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# Detection thresholds for quinine, PTC, and PROP measured using taste strips

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## Abstract

**Purpose** In clinical practice, when ability to perceive bitter taste is studied, quinine is preferred to phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) as taste stimulus, because many subjects are genetically non-tasters for PTC/PROP. However, it is poorly known how sensitive anterior (front) and posterior (back) parts of the tongue are to different bitter tastants that are detected by different bitter taste receptors (TAS2Rs). In the present study, we aimed to characterize sensitivity to bitter taste at front and back parts of tongue.

**Methods** We measured thresholds for quinine, PTC, and PROP using the "taste strips", employing seven concentrations of each stimulus both at front and back parts of tongue in 203 healthy participants (56% females, mean age 28 years).

**Results** Our data confirmed the hypothesis that the inability to perceive quinine was less frequent than the inability to perceive PTC and PROP: People can still perceive the bitter taste of quinine even if they are "non-tasters" for PROP/PTC. As expected, strong correlations between PTC and PROP thresholds were observed. Interestingly, correlations between thresholds for quinine and PTC/PROP also emerged. Overall, the detection thresholds were lower when measured at front part of the tongue.

**Conclusions** Our data suggest that determining taster status for quinine using paper "taste strips", applied to front part of the tongue, represents a suitable method for the screening for ageusia for bitter taste.

**Keywords** Taste threshold · Quinine · Phenylthiocarbamide · 6-*n*-Propylthiouracil · Clinical assessment

## Introduction

The human sense of taste comprises five different modalities: bitter, sweet, sour, salt, and umami. Among these, bitter perception has a particularly important role, as it protects us from ingesting a wide range of potential toxins present in food which typically taste bitter [1]. Bitter taste is mediated through a family of 25 bitter receptors (TAS2Rs) from the G protein-coupled receptor (GPCR) superfamily [2, 3]. The bitter taste receptors show considerable genetic variation [4]. For this reason, human population displays high variation in bitter taste perception which may have an impact on nutrient intake and overall appetite (for a review see [5]). The best characterized examples are the variable perception of bitter compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), which can be accounted for at the molecular level by polymorphic variants in the specific type 2 taste receptor, TAS2R38 [6, 7]. PTC and, its chemically related compound, PROP provide an extremely bitter taste to some subjects (tasters), but are tasteless or only slightly bitter to others (non-tasters) [8–10]. Approximately 15–30% of people are known to be non-tasters genetically [11–13].

The taste sensitivity for the related compounds PTC and PROP is highly correlated [7], which can be reconciled at the molecular level by their shared activation of TAS2R38 [6]. However, the generalization of PTC/PROP taster status as a predictor of sensitivity to other bitter compounds is controversial (e.g., quinine, caffeine, urea;

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[14]). Focusing on quinine, some investigations have found a significant positive relationship between PTC/PROP sensitivity and quinine sensitivity [15–18], whereas several other studies have failed to find such a relationship [14, 19–23]. However, these previous results were based mainly on suprathreshold ratings, not on threshold tests, which are the most widely used quantitative taste tests. In addition, among the studies which have used such threshold methods [24–27], no significant relationship was observed so far (but see also [18] for different results). The lack of concordance among studies suggests that the relationship between the ability to taste PTC/PROP and the perception of other bitter compounds is not completely understood.

Historical "tongue map", that persisted long in textbooks, suggested that each of the basic tastes was detected only in its own specific area, for example, bitter in the posterior part of tongue. However, Henkin and Christiansen [28] found that the palate was more sensitive to bitter taste (urea) than the tongue, and suggested that in prior studies, the localization of the bitter taste detection at the posterior tongue may have been in error due to confusion with taste in the palate. In addition, Sato et al. [29] argued that the tongue map could have resulted from misinterpretation of studies from early 1900s, where the differences between the different loci were actually small. Results from the study by Sato et al. [29], and from similar studies they discussed, did not provide support for the tongue map, but, instead, indicated that all basic tastes can be detected at all tested loci, although the sensitivity (i.e., detection threshold) can vary. In addition, Nordin et al. [30] showed that quinine was identified more often correctly as bitter when applied at the front (tip) and middle (midlateral) than the back (posteromedial) parts of the tongue. To our knowledge, prior taste sensitivity localization studies have employed only one compound—at different concentrations—per taste. In the case of bitter taste, one tastant may not capture all variation in the sensitivity to bitter taste in different parts of the tongue, because the ~25 bitter taste receptors (TAS2Rs) vary in molecules they detect [31] and specific bitter taste receptors may be unevenly distributed across the tongue. While it is known that sensitivity to different bitter taste stimuli can vary within an individual, the question whether the detection thresholds at front and back parts of the tongue show equal pattern for different bitter tastants remains open.

