Nonnutritive sweeteners are not supernormal stimuli

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BACKGROUND: It is often claimed that nonnutritive sweeteners (NNS) are ‘sweeter than sugar’, with the implicit implication that high-potency sweeteners are supernormal stimuli that encourage exaggerated responses. This study aimed to investigate the perceived sweetness intensity of a variety of nutritive sweeteners (sucrose, maple syrup and agave nectar) and NNS (acesulfame-K (AceK), rebaudioside A (RebA), aspartame and sucralose) in a large cohort of untrained participants using contemporary psychophysical methods.

METHODS: Participants (n = 401 total) rated the intensity of sweet, bitter and metallic sensations for nutritive sweeteners and NNS in water using the general labeled magnitude scale.

RESULTS: Sigmoidal dose–response functions were observed for all stimuli except AceK. That is, sucrose follows a sigmoidal function if the data are not artifactually linearized via prior training. More critically, there is no evidence that NNS have a maximal sweetness (intensity) greater than sucrose; indeed, the maximal sweetness for AceK, RebA and sucralose were signifi cantly lower than that for concentrated sucrose. For these sweeteners, mixture suppression due to endogenous dose-dependent bitter or metallic sensations appears to limit maximal perceived sweetness.

CONCLUSIONS: In terms of perceived sweetness, NNS cannot be considered supernormal stimuli. These data do not support the view that NNS hijack or overstimulate sweet receptors to produce elevated sweet sensations.

INTRODUCTION
Evolutionarily, sweet taste has enabled humans to make qualitative judgments about the energy density and nutritional quality of their food. Although sweet taste is no longer fundamentally needed for survival, sweet sensations are innately pleasurable across the lifespan.1 Nonnutritive sweeteners (NNS) have been utilized since the late 1800s2 as alternatives to evoke the desired sweetness in food products without the calories associated with mono- and disaccharides. More recently, consumption of NNS by both adults and children has increased greatly, as NNS are now used by 28–85% of the American population.3,4

Despite increasing use and renewed research interest in NNS, there is no standardized nomenclature for these compounds. The terms artificial, alternative, synthetic, low calorie, noncaloric, sugar-substitute, hyper-intense, high-intensity and high-potency have all been used roughly synonymously (for example, Swithers5) to describe NNS despite implicit differences in meaning. We choose to use NNS as a blanket term largely through a process of exclusion. For example, rebaudioside A (RebA) and monk fruit are plant extracts, therefore the terms artificial and synthetic are not appropriate; aspartame is metabolized while sucralose is not, therefore noncaloric and low calorie lack precision.

Critically, the term ’high intensity’ has been repeatedly misinterpreted in the scientific literature and popular press to imply that NNS are ‘sweeter than sugar’.6–9 However, there is no evidence to suggest that NNS are sweeter than natural carbohydrate sweeteners like sucrose. NNS are generally high-potency sweeteners, but potency is not synonymous with intensity, and the critical distinction between the two terms has strong implications for public health and health policy.

Specifically, referring to NNS as high-intensity sweeteners suggests they are some sort of supernormal stimulus. Originally described by Tinbergen and Perdeck,10 supernormal stimuli are exaggerated stimuli that evoke behavioral responses more effectively than the stimulus for which the response evolved. Describing NNS as high-intensity sweeteners rather than high-potency sweeteners implies NNS evoke a sweetness response greater than natural sugars like sucrose. Although it is often claimed NNS overstimulate sweet taste receptors,11–13 we fail to find evidence that NNS act as supernormal stimuli.

