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Bitter and Sweet Taste Tests are Reflective of Disease Status in Chronic Rhinosinusitis

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To the Editor

Recently, a growing body of literature has demonstrated expression of taste receptors throughout the body, with functions that extend far beyond the sensory capacity of the tongue.¹ Both bitter and sweet taste receptors are expressed in the airway, where they appear to play several important roles in innate immune defense.² The solitary chemosensory cell (SCC) is a discrete airway cell type that expresses both sweet (T1R2/3) and bitter taste receptors (T2Rs) capable of responding to bacterial products as well as the bitter compound denatonium.³ Stimulation of human SCC T2Rs elicits a Ca²⁺ response that causes immediate release of antimicrobial peptides (AMP's) from adjacent epithelial cells.⁴ Sweet receptor activation on the SCC by glucose blocks the signal transduction of SCC bitter receptors.⁸ Depletion of airway mucus glucose is a harbinger of bacterial infection, as the bacteria consume the sugar rapidly. It is postulated that this reduction in mucus glucose deactivates sweet receptors, which then release their inhibition of the response of the T2Rs to bitter microbial compounds.⁵

There is tremendous genetic variability in human taste receptor function.⁶ In the upper airway, this contributes to inherent weaknesses in respiratory defense. Genetic variations of T2R38 expressed on ciliated cells, as well as variations in functionality in bitter and sweet taste receptors on SCC's, correlate with disease severity in chronic rhinosinusitis (CRS).^{5,7,8} Thus, we hypothesize that individuals with insensitive bitter taste receptors or hypersensitive

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Conflict of Interest: The senior author (NAC) and penultimate author (DRR) have a patent pending "Therapy and Diagnostics for Respiratory Infection."

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sweet taste receptors, as assessed phenotypically with a taste test, will be more common in a CRS cohort.

With Institutional Review Board approval, we enrolled adult patients who met objective and subjective guidelines for the diagnosis of CRS. 93% of patients had CT confirmation of disease. All patients were recruited from the Department of Otorhinolaryngology-Head and Neck Surgery at the University of Pennsylvania starting on December 1, 2014. Selection for the study was limited to immune competent CRS patients over age 18 with endoscopic evidence of sinonasal inflammation (mucosal edema or polypoid degeneration) or overt mucopurulence. Exclusion criteria included patients with genetic disorders affecting mucociliary clearance, history of chemotherapy, immunodeficiencies, or rhinologic granulomatous disease. Basic demographic data were also collected from self-report, in addition to information regarding medical history and use of nasal therapeutics. Control subjects were family members of twins recruited in Twinsburg, Ohio at the 2015 Twins Days Festival. Each subject filled out basic demographic and respiratory disease questionnaires. Any controls with prior sinus surgery or a sinus infection treated with antibiotics or steroids in the previous 6 months were excluded from analysis.

Subjects tasted and rated two five-ml samples of several solutions including: 0.35 M sucrose (Suc), 0.25 M sodium chloride (NaCl), and 1.8 uM denatonium benzoate (DB).⁸ Distilled water was also used during the test. Taste intensity ratings for the two trials of each solution were averaged. A denatonium/sucrose combination score was obtained by first dividing each patient's denatonium and sucrose scores by their overall taste test score for all modalities, eliminating subjective differences in scale usage. These two proportions were then combined by taking one minus the sucrose proportion and then adding that value to the denatonium proportion.

Fisher's exact test was used to compare the control vs. CRS groups for all dichotomous and categorical covariates. General linear models were used to compare groups on continuous variables, including age and SNOT-22 scores. To obtain an unbiased estimate of the difference in taste intensity ratings between controls and CRS patients, propensity score methods were used. Propensity score modeling involves first calculating a score for each participant based on their probability of being either in the control group conditional on covariates. Then, CRS patients and control subjects with similar scores are compared. Once this is done, an unbiased estimate for the average difference in taste intensity ratings can be calculated. All tests were two-tailed, and used an alpha of 0.05. Stata 14.2 was used for statistical analyses.

A total of 328 CRS patients and 287 control subjects were enrolled in the study and had complete demographic and clinical data available (Table 1). The groups differed significantly on several variables. Thus, we included variables in the propensity score model that were both significantly related to our outcome (taste test) and to our predictor (control vs. CRS status), i.e. true confounders. These covariates included sex (male vs. female), age (continuous), and smoking status (never vs. ever). After the propensity scores were determined, the groups were found to be adequately balanced. We then determined an

unbiased estimate of differences in taste intensity ratings between the control, CRS without nasal polyps (CRSsNP), and CRS with nasal polyps (CRSwNP) groups.

Taste testing results by group are shown in Table 2 as both raw intensity ratings and estimated mean differences obtained with propensity score modeling. Compared to controls, CRSsNP patients rate denatonium (mean difference $-0.65 \pm .29$, $p < 0.05$) as having lower intensity overall. Conversely, CRSsNP and CRSwNP patients rated sucrose (mean difference CRSsNP 0.65 ± 0.25 , $p < 0.05$ and CRSwNP 0.65 ± 0.23 , $p < 0.01$) as having higher intensity when compared to control ratings. NaCl sensitivity was used as a non-bitter, non-sweet internal control, and intensity ratings of NaCl did not differ between control subjects and CRS patients. Based on the *in vitro* cell-based assays indicating opposing downstream physiologic effects of bitter and sweet taste receptor stimulation on SCC's,⁵ we also assessed a denatonium/sucrose combination score, as detailed in methods, which was highly different between CRS and control subjects (mean difference CRSsNP 4.94 ± 1.20 , $p < 0.001$ and CRSwNP 3.23 ± 1.07 , $p < 0.01$). Within the CRS cohort, none of the comorbidity variables examined detailed in Table 1 were independently associated with variations in taste intensity.

