Published in final edited form as:
Dev Psychobiol. 2003 September ; 43(2): 120–127. doi:10.1002/dev.10127.

Modification of Bitter Taste in Children

Julie A. Mennella, **M. Yanina Pepino**, and **Gary K. Beauchamp**
Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104-3308

Abstract

The palatability of oral medications, many of which are quite bitter, plays an important role in achieving compliance in pediatric patients. We tested the hypothesis that the addition of a sodium salt to some, but not all, bitter tasting liquids enhances acceptance and reduces the perceived bitterness in 7- to 10-year-old children and their mothers. For both children and adults, sodium gluconate significantly suppressed the perceived bitterness and enhanced the acceptance of urea and caffeine whereas the reverse was true for another bitter stimulus, Tetralone. Because children preferred salted solutions more than did adults, these data suggest that the use of sodium salts may be an especially effective strategy for reducing the bitterness of some medicines and facilitating compliance among pediatric populations. However, based on sodium's differential ability to inhibit bitterness, as has been shown here with children and adults, clearly each drug of interest must be evaluated separately.

Keywords

taste; bitter; salts; children; preference

Children and adults are subject to many of the same ailments and diseases and, by necessity, are often treated with the same drugs. However, only a small fraction of these drugs have been adequately tested in pediatric populations and consequently lack proper labeling for safety and efficacy (Committee on Drugs, American Academy of Pediatrics, 1995; Wilson, 1999). In concert with legislation that provides financial and marketing incentives for conducting pediatric studies, the Food and Drug Administration (1998) issued regulations entitled The 1998 Final Pediatric Rule requiring that applications from pharmaceutical companies for new drugs and biological products contain data to support pediatric use.

But industry and researchers have a problem. The problem lies in the fact that many medicines are quite bitter—a taste that is clearly aversive to infants (Kajuira, Cowart, & Beauchamp, 1992; Rosenstein & Oster, 1988; Steiner, 1977) and children (Berning, Griffith, & Wild, 1982; Lawless, 1985; Ramgoolam & Steele, 2002; Silbert & Frude, 1991). Indeed, it can be argued that if bitter taste sensitivity evolved, in part, to protect the organism from poisoning (Glendinning, 1994) and that most medicines are toxic substances, medicines, by their very nature, should be bitter and distasteful. In fact, bitter compounds are effective agents in deterring pediatric poisonings when used in conjunction with other preventive measures such as child-resistant closures (Rogers, 1994). Common methods of blocking distasteful bitter tastes with encapsulation can be ineffective for children since they often cannot or will not swallow pills or tablets (Steffensen, Pachaï, & Pedersen, 1998). Adding sugars may increase the palatability of some liquid medications, but chronic use of such medicine is problematic because of its association with excessive dental disease (Manley, Calnan, & Sheiham, 1994;

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Correspondence to: Julie A. Mennella, mennella@monell.org.

Pawar & Kumar, 2002). Moreover, the medical and dental communities have issued calls for the use of noncariogenic substitutes in children's liquid medicines (Manley et al., 1994).

An alternative method in suppressing the bitterness of oral medications may lie in the bitter suppressing ability of common sodium salts. In adults, sodium salts are effective in reducing the bitterness of some bittercompounds, including that of common drugs, presumably by acting at a peripheral taste level and not by cognitive effects (Bartoshuk, 1980; Breslin & Beauchamp, 1995, [1997]; Keast & Breslin, 2002; Keast, Breslin, & Beauchamp, 2001; Kroeze & Bartoshuk, 1985). Whether similar mechanisms are operative in young children remains unknown. To this end, we developed methodologies that were sensitive to the cognitive limitations of pediatric populations since the methods that were used to assess bitter suppression in adults (magnitude estimation) are clearly not suitable for research on young children. Based on previous research on adults (Breslin & Beauchamp, 1995), we then examined the preferences and behavioral responses of 7- to 10-year-old children for a range of bitter compounds alone or in combination with a sodium salt. We chose bitter stimuli that were either suppressed, but to varying degrees (e.g., urea: 76% suppression, caffeine: 55% suppression) or enhanced (Tetralone; iso-alpha acids found most commonly in beer) by the addition of sodium salts (Breslin & Beauchamp, 1995; Yokomukai, Breslin, Cowart, & Beauchamp, 1994). The children's mothers also were tested in tandem to obtain an estimate on how effective these new methods for children were in assessing the ability of salts to modify bitter taste in adults.

