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Relationship Between Bitter-Taste Receptor Genotype and Solid Medication Formulation Usage Among Young Children: A Retrospective Analysis

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Abstract

Background—Children often refuse to take medication in liquid formulation because of its unpleasant taste. Recent advances in taste genetics have provided some insight into individual differences in taste among children: due to their genotype, some prefer more intense sweetness and are more sensitive to bitter tastes and thus may have different needs for medication formulation.

Objective—The aims of this study were to: (1) test the a priori hypothesis that children with the bitter-sensitive genotypes are more likely to have experienced solid medication formulations than those with the bitter-insensitive genotype; and (2) conduct post hoc analyses to examine the relationship between genotype and most preferred level of sucrose in water because sweeteners are a common component of liquid formulations.

Methods—The following data were obtained from healthy, 3- to 10-year-old children who participated in 1 of 5 taste-research studies: taste genotype for alleles of the bitter-taste receptor *TAS2R38*; data from retrospective reports of solid medication formulation usage and favorite beverage; and most preferred level of sucrose in water, as determined psychophysically.

Results—Data from 448 children were included (245 girls, 203 boys; mean age, 7.8 years). Children with 1 bitter-sensitive allele (*TAS2R38 PP* or *AP* genotype) were more likely to have taken medication in solid formulation than were bitter-insensitive (*AA* genotype) children. Children with the *PP* genotype preferred higher concentrations of sucrose in water, and their favorite beverage contained more grams of sugar compared with children with the *AA* genotype.

Conclusions—Taste genotype was associated with experience with solid medication formulations and preference for more intense sweetness. This finding suggests that taste genetics might be an important factor in formulation choice and compliance in the pediatric population.

Keywords

bitterness; children; medication formulation; preference; sweetness; taste genetics

INTRODUCTION

Children and adults have many of the same illnesses and are treated with many of the same drugs, but approximately two thirds of these drugs lack labeling for efficacy and tolerability

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CONFLICTS OF INTEREST

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for children.¹ Although medications have different pharmacokinetic and pharmacodynamic effects in children than in adults, another important difference is often overlooked: children may perceive the taste of medication—which is often bitter—differently than adults.^{2–5} The lack of “child-friendly” formulations leaves children at an increased risk for suboptimal dosing due to lack of adherence to medication regimens and reduced access to new medicines.⁶

Many parents and pediatricians believe that taste is a central challenge of administering medicine to children: half of 500 parents surveyed indicated that their children refused to take their medication at some time, mostly because of its unpleasant taste,⁶ and >90% of pediatricians listed taste as a barrier to compliance to treatment of acute illness.⁷ Children experience sounds,⁸ smells,⁹ tastes,^{2–5} and irritants¹⁰ differently from adults. The difference in taste experience is especially striking, making the bad tastes of some medications problematic in children.

Within hours after birth, infants reject bitter-tasting liquids,¹¹ and children, especially those with a particular genotype,³ are more sensitive to bitter tastes than are adults.² Children also prefer sugar at higher concentrations than do adults.¹² The biology of taste in children—love of sweetness and rejection of bitterness—explains in part why formulations that are successful for children often contain sweeteners and why much effort is aimed at masking or blocking the inherent bitter qualities of drugs.¹³ Solid formulations, which encapsulate the bitter tastes of medicines, are impractical in children because the dosage often varies according to a child’s weight^{6,13–15} and because young children and infants often cannot or will not swallow pills or tablets.⁶ A better understanding of the biology of bitter taste perception may lead to better medication strategies for children.

The sensation of bitterness arises when drugs contact receptors on the surface of specialized cells in the taste buds of the tongue. During the past decade, research has reported 25 members in the TAS2R family of bitter-taste receptors. These receptors are selectively sensitive to particular compounds; for instance, the TAS2R38 receptor responds to propylthiouracil, a drug widely prescribed for hyperthyroidism.¹⁶ This particular receptor has 2 genetic forms; people with the inactive form are insensitive to the bitter taste of this drug. Findings from studies in children and their parents have suggested that the phenotype–genotype relationship for this receptor varies with age and that children with a particular genotype are more sensitive to bitter taste than are their parents with the same genotype.^{2,3}