The confusion between high potency and high intensity is understandable, given common marketing claims like ‘sucralose is 600 times sweeter than sugar’14 that are often repeated uncritically in the scientific literature. Although strictly correct in one sense, this phrasing is also a gross oversimplification that is misleading. It may be helpful to recall the critical distinction between potency and activity in pharmacology. Specifically, because NNS have high pharmacological potency with respect to receptor activation, they have very low psychophysical detection thresholds compared with bulk carbohydrate sweeteners. It takes a very small amount of these compounds to activate a receptor and elicit a sensation; accordingly, a metabolized compound like aspartame is able to provide sweetness without contributing a nutritionally meaningful amount of calories to the diet. With regard to their detection threshold, NNS are ‘sweeter’ than disaccharides like sucrose on a weight-to-weight basis. Nonetheless, this does not imply that high-potency sweeteners are high-intensity stimuli. That is, the psychophysical intensity (that is, the quantitative magnitude of a given sensation) is roughly equivalent to the pharmacological concept of activity. The important distinction between potency and activity can be...
illustrated with the opioids buprenorphine and morphine: buprenorphine has much greater potency than morphine, but the activity of buprenorphine is much less than morphine. Likewise, a sweetener may have a low detection threshold without being intensely sweet. Indeed, it is well known in the food industry that NNS may have low maximal sweetness (for example acesulfame-K (AceK), saccharin), which limits their utility. DuBois et al. demonstrated this in a dose–response (D–R) study for numerous nutritive sweeteners and NNS using a small trained panel (n = 18). They found that sweetness functions for NNS were hyperbolic, as perceived sweetness hit a ceiling and did not increase further as concentration increased. Conversely, monosaccharides, disaccharides and sugar alcohols showed a linear D–R function in their study, although they noted that this linearity was an artifact of the panelist training. Given that sweetness is primarily a G protein-coupled receptor-mediated phenomenon, we would expect a sigmoidal function if other intensity scaling methods were used.

In terms of measuring sweetness perception, magnitude estimation has been commonly used to collect intensity data in relation to sweet taste stimuli. Variation in magnitude estimation data may arise from either true perceptual differences or differences in how the participant uses numbers. The general labeled magnitude scale (gLMS) reduces this problem because it encourages participants to rate outside of the context of taste stimuli with the top anchor being ‘strongest sensation of any kind’. Surprisingly, relatively few studies have utilized the gLMS to quantify sweetness intensity perception (for example, Sartor et al., Thai et al. and Green et al.), despite the ability of the gLMS to generate putative ratio level data and allow more valid across-group comparisons.

Here, we sought to reexamine and characterize the sweetness intensity D–R functions of NNS (sucralose, AceK, RebA, aspartame) and ‘natural’ caloric sweeteners (sucrose, maple syrup, agave nectar) using modern psychophysical techniques. The present study had two specific goals. First, we revisit the question of whether NNS are able to elicit greater (more intense) sweet sensations than sucrose. Second, we provide new D–R function estimates determined from a large cohort of untrained participants.

MATERIALS AND METHODS
Overview of methods
The purpose of these series of experiments was to investigate the perceived sweetness of NNS (aspartame, AceK, RebA, sucralose) and nutritive sweeteners (sucrose, agave nectar and maple syrup). Data were collected in four experiments conducted on separate days and pooled, treating observations from each participant as independent measures. For each experiment, the same orientation procedures and testing methods were used. Sucrose concentrations remained constant across experiments to enable comparisons across days. In the fourth experiment, sucrose and aspartame were tested with two additional concentrations to better characterize the D–R functions.

Compusense five software, version 5.2 (Guelph, Ontario, Canada) was used for data collection. Presentation order of samples was counterbalanced using a Williams design. All tests were conducted at the Sensory Evaluation Center in the Department of Food Science at the Pennsylvania State University. Participants were provided with an explanation of the experiment in a brief orientation prior to testing in isolated testing booths. The orientation consisted of an overview of the gLMS with a warm-up using both imagined sensations (for example Hayes et al.), and presentation of prototypical exemplars of sweet, bitter and metallic stimuli. This orientation differs substantially from classical ‘trained panel’ approaches like Quantitative Descriptive Analysis or Spectrum Descriptive Analysis that use small numbers of participants and require tens or hundreds of hours of training to calibrate panelists to attributes and scale usage.

Participants
Reportedly healthy individuals (n = 401) were recruited from the Pennsylvania State University campus and surrounding area (State College, PA, USA) via email for their willingness to participate in a taste study. Participants were prescreened for eligibility. Eligibility criteria included: between 18 and 64 years old; not pregnant or breastfeeding; no known defects of smell or taste; no lip, cheek or tongue piercings; nonsmoker (had not smoked in last 30 days); no food allergies or sensitivities; no history of choking or difficulty swallowing. Participants were also required to provide 30–35 min of their time for the experiment. A new group of participants were recruited for each experiment described below from a database containing 1200+ individuals; however, due to limitations of our recruitment system, we did not actively exclude those who had participated in a prior experiment, so a small fraction may have participated in more than one study. Retained data are fully anonymized, so we are unable to estimate this proportion. Participants provided informed consent and were paid for their time. All procedures were approved by the Pennsylvania State University Institutional Review Board (protocol number #33164).

