“A Spoonful of Sugar Helps the Medicine Go Down”: Bitter Masking by Sucrose Among Children and Adults

Julie A. Mennella, Danielle R. Reed, Phoebe S. Mathew, Kristi M. Roberts and Corrine J. Mansfield

Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA

Correspondence to be sent to: Julie A. Mennella, Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA. e-mail: mennella@monell.org

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Abstract

Sweeteners are often added to liquid formulations of drugs but whether they merely make them better tasting or actually reduce the perception of bitterness remains unknown. In a group of children and adults, we determined whether adding sucrose to urea, caffeine, denatonium benzoate, propylthiouracil (PROP), and quinine would reduce their bitterness using a forced-choice method of paired comparisons. To better understand individual differences, adults also rated each solution using a more complex test (general Labeled Magnitude Scale [gLMS]) and were genotyped for the sweet taste receptor gene TAS1R3 and the bitter receptor TAS2R38. Sucrose suppressed the bitterness of each agent in children and adults. In adults, sucrose was effective in reducing the bitterness ratings from moderate to weak for all compounds tested, but those with the sensitive form of the sweet receptor reported greater reduction for caffeine and quinine. For PROP, sucrose was most effective for those who were genetically the most sensitive, although this did not attain statistical significance. Not only is the paired comparison method a valid tool to study how sucrose improves the taste of pediatric medicines among children but knowledge gleaned from basic research in bitter taste and how to alleviate it remains an important public health priority.

Key words: bitter taste, children, psychophysics, sucrose, TAS1R3

Introduction

Drugs given to young children are seldom administered alone but often as part of formulations delivered as liquids, because many children have difficulty swallowing pills or tablets. The resulting liquid formulations are complex mixtures that contain both the drug substance (commonly referred to as the active pharmaceutical ingredient or API) and excipients, including, but not limited to, sweeteners (Pawar and Kumar 2002). Sweeteners are added not just to medications but many products geared for children, for several reasons. First, sweeteners can function as gelling and bulking agents or emulsifiers (Mitchell 2006). Second, they impart a sweet taste that is highly preferred by children (Mennella et al. 2011a) and can drive acceptance of a variety of products, as evidenced by findings from scientific research (Mennella 2008), as well as the widespread use of sweeteners in medicines, foods, and beverages geared for pediatric populations. The liking of sweet-tasting liquids is evident within hours of birth (Desor et al. 1973), remains elevated during periods of maximal growth, and does not decrease to adult levels until mid-adolescence (Mennella et al. 2011a, 2014a). Third, to enhance the palatability of liquid formulations, one must diminish or eliminate the bad tastes of the APIs, since from an early age children have a well-developed ability to detect and reject bitter tastes (Kajiura et al. 1992; Mennella et al. 2003). In adults, the addition of sweeteners can make a formulation taste better not just because they impart sweetness but because they can reduce the bitterness of some APIs, as can salts in adults (Keast and Breslin 2002).

Psychophysical studies in adults suggest that the mode of action for bitterness suppression differs between sugars and salts. Sodium salts appear to suppress bitter taste in the periphery (receptor level), and this suppression is compound specific (Breslin and Beauchamp 1995; Keast and Breslin 2002; Keast et al. 2004; Narukawa et al. 2012). Sugars, on the other hand, act along the central gustatory pathway (cognitive level) and have been shown to suppress the bitterness of a range of bitter agents in adults (Lawless 1979; Kroeze and Bartoshuk 1985; Keast et al. 2004). In a landmark study, Kroeze and Bartoshuk (1985) compared...
perceptions of bitterness of quinine and salt or quinine and sucrose applied to the entire tongue (thus allowing for interaction at the receptor level) versus quinine applied to one side of the tongue and either salt or sucrose to the other. Because the 2 sides of the tongue are neurally independent prior to the thalamic level, no suppression should occur with the separate applications if sucrose works only in the periphery. Sucrose attenuated the perceive bitterness of quinine when the 2 compounds were applied simultaneously but independently to the 2 sides of the tongue, but sodium salts reduced bitterness only when applied to the same side of the tongue.

