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Lack of support for the inability to taste phenylthiocarbamide as an endophenotypic marker in patients with schizophrenia and their first-degree relatives

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Abstract

Objective: This study sought to replicate recent findings that both patients and relatives are significantly more likely to be phenylthiocarbamide (PTC) nontasters than healthy controls, and that within the patient group, nontasters have more severe positive and/or negative symptoms than tasters. Associations between PTC-tasting status and olfactory identification scores also were examined.
Method: PTC perception and olfactory identification were assessed in 48 patients with schizophrenia or schizoaffective disorder, 28 first-degree relatives, and 32 healthy volunteers.
Results: The three groups did not differ in PTC taste sensitivity. Findings did not change after: a sensitivity analysis that re-categorized participants who "possibly" tasted PTC, excluding Caucasian participants, or restricting the sample of patients to only those with schizophrenia. Among the patients, tasters and nontasters did not differ with regard to positive, negative, or general psychopathology symptoms. In the combined sample and the three groups separately, there were no associations between PTC-tasting status and olfactory identification scores.
Conclusions: This study, conducted specifically as an attempt to replicate previously reported findings, failed to provide support for PTC perception as an endophenotypic marker for schizophrenia. Further research is warranted.

Keywords: Phenylthiocarbamide; Psychosis; Schizophrenia

1. Introduction

Phenylthiocarbamide (PTC) is an antithyroid compound, and two specific genetic loci account for variance in perception of its bitter taste (Drayna et al., 2003; Guo and Reed, 2001; Kim et al., 2003; Reddy and Rao, 1989). Approximately one-third of the U.S. population is unable to taste the chemical (Guo and Reed, 2001; Yackinous and Guinard, 2001), though the prevalence of non-tasting may be greater among African Americans (Guo and Reed, 2001). PTC-nontasting status has been examined in people with several physical disorders (e.g., diabetes, peptic ulcer disease), as well as depression (Joiner and Perez, 2004), and five prior reports have examined PTC perception in patients with schizophrenia. In 1958, Constantinidis found that the inability to taste PTC was more common in patients with schizophrenia than in controls (Constantinidis, 1958). A decade later, Freire-Maia and coworkers

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reported a higher frequency of PTC-nontasting among males than females in a sample of 438 psychiatric patients, and a higher frequency of PTC-nontasting in psychiatric patients than in the general population (Freire-Maia et al., 1968). In 1992, Schlosberg and Baruch found a higher incidence of PTC-nontasting among 25 non-paranoid patients with schizophrenia compared to 25 patients with paranoid schizophrenia (Schlosberg and Baruch, 1992).

More recently, Moberg et al. (2005) found a higher prevalence of PTC-nontasting among 42 patients with schizophrenia (57%) and 12 of their healthy first-degree relatives (58%) compared to 23 healthy controls (22%). On the basis of those findings–the first to include first-degree relatives of patients with schizophrenia–the authors concluded that PTC-nontaster status may be an endophenotypic marker of an inherited neuronal vulnerability for schizophrenia. Additionally, within the patient group, they found that nontasters demonstrated higher total scores on the Scale for the Assessment of Positive Symptoms (SAPS) than tasters.

Moberg et al. (2007) then conducted a study to replicate the finding of an increased prevalence of nontasters in patients and family members in a larger independent sample, and to again examine possible clinical and symptom correlates of taster status in patients with schizophrenia. In that study, they again found a higher prevalence of PTC-nontasting among 67 patients with schizophrenia (57%) and 30 healthy first-degree relatives (60%) compared to 30 healthy controls (23%). Among the patients, nontasters had higher factor analysis-derived negative symptom scores and Schneiderian (first-rank) symptom scores than tasters. Olfactory identification also was assessed, as it was hypothesized that the well-documented deficits in olfactory function in schizophrenia might be associated with PTC taster status given the propinquity of smell and taste functions, as well as similarities in the underlying neuroanatomy. Patients who were nontasters were found to have poorer right nostril odor identification, as measured by the University of Pennsylvania Smell Identification Test.