Psychophysical scaling
A gLMS was used to measure the perceived intensities of sweetness, bitterness and metallic sensation for all stimuli. The gLMS ranges from 0 (no sensation), 1.4 (barely detectable), 6 (weak), 17 (moderate), 35 (strong), 51 (very strong) and 100 (strongest imaginable sensation of any kind). Data were collected using Compusense five software. Prior to rating test stimuli, all participants partook in a brief warm-up to familiarize the participants with the gLMS. The warm-up required participants to make overall intensity ratings for 15 imagined and/or remembered sensations that include oral and non-oral sensations. Generalizing the scale outside an oral context allows for more valid comparisons across individuals. More pragmatically, the gLMS also provides two other advantages over magnitude estimation: the gLMS does not require the same degree of numeracy on the part of participants, and gLMS data do not require the same extensive post-collection manipulation required by magnitude estimation data.

Stimuli
Taste stimuli. All stimuli were presented in 10-ml aliquots in 30-ml medicine cups at room temperature. Solutions were prepared at least 24 h prior to testing using reverse osmosis water and were stored at refrigerated temperature for a maximum of 5 days. Concentration ranges for sweeteners were determined from results of bench top testing.

Orientation stimuli. The orientation exemplars were 10 ml 292 mM sucrose (sweet), 0.032 mM quinine monohydrate dihydrate (bitter), and 292 mM sucrose/0.032 mM quinine mixture (sweet and bitter) and 1.7984 mM ferrous sulfate prepared by Katz (metallic), as used by Kamerud and Delwiche. Participants were told that they may or may not experience all sensations from the orientation samples during the session in the booth and that ‘they may receive samples that have more than one taste quality’. Participants were also instructed to avoid rating how much they ‘liked’ or ‘disliked’ samples and separate intensity from hedonic affect (liking).

Dose–response for nutritive sweeteners (experiments 1, 2 and 4). Participants rinsed with room temperature reverse osmosis water before and between each sample. Participants were provided with 45 s to rinse before the next sample. Five sucrose concentrations were used as constant stimuli across all sessions. In experiment 1, 102 participants rated the sweetness, bitterness and metallic intensity for five sucrose solutions (109.5, 219.1, 303.8, 400.0 and 818.0 mM), five aspartame solutions (0.23, 0.70, 1.0, 1.83 and 3.15 mM) and five RebA solutions (0.04, 0.25, 0.52, 1.03 and 1.55 mM). In experiment 2, 91 participants made the same attribute ratings for five NNS (sucralose, AceK, RebA and sucralose) and nutritive sweeteners (sucrose, agave nectar and maple syrup). Participants were provided with 45 s to rinse before the next sample. Five sucrose concentrations were used as constant stimuli across all sessions. In experiment 1, 102 participants rated the sweetness, bitterness and metallic intensity for five sucrose solutions (109.5, 219.1, 303.8, 400.0 and 818.0 mM), five aspartame solutions (0.23, 0.70, 1.0, 1.83 and 3.15 mM) and five RebA solutions (0.04, 0.25, 0.52, 1.03 and 1.55 mM). In experiment 2, 91 participants made the same attribute ratings for five NNS (sucralose, AceK, RebA and sucralose) and nutritive sweeteners (sucrose, agave nectar and maple syrup). Participants were provided with 45 s to rinse before the next sample. Five sucrose concentrations were used as constant stimuli across all sessions. In experiment 1, 102 participants rated the sweetness, bitterness and metallic intensity for five sucrose solutions (109.5, 219.1, 303.8, 400.0 and 818.0 mM), five aspartame solutions (0.23, 0.70, 1.0, 1.83 and 3.15 mM) and five RebA solutions (0.04, 0.25, 0.52, 1.03 and 1.55 mM). In experiment 2, 91 participants made the same attribute ratings for five NNS (sucralose, AceK, RebA and sucralose) and nutritive sweeteners (sucrose, agave nectar and maple syrup) using modern psychophysical techniques. The present study had two specific goals. First, we revisit the question of whether NNS are able to elicit greater (more intense) sweet sensations than sucrose. Second, we provide new D–R function estimates determined from a large cohort of untrained participants.