Tests of bitter tasting have been performed almost exclusively in adults. Because of the importance of taste in adherence and compliance of medication regimens among children (Giacofa et al. 2012), we recently expanded basic research on bitter taste blocking to pediatric populations (Mennella et al. 2003, 2014b). Consistent with studies in adults (Breslin and Beauchamp 1997; Keast and Breslin 2002; Keast et al. 2004), we found that the ability of 2 sodium salts (sodium gluconate [Na gluconate] and monosodium glutamate [MSG]) to block bitter taste was not only compound specific but, as we showed for the first time, also specific to the age of the subject. In general, if the blocker worked for a given bitter in children, it also worked for adults, but not vice versa. The bitterness of prophythidouracil (PROP), a member of one of the most studied class of bitter agents (Guo and Reed 2001), was not reduced by either blocker in either age group, and its ineffectiveness was independent of genotype of the PROP receptor (TAS2R38). Overall, these results suggest that the efficacy of blocking bitter tastes depends on both the age of the subject and the chemical nature of the blocker and bitter agent.

In the present study, we evaluated for the first time the efficacy of sucrose to reduce the bitterness of a broad array of bitter-tasting compounds in children. First, we tested the null hypothesis that there would be no systematic differences in the ability of sucrose to reduce bitterness between children and adults. Because of the lesser ability of children to understand complex psychophysical tasks, such as the general Labeled Magnitude Scale (gLMS; Bartoshuk et al. 2004), both age groups were tested with the same forced-choice, paired comparison method validated in previous studies (Mennella et al. 2003, 2014b). This method cannot determine how much the addition of sucrose decreases perceived bitterness, so mothers evaluated each solution using the gLMS method. We also genotyped subjects for 2 variants associated with bitter and sweet perception: the receptor for the bitter compound PROP (TAS2R38) and a sweet taste receptor gene (TAS1R3). These genetic variants explain person-to-person differences in the sensitivity to the bitter compound PROP (Bu et al. 2005; Mennella et al. 2011b) and the sensitivity or liking for sucrose in adults (Fushman et al. 2009; Mennella et al. 2012, 2014a).

Materials and methods

Participants

Women and their children, all of whom were between the ages of 5 and 12 years, were enrolled in a research study on bitter taste in children; previous data collected from some of these dyads have been published elsewhere (Mennella et al. 2014b). The mothers were given detailed descriptions of the study procedures of the “taste study” but were not told the goals of the study or hypotheses being tested. Women who were diabetic, pregnant, or lactating were not eligible; pregnancy tests were conducted on the day of testing to confirm nonpregnant status. Mothers also completed questionnaires regarding demographics and racial/ethnicity identity. All procedures and consent forms were approved by the Office of Regulatory Affairs at the University of Pennsylvania and the study complies with the Declaration of Helsinki for Medical Research involving Human Subjects. Written informed consent was obtained from the mother of each child participant, and written assent was obtained from children 7 or more years of age. The trial was registered at clinicaltrials.gov (NCT01407939).

Procedures

Participants were tested individually in rooms specifically designed for sensory testing. They were instructed to abstain from eating for at least 1 h; we recorded the time since they last ate and factored this into initial analyses to explore whether hunger could explain variation in the efficacy of sucrose in masking bitter. After training (see Training section), both adult and children subjects evaluated the bitterness of 5 food-grade generally recognized as safe (GRAS) bitter stimuli alone and in combination with sucrose using a forced-choice, paired comparison method validated in previous studies (Mennella et al. 2003, 2014b). Adults also were presented with each taste stimulus again and asked to rate the bitterness on a gLMS (Bartoshuk et al. 2004).

Stimuli

We selected 5 food-grade bitter agents (0.5 M urea, 0.008 M caffeine, 1.19 × 10^{-3} M quinine, 5.60 × 10^{-3} M PROP, 4.92 × 10^{-7} M denatonium benzoate [DB]; all from Spectrum Chemical Company) to match bitter compounds used in previous work to investigate the efficacy of sodium salts to reduce their bitterness in children. The concentration of bitter stimuli selected, which was in the moderately bitter range for adults, was based on pilot studies where we found that children would not participate in the task if more concentrated solutions were tasted. The concentration of sucrose used (0.6 M) has been shown to be most preferred by children as a group (Mennella et al. 2011a, 2014a). Deionized Millipore-filtered water (Millipore Milli-Q Academic model) was used to prepare the solutions and as a rinsing solution.
Solutions were stored in amber glass bottles and replaced at least every 2 weeks.