The aim of the present study was twofold: (1) to investigate the relationship between quinine, PTC, and PROP and (2) to explore the spatial organization of the tongue in response to different bitter tastants. We measured participants' thresholds by means of the "taste strips"—a method based on tastant-impregnated filter-paper strips which has several advantages in clinical practice (e.g., long shelf-life, convenience of administration, short-time needed for testing, and possibility to test each side of the tongue separately: [32])—at two sides of the tongue: frontal and posterior. We hypothesized that, based on measurements of detection threshold using the taste strips, (1) proportion of non-tasters would be lower in the case of quinine than PTC/PROP, (2) quinine thresholds would correlate with PTC/PROP thresholds, albeit not as strongly as PTC and PROP thresholds would correlate with each other, and (3) the front part of the tongue would be more sensitive to bitter taste stimuli than the back part and this might generalize to bitter stimuli in general.

## Materials and methods

### Participants

A total of 203 healthy participants (114 females) aged between 18 and 43 years (mean age: 28.1 years, SD: 6.5) was recruited for this study. All participants gave informed, written consent prior to the initiation of the study, and were selected after successfully completing the eligibility questionnaires. Volunteers with known illnesses, under medication, pregnant or lactating or reporting any kind of food allergies were not recruited for the current study. All aspects of the study were compliant with the Declaration of Helsinki. The Ethics Committee of the Medical Faculty at the TU Dresden approved the study (application number: EK930520).

### Bitter taste compounds

Participants were presented with seven different concentrations of three bitter tastants (quinine: article # P3755; PTC: article # Q1125; PROP: article # P3700000; all from Sigma-Aldrich, Darmstadt, Germany). The concentrations of the different tasting solutions are shown in Table 1.

**Table 1** Concentrations for quinine, PTC, and PROP

| Taste component | Concentrations (mg/l of water) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Quinine | 311.44 | 77.86 | 19.46 | 4.866 | 1.216 | 0.304 | 0.076 |
| PTC | 48.71 | 12.178 | 3.044 | 0.762 | 0.19 | 0.048 | 0.012 |
| PROP | 54.474 | 13.618 | 3.404 | 0.852 | 0.212 | 0.054 | 0.014 |

## Determination of the threshold

Thresholds were assessed for both the anterior (in the area of the tip of the tongue) and posterior (in the area of the circumvallate papillae) part of the tongue using a two-alternative, forced-choice staircase procedure. Administration of the taste stimuli was based on the principles used with the "taste strips" [32] with 1 $cm^2$ of filter paper being impregnated with a tastant. The dried filter papers were then applied to the tongue. The strips were prepared in 7 dilution steps. Dilutions in water were made in steps of 1:4; starting concentrations were as follows: quinine 24 mM, PTC 8 mM, and PROP 8 mM. On each trial, subjects were presented with pairs of taste strips, one of which was the strip containing the taste and the other of which was a blank. During each trial, subjects were asked to determine which of the strips contained a taste, after which they rinsed their mouths with Evian© water (Danone Waters, Frankfurt, Germany). The concentration of the strip presented increased after a single incorrect response and decreased after two consecutive correct responses. A reversal was considered to have occurred when the concentration sequence changed directions. The procedure was terminated when four reversals had occurred; the average of the four reversals was used as a measure of sensitivity. The interval between trials was 20–30 s to minimize desensitization. Participants were considered "non-tasters" when they were not able to perceive the stimuli at the highest concentration used. Tables 2 and 3 show the percentage of tasters and non-tasters for quinine, PTC and PROP when measured in the front and back part of the tongue, respectively.