SUBJECTS AND METHODS

Subjects

Mothers were recruited from advertisements in local newspapers. During the telephone interview, the mother was asked whether she and her child or, in some cases, children, would like to participate in a "taste study." The mothers (47.7% Caucasian, 38.6% African American, 4.6% Hispanic, 6.8% Asian, and 2.3% Other Ethnic Group; n=39) were, on average, 37.8 (±0.9) years and their children (26 girls, 15 boys) ranged in age from 7 to 10 years (8.8±0.2). All mothers reported that they and their children were healthy at the time of testing and were not taking any medications. Seven additional mother-children pairs began testing, but were excluded because the child could not understand the task (n=1) or did not comply with study procedures (n=6). The procedures used in this study were approved by the Office of Regulatory Affairs at the University of Pennsylvania. Informed consent was obtained from each mother, and assent was obtained from each child, prior to testing.

Stimuli

The bitter agents studied were 0.5 M urea (Sigma Chemical Company, St. Louis, MO), 0.08 M caffeine (Sigma) and 1.37×10^{-4} M Tetralone, iso-alpha acids found most commonly in beer (Kalsec, Kalamazoo, MI). The salt solution, 0.3 M sodium gluconate (Sigma), was chosen because previous research in adults revealed that it was highly effective at suppressing the bitterness of urea and caffeine and tasted less salty than sodium chloride (Breslin & Beauchamp, 1995). As shown in Table 1, the bitter and salt solutions consisted of a combination of the particular bitter agent (i.e., urea, caffeine, Tetralone) and sodium gluconate whereas the water solution used to prepare the solutions and as a rinsing solution was double-distilled, deionized (di) Millipore filtered water, hereafter referred to as water. Solutions were stored in amber glass bottles and replaced at least every 2 weeks.

Procedures

Children and their mothers were tested at the Monell Center in closed rooms specifically designed for sensory testing with a high air-turnover ventilation system. The mother and her child were tested individually in separate rooms using identical procedures. To ensure that subjects understood the concept of bitterness, subjects were presented with three reference solutions that were identified as sweet (0.3 M sucrose), salty (0.3 M sodium gluconate), and bitter (0.5 M urea). Then they were given a training session in which they received pairs of samples that differed in their sweetness and bitterness. Subjects were asked to focus only on the bitter taste and point to which of the pair tasted more bitter, rinsing their mouths with water two times after tasting each sample and four times between each pair. The pairs of solutions presented during the training session included: 1.0 M urea versus 0.5 M urea; 1.0 M urea versus 0.5 M urea + 0.3 M sucrose; 1.0 M urea + 0.3 M sucrose versus water; and 1.0 M urea + 0.3 M sucrose versus 0.5 M urea 0.3 M sucrose. In some cases, therefore, the more bitter solution also was sweet whereas in others it was not. Thus, the subject learned that in some cases the more bitter solution may be a complex mixture whereas in other cases it was not.

An age-appropriate, game-like task that was fun for children and minimized the impact of language development was used. Using a forced-choice procedure, each subject was presented with all possible pairs of the four solutions (e.g., 0.5 M urea, 0.3 M sodium gluconate, 0.5 M urea 0.3 M sodium gluconate, and water), one pair at a time, and was asked to indicate which of the pair tasted more bitter during one test session and which tasted better during another. After all pairs had been presented, subjects then were presented with the urea versus urea with sodium gluconate pairing to ensure that there were no learning biases in our experimental design. An aliquot of 2 ml of each solution was presented in a 30-ml polyethylene medicine cup (Delaware Valley Surgical Supply; Boothwyn, PA). At the end of the session, subjects were again presented with each of the four solutions and asked to rank them from most to least preferred. The order of presentation of the solutions was randomized within and between each pair of samples and between subjects. Subjects rinsed and expectorated with water two times after tasting each sample and four times between each pair. A 45-s interval separated each pair of solutions, and a 5-min interval separated the three test sessions. During these intervals, children were offered a sip cup containing water and a small, unsalted cracker to cleanse their palate.

Of the children and mothers tested, 21 pairs returned for 2 additional days of testing. In counterbalanced order, approximately half (n=10) of the children and their mothers were tested with the caffeine on the second and Tetralone on the third test day; the order was reversed for the remaining motherchild dyads. Eight additional mother-child pairs were tested for one additional testing; six of these pairs were tested with caffeine and two with Tetralone. The procedures and the sodium salt used were identical to that described earlier for urea, and the bitter agent used in the training session was identical to that used during that particular day of testing. Mothers also completed a variety of questionnaires, and were asked to indicate what type of formulation (e.g., liquids, pills, chewable) of medicine they give their child and whether the child had ever successfully swallowed medicine in pill form. Each child also indicated whether they ever tried sports drinks, such as Gatorade™ and Powerade™, and if so, whether they liked such salty drinks.

