3.18	1.70	0.05
	A886G	I269V	0.67	2.75	1.34	0.01

Figure 5 Genotype–phenotype associations. Results of association tests between genotype for each variable position (nucleotide and amino acid positions are both given). P indicates the probability of no association, r^2 indicates the coefficient of determination, and β indicates the effect size.

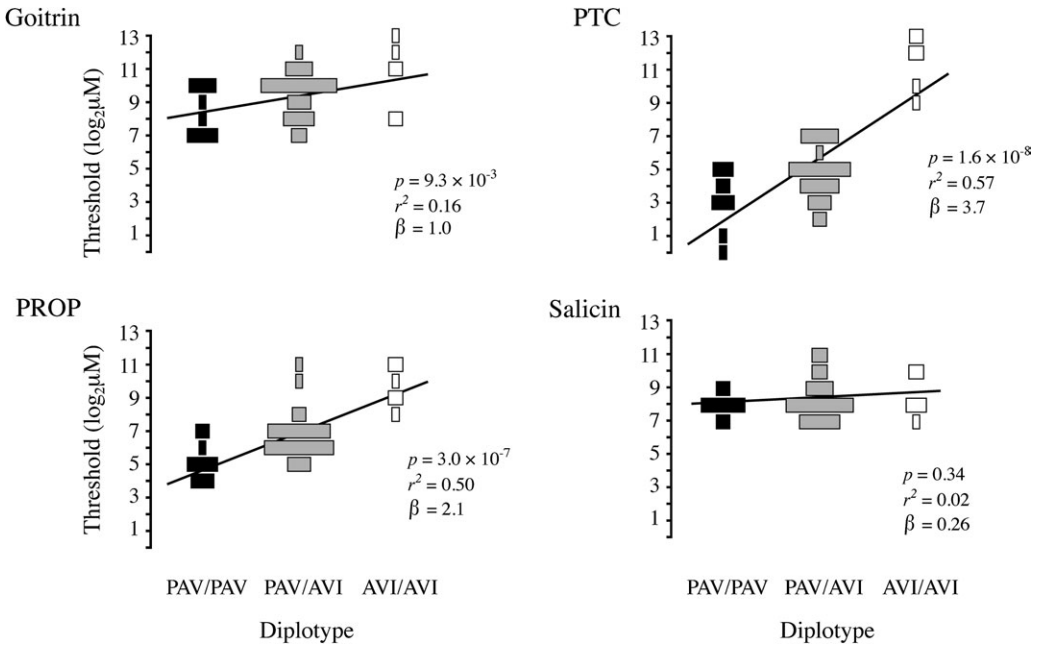

Figure 6 Diplotype–phenotype associations. The number of observations of each threshold for each diplotype are indicated by bar width. Analyses included only individuals with diplotypes composed of the 2 common alleles, AVI and PAV, which accounted for 40 of 50 subjects (80%) in the sample. Diplotypes composed of rare haplotypes, shown in Figure 4, were excluded.

sampled population. We also found that the effect size of *TAS2R38* diplotype was large, with the PTC association having a β of 3.7 and the PROP association having a β of 2.1.

The association between diplotype and goitrin response, like those involving PROP and PTC, was highly significant ($P = 9.3 \times 10^{-3}$). However, like the SNP-by-SNP associations, this association was appreciably weaker than those of PROP and PTC, with diplotype accounting for just 16% of the observed variance. And, like SNP-by-SNP effects, the effect size of the diplotype–goitrin association was smaller, with a β of 1.0.

The relative strengths of these associations were evident in distributions showing the representation of diplotypes at each observed phenotype (Figure 2). The distribution of PTC thresholds recapitulated the familiar strong distinction between modes, with one being composed entirely of AVI/AVI (i.e., nontaster) diplotypes and one being composed entirely of AVI/PAV and PAV/PAV (i.e., taster) diplotypes. This distinction was less clear for the PROP distribution, consistent with its having a weaker diplotype association than PTC, and nearly absent for the goitrin distribution. Thus, although a clean genotype–phenotype dichotomy

was observed for PTC, the trend in goitrin thresholds, while highly statistically significant, was far less obvious.

Allele-specific responses

Functional assays revealed that PTC, PROP, and goitrin elicit different dose–response profiles from the TAS2R38 receptor. As demonstrated previously, PROP and PTC both elicit strong responses from the PAV allele and no response from the AVI allele (Bufe et al. 2005b). We found that goitrin elicited a response from the PAV allele, but it was weaker than that of PROP and PTC (Figure 7). Goitrin elicited a lower maximum response and required a higher concentration to reach half-maximal response (EC_{50}) (65 μM vs. 1.1 and 2.1 μM) (Figure 7). This pattern is consistent with our phenotypic data, in which the mean thresholds of PAV/PAV homozygotes were 15.5, 49.6, and 268.8 μM for PTC, PROP, and goitrin, respectively. None of the tested compounds elicited significant responses from the AVI allele. Salicin did not elicit significant responses from either allele.