**Table 2** Percentage of tasters and non-tasters for quinine, PTC and PROP when measured in the front part of the tongue

| | Group | |
|---|---|---|
| | Non-tasters | Tasters |
| Quinine front | | |
| *N* | 7 | 196 |
| % | 3.4% | 96.6% |
| Standardized residuals | −3.6 | 1.3 |
| PTC front | | |
| *N* | 34 | 169 |
| % | 16.7% | 83.3% |
| Standardized residuals | 1.9 | −0.7 |
| PROP front | | |
| *N* | 33 | 170 |
| % | 16.3% | 83.7% |
| Standardized residuals | 1.7 | −0.6 |

**Table 3** Percentage of tasters and non-tasters for quinine, PTC and PROP when measured in the back part of the tongue

| | Group | |
|---|---|---|
| | Non-tasters | Tasters |
| Quinine back | | |
| *N* | 26 | 177 |
| % | 12.8% | 87.2% |
| Standardized residuals | −3 | 1.7 |
| PTC back | | |
| *N* | 52 | 151 |
| % | 25.6% | 74.4% |
| Standardized residuals | 0.8 | −0.4 |
| PROP back | | |
| *N* | 62 | 141 |
| % | 30.5% | 69.5% |
| Standardized residuals | 2.2 | −1.2 |

## Statistical analyses

Analyses were carried out using SPSS 21 (SPSS Inc., IL, USA). A Chi-square analysis was run to investigate whether the number of non-tasters (i.e., defined as people who obtained a score of 1 in the threshold) was less or more when using the different bitter taste compound (i.e., quinine, PTC, PROP). To assess the effect of the front vs back part of the tongue on threshold performance, a repeated-measure analysis of variance (rm-ANOVA) was used with "tastant" (quinine, PTC, and PROP) and "position" (front, back) as within-subject variables. Multiple comparisons were adjusted according to Bonferroni, and whenever the sphericity assumption was violated, Greenhouse–Geisser corrections were applied. The relationship between each binary combination of bitter taste compound was tested using Pearson's correlations. $p$ values below 0.05 were considered significant.

# Results

## Frequency of "non-tasters"

When testing in the front part of the tongue, a significant association emerged between the type of tastant and the number of tasters and non-tasters ($\chi^2 = 21.63$, $df = 2$, $p < 0.001$). Regarding quinine, significantly less people than expected were non-tasters ($p < 0.001$) (3.4% non-tasters vs 96.6% tasters). Regarding PTC, more people than expected were non-tasters ($p < 0.05$) (16.7% non-tasters vs 83.3% tasters). The standardized residuals were not significant for PROP (16.3% non-tasters vs 83.7% tasters). The Chi square was significant also when testing the back part of the

tongue ($\chi^2 = 19.22$, $df = 2$, $p < 0.001$). Again, when considering quinine, significantly less people than expected were non-tasters ($p < 0.01$) (12.8% non-tasters vs 87.2% tasters). Regarding PROP, more people than expected where non-tasters ($p < 0.05$) (30.5% non-tasters vs 69.5% tasters). The standardized residuals were not significant for PTC (25.6% non-tasters vs 74.4% tasters).

### Detection threshold for the bitter tastants measured at front and back parts of the tongue

The results of the rm-ANOVA showed a main significant effect of the type of tastant $F_{2,404} = 35.64$, $p < 0.001$. Scores were higher for quinine (mean = 3.92) as compared to PROP (mean = 3.58) and PTC (mean = 3.43) ($p < 0.001$). No significant differences emerged between PROP and PTC ($p = 1.00$). In addition, a significant main effect was found for the position $F_{1,404} = 94.5$, $p < 0.001$. The mean score obtained measuring the front part of the tongue (mean = 3.97) was higher as compared to the back part (mean = 3.17) ($p < 0.001$). The interaction between the "type of tastant" and the "position" was not significant $F_{2,404} = 0.32$, $p = 0.73$.

### Correlations between quinine, PTC, and PROP

As shown in Fig. 1, the quinine threshold measured in the front of the tongue showed significant correlations with the thresholds for PTC ($r = 0.71$, $p < 0.001$) and PROP ($r = 0.74$, $p < 0.001$). PROP and PTC were also significantly correlated ($r = 0.77$, $p < 0.001$). Regarding the thresholds measured in the back of the tongue, the same pattern was observed (Fig. 2). Quinine was significantly correlated with PTC ($r = 0.65$, $p < 0.001$) and PROP ($r = 0.72$, $p < 0.001$); PTC and PROP were also correlated ($r = 0.68$, $p < 0.001$).

## Discussion

We studied perception of bitter taste from quinine, PTC, and PROP, both at front (anterior) and back (posterior) part of the tongue, using the paper taste strips. Specifically, we first compared the proportions of "tasters" and "non-tasters" for quinine, PTC, and PROP ("non-tasters" being defined as individuals who are not able to perceive the stimuli at the highest concentration used). Second, we investigated the detection thresholds for the bitter tastants at front and back parts of the tongue, and how the thresholds correlated among tastants measured at different locations.