Statistical Analyses

Forced-Choice Pairwise Comparisons—The null hypothesis tested was that the addition of sodium gluconate to each of the three bitter stimuli did not alter its perceived bitterness or pleasantness. Because there were no significant differences in the children's and mothers' first and second comparisons of bitter versus bitter+salt (ps>0.18) for each of the three bitters (urea, caffeine, Tetralone) and for both types of comparison ("What tastes more bitter?" "What tastes better?"), data for these two comparisons were averaged.

The data for each of the three bitter stimuli were expressed as the proportion of children or mothers who chose one member of the pair as tasting either more bitter or better. Specifically, we determined the proportion of subjects who chose the bitter solution when compared to the bitter combined with sodium gluconate, sodium gluconate, or water solutions as well as the proportion of subjects who chose the bitter combined with sodium gluconate when compared to sodium gluconate or water solutions. Binomial distribution tests were then conducted to determine whether children's and mothers' performance for each of the pairs was above chance (i.e., the proportions were above the upper limit of the 95% confidence interval for 50% responses for a given member of the pair; see Siegel & Castellan, 1988).

Preference Ranking—The null hypothesis was that there were no systematic differences in children's or mothers' preference ranking between the four different solutions (bitter, bitter combine with sodium gluconate, sodium gluconate, water) for each of the three bitter compounds tested. To test this, each of the four solutions was ranked according to subject's preferences (1=most preferred; 4=least preferred). Data obtained from mothers were analyzed separately from children. Separate Friedman two-way nonparametric analyses were conducted on these preference ranking scores, one for each of the three bitter stimuli. When significant, multiple comparisons were performed to determine which differences among the solutions were significant (Siegel & Castellan, 1988). All summary statistics are expressed as means ±*SEM*, and levels of significance were $p<.05$.

RESULTS

Overview

Sodium gluconate (a salt) suppressed the bitterness and enhanced the acceptance of urea and, to a lesser extent, caffeine, in both children and adults (Table 2). In striking contrast, this same sodium salt enhanced the bitterness in children and decreased the liking of Tetralone in both children and adults. These data suggest that not only did the children understand the task but their responses were guided by the intensity of the bitter perception, not the complexity of the mixture. Specific results for each bitter compound and each pairing are summarized in Table 2 and the preference ranking data are presented in Figure 1. The present study also revealed that children prefer salt more than adults do.

Urea

Bitterness—As shown in Table 2, the majority of children and their mothers reported that urea seemed to taste more bitter when compared with either water (children: 85%; mothers: 87%) or the sodium gluconate solution (children: 61%; mothers: 77%), although the latter did not reach statistical significance in children (p=.08). The majority of mothers (73%) and children (66%) indicated that the solution combining urea with sodium gluconate tasted less bitter than the solution containing the same concentration of urea without the salt (*ps*<.05). This sodium salt suppressed the perceived bitterness of urea; both children and mothers responded at chance levels (children: 41%, mothers: 59%; $p<.10$) when asked to indicate whether the urea solution containing sodium gluconate tasted more bitter than sodium gluconate alone. However, bitter suppression was not complete since 71% of the children and 72% of the mothers chose urea and salt solution as tasting more bitter than water. That sodium gluconate contributes to the bitterness of the urea plus salt solution is suggested by the finding that 69% of the mothers indicated that the sodium gluconate tasted significantly more bitter than water.

Relative Preference—The addition of sodium gluconate to the urea solution increased its acceptance in children and adults since both groups chose the urea solution containing sodium gluconate as tasting better than the urea solution alone. As can be observed in Table 2, 70% of the children and 82% of the mothers indicated that urea combined with the salt tasted better than urea alone. Moreover, children and mothers responded at chance levels when presented with sodium gluconate and the urea combined with sodium-gluconate solutions. The significant differences in the preference-ranking scores of the four solutions by children, $F_r(3\ df)=55.65$, $p<.0001$, and mothers, $F_r\ (3\ df)=70.29$, $p<.0001$, further supports data obtained from the pairwise comparisons. As shown in Figure 1, urea was the least preferred solution for children, and its ranking was significantly higher (less preferred) than urea combined with sodium gluconate, sodium gluconate alone, or water; these latter three solutions were equally preferred by children. Mothers also ranked urea as least preferred, and it was less preferred than urea combined with sodium gluconate and water, but not sodium gluconate.

