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Non-nutritive sweetener consumption in humans: Effects on appetite and food intake and their putative mechanisms

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Abstract

Non-nutritive sweeteners (NNS) are ecologically novel chemosensory signaling compounds that influence ingestive processes and behavior. Only about 15% of the US population >2y/o ingest NNS, but the incidence is increasing. They hold the potential to moderate sugar and energy intake while maintaining diet palatability, but their use has increased in concert with BMI in the population. This association may be coincidental or causal where either mode of directionality is plausible. A critical review of the literature suggests the addition of NNS to non-energy yielding products may heighten appetite, but this is not observed under the more common condition where NNS is ingested in conjunction with other energy sources. Substitution of NNS for nutritive sweetener generally elicits incomplete energy compensation, but evidence of long-term efficacy for weight management is not available. The addition of NNS to diets poses no benefit for weight loss or reduced weight gain without energy restriction. There are long-standing and recent concerns that inclusion of NNS in the diet promotes energy intake and contributes to obesity. Most of the purported mechanisms by which this may occur are not supported by the available evidence, although some warrant further consideration. Resolution of this important issue will require long-term randomized controlled trials.

Keywords

nonnutritive sweeteners; sweeteners; diet sweeteners; appetite regulation; energy compensation

Introduction

Nutritive sweetener (NS) intake has increased markedly in the United States and globally over the past three decades, coincident with the increased incidence and prevalence of overweight and obesity (1). This has prompted considerable research on their role in energy balance. Numerous reviews (2–9) have attempted to summarize the literature, but no consensus has emerged. Nevertheless, recommendations have been made to moderate intake of NS (10,11). Given the contribution of sweeteners to food palatability and recognition that adherence to diets of moderate or low palatability is likely to be limited, one approach to limit intake is to substitute non-nutritive sweeteners (NNS) for NS in products and discretionary applications. The success of this approach is open to debate and requires resolution to determine best clinical practices and public health recommendations. This review describes recent trends in NNS use and current knowledge of their effects on short-term appetite and food intake, as well as longer term energy balance and body weight. More importantly, given the current controversy about

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NNS and energy balance, we critically review the reported mechanisms by which they may exert their effects on these outcomes.

Currently, five NNS are approved by the US Food and Drug Administration (FDA) — saccharin, sucralose, aspartame, acesulfame-K and neotame. In addition, stevia, a herb extract of intense sweetness, is used in limited applications. While research on NNS began more than a century ago, it was not until concerns about diabetes and weight control intensified that the food industry began to move NNS to market and to obtain regulatory approval for their inclusion in the diet (Table 1). Thus, there has been relatively little time to assess the long-term effects of these substances that mimic certain sensory properties (i.e., sweetness), but lack the energy value of the class of compounds that have provided the mainstay of dietary energy during human evolution. Cyclamate was designated as generally recognized as safe (GRAS) in 1958, but in 1969 it was banned in the US due to evidence that high concentrations in the diet were associated with bladder cancer in rats. Subsequent review of the evidence raised questions about the physiological relevance of the trials, but the sweetener remains unapproved in the US. Cyclamate is approved for use in the European Union and in more than 100 countries.

There are published safety standards for consumption of NNS. For example, the United States Food and Drug Administration, Joint Commission of Experts on Food Additives (JECFA) of the World Health Organization (WHO) and the Organization of Food and Agriculture (FAO), as well as the European Food Safety Agency (EFSA) have established Acceptable Daily Intakes (ADI) (Table 1). The FDA estimates the ADI equivalents to be 18 to 19 cans (1 can=12oz or 355ml) of diet cola for aspartame, 9 to12 packets of sweetener for saccharin, 30 to 32 cans of diet lemon-lime soda for acesulfame-K and 6 cans of diet cola for sucralose.

Consumption levels of NNS

Data on the amounts of NNS in foods and beverages are not readily accessible. Total estimates of tons of aspartame produced based on sales data are available, but there is no direct measure of use. Since all of the approved NNS are regarded as “GRAS”, producers and manufacturers are not required to provide content data on food labels or to release this information to federal agencies. There are a few studies that directly measured the amounts of NNS in foods, specifically beverages. For instance, one was a safety study undertaken in Hong Kong (12). It documented wide ranges of concentrations and multiple combinations of NNS in products, as would be expected since each product has different properties. Others in small selected samples have published overall NNS consumption but not content in specific foods (13–16).

Given the absence of reliable data on the concentrations of NNS in the food supply, estimates can only be derived from information about foods that contain them. In the present paper, two methods were used to identify foods that contain NNS: 1) based on an earlier toxicity study (17), that identified aspartame containing foods, we located these same foods in the US nutrient monitoring system food composition tables; 2) using food descriptions, keyword searches were conducted that included the terms: low-cal, low calorie, reduced calorie, dietetic, sugar-free, sugarless, sugar substitute, lite or light, sweetener, aspartame, splenda, sucralose, and stevia. The nutrient content of each of these items was then reviewed using the USDA food composition table to eliminate items with names that did not match their content.

Foods were initially grouped using the University of North Carolina (UNC) food-grouping system (18). It places foods and beverages into nutrient-based subgroups according to their fat and fiber content. However, these food groups varied widely with respect to added sugar values. To more accurately assess added NS and NNS in foods and beverages, the initial UNC food groups were further subdivided into sweetened with NS and NNS (i.e. the “soda” food group was divided into “soda, with sugar” and “soda, with non-nutritive sweetener” food groups).

Table 2 presents an estimate of foods with NNS. The added NS foods and beverages are readily measured and represent the total grams of food consumed for all Americans aged 2 and older on a per capita daily intake level. Thus, it is estimated that in 2003–2004, the average American consumed 585 g (20.5 oz) of beverages with added NS and 375 g of food with added NS. Over 66% of Americans consumed these beverages and the mean grams of energy-yielding beverage consumed by those who drank them was 872 g (30.5 oz). For foods, 90.3% of Americans consumed foods with added NS and the mean intake of these foods was 381 grams.