The current study attempted to replicate the findings of Moberg et al. (2005, 2007) by assessing PTC perception in a sample of patients with schizophrenia, their first-degree relatives, and healthy controls. Previous reports using a very similar sample of patients, relatives, and controls from this research group have demonstrated that relatives have intermediate scores between patients' and controls' scores on verbal memory domains (Compton et al., 2006) and neurological soft signs (Compton et al., 2007). Using a sample approximately 40% larger ($n=108$) than the original Moberg et al. (2005) sample, this study sought to test the following hypotheses and, in doing so, replicate the previous findings: (1) patients and relatives would be significantly more likely to be PTC-nontasters than healthy controls, and (2) among patients, nontasters would have a higher level of positive symptoms and/or negative symptoms than tasters. Given that the UPSIT also was administered to study participants, any associations between PTC-tasting status and olfactory identification scores were explored.

2. Method

Forty-eight patients with schizophrenia or schizoaffective disorder (28 men and 20 women), 28 first-degree relatives (5 men and 23 women), and 32 healthy volunteers (18 men and 14 women) were recruited as part of a study of several risk markers for schizophrenia. Based on the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID) (First et al., 1997), 17 patients (15.7%) were diagnosed with schizophrenia, paranoid type; 14 (13.0%) with schizophrenia, undifferentiated type; seven (6.5%) with schizoaffective disorder, bipolar type; five (4.6%) with schizoaffective disorder, depressed type; four (3.7%) with schizophrenia, disorganized type; and one (0.9%) with schizophrenia, catatonic type. Relatives included 11 mothers (39.3%), nine sisters (32.1%), four fathers (14.3%), three daughters (10.7%), and one brother (3.6%).

Based on the SCID, all included controls and relatives were free of current or past psychotic or mood disorders. Controls were excluded if they endorsed any family history (in first- or second-degree relatives) of such disorders. Exclusion criteria for all participants were: (1) inability to speak English, (2) a substance dependence diagnosis, (3) known or suspected mental retardation, (4) history of neurological disease or clinically significant head injury, and (5) presence of any active medical condition that could affect olfactory or gustatory perception (e.g., upper respiratory tract infection). The study was approved by the university's institutional review board, and all participants gave written informed consent.

As expected, there were significant differences in age among patients (mean=31.0, SD=9.9), family members (mean=44.0, SD=18.0), and controls (mean=38.5, SD=6.5; $F=11.97$, $df=2,105$, $p<0.001$). The three groups also differed with respect to gender (41.7%, 82.1%, and 43.8% females in the patient, relative, and control groups, respectively; $\chi^2=13.11$, $df=2$, $p=0.001$), as well as race (87.5%, 75.0%, and 100.0%

African American, respectively; $\chi^2=8.83$, $df=2$, Fisher's exact $p=0.006$).

Smoking status was assessed in all participants. Among smokers, nicotine dependence was assessed using the *Fagerström Test for Nicotine Dependence* (Heatherton et al., 1991). Patients' symptom levels were rated using the *Positive and Negative Syndrome Scale* (PANSS) (Kay et al., 1987). All patients were receiving antipsychotic medications (mostly second generation agents) at the time of assessment. The mean PANSS positive, negative, and general psychopathology scores were: mean=19.8, SD=5.0; mean=22.1, SD=6.4; and mean=39.3, SD=8.1, respectively. The UPSIT was used as a measure of olfactory identification ability (Doty et al., 1984) that has been used extensively in schizophrenia research (Moberg et al., 1999), though it was not administered unirhinally in the current study.

The following steps were taken to assess PTC perception: (1) a control strip of filter paper was placed on the tongue and then removed; (2) a PTC-impregnated strip of filter paper (same supplier) was placed on the tongue; (3) the subject was asked if he or she tasted anything (using a "no," "possibly," or "yes" response format) different from the control strip; and (4) they then were asked to rate the intensity of taste on a 100-mm visual analog line, ranging from 0 mm (no taste) to 100 mm (extremely strong taste). Regarding the latter, a clear bimodal distribution was not apparent. However, the 28 participants rating "no" had a much lower score for the intensity rating (mean=11.0, SD=16.3) compared with the 75 participants rating "yes" (mean=69.0, SD=25.8; $t=13.31$, $df=76.5$, $p<0.001$), which provides a validation for the two-fold approach. The five participants responding "possibly" (visual analogue mean=37.6, SD=24.9) were excluded from the initial analyses and then included in sensitivity analyses. Those responding "possibly" and giving an intermediate score on the visual analog scale were likely responding to the bland taste of the paper rather than having a true PTC sensitivity, which typically elicits a strong response among those who are able to taste it. Following the Moberg et al. (2005, 2007) methodology, commercially available (Carolina Biological Supply Company, Burlington, N.C.), odorless PTC paper allowed for standardization across administrations. The paper strips were impregnated with 0.007 mg of PTC.