Caffeine

Bitterness—As shown in Table 2, both mothers and children selected caffeine and caffeine combined with sodium gluconate as tasting more bitter than either water or the sodium-gluconate solution, although the latter was a trend in children ($p=.06$). Sodium gluconate significantly suppressed the bitterness of caffeine in 77% of the adult subjects; there was similar tendency in children (68%; $p=.06$). In comparison with urea, the bitterness of caffeine was not as well suppressed by the addition of sodium gluconate since both children (67%; $p=.06$) and adults (73%) chose the caffeine and salt mixture as tasting more bitter than salt alone. This is consistent with previous studies on adults (Breslin & Beauchamp, 1995).

Relative Preference—Sodium gluconate significantly increased the acceptance of caffeine in children, and there was a tendency for this to occur in mothers ($p=.06$). For the vast majority of children and mothers, water tasted better than caffeine and caffeine combined with sodium gluconate (see Table 2). In addition, there were significant differences in the preference-ranking scores of the four solutions in children, $F_r(3\ df)=39.09$, $p<.0001$, and mothers, $F_r(3\ df)=51.27$, $p<.0001$. As can be observed in Figure 1, caffeine and caffeine combined with sodium gluconate were the least preferred solutions of children and mothers (i.e., there were no significant differences between the ranking scores of these two solutions). Although water and sodium gluconate were equally preferred by children (ranking of water: 1.4±0.1; ranking of sodium gluconate: 2.1±0.2; *n.s.*), mothers significantly preferred water to the other three solutions. In addition, mothers preferred the sodium-gluconate solution when compared with caffeine, but not when compared with caffeine combined with sodium gluconate.

Tetralone

Bitterness—Mothers and children indicated that the Tetralone combined with sodium gluconate, as well as the same concentration of Tetralone alone, tasted more bitter than either sodium gluconate or water. However, unlike the data reported herein for urea and caffeine, the combination of Tetralone and sodium gluconate yielded enhanced bitterness in children. As presented in Table 2, 72% of the children selected Tetralone combined with the salt as more bitter than Tetralone alone.

Relative Preference—In contrast with the other two bitter agents (urea and caffeine), sodium gluconate diminished the acceptance of Tetralone in both children and mothers. Seventy-seven percent of the children and 72% of the mothers indicated that Tetralone tasted better than the same concentration of Tetralone combined with sodium gluconate. They also indicated that sodium gluconate and water tasted better than Tetralone alone or in combination with sodium gluconate (Table 2).

The preference-ranking scores of the four solutions were statistically significant for both children, $F_r(3\ df)=36.13$, $p<.0001$, and mothers, $F_r(3\ df)=45.10$, $p<.0001$. Tetralone alone and Tetralone combined with sodium gluconate were the least preferred solutions in both children and mothers (i.e., there were no significant differences between the ranking scores of these two solutions). Nevertheless, unlike that reported earlier for urea and caffeine, Tetralone was ranked intermediary between the solution of the bitter combined with sodium gluconate and sodium gluconate alone (Figure 1).

Sodium Gluconate

Relative Preference—When analyzing the data obtained from the pairwise comparisons as well as the rankedpreference scores, differences emerged between children and mothers when they were asked to choose whether the solution of sodium gluconate tasted better than water. During each of the three sessions (i.e., urea, caffeine, Tetralone), mothers consistently indicated that water tasted better than sodium gluconate (see Table 2), and as shown in Figure 1, their preference-ranking score for water (1.2±0.1) was significantly lower (e.g., more preferred) than sodium gluconate for each of the three test sessions (2.9±0.1 for urea session, 2.3±0.2 for caffeine session, and 2.2±0.2 for Tetralone session). Children, on the other hand, did not prefer water to sodium-gluconate solution during either the pairwise comparisons (see Table 2), or the preference-ranking procedures (Figure 1), thus suggesting that children, unlike adults, do not prefer water more than this salt.

To further examine the differences in preference for salty taste among children and adults, we determined the number of children (n=41) and mothers (n=39) who ranked sodium gluconate as one of their most preferred (Rank Score 1 or 2) or least preferred of the four solutions (Rank Score 3 or 4) during the first test session. More than half (56%) of the children, but only 22% of the mothers, ranked salt as one of their most preferred solutions. This difference between children and adults was significant, $\chi^2(1\ df)=9.09$, $p<.005$.

Accepted Formulation of Medication and Use of Sport's Drinks—Fifty-one percent of the mothers reported that they tried to give their child medication in a pill formulation, but only 29% routinely took medicine in pill form. The remaining children used liquid or chewable formulations or both. The majority of children (68%) reported that they had tried and liked drinking sport drinks, some of which contain approximately 0.2 M NaCl (e.g., Gatorade™).

