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Phenylthiocarbamide (PTC) perception in ultra-high risk for psychosis participants who develop schizophrenia: testing the evidence for an endophenotypic marker

Warrick J Brewer^a, Ashleigh Lin^{a,b,f}, Paul J Moberg^{c,d}, Gregory Smutzer^e, Barnaby Nelson^a, Alison R Yung^a, Christos Pantelis^b, Patrick D McGorry^a, Bruce I Turetsky^{c,d}, and Stephen J. Wood^f

^aOrygen Youth Health Research Centre, University of Melbourne, Melbourne, Australia

^bMelbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, and Melbourne Health, Melbourne, Australia

^cNeuropsychiatry Section, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

^dSmell and Taste Center, Department of Otorhinolaryngology: Head & Neck Surgery, University of Pennsylvania, Philadelphia, PA, USA

^eDepartment of Biology, Temple University, Philadelphia, PA 19122, USA

^fSchool of Psychology: University of Birmingham, Birmingham, UK

Abstract

Reports suggesting that schizophrenia participants are more likely to be phenylthiocarbamide (PTC) non-tasters when compared to controls have recently been controversial. If supported, a genetic-based phenotypic variation in PTC taster status is implicated, suggesting a greater illness risk for those participants with recessive alleles for the TAS2R38 receptor. Should PTC insensitivity be a schizophrenia endophenotype, then it would be expected in follow-up of ultra high-risk for psychosis participants who later develop schizophrenia (UHR-S). UHR-S were hypothesised to show reduced PTC sensitivity compared to those who were previously at risk, but did not transition (UHR-NP). PTC perception was assessed in 219 UHR participants at long-term follow-up, of whom 53 had transitioned to psychosis (UHR-P) during the follow-up period. Fifteen of the 219 participants were diagnosed with schizophrenia. Seventy-eight had a family history of psychotic disorder. No differences in PTC taster status were found in UHR participants based upon transition to psychosis status, schizophrenia diagnosis, or family history of schizophrenia. This report indicates that schizophrenia development among UHR participants is not associated with PTC tasting deficits and fails to support previous findings that inability to detect the bitter taste of PTC is a schizophrenia endophenotype.

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Correspondence: Assoc. Prof. Warrick J. Brewer, ORYGEN Youth Health Research Centre (Locked Bag 10), Parkville, Vic. 3052, Australia Phone: +613 9342 2800; Fax: +613 9342 2858; w.brewer@unimelb.edu.au.

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Keywords

TASTE; ENDOPHENOTYPE; PREDICTION; MENTAL ILLNESS; PSYCHOSIS; RISK

1. Introduction

Recent findings support long made suggestions that the ability to detect the bitter taste of phenylthiocarbamide (PTC) at suprathreshold amounts is reduced in participants with schizophrenia and their family members relative to controls (Constantinidis, 1958; Freire-Maia et al, 1968; Moberg et al., 2005; 2007). Moreover, non-tasters exhibited increased levels of negative and first-rank symptoms (Moberg et al., 2007). These results suggest greater illness risk and severity in those participants who cannot perceive the bitter taste of PTC (Reddy et al., 1989; Kim et al., 2003).

Phenotypic variation in PTC sensitivity correlates with single nucleotide polymorphisms in the *TAS2R38* bitter taste receptor gene that localizes to chromosome 7 (Kim et al., 2003). Each single nucleotide polymorphism encodes a different amino acid in the receptor protein (at amino acid positions 49, 262, 296, 80 (rare), and 274 (rare). Two predominant haplotypes for this gene exist at high frequency outside of sub-Saharan Africa (Kim and Drayna, 2004), and these two major haplotypes are primarily responsible for the taster and non-taster phenotypes for PTC (Kim et al., 2003).

In addition, a second locus for PTC detection has been reported on chromosome 16p (Reed, 2000). Moreover, recent investigations of the PTC receptor suggest that activation of stimulatory G-proteins are required for detecting this bitter tasting substance (Kim et al., 2003; Bufo et al., 2005; Behrens and Meyerhof, 2009). G-protein dysregulation has been strongly linked to the dopamine system of schizophrenia (Schreiber & Avissar, 2000).