Foods and beverages with added NNS were consumed by a relatively small proportion of the population. Beverages with NNS were consumed by 10.8% of the population and 5.8% consumed foods with NNS(See Table 2). Overall, only 15.1% of all Americans indicated that they consumed any food or beverage with NNS added in 2003–2004. The grams per consumer of the NNS beverages was 752 (26.2 ounces) or just 120 g below that for NS beverages. Among the foods with NNS, the amount consumed per capita was 233 g. Assuming the products containing NNS were equi-sweet to the comparable products with NS, this indicates NNS are adding the equivalent of over 60% of the sweetening contributed by NS. It corresponds to 53 grams per day or 862 kJ/d of sweetener in the average American over 2 years of age.

The consumption trends for NNS containing foods and beverages are clearly upward, but differ between categories. The proportion of consumers ingesting NNS in beverages remained relatively stable between 1989–2004 (6.9% increase), while the proportion of consumers of NNS in foods increased 81.2%, although, in 2004, this still represented only 5.8% of the population over 2 years of age. The amount of NNS ingested in beverages and foods by NNS consumers increased by 37.7% and 14.2%, respectively between 1989 and 2004. If anything, we expect that these figures for the proportion of the sample consuming foods with NNS's might be overestimated. The literature shows selected underestimation of less healthy more energy dense foods and overestimation of healthier ones (19–22). Following this logic, it is possible that amounts per consumer are also overestimated.

Association between NNS consumption and appetite, energy intake and BMI

The influence of NNS on appetite, energy intake, and body weight has been the topic of a number of scholarly reviews (8,9,23–30). While these authors represent different disciplines and are supported by various funding agencies, the consistencies in their findings are striking.

NNS and Appetite

Although there were reports to the contrary (31–33), earlier reviews faithfully summarized the preponderance of then existing evidence indicating acute exposure to NNS in vehicles providing little or no energy, such as water or chewing gum, augments hunger relative to effects of exposure to the vehicle alone (31,34–36). The interpretation of such trials was that the sweetness of NNS enhances post-ingestive hunger. However, a study of comparable design, using NaCl in soup, replicated the findings suggesting the phenomenon may be attributable, more generally, to oral exposure to a palatable stimulus in the absence of an energy load (37).

Subsequent studies explored the addition of NNS to energy-yielding foods, beverages or meals, and commonly observed no alteration of hunger relative to vehicle alone or vehicle sweetened with sucrose (38–40). This holds when the foods are equally energetic, sweet, and palatable indicating a lack of effect of sweetener type. Additional support for this latter finding is provided through studies reporting no effects on hunger when sweeteners are delivered via a nasogastric tube (41) or capsules (31,42–44) to eliminate orosensory stimulation. Some work suggests ingestion of aspartame in a capsule actually decreases hunger (42,43), although the validity of this observation and a likely mechanism remain to be established. Aspartame doses

were similar in trials noting effects or not. With the addition of this evidence, later reviews consistently concluded NNS have little effect on appetite (26,29,45).

Evidence that NNS promotes hunger when delivered without energy, but not when incorporated into an energy-yielding food requires this effect to be weighed in light of the fact the beverages are the primary source of NNS (46). This is a medium that commonly does not supply energy, but is most often ingested periprandially (39,47) negating the conditions apparently required for the rise in hunger. Further, if a rise of hunger is elicited, the question becomes, does this translate into increased energy intake?

Preload design trials are the most common approach for assessing appetitive effects on intake, but because, by design, they are short-term, they fail to reflect known (48–50) longer-term dietary compensation responses. Thus, their predictive value for energy intake over intervals likely to impact body weight is questionable. Due to this limitation, only evidence from human trials lasting at least 3 days is considered here.

NNS and Energy Intake

Based on modeling with data from the Beltsville One Year Dietary Study, it was predicted that carbohydrate replacement in core foods would result in increased fat and protein consumption (51), thereby offsetting a reduction of energy intake. The authors noted that their findings were predicated on substitution rather than addition of reduced carbohydrate products. While controlled feeding trials, where sugars were replaced with NNS, have yielded mixed support for the the model's predictions (52,53), a test in free-living populations has not occurred because consumers largely use products with NNS as additions to the diet. Absolute quantities of carbohydrates, sugars specifically, and NNS products have increased over the past two decades (2). Indeed, as a percent of energy intake, the contribution from carbohydrate has also risen (1,46).

There are reports from controlled trials in humans of enhanced energy intake following ingestion of a sweetened, non-caloric beverage (54–57). However, the preponderance of evidence indicates NNS exert no short-term effect on energy intake (28,35,58). Longer-term feeding trials generally indicate NNS use results in no change or reduced energy intake. Early feeding trials conducted in a metabolic ward indicated substitution of NNS for NS during 3d blocks resulted in incomplete energy compensation as intake was 14–23% lower than baseline (59). When the sucrose-sweetened products were re-introduced, energy intake exceeded baseline by 7.4% and 5.3% in the next two 3-day trial blocks. A subsequent trial that entailed reducing the energy content of an *ad libitum* diet by 25% for 12 days, though the use of NNS, revealed energy intake stabilized at 85% of baseline (52). However, baseline intake in this group was approximately 15.9MJ/d, raising questions about the ecological validity of the trial. Thus, these data suggest covert introduction of NNS can lead to a reduction of energy intake over days, but with uncertain sustainability. The covert manipulation and controlled test setting were appropriate for the hypotheses under study, but left open questions about extrapolation of the data to free-living individuals who largely know when they are consuming products with NNS.