DISCUSSION

For adults, the perceived bitterness of some bitter compounds is reduced when the compound is mixed with sodium salts (Breslin & Beauchamp, 1995, 1997; Keast & Breslin, 2002; Keast et al., 2001; Kroeze & Bartoshuk, 1985). We show here for the first time that this also is the case for children. In particular, sodium gluconate reduced the bitterness of urea, and the same tendency was evident for caffeine. In marked contrast, the reverse effect was true for the bitter compounds in the Tetralone mixture. Consistent with the reductions in perceived bitterness, children also reported that urea and caffeine, to which the sodium salt was added, tasted better than these bitter compounds alone. Again, the reverse was true for Tetralone.

The mechanisms underlying the ability of sodium gluconate to reduce bitterness are not known. Previous studies strongly suggested that the locus of the effect is at the periphery (Bartoshuk, 1980; Breslin & Beauchamp, 1995; Kroeze & Bartoshuk, 1985), most likely due to the sodium ion somehow interfering with the functioning of one or more bitter receptors. If this is the case, why does sodium gluconate differentially reduce the bitterness of some bitter compounds and enhance the bitterness of others? The answer to this question may lie in the recent findings that indicate there are multiple mechanisms underlying the sensory transduction of bitter compounds (Brand, 2000; Margolskee, 2002). There are multiple G-protein coupled bitter receptors (Adler et al., 2000; Chandrashekar et al., 2000; Matsunami, Montmayeur, & Buck, 2000), and bitter taste may be induced in some cases by nonreceptor interactions between bitter compounds and taste cells (Rosenzweig, Yan, Dasso, & Spielman, 1999). Consequently, sodium may interfere with some transductive processes, but not others.

Whatever the mechanism by which sodium reduces the bitterness of some bitter compounds and enhances the bitterness of others, it is clearly operative in 7- to 10-year-old children. There have been reports that sensitivity to tastes changes marginally between childhood and adulthood (Oram, Laing, Freeman, & Hutchinson, 2001). However, the most convincing and striking age-related differences in taste relate not to sensitivity but to preferences. That is, children prefer significantly higher concentrations of sweeteners and salt when compared with adults (Desor, Greene, & Maller, 1975). The latter tendency also was evident in the current study. For example, approximately 44% of the children, on average, preferred salt to water during the three sessions whereas this was the case for, on average, 19% of the mothers (Table 2). Likewise, 56% of the children, but only 22% of the mothers, ranked the salted solution as one of their top two most preferred solutions.

Sodium salts, particularly sodium chloride (i.e., table salt), impart a desirably salty taste to foods. But salt also appears to have other important functions in cuisine. In particular, relatively small amounts of salt are reported to “enhance” or increase palatability of many foods (Kemp & Beauchamp, 1994). One mechanism underlying this increase in palatability of salted foods may be via the suppressing activity of sodium on bitter taste. For example, the intensity of sweetness is enhanced by the addition of a sodium salt to a sweet-bitter mixture, presumable by blocking bitterness and thereby releasing sweetness from suppression (Breslin & Beauchamp, 1997). Intense sweeteners are used, but often unsuccessfully, to mask the bitterness in children’s formulations of medicines. We suggest that the addition of sodium salts to these concoctions, in selected cases, might be expected to improve their acceptability by children.

Bitter-tasting substances elicit innately determined rejection reflexes in nonhuman animals as well as in humans (Rosenstein & Oster, 1988; Steiner, 1977; Steiner, Glaser, Hawilo, & Berridge, 2001). Presumably, this rejection reflex evolved for the mutual protection of both animal and plant—to protect the animal from poisoning (most, but not all, bitter compounds in nature are toxic to some degree.) and protect the plant from being eaten. As indicated in the Introduction, most pharmaceutical preparations taste bitter, and when children cannot or will not take medicines in encapsulated form (Steffensen et al., 1998), a way of reducing this innately rejected sensory stimulus becomes medically significant. Failure to consume medication may do the child harm, and in some cases, may be life threatening (Van Dyke et al., 2002).

CONCLUSIONS

The current study indicates that it may be effective to use sodium salts to suppress the bitterness of some pharmaceuticals. Based on the differential ability of a sodium salt to inhibit bitterness, clearly each drug of interest must be evaluated separately to determine whether sodium salts are effective at inhibiting bitterness (see also Breslin & Beauchamp, 1995). With progress in understanding how bitter taste is transduced and how sodium acts to suppress bitterness, it may be possible to predict the efficacy of sodium as a specific bitter blocker based on the structure of the drug of interest. There are other compounds that are reported to reduce bitterness (e.g., phosphatidic acid beta-lactoglobulin, PALG) (Katsuragi, Sugiura, Lee, Otsuji, & Kurihara, 1995), but it is questionable whether they are superior to sodium. However, superior bitter-taste-inhibiting compounds may be discovered when knowledge of the mechanistic processes underlying bitter taste perception is more fully known. Such compounds instead of, or in combination with, sodium salts should aid in increasing the acceptability of many drugs, thereby benefiting children with illnesses.