In an attempt to replicate the findings of Moberg et al. (2005; 2007), Compton and colleagues (2007) failed to support PTC taster status as an endophenotypic marker for schizophrenia. One possible explanation for these contradictory findings is that previous reports linking PTC taster status and schizophrenia did not assess participant response to a control filter paper that contained no tastant as employed by Compton et al. (2007). Whilst it may be speculated that schizophrenia participants are more likely to state that they can taste something if they are not presented with a negative control it remains unclear as to whether the older studies instructed the participants that the PTC paper (or strips) would have an expected bitter taste. If the studies did not, then the subject might give a positive response, due to a background (non-bitter) taste. This might occur more frequently in participants diagnosed with schizophrenia, which might skew the data. Moreover, the research to date has been confined to chronically unwell participants where long term medication use may be a confound, or their first degree relatives. The specificity and sensitivity of PTC and the related compound *n*-propylthiouracil (PROP) on bitter taste perception in other psychotic disorders remains unclear. If PTC taster status is a clear endophenotype, then this finding would be expected in ultra high-risk (UHR) for psychosis participants who later develop schizophrenia. The current study examined PTC taster status in an UHR for psychosis group, assessed at follow-up as part of a larger study. We hypothesised that of those participants who had made the transition to psychosis generally (UHR-P), only those with the more specific diagnosis of schizophrenia (UHR-S) would show reduced PTC sensitivity at follow up compared to those who were previously at risk for psychosis but did not transition (UHR-NP).

2. Method

2.1 Participants

Participants included 219 individuals identified as being at UHR for psychotic disorder at the PACE clinic in Melbourne, Australia, between 1993 and 2006. These individuals were reassessed as part of a large follow-up study at PACE. Following approval by Melbourne Health Research & Ethics Committee, all participants provided written informed consent.

At baseline, all participants were aged 15–30 years and met the PACE UHR criteria, as assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005). These criteria are 1) attenuated positive symptoms (APS), 2) brief limited intermittent psychotic symptoms (BLIPS), and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or a history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning. These criteria have previously been operationalized (Yung et al., 2003; 2004). Exclusion criteria for PACE are a previous psychotic episode (treated or untreated), an organic cause for presentation or past anti-psychotic exposure equivalent to a total haloperidol dose of >50 mg.

For inclusion in research at PACE, participants must have normal (or corrected-to-normal) vision and hearing, and speak English as their preferred language. A history of significant head injury, seizures, and neurological diseases were exclusion criteria for this study.

2.2 Measures and Procedure

Participants were reassessed between September 2007 and August 2009. In this study, all participants were reassessed with the CAARMS (Yung et al., 2005) to determine transition to psychosis, and the Structured Clinical Interview for DSM-IV Axis I disorders (SCID; First et al., 1996) to determine diagnosis. Family history of psychiatric disorders was assessed with an abbreviated form of the Family Interview for Genetic Studies (FIGS; Maxwell, 1992). PTC sensitivity was tested with novel edible taste strips that were prepared from pullulan-hydroxypropyl methylcellulose solutions (at a wt/vol ratio of 92% pullulan and 8% hydroxypropyl methylcellulose) that were dried to a thin film at room temperature (Smutzer et al., 2008). The amount of PTC tastant that was incorporated in a 2.54 cm × 2.54 cm (one inch square) taste strip was 667 nanomoles. Control strips were identical to PTC strips except that no PTC was added to the control solution. Fluorescence intensity measurements of a random sample of edible strips have shown that tastants are uniformly distributed in the strips (Smutzer et al., 2008; Desai et al., 2011).

Participants were instructed to place the control strip (containing no tastant) on their tongue. Once the strip had completely dissolved, the process was repeated with a PTC taste strip, without participants closing their mouths. Participants were asked if they tasted anything and then whether the two strips tasted the same or tasted different. If the participant tasted a difference, they were asked to describe how it was different from the first control strip. All participants gave a qualitative response to the taste of the second PTC strip. They were then asked to rate the taste intensity rather than indicate bitterness on a 100-mm non-calibrated, visual analogue scale. This scale ranged from “no taste” to “very strong taste.”

3. Results

The mean age of the sample was 25.79 (SD=5.09) years. Table 1 lists the percentages of UHR participants who could or could not detect the taste of PTC. No gender effect was found for PTC sensitivity in this study. Fifty-three (24.2%) of the participants had made a transition to psychosis during the study follow-up period. Fifteen (6.8% of the total UHR sample) received a diagnosis of schizophrenia. Of the remaining 38 UHR-P participants, 3

(1.4%) had bipolar with psychotic features; 1 (0.4%) schizoaffective disorder, 4 (1.8%) major depressive disorder with psychotic features; 1 (0.4%) delusional disorder; 2 (0.9%) substance induced psychotic disorder; 6 (2.7%) psychotic disorder NOS. Here we report current or lifetime diagnosis at follow-up interview (last known diagnosis), in order to mitigate diagnostic change early in the history of the disorder (Schwartz et al., 2000; Veen et al., 2004). A number of participants who had transitioned previously were in remission and did not meet diagnostic criteria for a psychotic disorder when asked about experiences since they were last seen at PACE. The total number of participants with a family history of psychosis was 78. All PTC tasters rated the strength of taste in the top quartile on the uncalibrated 100 mm line indicating perception as 'strong-very strong'. PTC non-tasters rated predominately in the lowest two quartiles.