Our data indicated that inability to perceive quinine was less frequent than the inability to perceive PTC and PROP. This was especially the case when the threshold was measured in the front part of the tongue. When measured in this way, only 3.4% of our participants were "non-tasters" for quinine, whereas the proportion of "non-tasters" was 16.7% and 16.3% for PTC and PROP, respectively. This suggests that approximately 1 out of 10 people can perceive bitter taste from quinine even if they are "non-tasters" for PTC/

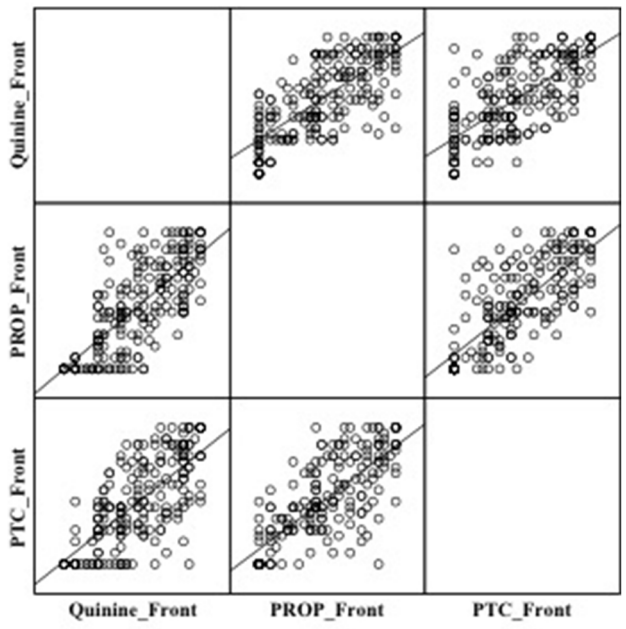


**Fig. 1** Scatterplots depicting the relationship between the detection thresholds for the bitter tastants measured in the front part of the tongue

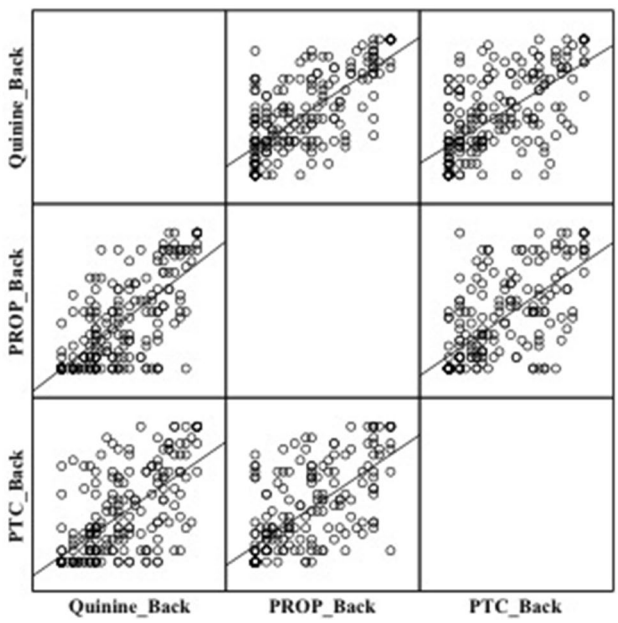


**Fig. 2** Scatterplots depicting the relationship between the detection thresholds for the bitter tastants measured in the back part of the tongue

PROP. In addition, of the seven individuals who were "non-tasters" for quinine, all of them were also "non-tasters" for PTC and PROP, implying that they may have ageusia to bitter (i.e., general inability to perceive bitter taste). Among the 169 people who were able to detect PTC and among the 170 who were able to detect PROP, none were non-tasters for quinine. This suggests that testing for quinine taster status (instead of PTC/PROP) would very rarely misclassify someone as ageusic to bitter. However, because of the multitude of bitter tastants and receptors detecting them, screening with quinine alone cannot be regarded as the perfect method for reliably identifying ageusia to bitter. Nevertheless, assessing quinine taster status will leave relatively few "non-tasters" to be examined for ageusia using more thorough methods, including whole-mouth testing and several different bitter taste stimuli.