In partial response to these concerns, a later three arm, cross-over design study monitored the energy intake and body weight of 30 free-living, normal weight, males and females who were provided 1150 g/d of soda with NS, NNS or no soda, each for three weeks (60). Relative to the no soda condition, daily energy intake rose significantly with NS and declined with the NNS. However, poor dietary compensation for beverages with different energy sources has been reported (61) so attributing the effects to sweetness or sweetener is not possible. This concern was addressed in another cross-over design trial that monitored the intake of 14 free-living males for two 10-day periods when they were provided three meals per day containing

sucrose sweetened beverage and solid food products or counterparts containing NNS (aspartame and acesulfame K) (53). For the 10 participants ingesting NS followed by products with NNS, energy intake was consistently lower with the NNS intervention, although it still averaged about 12.41MJ/d. Mean dietary compensation was approximately 42%, but was marked by high individual variability with responses ranging from reverse compensation to about 90%.

A more recent trial (62), examined the effects of a 10-week intervention where overweight males and females were required to consume specific minimum amounts of sucrose or NNS products daily, but otherwise intake was *ad libitum*. In the sucrose group, 70% of sugar was provided via beverages and in the NNS group, the value was 80%. The diets provided 3.4MJ of sucrose/d or 1.0MJ of NNS products/d. Mean energy intake rose in the sucrose group by approximately 1617 kJ/d (16.4%) and declined by 439 kJ/d (4.8%) in the NNS group. There was a significant group difference, but the change in energy intake of the NNS group over the trial was not statistically significant.

Thus, short-term trials of NNS consumption provide mixed evidence for reduced energy intake, while longer-term trials consistently indicate their use results in incomplete compensation and slightly lower energy intake. The latter studies are arguably the more nutritionally relevant. These conclusions are consistent with those of prior reviewers (9,23,24,26–29,45,63).

NNS and BMI

The primary interest in effects of NNS on feeding is based on the assumption that a stimulatory effect will result in weight gain or reduced weight loss in those attempting to lose weight. The pendulum of concern about the contribution of NNS use on body weight has made a full cycle in the past two decades. The potential for NNS consumption to promote weight gain drew attention in 1986 based on findings from an American Cancer Society (ACS) survey conducted over one year with 78,694 women 50–69 years of age (64). After controlling for initial body weight, those who used NNS were significantly more likely to gain weight than non-users. However, the authors noted that mean weight changes differed by less than two pounds between users and non-users, so no conclusion was actually drawn regarding long-term effects on weight change. Despite the conservative interpretation of the data, the hypothesis generated considerable debate. Although some additional supporting data were published (65), the noted shortcomings in the ACS data (66) and proposed alternative explanations of the findings (e.g., the association was equally well explained by reverse causality) combined with the publication of data from shorter-term [i.e., 10 days (53); 3 weeks (60); 10 weeks (62); 12 weeks (58); 16 weeks (67)] intervention trials that failed to support the original hypothesis, allayed concerns. Inverse associations were also reported in some observational studies (68).

The largest intervention trial with NNS aimed to promote weight loss through substitution of NNS for sucrose in the diet (69). A sample of 163 adults participated in a 3-week run-in, 16-week intervention, 1-year maintenance, and 2-year follow-up. At the end of the intervention, there was no difference in weight loss between groups using and avoiding aspartame, but the former group better maintained the loss during the subsequent 2 years. While the reports of Stellman and Garfinkel (1986) and Blackburn (1999) are often cited as support for antithetical views about the role of NNS in weight loss, in fact, they draw essentially the same conclusions. The former group stated, “These data do not support the hypothesis that long-term AS [aspartame] use either helps in losing weight or prevents weight gain.” While the latter stated, “… the use of aspartame-containing foods and beverages is as effective at promoting weight loss as the same diet, exercise, and behavior program devoid of aspartame-containing products.” This lack of clear evidence for efficacy or exacerbation of weight gain, coupled with increasing concern about the role of fat in the diet, diverted attention away from the issue.

However, with the popularity of higher fat diets and renewed implication of carbohydrate in obesity incidence and prevalence during the late 1990's and early 2000's, attention was again focused on a role for NNS. Since this reversal, no new large scale intervention trial has been published and, as before, the recent observational evidence has failed to clarify the issue. An analysis of data from the Nurses Health Study (70), which had previously suggested a direct association between NNS use and body mass index (BMI) (71), noted no differences in risk of weight gain with long-term consumption of soda with NNS and those who increased intake had a lower weight gain than those decreasing use. In contrast, findings from the San Antonio Heart Study indicate there is a direct relationship. This trial recruited 5,158 adults and completed 3,682 (74%) between 1979 and 1988 (72). After controlling for baseline BMI, age, ethnicity, gender, years of education, and socio-economic status, a dose response relationship was noted between NNS beverage consumption and the incidence of overweight/obesity among individuals with baseline BMI <25 kg/m^2 as well as those with baseline BMI <30 kg/m^2. Significantly elevated odds ratios were noted for individuals consuming 11–21 or ≥22 NNS beverages per week (1.60 and 1.79 in the former group and 1.92 and 2.08 in the latter group). The mean BMI gain was 1.47kg/m^2 in the combined group of NNS users and 1.01kg/m^2 in nonusers. NNS use and BMI gains were higher in dieters (1.97 kg/m^2) than non-dieters (1.26kg/m^2) that used NNS beverages, although the rise among non-dieters was still significant. While reverse causality remains a likely explanation for a portion of the findings, changes noted for non-dieting, normal weight individuals fits less well with this interpretation. Whether these findings hold when total NNS use is considered is an important question. Limiting analyses to NNS beverage use may bias the data towards significant effects as this is a medium more consistently associated with NNS augmentation of appetite and intake (27).

Thus, intervention trials consistently fail to document that NNS promote weight gain and observational studies provide only equivocal evidence that they may. Reflecting these findings, conclusions from prior reviews are ambivalent about a contribution of NNS to weight gain (9,23,24,26–29,45,63). Nevertheless, concern about their use persists. This is fueled by existing and evolving evidence for plausible mechanisms. They appear to be afforded greater weight given the noted methodological difficulties in documenting associations between NNS use, feeding, and BMI. Thus, a critical examination of commonly evoked mechanisms linking NNS to appetite and feeding should help clarify the issue.