As shown in Table 1, no statistical differences were detected in PTC taster status between those who did (UHR-P) or did not (UHR-NP) make the transition to psychosis. Secondly, those who received a diagnosis of schizophrenia in the UHR-P cohort reported no difference in PTC sensitivity when compared to those who did not have a diagnosis of schizophrenia. Also, no differences in PTC taster status between those with or without a family history of diagnosed psychiatric disorder were observed. For those UHR clients with or without a family history of psychotic-spectrum disorder more specifically, no difference in PTC taster status was found.

4. Discussion

This study is the first to test PTC sensitivity in a cohort of participants who were originally identified as being at ultra-high risk for psychosis. PTC taster status at follow-up examinations did not discriminate those who later developed psychosis or schizophrenia from those who did not develop psychosis. Furthermore, a family history of either general psychopathology or more specifically psychosis-spectrum disorder was not associated with reduced PTC sensitivity. Therefore, findings in this large UHR cohort do not support previous reports of a higher prevalence of PTC non-tasters among participants with a diagnosis of schizophrenia. Rather, these results suggest that the development of schizophrenia and other psychotic disorders is not associated with PTC taster status.

Our psychophysical protocol was similar to that reported by Compton et al. (2007) where a comparison strip was administered before presentation of a PTC-containing strip. This protocol was not followed in previous reports, and we reiterate the point that schizophrenia participants are more likely to report that they have tasted something when there is no comparable reference and it remains unclear as to whether the older studies instructed the participants that the PTC paper (or strips) would have an expected bitter taste which further confounds the procedure. In addition, the number of participants with chronic schizophrenia in the Compton et al. (2007) study were similar in the reports by Moberg et al. (2005; n = 42): [Compton et al. (2007; n = 48)] except that 11.5% of the Compton cohort was diagnosed with schizoaffective disorder. Only forty-three percent of the cohort of Moberg et al. (2005) were tasters of PTC, which was subsequently replicated in a larger independent sample (Moberg et al., 2007; n = 67, 43%). In contrast, the proportion of PTC tasters in the Compton cohort of schizophrenia participants was considerably higher at 69.6%. Compton et al. (2007) further suggested that medication status may explain in part the discrepancy of PTC taster status in their subject population when compared to the findings of Moberg et al. (2005; 2007).

Findings from the current study, albeit from a relatively small number who were diagnosed with schizophrenia (n = 15), suggest that 86.7% (n = 13) could taste PTC during treatment at the PACE clinic. Regarding our larger total cohort, 78 clients (35.6%) reported a family

history of psychosis, of whom 69.2% were PTC tasters. This proportion of PTC tasters is similar to that generally reported for healthy Caucasians (Mascie-Taylor et al., 1983). This finding is also similar to the proportion of first-degree relatives who were tasters in the Compton et al. (2007) study. Our findings are also consistent with the enhanced methodology employed by Compton et al. (2007) and, as such, do not support PTC insensitivity as an endophenotypic marker for schizophrenia.

Other factors may influence the disposition of PTC taster status as our cohort ages. For example, potential epigenetic changes such as cytosine methylation in the *TAS2R38* gene, or changes in histone modifications, have not been examined. Additional factors may include the methodology used to present PTC, chronicity, or ethnicity of the subject population (Drayna, 2005). Further research in a large first-episode cohort is warranted, where larger numbers of participants with schizophrenia can be compared to true age-matched controls.

One caveat to the current findings must be noted. It has been reported that psychophysical testing by means of papers or strips impregnated with PTC may lead to a high incidence of false positive responses from insensitive participants (Lawless, 1980). This finding appears to arise from variability in the procedures employed to accurately classify participant responses as to whether they “taste something.” A more reliable way for future studies to resolve some of the discrepancies is to identify *TAS2R38* haplotypes in neuropsychiatric and control populations. Provided that the delivery method for PTC has been successfully validated (GS, submitted), genetic analysis of the PTC receptor would circumvent any procedural differences. This genetic data would directly address, on a genetic level, the question of taster-non-taster status in this clinical population.

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Table 1

	Taste response		Estimate [*]	
Variables	Same (%)	Different (%)	χ^2	<i>p</i> -value
Gender				
Male	24.7	75.3	0.26	0.6
Female	27.8	72.2		
Transitioned to psychosis (UHR-P)? (<i>N</i> = 53)				
Yes	22.6	77.4	0.53	0.5
No	27.7	72.3		
Diagnosis of schizophrenia (UHR-S)? (<i>N</i> =15)				
Yes	13.3	86.7	1.04	0.3
No	26.3	73.7		
FH of psychopathology?				
Yes	23.7	76.3	0.10	0.3
No	29.7	70.3		
FH of psychotic disorders?				
Yes	25.5	74.5	0.03	0.9
No	26.7	73.3		

Notes: FH = family history.

^{*}
df = 1.