Acknowledgments

This research was support by NIH Grant HD37119, and the research apprenticeship of Ms.Tiffany Teel was supported by grants from the Annenberg Foundation and Mrs. Patricia Kind. We thank Dr. Paul Breslin for his comments and discussion throughout the project, and acknowledge the excellent technical support of Ms. Nadia MacFarlane, Ms. Tiffany Teel, and Mr. Christopher Tharp.

Contract grant sponsor: NIH

Contract grant number: HD 37119

Contract grant sponsor: Annenberg Foundation

Contract grant sponsor: Mrs. Patricia Kind

REFERENCES

Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS. A novel family of mammalian taste receptors. Cell 2000;17:693–702. [PubMed: 10761934]

Bartoshuk, LM. Sensory analysis of the taste of NaCl. In: Kare, MR.; Fregly, MJ.; Bernard, RA., editors. Biological and behavioral aspects of salt intake. Academic Press; New York: 1980. p. 83-98.

Berning CK, Griffith JF, Wild JE. Research on the effectiveness of denatonium benzoate as a deterrent to liquid detergent ingestion by children. Fundamental and Applied Toxicology 1982;2:44–48. [PubMed: 7185601]

Brand JG. Within reach of an end to unnecessary bitterness? Lancet 2000;358:1371–1372. [PubMed: 11052575]

Breslin PAS, Beauchamp GK. Suppression of bitterness by sodium: Variation among bitter taste stimuli. Chemical Senses 1995;20:609–623. [PubMed: 8788095]

Breslin PAS, Beauchamp GK. Salt enhances flavor by suppressing bitterness. Nature 1997;387:563. [PubMed: 9177340]

Chandrashekar J, Mueller KL, Hoon MA, Adler E, Felg L, Guo W, Zuker CS, Ryba NJ. T2Rs function as bitter taste receptors. Cell 2000;100:703–711. [PubMed: 10761935]

Committee on Drugs; American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 1995;95:286–294. [PubMed: 7838651]

Desor JA, Greene LS, Maller O. Preference for sweet and salty in 9- to 15-year-old and adult humans. Science 1975;190:686–687. [PubMed: 1188365]

Food and Drug Administration. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. Final Rule (63 FR 66632; Dec. 2). 1998

Glendinning JI. Is the bitter rejection response always adaptive? Physiology & Behavior 1994;56:1217–1227. [PubMed: 7878094]

Kajuira H, Cowart J, Beauchamp GK. Early developmental changes in bitter taste responses in human infants. Developmental Psychobiology 1992;25:375–386. [PubMed: 1526325]

Katsuragi Y, Sugiura Y, Lee C, Otsuji K, Kurihara K. Selective inhibition of bitter taste of various drugs by lipoprotein. Pharmaceutical Research 1995;12:658–662. [PubMed: 7479549]

Keast RSJ, Breslin PAS. Modifying the bitterness of common oral pharmaceuticals with cations and anion series of salts. Pharmaceutical Research 2002;19:1019–1026. [PubMed: 12180534]

Keast RSJ, Breslin PAS, Beauchamp GK. Suppression of bitterness using sodium salts. Chimia 2001;55:441–447.

Kemp SE, Beauchamp GK. Flavor modification by sodium chloride and monosodium glutamate. Journal of Food Science 1994;59:682–686.

Kroeze JHA, Bartoshuk LM. Bitterness suppression as revealed by split-tongue taste stimulation in humans. Physiology & Behavior 1985;35:779–783. [PubMed: 4080842]

Lawless H. Sensory development in children: Research in taste and olfaction. Journal of the American Dietetic Association 1985;85:577–584. [PubMed: 3886763]

Manley MC, Calnan M, Sheiham A. A spoonful of sugar helps the medicine go down? Perspectives on the use of sugar in children's medicines. Social Science & Medicine 1994;39:833–840. [PubMed: 7973879]

Margolskee RF. Molecular mechanisms of bitter and sweet taste transduction. Journal of Biological Chemistry 2002;4:1–4. [PubMed: 11696554]

Matsunami H, Montmayeur JP, Buck LB. A family of candidate taste receptors in human and mouse. Nature 2000;6:552–553.