Bitter-taste receptors are genetically extremely diverse,¹⁶ so one would not expect every child (or adult) to be equally sensitive to the taste of a particular drug.² This may explain why some children refuse to take some medicines and others readily comply.⁶ Young children are almost always given liquid formulations, if available—95% of children have been exposed to a liquid medication by age 2 years.¹⁷ However, children who are most sensitive to bitterness due to their taste genotypes may be more likely to try solid formulations (pills). Therefore, in the present study, children underwent genotyping for a particular bitter-taste receptor, and the relationship between their genotype and having tried solid forms of medication was determined. Also, because children with bitter-sensitive genotypes might more strongly desire formulations that mask bitterness with sweeteners, sweet preference was measured using a laboratory test, and the sugar content of each child’s reported favorite beverage was recorded. The long-range goal of the present study was to provide an understanding of how compliance with different formulations of medication is affected by the taste sensitivity of a child, and therefore to gain insight into how to better develop medicines for pediatric populations.

METHODS

Participants

The study population consisted of healthy, 3- to 10-year-old children and their mothers who participated in 1 of 5 taste-research studies at the Monell Chemical Senses Center (Philadelphia, Pennsylvania) between 2003 and 2010. Participants were pooled from multiple studies to provide enough power for genotype–phenotype analysis. The total study population included healthy children between the ages of 3 and 19 years; however, for the present analysis, children who were 3 to 10 years of age were selected because age is a key factor in the ability of a child to swallow a pill (the majority of children over the age of 10 years are easily able to swallow a pill¹⁷). Genotype–phenotype association studies require that subjects be genetically unrelated,¹⁸ so if >1 child from a family was tested, data were included from the first child of the sibling pair from whom data were available. None of the children were excluded from analyses for any other reasons. All of the children underwent genotyping.

All of the studies, procedures, and analyses were approved by the Office of Regulatory Affairs at the University of Pennsylvania, Philadelphia, Pennsylvania. Informed consent was obtained from each adult, and assent was obtained from each child aged ≥ 7 years.

Medication Formulation History

Mother–child dyads were queried about whether the child had ever taken medication in pill/tablet (encapsulated or solid) formulation. Children were categorized as those who had or had not taken medication in a solid formulation.

Taste Testing and Queries

Following acclimation to the room and personnel and a 1-hour fast, children were individually tested at Monell in a closed room specifically designed for sensory testing. Sucrose preferences were determined using a forced-choice, paired-comparison tracking procedure that is sensitive to the cognitive limitations of children.¹⁹ Participants were presented with pairs of solutions of sucrose at differing concentrations (3, 6, 12, 24, and 36 g/dL). They tasted and expectorated each solution and pointed to the one they liked better. The procedure continued until the participant either chose the solution with a given concentration when it was paired with both a higher and a lower concentration or chose the solution with the highest or lowest concentration 2 consecutive times.

Children were also queried about their favorite beverages. Specifically, they were asked, “What is your favorite beverage in the whole world?” and “Which beverage do you ask your mom to buy the most?” The sugar content of their favorite beverages was determined from product labels.

Genotype Analyses

Cheek cells were obtained from children via swab (Buccal Amp, Epicenter, Madison, Wisconsin) or saliva collection (Oragene, DNA Genotek Inc., Kanata, Ontario, Canada), and genomic DNA was extracted following the instructions from the manufacturer. Alleles of *TAS2R38* (accession no. AF494231) were genotyped using real-time polymerase chain reaction single-nucleotide polymorphism genotyping assays (rs713598, rs1726866, and rs10246939; Applied Bio-systems, Foster City, California). Although this gene has 3 variant sites associated with bitter-sensitivity, they are in strong linkage disequilibrium.²⁰ Therefore, children were grouped by the first variant site, *A49P* (alanine [A] changed to proline [P] at position 49). Children were identified as homozygous for the bitter-insensitive allele (*AA*), homozygous for the bitter-sensitive allele (*PP*), or heterozygous (*AP*).