Training
To ensure that subjects understood the concept of bitterness, they were presented with 3 reference solutions that were identified as salty (0.3 M Na gluconate), sweet (0.3 M sucrose), and bitter (0.5 M urea). Although Na gluconate tastes less salty than sodium chloride, we chose this as our reference solution because our prior work in children revealed that it was highly effective at suppressing the bitterness of some but not all bitters (Mennella et al. 2003, 2014b). Then subjects were given a training session in which they received pairs of samples that differed in their sweetness and bitterness (Mennella et al. 2003); in some cases the more bitter solution was also sweet. Thus, the subjects learned that in some cases the more bitter solution may be a complex mixture.

Forced-choice paradigm: children and adults
To test the hypothesis that the addition of sucrose decreased bitterness of a variety of bitter agents, we used an age-appropriate, game-like task that was fun for children and minimized the impact of language development. Using a forced-choice procedure, each subject was presented with all possible pairs of 4 solutions (e.g., urea, sucrose, urea + sucrose, and water), 1 pair at a time, and was asked to indicate which of the pair tasted more bitter; the pairing of sucrose versus water, like all other pairs, was done once yielding a total number of pairings to 26. Procedures were identical for both children and their mothers. An aliquot of 5 mL of each solution was presented in a 30-mL polyethylene medicine cup. The order of presentation of the solutions was randomized within and between each pair of samples and between subjects. Subjects rinsed their mouth and expectorated with water 2 times after tasting each sample and 4 times between each pair. A 60-s interval separated each pair of solutions. During these intervals, subjects were offered a small unsalted cracker to cleanse their palate and a sip cup containing water for rinsing.

gLMS: adults only
We presented each adult participant, in randomized order, the bitter agent alone, the bitter with sucrose, sucrose alone, and water, and they rated their bitterness on a gLMS (Bartoshuk et al. 2004), using Compusense five Plus software (Compusense, Inc.). The gLMS is a psychophysical tool that requires subjects to rate the perceived intensity along a vertical axis lined with adjectives that are spaced semi-logarithmically, based upon experimentally determined intervals, to yield ratio-quality data (Bartoshuk et al. 2004). To ensure that differences in perception were specific to taste sensations and not differences in how the scales were used, the adults were asked to use the gLMS to rate the heaviness of 6 opaque, sand-filled jars of differing weights. Heaviness ratings were then used to normalize taste intensity ratings using previously described methods (Keast and Roper 2007).

Genotyping
Subjects provided DNA samples extracted from saliva (Genotek). DNA samples were used as a template in Taqman assays (Applied Biosystems). Genotypes for the bitter taste receptor gene TAS2R38 (rs713598; AA, AP, and PP) and a sweet receptor gene TAS1R3 (rs35744813; CC, CT, TT) and were assayed using previously established methods (Mennella et al. 2005, 2012). For TAS2R38, A is the insensitive allele. For TAS1R3, of 3 genotypes at this locus, TT is associated with a poorer ability to detect low concentrations of sucrose compared with the CC genotype. The genotype allele frequencies were compared against earlier studies from a similar population (Mennella et al. 2011b).

Statistical analyses
For the paired comparison data, 1 null hypothesis tested was that there were no systematic differences in bitterness ranking between the 4 different solutions (bitter, bitter plus sucrose, sucrose, and water) for each of the 5 bitter compounds tested (urea, caffeine, quinine, PROP, and DB). A second null hypothesis tested whether there were no systematic differences between children's and mothers' bitterness ranking of the 4 different solutions. To this end, we focused on each bitter stimulus separately. First, we determined the number of times that each subject chose each of the 4 solutions as tasting more bitter (Supplementary Table I for more details of ranking procedure and analysis). From these data, we ranked the 4 solutions according to the subject's selections, where 1 was the least chosen (least bitter) and 4 was the most chosen (most bitter). Data obtained from mothers were analyzed separately from children. Separate Friedman 2-way nonparametric analyses were conducted on these bitter ranking scores, 1 for each of the 5 bitter stimuli. When significant, multiple comparisons were performed to determine which differences among the solutions were significant (Siegel and Castellan 1988).