Our results also show that the thresholds measured from the front were lower than those from the back part of the tongue. This pattern did not significantly differ for the three bitter tastants. Overall, our data support the validity of the taste strip method employing quinine, PTC, and PROP applied especially to the front part of the tongue [32, 33] for the clinical assessment of bitter taste function. As many people are non-tasters for PTC and PROP, the use of quinine becomes recommended. However, our observation of difference in sensitivity to bitter taste in front and back parts of the tongue should be interpreted with caution. Testing the middle of the back part of the tongue using taste strips is challenging due to the risk to gag reflect when that area is touched. For example, Nordin et al. [30] observed that when quinine was applied to the posteromedial part of the tongue, the frequency of identifying the taste as bitter was close to chance level.

Taste strips test in the aforementioned three studies used four concentrations of quinine and the task of the participant was to name the taste, whereas in the present study, we measured detection threshold using seven concentrations both at front and back parts of the tongue. Therefore, using more comprehensive testing, our results support the use of basic elements of the original taste strips test: quinine as the bitter taste stimulus, impregnated paper strips as the stimulus delivery method, and the front part of the tongue as the location, where the test was applied.

Genetic variation in receptor TAS2R38 has been shown to be strongly associated with sensitivity to PTC and PROP [6]. It appears that TAS2R38 is the only taste receptor that detects PTC and PROP [31]. Reed et al. [34] found that the sensitivity to quinine has also been associated with genetic variation in a bitter taste receptor, namely, TAS2R19. However, they reported that the peak association accounted for only 5.8% of the variance in perceived intensity of quinine HCl (at $1.81 \times 10^{-4}$ M), whereas the peak association of TAS2R38 accounted for much larger proportion, 45.9%, of the variance in perceived intensity of PROP (at $6.0 \times 10^{-4}$ M). According to Meyerhof et al. [31], altogether, nine TAS2R receptors are stimulated by quinine in a cell model. Thus, the perception of quinine seems to be secured by more receptor types than PTC/PROP and, therefore, less susceptible to individual deleterious genetic variants in receptors. Taken together, these results provide further support for the choice of quinine as the test stimulus for testing overall ability to perceive bitter taste.

Regarding the correlations between the detection thresholds, we observed a strong correlation between PTC and PROP thresholds, as expected [7]. This is probably due to detection of both PROP and PTC exclusively by the same taste receptor, *TAS2R38* [6, 31]. However, Bufe et al. [6] observed that the variation in this receptor predicted less variance for perceived PROP bitterness than for PTC bitterness. This led them to conclude that suprathreshold sensitivity to PROP is under additional genetic and environmental controls and the PROP is not interchangeable with PTC.

We observed rather strong correlations between thresholds for quinine and PTC/PROP. This association probably reflects the common general basis of bitter taste perception. According to Meyerhoff et al. [31], quinine did not stimulate *TAS2R38*, that was the only receptor activated by PTC and PROP. It should be noted that the "sensitive" variant of *TAS2R38* (haplotype PAV) that has been associated with sensitivity to PTC/PROP is generally more common than the "insensitive" variant (AVI) and most often a person needs to be homozygous for the "insensitive" variant (i.e., have the AVI/AVI genotype) to be a "non-taster" (Bufe et al. [6]). Consistently, in the present study, the "non-tasters" of PTC/PROP were a clear minority, with about 15% of the study subjects. The relatively high correlation among all measured thresholds implies that despite the potential differences in specific receptors for the studied tastants, their perception also shares common mechanisms.

Three methodological considerations need to be addressed in the present study: first, we used detection threshold for a measure of sensitivity to bitter taste, and second, we measured the thresholds separately for front and back parts of the tongue. Another method to assess sensitivity is to measure suprathreshold responses, that is, the magnitude of perceived intensity for stimuli at higher concentrations. Although suprathreshold responses may be more relevant measures in the context of food perception and preferences [35], thresholds are more applicable in clinical settings, where tests are used for screening of taste disorders such as ageusia. Third, no salivary or plasma samples were taken, so no genetic analyses could be used to determine actual genetic make-up of the bitter tastant classifications of the subjects.

## Conclusions

All in all, our results suggest applicability of taste strips at the front part of the tongue for quick detection threshold measurement for quinine and PTC/PROP. The results provide also further support for using quinine as the stimulus for screening of ageusia for bitter taste in clinical settings. Almost all our participants were capable to detect quinine, even if some were PTC/PROP "non-tasters." Of those seven individuals who were "non-tasters" for quinine, virtually, no one detected PTC and PROP either, implying that these individuals may be ageusic to all bitter tastants. This suggests that testing for quinine would rarely misclassify people as ageusic to bitter. However, a further study employing a group of patients with diagnosed ageusia to bitter taste, in addition to control subjects with intact gustatory function, should confirm sensitivity and specificity of the method.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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