Mechanisms by which NNS may aid in weight management

NNS have been introduced into the food supply to achieve several aims. From an economics perspective, NNS may be less expensive than NS and supplies are more reliable, resulting in reduced product cost, hence profitability to the food industry (73). NNS may also yield products with desirable sensory properties (74) not easily achieved with NS and thereby increase product sales. Health considerations are also a driving force. NNS provide greater food choice to diabetic individuals attempting to moderate their ingestion of NS. They also provide options to healthy consumers interested in limiting NS consumption for reasons unrelated to energy balance (e.g., dental health, behavioral disorders), although, clearly, concerns have been voiced about the health effects of NNS use as well. Perhaps the most widely recognized function of NNS in the food supply is to help maintain the palatability of foods reduced in energy and, as a consequence, aid weight management.

On a metabolic level, there are no data indicating intrinsic properties of NNS modify energy balance independently of their influence on macronutrient and energy intake. With respect to the former, if it is assumed that substitution of NNS for NS only results in decreased carbohydrate intake, the fat and protein to carbohydrate ratios of the diet would increase. While weight loss is achievable on energy restricted diets of varying macronutrient composition (75), recent evidence supports the efficacy of an unrestricted diet with elevated fat and protein

to carbohydrate ratios (76,77). However, the degree to which NNS may contribute to this macronutrient shift is not established and could be low in free-living individuals where trends indicate NNS are commonly used as dietary additions rather than substitutes for NS (2). The preponderance of research on NNS and weight management has focused on their ability to promote negative energy balance through maintenance of the appeal and consumption of an energy diluted food. It is an uncontested maxim that, with free choice, consumers will not purchase or consume products on a chronic basis that do not meet their sensory expectations.

Mechanisms by which NNS may stimulate appetite Cephalic Phase Stimulation

Neurally-mediated physiological responses to sensory stimulation reportedly prime the body to optimize the digestion of foods and the absorption and use of the energy and nutrients they yield (78–80). There are hypotheses that lack of activation of cephalic phase responses may increase the risk of obesity (81). Conversely, others hypothesize that activation of cephalic phase responses, through eating in general (82,83) or exposure to sweet items in particular (84), will be problematic by stimulating appetite and intake. One proposed mechanism for the latter view entails a NNS exposure effect on insulin secretion and glucose metabolism. However, supportive evidence is lacking. An independent effect of sweetness stimulation on insulin release in humans has been reported in some studies (85,86), but not others (87–90). This may be due, in part, to sweetener differences in effectiveness since a cephalic phase insulin response (CPIR) has been reported in humans with glucose and saccharin (86,87) but not with aspartame (88,90–92).

Still, if sweet exposure provided through a NNS does prompt a rise of insulin, it cannot be assumed this will enhance hunger. Elevated levels of insulin in the brain decrease feeding in animals and hunger responses in humans do not track insulin concentrations during euglycemic clamp studies (93). Clamp studies also show that hunger does not track glucose concentrations. However, if glucose was an appetitive signal, a decline of hunger due to NNS stimulation of insulin is unlikely because the CPIR moderates glucose excursions (94,95) rather than augmenting swings. Moreover, there are other cephalic phase responses that could counter mechanisms promoting hunger. For example, the thermogenic response, particularly to palatable stimuli (96), is associated with reduced hunger (97), although not consistently (98). As with the CPIR, this response may not be elicited by all sweeteners [e.g., aspartame (99)]. Taken together, there is inadequate support that NNS stimulate hunger via cephalic phase responses.

Nutritive and osmotic effects

The stomach provides primarily volumetric-based appetitive signals whereas the intestines are more responsive to nutrient cues (100,101). However, these properties are not absolute as there are intestinal osmoreceptors and gastric chemoreceptors (102). Gastric distention promoted by mechanical inflation of a balloon (103,104) or nutritive fill (41,105) is associated with enhanced satiety. Within a beverage type, those containing NS have higher energy content and osmotic load (106). Beverages of higher energy density empty from the stomach more slowly (102,107), independent of osmotic effects (108,109). Similarly, the gastric emptying rate is reduced with higher osmotic challenges (110–112) independently of energy content (113). Activation of both gastric stretch and intestinal nutrient signals results in synergistic effects on satiety (101,114). Consequently, beverages with NNS may be hypothesized to weaken satiety properties associated with NS. However, the absolute importance of these properties is uncertain.

The osmotic effects on gastric emptying are transient. Within 30 minutes of ingestion of beverages with marked differences in osmotic load, emptying rates equilibrate as the greater gastric volume generated by the high osmotic load itself promotes increased emptying (113). Further, nutritive effects are inconsistent. Sucrose empties from the stomach more quickly than an iso-energetic load of maltose, yet the former results in greater fullness (41). Also an iso-energetic and iso-osmotic load of fructose empties more quickly than a load of glucose (115). Thus, the nature of the sweetener is also a factor. Ultimately, the gut is only one source of a highly redundant matrix of appetitive signals and its contribution may be over-ridden by cognitive, sensory, metabolic, and other sources of input (116). Long-term gastrectomized individuals differ little from healthy controls in appetitive sensations and food intake regulation (117). Thus, changes in the osmotic and nutrient properties of foods and beverages through substitution of NNS for NS would not be predicted to enhance hunger or diminish satiety.

Gut peptide response

Dietary macronutrients are differentially effective at stimulating the release of gut peptides. Carbohydrate is an adequate stimulus for secretion of glucagon-like peptide -1 (GLP-1) (118–120), a potent incretin and satiety factor (121,122). Failure of a NNS to elicit the release of such peptides could theoretically result in lower satiety and augmented energy intake. Recent evidence suggests receptors with properties similar to sweet taste receptors on the tongue are present in the GI tract and involved in GLP-1 release (123). The NNS sucralose is a ligand for the gut receptor and elicits GLP-1 secretion (123). However, just as aspartame was not an effective elicitor of cephalic phase responses, it also is not effective for GLP-1 secretion (124). Thus, with these data, the hypothesis that NNS will be less effective stimuli for carbohydrate responsive satiety hormones is uncertain. There may be compound specificity in responsiveness.