For the gLMS data, we determined a standardization factor; each subject's average intensity for heaviness was divided by the grand mean for heaviness across weight levels and subjects. Each individual's bitter taste intensity ratings were then divided by her personal standardization factor to eliminate scale-use bias. Because these data were skewed, they were square-root transformed to approximate a normal distribution before analyses. To determine whether there was concordance in the outcomes from analyses of paired-comparison data with gLMS data in adults, we conducted separate repeated-measures ANOVAs for each of the 4 solutions for each bitter agent. An efficacy score was calculated by subtracting the rating of the bitter plus sucrose from
rating of the bitter compound alone [i.e., bitter − (bitter + sucrose)]. Larger numbers represent more efficient suppression of bitterness.

Additional ANOVA analyses were conducted to determine how well sucrose worked in masking bitter tastes among those with different sweet receptor genotypes (TAS1R3). These analyses used the efficacy score separately for each bitter agent and with unrelated adults. Relatedness among the majority of adult subjects was ascertained by preliminary genotypes from the HumanOmni2.5m-8v1-1 platform from a separate genome-wide association study currently in progress. DNA samples that had a proportion of genotypes identical-by-state commensurate with first- or second-degree kinship were considered to be related. Sucrose efficacy in reducing PROP bitterness was also evaluated in unrelated adult subjects grouped by TAS2R38 genotype. When ANOVAs revealed significant effects, post hoc Fisher least significant difference analyses were conducted. All summary statistics are expressed as mean ± standard error of the mean (SEM), and levels of significance were \( P < 0.05 \).

### Results

#### Subject characteristics and completion of the tasks

Table 1 provides the demographic and characteristics of the sample, which reflects the diversity of race/ethnicity and educational levels of the city of Philadelphia (Pew Charitable Trust 2011). The mothers (\( N = 109 \)) were 35.6 ± 0.8 years of age, and their children (81 girls, 60 boys) ranged in age from 5 to 12 years (8.8 ± 0.2), with 82 singletons, 22 sibling pairs, and 5 sibling triads. Not all subjects completed all tasks. While the vast majority of mothers completed the paired comparison (98.2%) and the gLMS (97.2%) tasks for each of the 5 bitters (Table 1), we have only partial data for the paired comparison task for 2 women because they were nauseated after tasting DB and did not complete testing. Of the 141 children, 22 (15.6%) did not understand the task or comply with study procedures and thus were excluded from final analyses; those excluded were younger in age than the remaining children [9.1 ± 0.2 years vs. 7.3 ± 0.3 years; \( F(1, 139) = 21.66; P < 0.00001 \)]. Five children provided partial data either because they were nauseated after tasting DB (\( N = 2 \)) or PROP (\( N = 1 \)) or because of a lab error (\( N = 2 \)). The genotype frequencies of TAS1R3 and TAS2R38 genotypes were similar to those in other studies of similar populations (Mennella et al. 2010, 2012; Supplementary Table II).

#### Efficacy of sucrose by bitter agent

Null hypotheses tested were that there were no systematic differences in children’s or mothers’ ranking between the 4 different solutions (bitter, bitter + sucrose, sucrose, and water) and for each bitter compound tested. Sucrose significantly