CRS has a tendency to run in families, suggesting that there is a strong genetic component to the disease.⁹ While the cause of CRS is controversial, it is thought that there is a microbial contribution to the disease. Genetic variation in bitter and sweet taste receptor function has been previously implicated in disease status and disease severity in chronic rhinosinusitis.^{5,7,8} In the present study, we demonstrate that phenotypic taste test differences exist between control and CRS patients across bitter and sweet compounds detected by SCC's. Patients with CRSsNP are significantly more likely to be less sensitive to denatonium, a broad T2R agonist, and those with CRSsNP and CRSwNP are more sensitive to sucrose, a T1R2/3 agonist. Physiologically, this may reflect a decreased SCC response to bitter microbial products in the airway in CRS patients, and a compounding effect of an increased sensitivity to glucose in this same cohort. Patients with increased sensitivity to glucose will potentially inhibit SCC T2R function at lower airway glucose concentrations, i.e., early infection, due to a higher affinity of T1R2/3. Importantly, CRS and control subjects did not differ in taste perception of NaCl, a compound unassociated with bitter or sweet taste receptors. While the study incorporates statistical considerations to eliminate potential confounders, there is a possibility that taste is affected by other variables. Continued investigations are necessary to optimize compound concentrations used in taste testing to build a predictive model. The ability to assess airway taste receptor variation with an inexpensive taste test has broad implications, as differences in airway taste receptor function may reflect impaired innate immunity and predisposition to certain respiratory infectious/inflammatory disorders.

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Highlights

Genetic variation in upper airway taste receptor function correlates with susceptibility to infection and severity of rhinosinusitis. We demonstrate that phenotypic assessment with a taste test appears to be reflective of clinical disease status in rhinosinusitis.

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Table 1

Demographic and clinical data for CRS and control subjects. Abbreviations: AERD (Aspirin Exacerbated Respiratory Disease), AFS (Allergic Fungal Sinusitis), AR (Allergic Rhinitis), ASA Sens. (Aspirin Sensitivity), DM (Diabetes Mellitus), GERD (Gastroesophageal Reflux Disease), OSA (Obstructive Sleep Apnea), FESS (Functional Endoscopic Sinus Surgery).

	CRS	Control	<i>P</i>
Total Enrollment	328	287	
Female – N (%)	129 (39%)	166 (58%)	<0.001
Race – N (%)			0.787
White	289 (88.1%)	249 (87.1%)	
Non-White	39 (11.9%)	38 (12.9%)	
Ethnicity – N (%)			0.003
Hispanic	3 (1%)	15 (5.2%)	-
Non-Hispanic	325 (99.1%)	272 (94.8%)	-
Smoker – N (%)			<0.001
Never	197 (60.1%)	236 (82.2%)	
Ever	131 (39.9%)	51 (17.8%)	
Comorbidities – N (%)			
Asthma	162 (49.4%)	41 (14.4%)	<0.001
AERD	42 (12.8%)	-	-
AFS	14 (4.3%)	-	-
AR	248 (75.6%)	-	-
ASA Sens.	46 (14.0%)	-	-
DM	24 (7.3%)	-	-
GERD	111 (33.8%)	-	-
Hypertension	92 (28.0%)	-	-
OSA	45 (13.7%)	-	-
Nasal Polyps – N (%)	186 (56.7%)	-	-
Prior FESS – N (%)			
Primary	131 (39.9%)	-	-
Revision	197 (60.1%)	-	-
	Mean (SD)	Mean (SD)	
Age at Enrollment	48.6 (15.3)	40.4 (15.4)	<0.001
SNOT-22	46.6 (22.2)	10.6 (12.2)	<0.001
BMI	28.0 (5.3)	-	
Lund-Mackay CT	12.3 (6.0)	-	

Left: Taste intensity testing results (raw mean score) in control, CRS without nasal polyps (CRS_{NP}), and CRS with nasal polyps (CRS_{wNP}) patients.

Right: Propensity score modeling-adjusted differences between control and CRS groups reported as adjusted difference (standard error).

	Raw Taste Intensity Scores			Propensity Score Modeling--Adjusted Differences			
	Control	CRSsNP	CRSwNP	Control vs. CRSsNP	p	Control vs. CRSwNP	p
Denatonium	8.89	7.97	8.17	0.65 (0.29)	0.027	0.32 (0.25)	0.197
Sucrose	5.99	6.43	6.44	-0.65 (0.25)	0.011	-0.65 (0.23)	0.005
NaCl	6.67	6.44	6.68	-0.06 (0.27)	0.824	-0.22 (0.23)	0.356
Comb. Score	10.86	5.89	7.03	4.94 (1.20)	<0.001	3.23 (1.07)	0.003