Palatability

A primary motivation to add NNS to foods or beverages is to enhance their palatability. Often they are added to improve the acceptability of low or energy–reduced foods or diets with the aim of increasing their intake over more energy-dense versions. NNS may also be added to items with real or perceived health benefits independent of their energy content (e.g., high fiber or nutrient fortified foods) or with desired physiological effects (e.g., caffeinated products) to promote intake. In any case, the assumption is that palatability stimulates hunger and/or reduces satiation/satiety and thereby facilitates intake. However, support for this view is very limited. One report noted hunger increased in anticipation of eating a preferred food (125), but most trials have monitored appetite within an eating occasion. As reviewed previously (126), greater palatability has been associated with augmented (125,127), unchanged (128), or diminished (129,130) hunger after controlling for intake. Studies monitoring appetitive effects beyond the meal (e.g., rebound hunger) have also yielded mixed findings (125,130–132). Thus, there is inconclusive evidence that palatability influences appetitive sensations. Part of the explanation may be that the relationship is not static and with repeated exposures to a food, its hedonic tone changes (133). Generally, the acceptability of less palatable foods improves with familiarity.

Mechanisms by which NNS may enhance energy intake or balance

NNS substitution for NS may increase fat intake

Strictly replacing NS with NNS will, by definition, result in a higher proportion of energy from fat in the diet. Less straightforward are claims that NNS use may preferentially stimulate an absolute increase of fat intake. Based on mathematical modeling, a reduction of 20 grams of NS in core foods through the substitution of NNS would shift food choice and result in an increase of 10 g of fat and 6 g of protein in the diet. From an energy balance perspective, this

leads to little change (about 100kJ), but there are data suggesting the energy from iso-energetic diets that are higher in fat may be more efficiently used (134,135). It is important to emphasize two points in this model: first NNS are substituted for NS rather than being added to the diet; and second, the substitutions are made in core foods that provide energy from fat and/or protein as well. Given the increased use of NNS has not been accompanied by a reduction of NS, as documented elsewhere (1,46), the assumption that NNS are used as a substitute for NS likely does not hold. Second, the replacement of foods providing energy only in the form of sugars, such as sodas, would not influence the intake of other macronutrients.

Intervention trials provide limited support for the modeling prediction of increased fat intake and they do not confirm an impact on body weight. In a metabolic ward study (52), covert reduction of NS intake, by substitution with NNS, prompted energy compensation and an 18% increment in fat relative to baseline. However, total energy intake remained at only 85% of baseline suggesting the increment in fat would not pose a threat to weight gain. In a short-term trial with free-living adults, the substitution of NNS for NS, accounting for a 2092kJ/d energy reduction, resulted in an 11% increase in fat intake over 10 days (53). However, mean total energy compensation was only 50% so participants still consumed less energy than baseline and, again, an adverse effect on body weight would not be predicted. Several acute feeding trials, testing the effects of beverages containing NNS or NS on intake, noted no significant changes of dietary fat or energy intake (55,136). A 4-week intervention where adults were provided supplementary beverages containing either NS or NNS revealed no change of fat intake with either beverage. Additionally, NNS use for 10 weeks in free-living adults was not accompanied by significant shifts of macronutrient or energy intake or body weight (137). Taken together, published evidence does not indicate that NNS use leads to increased fat consumption resulting in greater energy intake. An enhanced efficiency of energy use with a higher proportional fat composition of the diet would likely be offset by incomplete energy compensation.

Informed use leads to over compensation

Nutrient labeling allows consumers to make informed decisions about the nutritive quality of their diet, but this may be counter-productive if the information is not correctly interpreted. Labeling foods as lower in energy could lead consumers to alter their feeding behavior and paradoxically increase energy intake. This may occur if the expected savings in energy attributed to the substitution of an energy diluted product is greater than any subsequent indulgence rationalized by the prior savings. This may also hold if information about an energy reduction leads to the mistaken belief that such products may be added to the diet without consequence. Acutely, beliefs about the energy content of foods may exert stronger effects on hunger than their true energy value (138) and coupling knowledge of energy loading with activation of digestive processes augments satiety responses relative to physiological challenges alone (139). Short-term studies have yielded mixed data on expectations and intake. In one crossover trial (140), participants ingested breakfast cereals that contained no sweetener, sucrose, or aspartame. The sweet versions were matched on energy, sweetness, and palatability. Half of the participants were informed about the sweetener used and half were not. Informed aspartame use was associated with a non-significant, but noteworthy, increase of total daily energy intake. Compared to informed sucrose use, the increment was 937kJ/d and with uninformed aspartame use, the increment was 791/d. However, other work has failed to observe this effect (55,141,142). In a long-term trial where participants were motivated to maintain weight loss, NNS use was associated with lower weight re-gain. The importance of this mechanism remains poorly characterized. It is not specific to sweeteners or sweetness. Indeed, more pronounced effects may occur with manipulated expectations of fat content (143,144) where small errors lead to larger energy differences due to the higher energy density of fat. In

this instance, the purported problem stems from an inappropriate use of NNS rather than an inherent problem with such products.

Loss of signal fidelity

Sweetness is inherently pleasant (145), but the sensation acquires salience through associative learning. That is, based upon acquired knowledge of the metabolic consequence of ingesting a food through previous exposures, its sensory properties signal information about the impending metabolic challenge posed by ingestion of the item. This allows decisions about what type and quantity of food to eat as well as initiation of an appropriate post-ingestive physiological response (146). Combined, such a homeostatic system contributes to maintenance of energy balance.