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adults (( N = 109 ))</th>
<th>Children (( N = 141 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>109 women</td>
<td>81 girls, 60 boys</td>
</tr>
<tr>
<td>Age, years (mean ± SEM)</td>
<td>35.6 ± 0.8</td>
<td>8.8 ± 0.2</td>
</tr>
<tr>
<td>Race/ethnicity [% (n)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16.5% (18)</td>
<td>10.6% (15)</td>
</tr>
<tr>
<td>Black</td>
<td>66.1% (72)</td>
<td>59.6% (84)</td>
</tr>
<tr>
<td>Hispanic/Latino/Latina</td>
<td>6.4% (7)</td>
<td>17.0% (24)</td>
</tr>
<tr>
<td>Asian</td>
<td>1.8% (2)</td>
<td>1.4% (2)</td>
</tr>
<tr>
<td>Other/more than 1 race</td>
<td>9.2% (10)</td>
<td>11.4% (16)</td>
</tr>
<tr>
<td>Socioeconomic data, adults only [% (n)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College graduate (or higher)</td>
<td>46.8% (51)</td>
<td></td>
</tr>
<tr>
<td>&gt;$75,000</td>
<td>12.8% (14)</td>
<td></td>
</tr>
<tr>
<td>Completion of psychophysical (paired comparison) task [% (n)]</td>
<td>98.2% (107/109)</td>
<td>82.3% (116/141)*</td>
</tr>
<tr>
<td>Understood and completed task/total tested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Understood but incomplete data because subject got sick during testing</td>
<td>1.8% (2/109)</td>
<td>2.1% (3/141)</td>
</tr>
<tr>
<td>Did not understand task or was noncompliant</td>
<td>0% (0/109)</td>
<td>15.6% (22/141)</td>
</tr>
<tr>
<td>Completion of gLMS task (adults only)</td>
<td>100% (106/106)*</td>
<td></td>
</tr>
</tbody>
</table>

*Partial data for 2 children due to lab errors.
*Three women did not participate in gLMS testing.
suppressed the bitterness of all 5 bitter agents in both children and adults (all \( F_1 \) values < 0.001; Table 2). For each of the 5 bitter agents, children and mothers chose each of the bitter agents as tasting more bitter compared with bitter + sucrose, sucrose alone, or water alone. Water was more likely to be chosen as tasting more bitter than sucrose in children but not adults (Table 2), but when asked which tasted better, sucrose or water, there was no age-related difference in preferring taste of sucrose to water (81.0% vs. 77.1%, \( P = 0.28 \)).

In adults, findings from the gLMS method paralleled the findings from the paired comparison tasks for each of the 5 bitter agents (Table 2). Unlike the paired comparison tasks, the gLMS data allowed us to calculate differences to determine how much lower the bitterness ratings were when sucrose was added. In no case did the bitterness of the bitter + sucrose mixture decrease to that of sucrose alone, but the reduction in bitterness (i.e., efficacy score) was substantial. Ratings on the gLMS scale decreased, on average, as follows: urea, 7.4 ± 9.1; caffeine, 7.9 ± 9.7; quinine, 7.2 ± 9.9; PROP, 4.8 ± 9.5; and DB, 3.5 ± 13.1. These differences represent a reduction of gLMS ratings for urea from 10.3 to 2.9; caffeine, from 11.3 to 3.4; quinine, from 12.1 to 4.9; PROP, from 13.0 to 8.1; and DB, from 22.8 to 19.3. The gLMS values (on a labeled log scale) represent changes from ratings of moderate to ratings of weak. On average, sucrose was the most effective for caffeine and the least effective for DB.

### Effects of TAS2R38 and TAS1R3 genotypes

To determine whether genotype was related to the efficacy of sucrose in reducing the bitterness of PROP, adult subjects were grouped by TAS2R38 genotype (rs713598). Because 11 adults were related (e.g., sisters and/or cousins), 1 member of each family was selected randomly to be included in genetic association analysis, resulting in a final sample size of 100 adult subjects for this analysis. Although the results were in the expected direction, TAS2R38 genotype was not related to the efficacy of sucrose in masking the bitterness of PROP \([F(2, 97) = 2.14, P = 0.123]\). Bitterness gLMS ratings decreased from 2.36 ± 2.31 to 0.80 ± 1.98 in people with the AA genotype, from 12.75 ± 1.63 to 7.30 ± 1.40 among heterozygotes, and from 24.95 ± 2.51 to 18.02 ± 2.15 in those with the PP genotype.