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104, 140 and 280 g l\(^{-1}\)). In experiment 3, participants wore nose clips to minimize any influence of volatiles on perceived sweetness (for example Frank et al.,\(^{34}\) Schifferstein et al.\(^{35}\) and Bartoshuk et al.\(^{36}\)). Nutritive sweeteners were measured on a weight-to-volume basis (g l\(^{-1}\)) as they contain a variety of sugars and other components.\(^{37,38}\)

The sweetener concentrations used in Experiments 1–4 are summarized in Supplementary Table 1.

Procedure

Participants received brief instruction on the gLMS and taste exemplars in a waiting room. After this orientation, the participants entered isolated computerized testing booths. Once in the booths, participants completed a scaling warm-up procedure on the computer, rating imagined or remembered sensations (for example Hayes et al.\(^{26}\)). Following the scale warm-up, participants received a tray of 15 samples (Test 1, 2 and 3) or 12 samples (Test 4). Participants were instructed to put the entire sample in their mouth, swish for 5 s to obtain total mouth coating and spit the sample out. Participants then waited 10 s to allow the sensation to peak in their mouth, swish for 5 s to obtain total mouth coating and spit the sample out. Participants received brief instruction on the gLMS and taste exemplars in a waiting room. After this orientation, the participants entered isolated computerized testing booths. Once in the booths, participants completed a waiting room. After this orientation, the participants entered isolated computerized testing booths. Once in the booths, participants completed a scaling warm-up procedure on the computer, rating imagined or remembered sensations (for example Hayes et al.\(^{26}\)). Following the scale warm-up, participants received a tray of 15 samples (Test 1, 2 and 3) or 12 samples (Test 4). Participants were instructed to put the entire sample in their mouth, swish for 5 s to obtain total mouth coating and spit the sample out. Participants then waited 10 s to allow the sensation to peak before making intensity ratings; 45 s breaks between samples were enforced via software to minimize potential carry over and lingering. Ad libitum reverse osmosis rinse water was also provided.

Statistical analysis

D–R functions were fit using GraphPad Prism 5.0C for OSX (GraphPad Software, San Diego, CA, USA). Descriptive and inferential statistics were calculated using SPSS statistical software. Because sweetness perception is a receptor-mediated process,\(^{17}\) D–R functions for sucrose, aspartame, RebA, sucralose, maple syrup and agave nectar were fit a priori using the Hill Equation:

\[
R = R_{\text{min}} + \frac{R_{\text{max}} - R_{\text{min}}}{1 + 10^{\frac{\log_{10}(C) - C_H}{C_V - C_H}}}
\]

where \(R\) is the mean response (perceived intensity) across participants and \(C\) is the stimulus concentration. In this model, \(R_{\text{max}}\) is top of the curve, \(R_{\text{min}}\) is the bottom of the curve, the point halfway between min and max is EC50 and the slope of the linear portion of the model is the HillSlope.

RESULTS

Dose–response functions for nutritive sweeteners are not linear

Mean D–R functions for caloric and NNS in a large number of participants are shown in Figure 1. As expected, all four NNS are left shifted compared with sucrose, indicating they have higher potency. Notably, both caloric sweeteners and NNS are well described by a constrained Hill-type equation, with the exception of AceK. Present data partially conflict with prior reports: in 18 highly trained assessors, sugars and sugar alcohols showed linear D–R functions, whereas high-potency sweeteners were best described by Hill-type models.\(^{16}\)

Sugars have higher maximal sweetness than nonnutritive sweeteners

As shown in Figure 1 and Table 1, the caloric sweeteners (sucrose, agave nectar and maple syrup) all had higher \(R_{\text{max}}\) values (estimated maximal sweetness) than the NNS, indicating NNS are not supernormal stimuli as compared with sucrose. To corroborate this, we also used the maximal observed sweetness for each NNS (Supplementary Table 3) rather than the estimated \(R_{\text{max}}\) values in Table 1, testing for differences compared with sucrose. The sweetness of RebA was significantly lower than that of sucrose (t(513) = 5.94; \(P < 0.0001\)). Likewise, the maximal observed sweetness for aspartame was lower than that of sucrose.