Statistical Analyses

All analyses were conducted using Statistica version 10 (StatSoft, Inc., Tulsa, Oklahoma). χ^2 analysis²¹ was used to test the a priori hypothesis that there would be an association between *TAS2R38* genotype and experience with solid formulations of medication. Because most solid formulations for children taste sweet, a post hoc analysis was conducted to examine the association between *TAS2R38* genotype and sucrose preference, as well as the sugar content of each child's favorite beverage using ANOVA with a general linear model.²¹ All summary statistics are presented as mean (SE).

RESULTS

The sample consisted of 448 children (245 girls, 203 boys; mean [SE] age, 7.8 [0.1] years; black, 52.2%; white, 28.1%; other race/ethnicity, 19.6%; Table I). Because of differences among studies, 256 children (57%) underwent both phenotyping for sucrose preference and were queried about medication usage, 111 (25%) underwent phenotyping only, and 81 (18%) provided only retrospective, self-reports of solid medication usage. Genotyping revealed that 31% of children had the *AA* (bitter-insensitive) genotype, 49% had the *AP* genotype, and 19% had the *PP* genotype. Of the 337 children interviewed regarding medication formulation, 158 (47%) had taken a solid formulation at least once.

Children with the *PP* or *AP* genotype were more likely to have taken medicine in a solid formulation than were children with the *AA* genotype (52% vs 36%; $\chi^2 = 7.88$; $df = 2$; $P = 0.02$; Figure). Children with the *PP* genotype preferred higher concentrations of sucrose in water than did children with the *AA* genotype, and children with the *AP* genotype had an intermediate preference ($F_{(2, 364)} = 4.36$; $P = 0.01$; Table II). Children with the *PP* genotype also tended to prefer beverages containing more sugar than did children with the *AA* genotype, with the favorite beverages of children with the *AP* genotype being intermediate ($F_{(2, 304)} = 2.86$; $P = 0.06$). However, there was no relationship between the level of sucrose most preferred and whether the children had taken medication in a solid formulation ($P = 0.3$).

DISCUSSION

The primary objective of the present study was to explore the association between bitter-taste receptor *TAS2R38* genotype and experience with medication in solid formulations (pills). Children with bitter-sensitive (homozygous *PP* and heterozygous *AP*) genotypes were more likely to have taken medication in a solid formulation than were children with the bitter-insensitive (*AA*) genotype.

Children are typically given medication in a liquid formulation when available,¹⁷ and the palatability of the formulation is the most common obstacle for adherence to therapeutic regimens.^{6,7} The resistance to taking bitter liquid formulations may affect compliance and therefore may motivate bitter-sensitive children or their parents to try medications in pill formulations as an alternative; this is an important area for future research.

Because many liquid formulations have added sweeteners to increase palatability,¹³ a secondary objective was to examine the relationship between *TAS2R38* genotype and preference for sucrose in water and sugar content of the children's favorite beverages. Children with the *PP* genotype preferred higher levels of sucrose in water in the laboratory setting and reported liking beverages with higher concentrations of sugar than did children with the *AA* genotype. Bitter-sensitive children may prefer higher levels of sweetener in liquid formulations or require more sweetness to effectively mask the bitterness of some

drugs. These differences in sweet preference may also contribute to individual differences in compliance when taking medications in liquid formulation, most of which taste sweet.

Although there are 25 known bitter-taste receptors, in the present study, variation was genotyped in only 1. Although this receptor is unlikely to be sensitive to the wide range of bitter compounds in medications taken by children,²² in the present study, genetic variation in this 1 receptor was associated with whether the children had ever taken a medication in pill/tablet (encapsulated or solid) formulation. Alleles of this particular receptor may be a proxy for general taste ability,^{23,24} or because bitter-taste receptor genes occur in tightly linked clusters,²⁵ genetic variation in this receptor may be related to variation in other receptors. This particular receptor may also respond more broadly than previously understood—drugs commonly used in children's medications have not been widely tested in assays designed to understand such receptor-ligand interactions. Further study of the relationship between *TAS2R38* genotype and liquid formulation intake and compliance is warranted.

The relationship between *TAS2R38* genotype and sweet preference in children remains unknown. This genotype could be a marker for ethnic and racial groups that differ in sweet preference.^{26,27} However, although there are marked differences in ancestral populations in genotype within this bitter-taste receptor,^{16,28} the sample in the present study had no ethnic/racial differences in allele frequency (data not shown). Another possibility is that the receptive range of this receptor might include sugars such as sucrose; however, based on a literature search, no data are available to evaluate this possibility. Nonetheless, the findings from the present study suggest individual differences in the level of sweetness most preferred, which may play an important role in a child's acceptance of liquid formulations with added sweeteners.