Two additional subjects could not be genotyped for TAS1R3 (rs35744813), perhaps due to genetic variants in the

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#### Table 2 Efficacy of sucrose in reducing perceived bitterness: bitterness rankings using forced-choice paired comparison method (children and adults) or bitter taste intensity ratings using gLMS methods (adults only) and summary of post hoc analyses

<table>
<thead>
<tr>
<th>Age group/method</th>
<th>Bitter stimulus</th>
<th>Bitter</th>
<th>Bitter + sucrose</th>
<th>Sucrose</th>
<th>Diluent</th>
<th>Statistical analysis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired comparison ranking²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>U</td>
<td>3.7 ± 0.05³</td>
<td>2.0 ± 0.08³</td>
<td>1.9 ± 0.09³</td>
<td>2.4 ± 0.07³</td>
<td>( F(3, 312) = 157.17, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>CAF</td>
<td>3.7 ± 0.05³</td>
<td>2.3 ± 0.07³</td>
<td>1.7 ± 0.08³</td>
<td>2.3 ± 0.08³</td>
<td>( F(3, 312) = 173.91, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>Q</td>
<td>3.7 ± 0.06³</td>
<td>2.4 ± 0.08³</td>
<td>1.6 ± 0.07³</td>
<td>2.3 ± 0.08³</td>
<td>( F(3, 312) = 173.53, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>PROP</td>
<td>3.6 ± 0.07³</td>
<td>2.3 ± 0.08³</td>
<td>1.8 ± 0.08³</td>
<td>2.3 ± 0.08³</td>
<td>( F(3, 312) = 133.69, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>DB</td>
<td>3.7 ± 0.05³</td>
<td>2.9 ± 0.06³</td>
<td>1.4 ± 0.07³</td>
<td>1.9 ± 0.06³</td>
<td>( F(3, 312) = 225.18, P &lt; 0.0001 )</td>
</tr>
<tr>
<td>Adults</td>
<td>U</td>
<td>3.9 ± 0.04³</td>
<td>2.1 ± 0.06³</td>
<td>1.9 ± 0.09³</td>
<td>2.1 ± 0.08³</td>
<td>( F(3, 312) = 172.34, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>CAF</td>
<td>3.9 ± 0.03³</td>
<td>2.6 ± 0.07³</td>
<td>1.7 ± 0.07³</td>
<td>1.8 ± 0.08³</td>
<td>( F(3, 312) = 203.39, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>Q</td>
<td>3.9 ± 0.03³</td>
<td>2.5 ± 0.07³</td>
<td>1.7 ± 0.07³</td>
<td>1.9 ± 0.08³</td>
<td>( F(3, 312) = 198.09, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>PROP</td>
<td>3.6 ± 0.06³</td>
<td>2.6 ± 0.09³</td>
<td>1.9 ± 0.08³</td>
<td>1.9 ± 0.09³</td>
<td>( F(3, 312) = 134.65, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>DB</td>
<td>3.7 ± 0.05³</td>
<td>3.1 ± 0.06³</td>
<td>1.6 ± 0.06³</td>
<td>1.6 ± 0.06³</td>
<td>( F(3, 312) = 234.06, P &lt; 0.0001 )</td>
</tr>
<tr>
<td>gLMS (adults only)³</td>
<td>U</td>
<td>10.2 ± 0.91³</td>
<td>2.9 ± 0.65³</td>
<td>0.9 ± 0.24³</td>
<td>0.8 ± 0.16³</td>
<td>( F(3, 312) = 71.88, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>CAF</td>
<td>11.2 ± 0.94³</td>
<td>3.4 ± 0.67³</td>
<td>0.9 ± 0.24³</td>
<td>0.8 ± 0.16³</td>
<td>( F(3, 312) = 77.90, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>Q</td>
<td>12.1 ± 1.01³</td>
<td>5.0 ± 0.71³</td>
<td>0.9 ± 0.24³</td>
<td>0.8 ± 0.16³</td>
<td>( F(3, 312) = 82.69, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>PROP</td>
<td>13.1 ± 1.37³</td>
<td>8.2 ± 1.15³</td>
<td>0.9 ± 0.24³</td>
<td>0.8 ± 0.16³</td>
<td>( F(3, 312) = 57.49, P &lt; 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>DB</td>
<td>22.7 ± 1.34³</td>
<td>19.1 ± 1.28³</td>
<td>0.9 ± 0.24³</td>
<td>0.8 ± 0.16³</td>
<td>( F(3, 312) = 191.35, P &lt; 0.0001 )</td>
</tr>
</tbody>
</table>

¹df, degrees of freedom. CAF, 0.008 M caffeine; DB, 4.92 × 10⁻⁷ M DM; PROP, 5.60 × 10⁻⁷ M propylthiouracil; Q, 1.19 × 10⁻⁴ M quinine; U, 0.5 M urea. Sucrose solution was 0.6 M; diluent was deionized water.