![Figure 1](image)

Figure 1. Mean D–R functions for nonnutritive (left) and nutritive (right) sweeteners. The y axis indicates perceived sweetness on a gLMS (see text). Data were pooled across experiments. Total numbers of participants per stimulus were: (sucrose: \(n = 401\)), (aspartame, solid squares \(n = 216\); open squares \(n = 102\)); (RebA, \(n = 114\)) (AceK, \(n = 91\)), (sucralose, \(n = 91\)), (maple syrup, \(n = 94\)), (agave nectar, \(n = 94\)). The dashed horizontal line is provided for context: it roughly represents the approximate sweetness of Kool-aid (10.5% w/v sucrose), which also contains citric acid.

| Table 1. Hill equation dose–response parameters for sucrose, agave nectar, maple syrup, aspartame, RebA and sucralose |
|----------------|--------|---------|--------|--------|--------|--------|--------|
| Sweetener      | \(R_{\text{max}}\) | SE      | Hill Slope | SE      | LogEC\(_{50}\) | SE      | EC\(_{50}\) | \(R^2\) |
| Maple syrup    | 50.7   | 7.01    | 1.32     | 0.24    | 1.53     | 0.12    | 33.86    | 0.40   |
| Agave nectar   | 45.4   | 3.50    | 1.60     | 0.26    | 1.34     | 0.06    | 21.9     | 0.39   |
| Sucrose        | 42.8   | 3.90    | 1.65     | 0.19    | 2.60     | 0.06    | 400.6    | 0.30   |
| Aspartame      | 33.4   | 3.22    | 1.15     | 0.14    | 0.37     | 0.09    | 2.33     | 0.34   |
| Sucralose      | 34.6   | 7.87    | 1.34     | 0.48    | 0.30     | 0.19    | 1.99     | 0.18   |
| RebA           | 22.2   | 2.54    | 1.19     | 0.33    | 0.67     | 0.13    | 0.21     | 0.17   |

All values represent means. EC\(_{50}\) is half of the concentration needed to evoke the maximal perceived sweetness rating; values are in grams per liter for the nutritive sweeteners, and mM for the NNS. \(R_{\text{max}}\) and SE estimated from the fitted equations were tested via one-way ANOVA using summary statistics with appropriate \(n\)’s, assuming \(n = 102\) for aspartame. The \(R_{\text{max}}\) values were significantly different (\(P < 0.05\)) across sweeteners.
(t(501) = 2.03; P < 0.043). Finally, the maximal observed sweetness for sucralose tended to be lower (t(490) = 1.73; P = 0.08) than that of sucrose. (All tests were two-tailed.) Collectively, there was no evidence to suggest NNS were sweeter than sucrose.

The mechanism by which many NNS are unable to show the same efficacy (maximal intensity) as the caloric sweeteners is unknown, but it may be partially due to mixture suppression of sweetness by bitter39 or metallic sensations. Figure 2 shows the mean D–R functions for sweetness and bitterness. For AceK, sucralose and RebA, bitterness increases with concentration, eventually equaling or surpassing perceived sweetness. In contrast, Figure 2 shows that aspartame has a similar function to that of sucrose, maple syrup and agave nectar (see Supplementary Figure 1); bitterness is minimal and does not increase with concentration.

**DISCUSSION**

Present data make several important contributions to extant literature. First, these data indicate that NNS are not supernormal stimuli. That is, they do not evoke sweet sensations that are more intense than sucrose. Second, we find that carbohydrate sweeteners exhibit sigmoid concentration–response functions, as would be expected given this is a receptor-mediated process, and not linear functions as reported previously.