Oram N, Laing DG, Freeman MG, Hutchinson I. Analysis of taste mixtures by adults and children. Developmental Psychobiology 2001;38:67–77. [PubMed: 11150062]

Pawar S, Kumar A. Issues in the formulation of drugs for oral use in children. Role of excipients. Pediatric Drugs 2002;4:371–379. [PubMed: 12038873]

Ramgoolam A, Steele R. Formulations of antibiotics for children in primary care effects on compliance and efficacy. Pediatric Drugs 2002;4:323–332. [PubMed: 11994037]

Rogers GC Jr. The role of aversive bittering agents in the prevention of pediatric poisonings. Pediatrics 1994;93:68–74. [PubMed: 8265327]

Rosenstein D, Oster H. Differential facial responses to four basic tastes in newborns. Child Development 1988;59:1555–1568. [PubMed: 3208567]

Rosenzweig S, Yan W, Dasso M, Spielman AI. Possible novel mechanism for bitter taste mediated through cGMP. Journal of Neurophysiology 1999;81:1661–1665. [PubMed: 10200202]

Siegel, S.; Castellan, NJ. Nonparametric statistics for the behavioral sciences. Vol. 2nd ed.. McGraw-Hill; New York: 1988.

Silbert JR, Frude N. Bittering agents in the prevention of accidental poisoning: Children's reactions to Denatonium Benzoate (Bitrex). Archives of Emergency Medicine 1991;8:1–7. [PubMed: 1854387]

Steffensen GK, Pachaï A, Pedersen SE. Peroral medinsk behandling af borner der problemer? [Peroral drug administration to children: Are there any problems?]. Ugeskr Laefer 1998;160:2249–2252.

Steiner, JE. Facial expressions of the neonate infant indication the hedonics of food-related chemical stimuli. In: Weiffenbach, JM., editor. Taste and development: The genesis of sweet preference. U.S. Government Printing Office; Washington, DC: 1977. p. 173-189.

Steiner JE, Glaser D, Hawilo ME, Berridge KC. Comparative expression of hedonic impact: Affective reactions to taste by human infants and other primates. Neuroscience and Biobehavioral Reviews 2001;25:53–74. [PubMed: 11166078]

Van Dyke RB, Lee S, Johnson GM, Wiznia A, Mohan K, Stanley K, Morse EV, Krogstad PA, Nachman S, Pediatric AIDS Clinical Trials Group Adherence Subcommittee Pediatric AIDS Clinical Trials Group 277 Study Team. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. Pediatrics 2002;109:e61. [PubMed: 11927734]

Wilson JT. An update on the therapeutic orphan. Pediatrics 1999;104:585–590. [PubMed: 10469794]

Yokomukai Y, Breslin PAS, Cowart BJ, Beauchamp GK. Sensitivity to the bitterness of iso-alpha-acids: The effects of age and interactions with NaCl. Chemical Senses 1994;19:577.