Discussion

It has long been observed that taste responses to PROP and PTC are associated with responses to, and preferences for, cruciferous vegetables such as cabbage, broccoli, and brussels sprouts (Duffy 2007). These associations are thought to be driven, in part, by similarities between the taste properties of these compounds and compounds found naturally in crucifers (Sandell and Breslin 2006). Our findings support this suggestion: associations between threshold responses to goitrin, PROP, and PTC are highly significant ($P < 0.001$) and strong ($r_s > 0.45$). Taste responses to goitrin are particularly

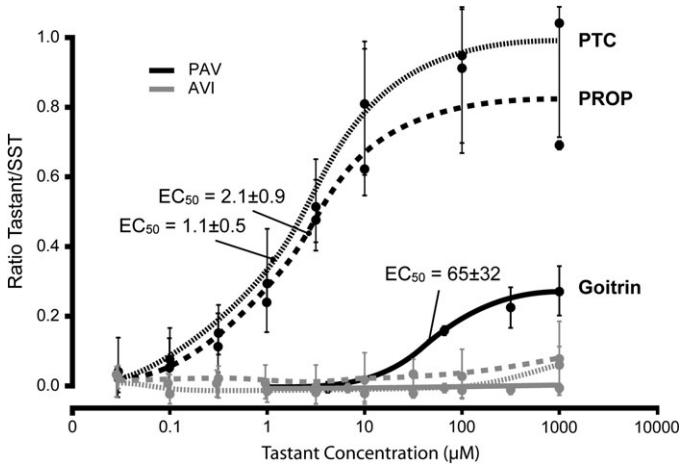

Figure 7 Functional assays. Curves indicate dose–response profiles of the AVI and PAV alleles to PTC, PROP, and goitrin (curves for PTC and PROP are redrawn from Bufe et al. (2005b)). Goitrin elicited both a lower maximal response from the PAV allele than did PTC and PROP and reached half-maximal response (EC_{50}) at a higher concentration (65 μM vs. 1.1 and 2.1 μM). None of the 3 test compounds elicited response from the AVI allele.

similar to those of PROP, the most widely used marker in studies of bitter taste psychophysics and diet. This suggests that past efforts to connect bitter taste responses and food preferences have utilized a remarkably similar, albeit imperfect, surrogate for a compound actually found in many bitter vegetables (Duffy and Bartoshuk 2000; Duffy 2007).

Our findings also support the hypothesis that variation in taste responses to goitrin, like responses to PROP/PTC, is mediated by mutations in *TAS2R38*. Associations between *TAS2R38* genotype/diplotype and response to goitrin were highly significant ($P < 0.001$), and the AVI and PAV alleles vary in functional response to goitrin in vitro. However, variation in *TAS2R38* accounted for far less variance in goitrin threshold (<20%) than for PROP and PTC (>50%) and elicited a weaker response from the PAV allele than did the other 2 compounds. Thus, substantial variance remains unexplained. An important possibility is that variation in genes other than *TAS2R38*, such as other *TAS2R* genes or genes encoding other components of the taste transduction pathway such as G-protein subunits, ion channels, and others, affect goitrin responses. Some evidence suggests that variation in the *TAS2R1* or *TAS2R4* genes might play such a role (Reed et al. 1999; Chandrashekar et al. 2000; Meyerhof et al. 2010). Dissecting these factors will require more extensive genotyping, phenotyping, and functional assays.

Evidence that taste responses to goitrin are mediated, at least in part, by *TAS2R38* lends credence to the longstanding hypothesis that connections between bitter taste responses to PROP, PTC, and phenotypes such as vegetable consumption are driven specifically by variable responses to phytogoitrogens themselves not just by generic variation in bitter taste response (Greene 1974; Drewnowski and Rock 1995; Duffy and Bartoshuk 2000; Guo and Reed 2001; Dinehart et al. 2006; Sandell and Breslin 2006). However, the weakness of the relationship between goitrin and *TAS2R38* raises questions. In particular, it seems implausible that associations between *TAS2R38* and endpoint phenotypes such as taste responses to whole vegetables and dietary preferences could be due solely to its interactions with goitrin. A hypothetical explanation for this is that TAS2R38 responds not just to goitrin but to many of the related compounds arising from glucosinolate–myrosinase reactions. Thus, bitter taste responses to cruciferous vegetables might be better described as an aggregate function of interactions between TAS2R38 and multiple agonists simultaneously.

Ultimately, preferences and consumption of whole foods depend on myriad interacting factors (Duffy 2007). Aspects of oral sensation such as taste intensity, hedonic response, and texture are all important. Variation in these factors results in variable response and acceptance. Our findings point to inherited variation in taste responses to goitrin, and possibly other products of glucosinolate–myrosinase reactions, as playing a contributing role in these processes. The consequences of this relationship are likely complex. Although exposure to phytogoitrogens probably has few health costs,

and might even have health benefits, in populations with adequate nutrition (Fahey et al. 2001; Basson et al. 2005), exposure has been implicated as a precipitating factor in TH deficiencies when predisposing influences such as iodine deficiency are present (Greene 1973, 1974; Vanderpas 2006). Thus, the net effects of interactions between TAS2R38 and phytogoitrogens likely involve countervailing pressures between nutrition and toxic exposure.

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