NNS are not supernormal stimuli. Although NNS have low psychophysical detection thresholds compared with sugars, it is not valid to use thresholds or the dose over threshold to estimate the perceived intensity of these sweeteners.36,40,41 Indeed, in 1948, Lichtenstein42 noted that comparing thresholds provides invalid information concerning the relative sweetness of sweet stimuli above threshold levels. The D–R functions obtained here indicate that NNS are more potent but have lower activity than sucrose, maple syrup and agave nectar, even near maximal concentrations. The lack of activity in the perceived sweetness intensity of AceK, sucralose and RebA is likely a function of increasing bitterness with concentration. Bitterness is a side taste that is associated with many NNS including RebA and AceK.43,44 In contrast to prior reports that indicate sucralose has minimal bitterness,44 we find clear evidence that sucralose is bitter, consistent with unpublished data showing sucralose can activate bitter receptors (hT2Rs) in vitro. Notably, the bitterness of sucralose and AceK are sufficiently intense to depress sweetness ratings. That is, endogenous bitterness not only provides a ceiling on maximal sweetness, but can actually reverse the slope of the function at the highest concentrations. Similar effects have been shown recently for the steviol glycoside Rubusoside.45 Here, the D–R function for RebA is suggestive of this pattern: accordingly, we would expect a similar reversal if higher concentrations were used. In contrast, aspartame lacks any bitterness, showing a pattern like sucrose, maple syrup and agave nectar. The absence of bitterness in aspartame as well as its similar taste qualities to sucrose is well documented in the literature.46–48

Furthermore, the nutritive sweeteners sucrose, maple syrup and agave nectar follow sigmoidal, not linear, functions. The literature disagrees whether nutritive sweeteners like saccharides and sugar alcohols follow linear functions in which intensity increases as a function of concentration16,49–52 or whether sugars diverge from linearity.20 Present data support the existence of sigmoidal D–R functions, consistent with the underlying biology.17

The previously reported linearity of the sucrose D–R function is likely a result of extensive panel training with reference samples16 or the choice of regression model. To prevent artifactual linearity in our data, we avoided extensive panel training (for example Sensory Spectrum universal scaling) by using the gLMS. It is typically claimed that the gLMS generates ratio level (for example, Sensory Spectrum universal scaling) by using the gLMS. It is typically claimed that the gLMS generates ratio level comparable to magnitude estimation, although it should be noted this assumption is based on a limited number of studies. Nonetheless, present data show that using the gLMS enables successful sweetener differentiation. Also, these data suggest the gLMS can be used to efficiently generate D–R functions in a large number of naive participants, precluding the need for labor-intensive forced choice methods (for example, Fry et al.53) or use of highly trained assessors (for example, DuBois et al.16).

![Figure 2](image-url)

*Figure 2. Dose–response functions for sweetness and bitterness in four NNS on a gLMS scale. Solid lines (squares) indicate perceived sweetness; dotted lines (triangles) indicate perceived bitterness; dotted lines (diamonds) indicate metallic sensations. Numbers of participants per stimulus were: (aspartame, solid squares n = 216; open squares n = 102); (RebA, n = 114), (AceK, n = 91), (sucralose, n = 91).*
CONCLUSION

Our data indicate that NNS are not supernormal stimuli with regard to perceived sweetness intensity. That is, although NNS may have greater binding affinity to sweet receptors, this does not imply that NNS overstimulate sweet receptors as has been implied previously. We also show that nutritive sweeteners (sucrose, maple syrup and agave nectar) do not follow linear D–R functions as previously described in the literature; instead, they follow the sigmoidal D–R function one would expect from receptor dependent phenomenon. Present data also clarify the bitter and metallic functions of the NNS as a function of concentration, although we must point out that the use of such high concentrations of NNS in commercial applications would be unlikely. Also, we should note that present stimuli were presented in a simple aqueous model system; whether they might behave differently in mixtures with each other or in real foods remains to be tested. Nonetheless, AceK, sucralose and ReBa are not ‘sweeter than sugar’ in that they do not surpass the perceived sweetness intensities of natural sweeteners like sucrose, maple syrup and agave nectar. Finally, we do not take a broader position on the safety of NNS (cf. Fitch and Kelm and Schifman), the nutritional consequences of NNS intake (for example, the energy signaling/decoupling hypothesis) or the role of extraoral taste receptors.

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