Research to further characterize how taste-receptor genotype and other aspects of taste phenotypes relate to pediatric medication formulations and compliance is necessary to gain insight into how to better develop medicines for pediatric populations. Such research could be incorporated into pediatric clinical trials to help understand individual compliance during the trials and to expand the understanding of the role of taste genetics in behavioral choices.

CONCLUSIONS

Children with bitter-sensitive (homozygous *PP* and heterozygous *AP*) *TAS2R38* genotypes were more likely to have taken medication in solid formulation than were children with the bitter-insensitive (*AA*) genotype. Additionally, children with the *PP* allele preferred higher levels of sucrose in laboratory testing and higher levels of sugar in beverages. Together, these findings suggest that taste genetics may play an important role in a child's acceptance of various liquid medications and experience with solid formulations.

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References

1. US Government Accountability Office. Pediatric drug research: studies conducted under Best Pharmaceuticals for Children Act: report to congressional committees. Washington, DC: GOA; 2007.
2. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics*. 2005; 115:e216–e222. [PubMed: 15687429]
3. Mennella JA, Pepino MY, Duke FF, Reed DR. Age modifies the genotype-phenotype relationship for the bitter receptor TAS2R38. *BMC Genet*. 2010; 11:60. [PubMed: 20594349]
4. Blakeslee AF. Genetics of sensory thresholds: taste for phenyl thio carbamide. *Proc Natl Acad Sci U S A*. 1932; 18:120–130. [PubMed: 16577422]
5. Negri R, Di Feola M, Di Domenico S, et al. Taste perception and food choices. *J Pediatr Gastroenterol Nutr*. 2011 Dec 23. [Epub ahead of print].
6. Milne CP, Bruss JB. The economics of pediatric formulation development for off-patent drugs. *Clin Ther*. 2008; 30:2133–2145. [PubMed: 19108801]
7. American Academy of Pediatrics. [Accessed December 15, 2011] Periodic Survey #44: Patient compliance with prescription regimens. <http://www.aap.org/research/periodicsurvey/ps44bexs.htm>
8. Schneider BA, Trehub SE, Morrongiello BA, Thorpe LA. Developmental changes in masked thresholds. *J Acoust Soc Am*. 1989; 86:1733–1742. [PubMed: 2808922]
9. Dorries KM, Schmidt HJ, Beauchamp GK, Wysocki CJ. Changes in sensitivity to the odor of androstene during adolescence. *Dev Psychobiol*. 1989; 22:423–435. [PubMed: 2759357]
10. Patil S, Maibach HI. Effect of age and sex on the elicitation of irritant contact dermatitis. *Contact Dermatitis*. 1994; 30:257–264. [PubMed: 8088137]
11. Steiner JE, Glaser D, Hawilo ME, Berridge KC. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. *Neurosci Biobehav Rev*. 2001; 25:53–74. [PubMed: 11166078]
12. Ventura AK, Mennella JA. Innate and learned preferences for sweet taste during childhood. *Curr Opin Clin Nutr Metab Care*. 2011; 14:379–384. [PubMed: 21508837]
13. Nahata MC, Allen LV Jr. Extemporaneous drug formulations. *Clin Ther*. 2008; 30:2112–2119. [PubMed: 19108799]
14. Allen LV Jr. Dosage form design and development. *Clin Ther*. 2008; 30:2102–2111. [PubMed: 19108798]
15. European Medicines Agency. EMA. 2006. Formulation of choice for the paediatric population.
16. Bufe B, Breslin PA, Kuhn C, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr Biol*. 2005; 15:322–327. [PubMed: 15723792]
17. Polaha J, Dalton WT 3rd, Lancaster BM. Parental report of medication acceptance among youth: implications for everyday practice. *South Med J*. 2008; 101:1106–1112. [PubMed: 19088518]
18. Khoury, MJ.; Beaty, TH.; Cohen, BH. *Fundamentals of Genetic Epidemiology*. New York, NY: Oxford University Press; 1993.
19. Mennella JA, Lukasewycz LD, Griffith JW, Beauchamp GK. Evaluation of the Monell forced-choice, paired-comparison tracking procedure for determining sweet taste preferences across the lifespan. *Chem Senses*. 2011; 36:345–355. [PubMed: 21227904]
20. Kim UK, Jorgenson E, Coon H, et al. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science*. 2003; 299:1221–1225. [PubMed: 12595690]
21. Howell, DC. *Statistical Methods for Psychology*. 5. Pacific Grove, Calif: Duxbury/Thomson Learning; 2002.
22. Meyerhof W, Batram C, Kuhn C, et al. The molecular receptive ranges of human TAS2R bitter taste receptors. *Chemical Senses*. 2009; 35:157–170. [PubMed: 20022913]