3. Results

Given the differences between patients, relatives, and controls with regard to age, gender, and race, it was important to first determine whether these demographic variables were associated with PTC sensitivity. For each variable, there was no association with PTC-tasting status (age: $t=1.02$, $df=101$, $p=0.31$; gender: $\chi^2=0.01$, $df=1$, $p=0.92$; race: $\chi^2=0.13$, $df=1$, Fisher's exact $p=1.0$). Additionally, PTC-tasting status was not related to smoking status ($\chi^2=0.05$, $df=1$, $p=0.82$), nor was it related to the level of nicotine dependence among smokers (Mann–Whitney U test: $z=0.75$, $p=0.49$).

Regarding the first hypothesis, patients and relatives were no more likely to be PTC-nontasters than controls ($\chi^2=0.49$, $df=2$, $p=0.78$). Proportions of tasters from

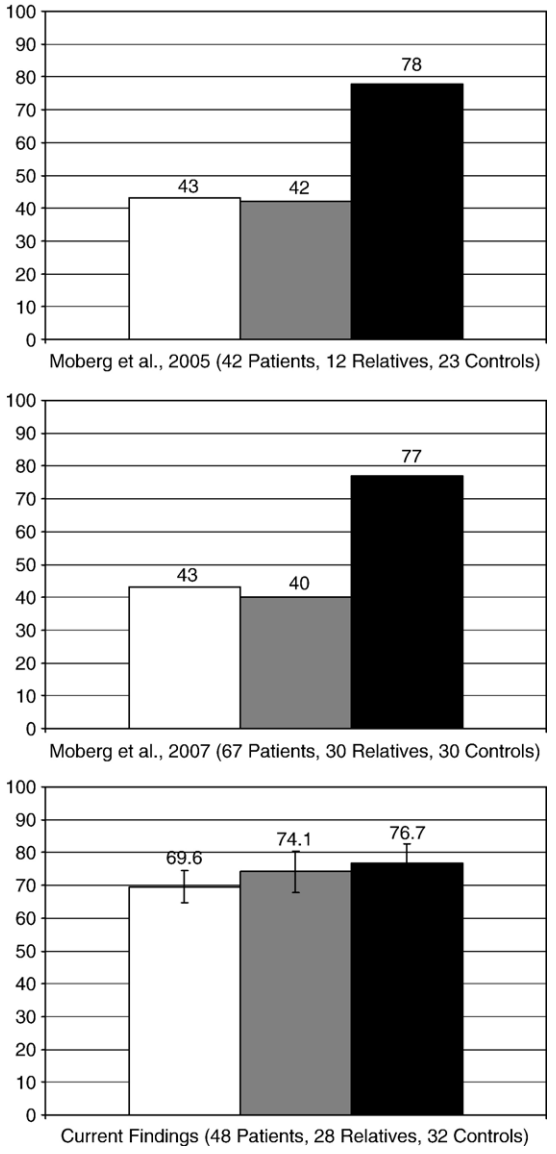

Fig. 1. Proportion of tasters of phenylthiocarbamide (PTC) among patients with schizophrenia (and schizoaffective disorder in the current study) (white), first-degree relatives (gray), and healthy controls (black). Sample sizes are shown in parentheses.

this sample and from the two studies by Moberg et al. (2005; 2007) are shown in Fig. 1. Further, the Kruskal–Wallis test revealed no significant differences in median scores on the visual analogue scale across the three groups ($\chi^2=2.58$, $df=2$, $p=0.28$). Among the tasters only, there were no differences in the visual analogue rating across the three groups ($\chi^2=2.32$, $df=2$, $p=0.31$) or by gender (Mann–Whitney U test: $z=0.92$, $p=0.36$).