²All Friedman statistical tests of rank tests \((F_1)\) were significant at \( P < 0.0001 \). Different letters indicate rankings that are statistically different from each other within each row.

³Rankings for bitterness range from 1 (least) to 4 (most).

⁴Ratings using gLMS scale range from 0 to 94, with the anchors falling approximately at these values: no sensation (N5) = 0, barely detectable (BD) = 1.37, weak (W) = 5.76, moderate (M) = 16.27, strong (S) = 33.48, very strong (VS) = 50.41, strongest imaginable (SI) = 94.53. Data are represented as least square mean ± SEM. Data were square-root transformed prior to analyses.
Discussion

We show for the first time that sucrose suppressed the bitterness of a range of moderately bitter stimuli in children like it does in adults (Lawless 1979; Kroeze and Bartoshuk 1985; Keast et al. 2004; Mennella et al. 2014b). Sucrose suppressed bitterness to different extents for each particular bitter compound, but for some bitter agents the effect of sucrose was marked; for instance, it substantially lowered bitterness ratings for caffeine. There was variation among people and among bitter agents in the ability of sucrose to suppress bitterness, but for some people and for some compounds, sucrose is an unequivocally effective masker of bitter taste.

The findings also reveal that sucrose was much more effective overall in suppressing bitterness than were sodium salts (Stevens 1996). While sucrose reduced the bitterness of all 5 bitter agents in both children and adults, past research in this population revealed that the efficacy of Na gluconate and MSG was specific to both compound and age (Table 3). Taken together, these data suggest that not only did the children understand the task but confirm previous reports that their responses were guided by the intensity of the bitter perception, not the complexity of the mixture (Mennella et al. 2003, 2014b).

The present study also highlights how bitter agents are unpleasant to some individuals not just because of their taste: 3 children and 2 adults could not complete testing because they were nauseated after tasting (but not swallowing) DB or PROP. A recent study in healthy adults found that nausea can result, in some but not all subjects, after tasting something bitter (without swallowing); the nausea may be due, in part, to bitter-induced gastric dysrhythmia (Peyrot des Gachons et al. 2011). Such findings highlight individual differences in aversive properties of bitter agents, the diverse location of bitter receptors (Behrens and Meyerhof 2010), and the formidable task that lies ahead to make liquid formulations of drugs more palatable to the pediatric palate (Mennella et al. 2013).

Women with an insensitive form of the sweet receptor received less benefit from the masking effects of sucrose, at least for some bitter compounds. The genetic diversity in sweet perception and its efficacy in masking bitter may explain in part why sweetened medicines are better tolerated by some than others and further suggest that medicine formulations could be matched to genotype so that people who need less sugar to mask the bitterness would not have to take overly sweetened formulations. But while sugars and salts are effective in reducing bitterness, we acknowledge that concerns about the negative consequences of consuming excess sodium and intolerance of sugars for some children may limit the usefulness of this approach.

Added sucrose creates oral health concerns, particularly with repeated nocturnal dosing, and use of sucrose-sweetened medicines has been linked to dental caries (Roberts and Roberts 1979; Feigal et al. 1984; Greenwood et al. 1984; Manley et al. 1994; Bigeard 2000). These concerns are responsible, in part, for the general decrease in sugar content in prescription medications in recent decades (Maguire and Rugg-Gunn 1997; Baqir and Maguire 2000). While both the medical and dental communities have issued calls for use of noncariogenic, nonnutritive (NNS) substitutes in children’s

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**Table 3** Summary of efficacy of Na gluconate, MSG, and sucrose in reducing bitterness in adult and pediatric populations (ranking scores)