NNS, and other means of diluting the energy density of foods, pose a challenge to this system. Repeated exposure to low-energy, NNS foods could lead to a non-cognitive expectation that their consumption would contribute little energy to the diet. Thus, if presented with a higher energy version with similar sensory properties, intake may reflect the expected, rather than the true energy value, leading to greater energy consumption. This has been demonstrated in a recent trial in rats where chow energy intake was higher after ingestion of a pre-meal with a flavor previously paired to a low-energy food compared to when the same preload had a flavor previously paired to a comparable high-energy food (147). There are also preliminary data in humans documenting the effect, albeit not solely through manipulation of sweeteners (148, 149). However, the long-term nutritional consequences of such misguided feeding are uncertain. The frequency of exposures to these conditions is likely to be low and energy compensation may occur at a later time point. Further, associative learning is continuous so each exposure to a food results in a recalibration of the sensory signal's meaning and, as a consequence, its influence on intake.

Another variation on this concept entails repeated pairings between a single sensory property, such as sweetness, and inconsistent metabolic consequences. Here, again the predictability of the signal may be compromised (84,150,151). Recent provocative findings from rat models suggest diminished predictability results in positive energy balance. In one set of studies (152), two groups of rats were provided sweet solutions overnight for 10 nights. In one group, they were sweetened with either 10% glucose or sucrose, so their sweet exposures were consistently paired with energy. The other group received 10% glucose or 0.3% saccharin and, as a result, sweetness was inconsistently associated with energy. This was followed by an acute feeding test where a sweet, chocolate-flavored caloric beverage premeal was consumed followed by *ad libitum* access to chow. While intake of the sweet premeal was comparable for both groups, those that received inconsistent pairings consumed more energy from the chow than the group receiving consistent pairings. Thus, when a sensory cue such as sweetness, lacks predictive power, energy regulation is disrupted and is biased towards positive balance. The longer-term implications of this acute trial were demonstrated in a subsequent 5 week study (151). The rats receiving inconsistent training consumed more energy, gained more body weight and more body fat due to a weaker dietary compensation response. It is unclear whether these findings can be extrapolated to humans who eat a more varied diet and where non-nutritively sweetened foods may be ingested concurrently with high energy foods (e.g., diet soda with a hamburger, non-nutritively sweetened coffee with pie). Under such conditions, associative learning would be considerably more complicated and subtle (e.g., will signal veracity be compromised if a meal contains 4184kJ versus 5021kJ by the substitution of a NNS beverage for one with a NS)?

Beverages sweetened with NNS are most commonly consumed with food (47). Other recent evidence indicates that learning does occur in humans, but is counter to predictions from the

animal studies (153). Participants reported consuming beverages containing NNS alone on at least some occasions, so their energy-taste associations would be inconsistent. In short-term tests, participants failed to report increased appetite or energy intake in response to NNS exposure whereas NNS non-users reported heightened appetite and energy intake following such stimulation. These findings indicate inconsistent NNS exposure (paired or not paired with energy) from beverages results in blunted responses to their consumption and no elevation of risk for weight gain. However, this work explored only one source of exposure, beverages, and short-term, one day, responses. The implications of chronic, widespread use of NNS on taste-energy associations and their influence on appetite and feeding are questions open to study.

Water effects

Given that a high proportion of NNS are consumed in beverage form (see Table 2), effects of hydration state on feeding are relevant. A reciprocal association between food and water intake is widely recognized. Animals reduce food intake when water restricted, and reduce water intake when food deprived (154). Similar responses are observed in humans (155). However, hydrational effects on feeding are also apparent in animals provided *ad libitum* access to food and water (156). This relationship prompted an early hypothesis that obesity stemmed from excess fluid consumption, independent of energy provided by the fluids (157). That is, drinking begets eating. Approximately 75% of beverage consumption is peri-prandial (47). Drinking may facilitate eating by numerous mechanisms including dilution or buffering of intense and/or irritating stimuli, thereby improving food palatability (158), and aiding deglutition (159, 160). The hypothesis is that drinking may initiate eating events to address the osmotic challenge posed by hypotonic beverage ingestion. There has been considerable research on feeding induction of drinking, but much less on the reverse (161–163). Whether NNS stimulate drinking and, as a consequence, compensatory eating, has not been adequately evaluated.

Activation of reward systems

The concept of reward in feeding is difficult to define (164), and is proposed to be multi-faceted with elements of liking, wanting, and learning (165). Sweetness is a prototypical stimulus to document each of these elements (166). There is increasing recognition that reward systems activated by the anticipation and actual act of feeding interact with, and may dominate, appetitive systems in modulating food and beverage consumption (166–168). One way to operationalize reward is to document effects of sensory exposures on its neural substrates. Sweetness is an effective stimulus for the release of mediators of reward such as dopamine (169–171) and opioids (172,173) that may stimulate food intake. However, the view that sweet foods are preferred and consumed because of the activation of these systems is only one proposed mechanism. Higher intake may also be due to a lack of responsiveness of these systems (171,174). Thus, over-eating can stem from a lower reward value of foods or motivation to seek them (175,176).

Recently, it was proposed that these phenomena co-exist (171), but it may also be argued that the data are presently more descriptive than mechanistic. Behaviorally, common experience indicates that food palatability can initiate eating in the absence of energy need and increase energy intake within a meal (125,127,177–179). Reduced palatability during a meal is not a primary determinant of its termination (180). While there is no evidence NNS are uniquely able to stimulate feeding acutely, their addition to an energy-yielding food or meal has been associated with greater intake (45,181,182). The effect is magnified if intake occurs when individuals are hungry (179) and persists, albeit to a lesser degree, in a state of higher satiety (183). Whether longer term intake is increased by this mechanism is not established. With repeated exposure, less palatable foods gain acceptability and intake can match initially

preferred items (133). Similarly, palatability may decline for foods with high hedonic quality with frequent exposure (184,185).

Individuals with heightened reward sensitivity may be at particular risk for palatability driven feeding as preliminary evidence indicates this characteristic is directly related to food intake and BMI (170,186). However, it cannot be assumed that obese individuals derive greater pleasure from foods (168,187). Indeed, some work indicates there are no differences between lean and obese individuals (188,189) or that the former actually provide higher hedonic ratings to a standard list of foods (190). The evidence may be stronger that obese individuals express a stronger desire, “wanting” to eat than pleasure, “liking” from doing so (191).