In order to provide a sensitivity analysis given that five participants had responded as "possibly" tasting PTC, this small group was combined with nontasters. Repeating the analysis revealed no differences in PTC perception across the two groups ($p=0.85$). This subgroup then was combined with the taster group, and re-analysis again revealed no significant differences ($p=0.76$). To confirm that findings were not influenced by slight differences in racial composition, the 13 Caucasian participants were excluded. This did not change primary findings (70.0% of patients, 70.0% of relatives, 70.6% of controls were tasters) or the results of the sensitivity analyses. Finally, to confirm that findings were not influenced by diagnostic heterogeneity, the 13 patients with schizoaffective disorders were excluded. Again, this had no impact on the findings (74.3% of patients, 74.1% of relatives, and 76.7% of controls were tasters).

Regarding the second hypothesis, among the patients, tasters and nontasters did not differ with regard to PANSS positive (and the hallucination and delusion items individually), negative, or general psychopathology scores. Also, in the combined sample and the three groups separately, there were no associations between PTC-tasting status and olfactory identification scores as measured by the UPSIT.

4. Discussion

Despite using a slightly larger sample of patients, relatives, and controls, as well as a remarkably similar methodology, this study failed to replicate the findings of Moberg et al. (2005). Whereas Moberg et al. (2007) replicated their prior finding in a larger independent sample, the present study did not replicate their results. In the current study, relatives and patients were no more likely to be PTC-nontasters than healthy controls, and within the patient group, nontasters did not have a higher level of positive symptoms (or negative symptoms) than tasters. Within the patient group, and the relative and control groups, there were no associations between PTC-tasting status and UPSIT scores. Thus, the present report does not support the notion that inability to taste PTC is an endophenotypic marker for schizophrenia or that PTC sensitivity is associated with clinical symptomatology or olfactory identification ability.

There are several potential explanations for the discrepant findings. As suggested by Guo and Reed (2001) when they discussed reports of relationships between PTC tasting and diseases more generally, initial reports of associations that are later not replicated may be due to chance/spurious associations. Insufficient statistical power should be considered, though the sample size of the current study was slightly larger than that of Moberg et al. (2005), and the current findings did not reveal even a suggestion of a difference across groups. Given that PTC-tasting has been linked to specific genetic loci (Drayna et al., 2003; Guo and Reed, 2001; Kim et al., 2003; Reddy and Rao, 1989), the effect of admixture and population stratification must be considered in larger studies that use ancestry-informative genetic markers.

Although the current study used a methodology very similar to that of Moberg et al. (2005, 2007), important sample differences may have been present. For example, the 42 patients in Moberg et al. (2005) were either receiving atypical antipsychotic agents (60%), conventional agents (14%), or were unmedicated at the time of testing (26%). In their second report (Moberg et al., 2007), the 67 patients were receiving atypical agents (54%), conventional agents (25%), or a combination of both types (21%). The current study unfortunately did not collect complete data on current medication status, though all patients were prescribed antipsychotic agents, and the majority was on atypical agents. It cannot be excluded that differences in medication status accounted for the discrepant findings; however, there is no research evidence indicating that the type of antipsychotic agent has an effect on PTC-tasting ability.

With regard to the current findings of no evidence for an association between PTC perception and symptoms, it should be noted that Moberg et al. (2005, 2007) rated psychopathological symptoms using the SAPS and the Scale for the Assessment of Negative Symptoms (SANS) (or symptom dimensions derived from factor analyses including these scales), whereas the current study used PANSS subscale scores. Although there is evidence for relatively high correlations/convergent concurrent validity between these two methods for measuring symptoms (Kay et al., 1988; Norman et al., 1996), it cannot be excluded that the use of different measures could yield different associations between PTC-tasting status and symptom scores.

Given the mixed findings to date, whether PTC insensitivity is a risk marker for schizophrenia cannot be concluded. Studies that genotype relevant loci, and

studies involving larger sample sizes that would allow for better control of potential confounders such as race, are needed. Future studies should consider several methods for assessing sensitivity to PTC given some evidence that use of impregnated paper may lead to false positive responses in some nontasters (Lawless, 1980). To exclude potential medication effects, as well as any effects related to chronicity, PTC-tasting status should be studied in first-episode, antipsychotic-naïve samples, as well.

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Contributors

Each of the below contributors has made a substantial contribution to the research and the drafting of the manuscript and has approved the manuscript for submission.

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Conflict of Interest

The authors know of no conflicts of interest pertaining to this manuscript.

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