<table>
<thead>
<tr>
<th>Bitter agent</th>
<th>Blocking/masking agent by age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na gluconate</td>
</tr>
<tr>
<td></td>
<td>Children</td>
</tr>
<tr>
<td><strong>Urea</strong></td>
<td>↓</td>
</tr>
<tr>
<td><strong>Caffeine</strong></td>
<td>--</td>
</tr>
<tr>
<td><strong>Quinine</strong></td>
<td>↓</td>
</tr>
<tr>
<td><strong>Denatonium</strong></td>
<td>--</td>
</tr>
<tr>
<td><strong>PROP</strong></td>
<td>--</td>
</tr>
</tbody>
</table>

Symbols: ↓, decreased bitterness; ↑, increased bitterness; --, no effect on bitterness.

*From Mennella et al. (2014b).*
medicines because of oral health concerns, it is important to note that some NNS (e.g., saccharin, aspartame, acesulfame-K, cyclamate) have a bitter taste component and, to some, an aversive metallic aftertaste, particularly at higher concentrations that may be needed to mask the APIs (Riera et al. 2007). Further, some nonnutritive sweeteners may interfere with physiological responses that control homeostasis and affect the microbiome (Suez et al. 2014). Even though NNS may provide an alternative to nutritive sweeteners, their palatability as well as efficacy in bitter reduction among pediatric populations has yet to be experimentally determined.

In addition to sweeteners, most liquid formulations contain flavor volatiles such as bubble gum and berry flavors. In a novel research program combining horticulture, chemistry, metabolomics, and psychophysics, researchers found that some, but not all, of the aroma volatiles of the tomato (Tieman et al. 2012) and the strawberry (Schwieterman et al. 2014) contributed to perceived sweetness independent of the plant’s sugar content. This not only suggests that volatiles may be an under-appreciated way to increase perception of sweetness without adding sugar but also raises questions as to whether some of the volatile flavors, so common in pediatric formulations, contribute to suppressing bitterness. This is an important area for future research.

Validating methodologies to measure palatability and acceptability among pediatric patients, depending upon the task at hand and what is to be measured, remains an important approach to developing medicine formulations acceptable to the pediatric palate by understanding how to block unwanted tastes (Tuleu and Breitkreutz 2013). The present study established that valid psychophysical assessments of liquids in pediatric patients can be obtained. However, this method was specific to the question of whether a blocker or masker, in this case sucrose, was effective in reducing bitterness of moderately or weak bitter tasting stimuli, and must be adapted to study other dimensions of children’s taste perceptions and palatability.

Our findings, along with findings that bitter taste perception varies with age (Mennella et al. 2010, 2014b), that the efficacy of sodium salts to block bitter taste is age and compound specific (Mennella et al. 2014b), and that the site of action of the suppressing effects of sugars is central but for sodium salts is peripheral (Kroeze and Bartoshuk 1985), raise important concerns about the applicability of electronic tongue systems in assessing the ability of salts and sugars to suppress the bitter taste of APIs (Choi et al. 2014). As presented herein and recently reviewed (Mennella et al. 2013), given the numerous and varied components of peripheral and central mechanisms involved in the mediation of bitter taste and the different modes of action of putative blockers/masking agents such as salts and sugars, respectively, the ability of an artificial sensor to model and predict the properties of this complex biological system is questionable.

More than 2 decades ago, Stevens (1996) commented that although sugar works better than salt in suppressing the bitter taste of quinine, there is a caveat, especially when related to foods or pharmaceuticals: “No amount of sugar or salt may suffice to eliminate or even reduce sufficiently unwanted sour or bitter. In the practical world of the food scientists, it may sometimes be more realistic to reduce the unwanted components in other ways.” Given the numerous and varied components of peripheral and central mechanisms involved in the mediation of bitter taste and the age-related changes in bitter perception (Mennella et al. 2013), the task ahead of us is challenging but remains an important public health priority that has the potential for major impact on the health of our children.

Supplementary material
Supplementary material can be found at http://www.chemse.oxfordjournals.org/

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Conflict of interest
The authors declare that no competing interests exist.

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Baqir W, Maguire A. 2000. Consumption of prescribed and over-the-counter medicines with prolonged oral clearance used by the elderly in the


Bitter Masking by Sucrose