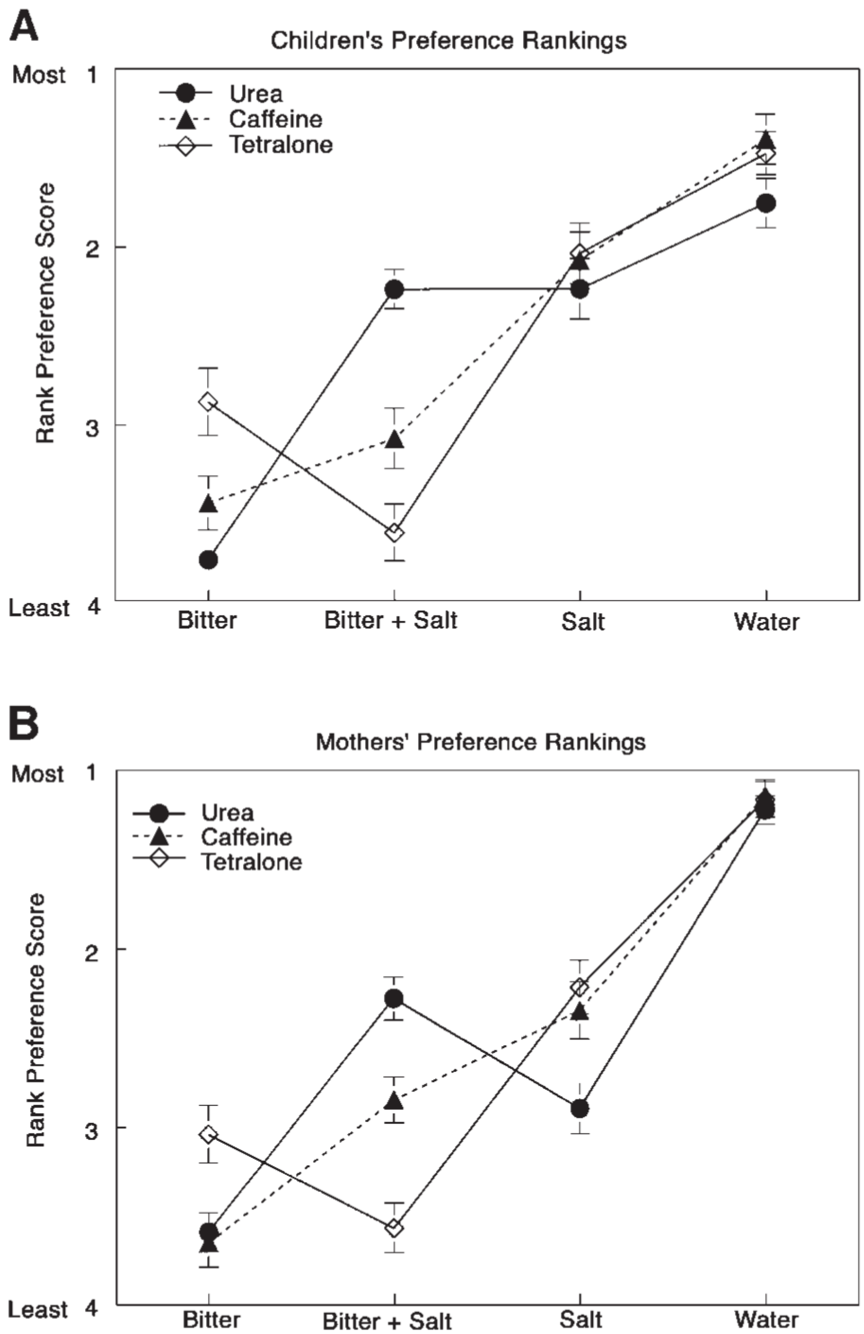

FIGURE 1.

Mean preference ranking scores (1=most preferred; 4=least preferred) of the four different solutions (bitter, bitter combined with sodium gluconate, sodium gluconate, water) for each of the three bitters (● 0.5 M urea, ▲0.08 M caffeine, ◇ 1.37×10^{-4} M Tetralone). Data obtained from children are presented in Panel A and mothers in Panel B.

Table 1

Experimental Stimuli

	Bitter Stimuli		
	Urea	**Caffeine**	**Tetralone**
Bitter	0.5 M urea	0.08 M caffeine	1.37×10^{-4} M Tetralone
Salt	0.3 M sodium gluconate	0.3 M sodium gluconate	0.3 M sodium gluconate
Bitter+salt	0.5 M urea+0.3 M sodium gluconate	0.08 M caffeine+0.3 M sodium gluconate	1.37×10^{-4} M Tetralone+0.3 M sodium gluconate
Water	Double distilled	Double distilled	Double distilled

Table 2

Bitter Taste Perception and Preferences in Children and Adult

	Children			Mothers		
	Type of bitter					
Pair-wise comparison	Urea	Caffeine	Tetralone	Urea	Caffeine	Tetralone
What tastes more bitter?						
Bitter vs. Bitter+Salt	66*	68	28*	73*	77*	37
Bitter vs. Salt	61	67	74*	77*	73*	91*
Bitter vs. Water	85*	100*	91*	87*	92*	91*
Bitter+Salt vs. Salt	41	69*	78*	59	73*	87*
Bitter+Salt vs. Water	71*	77*	96*	72*	96*	96*
Salt vs. Water	54	58	65	69*	69*	57
Subjects (n)	41	26	23	39	26	23
What tastes better?						
Bitter vs. Bitter+Salt	30*	30*	77*	18*	33	72*
Bitter vs. Salt	30*	35	26*	26*	12*	22*
Bitter vs. Water	20*	4*	17*	10*	8*	0*
Bitter+Salt vs. Salt	54	23*	17*	56	19*	4*
Bitter+Salt vs. Water	39	31*	9*	26*	12*	4*
Salt vs. Water	37	46	48	31*	12*	13*
Subjects (n)	41	26	23	39	26	23

Note. Values are expressed as %, unless otherwise indicated (n). Children and mothers who indicated when the bitter solution, bitter solution combined with sodium gluconate, or sodium gluconate tasted "more bitter" or "better" when compared to each other, salt, or water. Bitter solutions were 0.5 M urea, 0.08 M caffeine, and 1.37×10^{-4} M Tetralone. The salt solution was 0.3 M sodium gluconate. The percentage refers to number of subjects that chose the solution that is underlined when compared to non-underlined solution of the pair.

* $p<.05$.