The importance of post-ingestive learning in establishment of food preferences has been well documented (192) and often attributed to flavor cues. However, recent findings raise questions about the role of sweet taste in reward-mediated feeding. The neural substrates of reward are also activated in sweet-blind ($trpm5^{-/-}$ knock-out) mice due to the energy provided by sucrose (193). In this model, NNS is not as effective at stimulating dopamine release, or either flavor conditioning or promoting intake. Existing evidence does not support nor refute a role for NNS enhanced palatability on reward motivated feeding.

Training the palate: learning to like the familiar

There is an old adage that ‘we like what we eat more than eat what we like’. This statement highlights the fact that while there are inherently pleasant (e.g., sweetness) and unpleasant (e.g., bitterness) sensations (194–196), their influence on ingestive behavior is commonly overwhelmed by learned flavor preferences (197,198). This is best exemplified by the wide variety of cuisines in a global population with largely common inherent hedonic predilections. A primary mechanism by which flavor preferences are entrained is through repeated exposure. This phenomenon has been most clearly described for salt and fat. Observational data indicate there is a direct association between customary salt intake and the preferred concentration of salt in food (199). Some evidence suggests a more specific association between use of discretionary salt and intake (200) which underscores the contribution of sensory exposure. Experimentally, the required addition of salt to food, which increases sensory exposure to the taste, leads to a preference for higher levels of salt in food (201). In contrast, no hedonic shift occurs when adding the same quantity of salt to the diet via capsule, which matches the metabolic challenge posed by salting food, but without the same sensory exposure.

With the exception of extreme sodium depletion (202), systematic reduction of salt exposure for more than several weeks has the opposite effect (203–205). Similarly, placing individuals on the same reduced-fat diet where one group is deprived of sensory exposure to fats while another is allowed to use fat replacers to simulate continued sensory exposure, leads to a preference for lower fat levels in foods in the former group, but not the latter (206,207). Generally, these hedonic shifts occur without changes of sensitivity to or intensity perception of the sensory qualities and typically require about 8–12 weeks to manifest. With respect to sweetness, several (208–212) although not all (207) observational studies note a significant association between hedonic ratings for sweet items and customary sweetener exposure. Infants repeatedly provided sweetened water early in life exhibit a heighten acceptance of sweetened water at two years of age (208). This preference is not apparent for a novel fruit-flavored beverage, indicating the effect is food specific. However, ethnographic studies suggest learned sweet preferences in children generalize, at least across beverages (209). Broader associations have also been noted between the percent of energy ingested from predominantly sweet foods and beverages and optimal concentrations of sweetness in foods in adults (213). Measures of sweet liking permitted classification of individuals into tertiles of intake of sweet food intakes or percent of energy from predominantly sweet items with 94–100% accuracy. In other work,

the dietary sweetness level, calculated as the gram sum of fructose, sucrose, and alternative sucrose equivalents, correlated with peak hedonic ratings of a fruit-flavored beverage containing graded sucrose concentrations (211). These observations are supported by limited data from a controlled intervention trial where 59 children (mean age 9.2±0.9 years) and 46 young adults (mean age 22±2.0 years) were exposed to a sweetened orange-drink for 8 consecutive days and then tested for their preferred sweetness level of the beverage and a sweetened yogurt (212). A significant increase in preferred sweetness level for the beverage and a trend in this direction for the yogurt were observed in the children, but not the adults. Interestingly, a similar effect was not noted for a comparable manipulation of sourness. However, this may be attributable to the short duration of exposure, as acceptance of novel sweet items is more rapid than acceptance of novel sour items (214).

Collectively, these observations suggest that repeated exposure to a taste or flavor leads to increased acceptance for foods or beverages characterized by the taste or flavor and that the desired intensity of the sensation is directly related to the concentration of the compound responsible for the sensation in dietary items. Further, the sensory property may exert a stronger influence on the preferred concentration of a taste or flavor compound in a food than the metabolic effect of consuming the relevant compound. Thus, repeated exposure to NNS would be expected to establish and maintain a preference for sweet items in the diet. To the extent that NNS are included in energy-yielding items and that the liking for sweetness contributes to intake, their use may be predicted to contribute to energy intake. Generally, there is a direct relationship between hedonic ratings for foods and intake (126). Amelioration of a learned liking for a highly sweetened diet will likely require restricting exposure to sweet foods and beverages, including those that are not significant sources of energy. Such an approach clearly conflicts with one that encourages the use of NNS to dilute the energy content of the diet while maintaining its palatability. It may be that each approach holds merit, but for different sub-sets of the population who are consuming energy from sweet items in excess of need for different reasons (e.g., reward sensitivity, economics).

Inherent liking

There is widespread agreement that sweetness is an inherently pleasant sensation (145,215). However, there is marked individual variability in its behavioral manifestation (183,216). This has prompted exploration of the genetic basis of sweet taste. To date, there is little evidence of a heritable component for the ability to detect or rate the intensity of sweetness and only slightly more support for individual differences in hedonics (217). There are several recent reports of a genetic basis for sugar intake (218,219) that may be mediated by sweetener-sensing mechanisms (220,221). There are receptors in the intestine, analogous to sweet taste receptors (TR1's) in the oral cavity, that increase glucose transport via rapid glucose transporter type 2 (GLUT2) insertion into enterocyte cell membranes when activated by NS and NNS (220). Thus, to the extent that GLUT2 activity is associated with obesity (222), substitution of NNS for NS may offer no health advantages. Identification of a polymorphism of GLUT2 revealed individuals that were Ile carriers had higher intakes of sugars from items such as baked goods and chocolate, but not inherently sweet items such as fruit. This suggests that even if there is an inherent predisposition to ingest sweet items, it will be modulated by non-physiological factors such as food availability, health concerns and custom (223) and, possibly, other inherited traits influencing food choice [e.g., neophobia (224)].