23. Bartoshuk LM, Duffy VB, Reed D, Williams A. Supertasting, earaches and head injury: genetics and pathology alter our taste worlds. *Neurosci Biobehav Rev.* 1996; 20:79–87. [PubMed: 8622833]
24. Hayes JE, Bartoshuk LM, Kidd JR, Duffy VB. Supertasting and PROP bitterness depends on more than the TAS2R38 gene. *Chemical Senses.* 2008; 33:255–265. [PubMed: 18209019]
25. Adler E, Hoon MA, Mueller KL, et al. A novel family of mammalian taste receptors. *Cell.* 2000; 100:693–702. [PubMed: 10761934]
26. Desor JA, Greene LS, Maller O. Preferences for sweet and salty in 9- to 15-year-old and adult humans. *Science.* 1975; 190:686–687. [PubMed: 1188365]
27. Pepino MY, Mennella JA. Factors contributing to individual differences in sucrose preference. *Chemical Senses.* 2005; 30(Suppl 1):i319–i320. [PubMed: 15738179]
28. Campbell MC, Ranciaro A, Froment A, et al. Evolution of functionally diverse alleles associated with PTC bitter taste sensitivity in Africa. *Mol Biol Evol.* 2012 Feb 16. [Epub ahead of print].

Figure.

Percentages of children who had taken medicine in solid formulation, by *TAS2R38* bitter-taste genotype (N = 337). Children with 1 (*AP*) or 2 (*PP*) bitter-sensitive alleles were more likely to have taken medicine in a solid formulation than were children with the bitter-insensitive (*AA*) genotype ($\chi^2 = 7.88$; $df = 2$; $P = 0.02$).

Table I

Characteristics of children included in the study (N = 448).

Characteristic	Value
Age, y	
Mean (SE)	7.8 (0.1)
Range	3.1–10.9
Male sex, no. (%)	203 (45.3)
Race/ethnicity, no. (%)	
Black	234 (52.2)
White	126 (28.1)
Other	88 (19.6)
<i>TAS2R38 A49P</i> bitter-taste genotype, no. (%)	
<i>AA</i> (bitter-insensitive)	140 (31.3)
<i>AP</i>	221 (49.3)
<i>PP</i>	87 (19.4)
Taken medicine in solid formulation, * no. (%)	158/337 (46.9)
Sweet preference measure, * g/dL	
Preferred concentration of sucrose in water (n = 367)	
Mean (SE)	18.6 (0.6)
Range	3.0–36.0
Sugar content of favorite beverage (n = 307)	
Mean (SE)	9.9 (0.2)
Range	0.0–18.3

* Participants were pooled from multiple studies; because of differences among studies, these data are from a subset of children.

Table II

Relationship between the *TAS2R38* bitter-taste genotype and sweet preference. Data are mean (SE) g/dL.

Sweet Preference Measure	<i>TAS2R38</i> Genotype			Statistical Analysis
	AA (Bitter-Insensitive)	AP	PP	
Preferred concentration of sucrose in water (n = 367)	16.0 (1.1)	19.2 (0.8)	20.8 (1.3)	$F_{(2, 364)} = 4.36; P = 0.01$
Sugar content of favorite beverage (n = 307)	9.2 (0.4)	9.9 (0.3)	10.8 (0.6)	$F_{(2, 304)} = 2.86; P = 0.06$