Summary

From an evolutionary perspective, NNS are a novel dietary stimulus that has been introduced to our diets in only the last few decades. Although the safety of approved NNS has been established with respect to acute toxicity and longer-term pathologies (e.g., carcinogenesis),

their influence on appetite feeding, energy balance, and body weight has not been fully characterized. Questions remain regarding effects of both properties of the compounds themselves (e.g., sweet, palatable) and the way consumers choose to use them (dietary additions rather than substitutes). Despite widespread concern about overweight and obesity and the ready availability of NNS for discretionary use and in products, only about 15% of the population ingests them. However, this number is growing so the implications of their use in addressing overweight and obesity requires more complete understanding.

Early acute feeding studies indicate that their inclusion in products that provide little or no energy is associated with heightened hunger, but subsequent work showed that when incorporated into energy-yielding products, this does not occur. Because beverages containing NNS are commonly consumed with foods, augmented hunger may not be a concern. Further, it is unclear that heightened hunger necessarily translates into increased energy intake. Longer-term feeding trials exploring the effects of substitution of NNS for NS in the diet suggest energy compensation is incomplete, resulting in 5–15% reductions of daily energy intake. However, evidence that NNS use in free-living individuals results in improved weight loss or maintenance is lacking. This void has permitted speculation that NNS ameliorate or, more commonly, exacerbate the problem of positive energy balance. A critical review of the literature, addressing the mechanisms by which NNS may promote energy intake, reveals none are substantiated by the available evidence.

There is no clear evidence that NNS augments appetite by activating cephalic phase responses, altering osmotic balance, or enhancing food palatability. Indeed, there is emerging evidence that selected NNS may stimulate the release of satiety hormones, though the link between these hormones and energy intake in free-living individuals is also open to debate. With respect to energy intake, there is no substantive evidence that inherent liking for sweetness or NNS activation of reward systems is problematic. NNS use may result in greater proportional energy contributions from fat, but work on this issue also indicates total energy intake is moderated by NNS and the latter is the dominant factor with respect to body weight. Knowledge of NNS use has been shown to result in energy compensation or even over-compensation in short-term trials, but less so with chronic use. This may be because those who compensate, and therefore fail to achieve weight goals, cease NNS use so only those less susceptible to cognitive influences remain to be evaluated. The concept that NNS use disrupts responsiveness to signals aiding energy balance has been substantiated theoretically, but there is no evidence available to assess the validity of the mechanism in humans. The question of whether drinking is promoted by the appeal and availability of NNS-containing beverages and thus stimulates eating leading to positive energy balance remains unsettled. Use of NNS likely promotes a preference for higher sweetener levels of foods and beverages, but whether this compromises efforts to reduce energy intake has not been explored. Taken together, the evidence summarized by us and others suggests that if NNS are used as substitutes for higher energy yielding sweeteners, they have the potential to aid in weight management, but whether they will be used in this way is uncertain. This will require additional information about NNS use patterns, clarification of remaining potential counter-productive mechanisms, and long-term randomized, controlled trials in free-living populations.

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Table 1

Date of discovery and approval of currently marketed NNS and their Acceptable Daily Intakes (ADI).

Sweetener	Year Discovered	Year Approved for Use in Foods	JECFA ADI (mg/kg body weight)	EFSA ADI (mg/kg body weight)	FDA ADI (mg/kg body weight)	NFI DVFA (mg/kg body weight)
Acesulfame - K	1967	1988	15	9	15	40
Aspartame	1965	1981	40	40	50	15
Cyclamate[a]	1937	1958	111	7	NA	11
Saccharin	1879	1977	5	5	5	5
Sucralose	1976	1998	15	15	5	15
Neotame	1965	2002	0–2	1	18	

Note: Joint Commission of Experts on Food Additives (JECFA) of the World Health Organization and the Organization of Food and Agriculture; European Food Safety Agency (EFSA); Food and Drug Administration (FDA) Acceptable Daily Intake(ADI); National Food Institute (FDI) Danish Veterinary and Food Administration,(DVFA).

[a]Cyclamate has been banned in the United States since 1969.

Table 2

Trends in consumption of foods and beverages with either added nutritive sweeteners (NS)[#] or non-nutritive sweeteners (NNS) among Americans ≥ 2 years[*]

Year	Foods Containing Added NS			Foods Containing NNS		
	Grams per capita	% of pop. Consuming	Grams per consumer	Grams per capita	% of pop. Consuming	Grams per consumer
Beverages						
1965	190	41.1	455	10	2.5	368
1977	242	49.5	491	22	4.8	417
1989–91	302	50.5	581	71	10.1	546
1999–2000	599	67.6	881	109	9.1	736
2001–2002	568	66.2	857	108	9.4	711
2003–2004	585	66.6	872	129	10.8	752
Foods						
1965	396	94.2	398	1	0.8	60
1977	352	95.4	357	1	3.8	23
1989–91	376	94.3	383	7	3.2	204
1999–2000	381	90.0	388	19	4.9	305
2001–2002	357	89.9	363	15	5.2	232
2003–2004	375	90.3	381	17	5.8	233
Total						
1965	586	94.3	589	11	3.3	304
1977	594	95.8	599	23	8.0	258
1989–1991	677	95.5	683	78	12.7	493
1999–2000	979	91.6	987	128	12.9	658
2001–2002	924	91.2	931	123	13.5	619
2003–2004	960	91.5	963	146	15.1	663

[*] Utilizing the Nationwide Food Consumption Surveys for 1965, 1977–78, and 1989–91 and the NHANES for 1999–2000, 2001–2, and 2003–4. The results are all weighted to be nationally representative.

[#] Nutritive sweeteners include a wide variety of monosaccharides (glucose and fructose) and disaccharides (sucrose and saccharose), which exist either in a crystallized state as sugar or in thick liquid form as syrups. Included in sweeteners are maple sugar and syrups, caramel, golden syrup, artificial and natural honey, maltose, glucose, dextrose, isoglucose (also known as high-fructose corn syrup), other types of fructose, sugar confectionery, and lactose.