

Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms^{1–3}

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ABSTRACT

Nonnutritive sweeteners (NNS) are ecologically novel chemosensory signaling compounds that influence ingestive processes and behavior. Only about 15% of the US population aged >2 y ingest NNS, but the incidence is increasing. These sweeteners have the potential to moderate sugar and energy intakes while maintaining diet palatability, but their use has increased in concert with BMI in the population. This association may be coincidental or causal, and either mode of directionality is plausible. A critical review of the literature suggests that the addition of NNS to non-energy-yielding products may heighten appetite, but this is not observed under the more common condition in which NNS is ingested in conjunction with other energy sources. Substitution of NNS for a 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 occurs are not supported by the available evidence, although some warrant further consideration. Resolution of this important issue will require long-term randomized controlled trials. *Am J Clin Nutr* 2009; 89:1–14.

INTRODUCTION

The intake of nutritive sweeteners (NS) has increased markedly in the United States and globally over the past 3 decades, coincident with the increased incidence and prevalence of overweight and obesity (1). This has prompted considerable research on the role of NS 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 the 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 nonnutritive sweeteners (NNS) for NS in products and discretionary applications. The success of this approach is open to debate and requires resolution to determine the best clinical practices and public health recommendations. This review describes recent

trends in the use of NNS 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 NNS and energy balance, we critically reviewed the reported mechanisms by which they may exert their effects on these outcomes.

Currently, 5 NNS are approved by the US Food and Drug Administration (FDA): saccharin, sucralose, aspartame, acesulfame-K, and neotame. In addition, stevia, an herb extract of intense sweetness, is used in limited applications. Although 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, which mimic certain sensory properties (ie, 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 was banned in the United States in 1969 because of evidence that high concentrations in the diet were associated with bladder cancer in rats. Subsequent review of the evidence has raised questions about the physiologic relevance of the trials, but the sweetener remains unapproved in the United States. Cyclamate is approved for use in the European Union and in more than 100 countries.

There are published safety standards for the consumption of NNS. For example, the US FDA, the Joint Commission of Experts on Food Additives (JECFA) of the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the European Food Safety Agency (EFSA) have

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² Supported by PHS grant no. 1 R01 DK 063185 and the USDA HATCH grant 0172514/INDO0840-55 (to RM) and grants R01-HD39183, R01-HD041375, and R01 HD030880 (to BP).

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Received August 6, 2008. Accepted for publication October 22, 2008.

First published online December 3, 2008; doi: 10.3945/ajcn.2008.26792.

TABLE 1Date of discovery and approval of currently marketed nonnutritive sweeteners (NNS) and their Acceptable Daily Intake (ADI)¹

Sweetener	Year discovered	Year approved for use in foods	JECFA ADI	EFSA ADI	FDA ADI	NFI DVFA
			mg/kg body wt	mg/kg body wt	mg/kg body wt	mg/kg body wt
Acesulfame-K	1967	1988	15	9	15	40
Aspartame	1965	1981	40	40	50	15
Cyclamate	1937	1958	111	7	NA ²	11
Saccharin	1879	1977	5	5	5	5
Sucralose	1976	1998	15	15	5	15
Neotame	1965	2002	0–2	1	18	

¹ JECFA, Joint Commission of Experts on Food Additives of the World Health Organization and the Food and Agriculture Organization; EFSA, European Food Safety Agency; FDA, Food and Drug Administration; DVFA, Danish Veterinary and Food Administration; NA, not available.

² Cyclamate has been banned in the United States since 1969.

established Acceptable Daily Intakes (ADIs) (Table 1). The FDA estimates the ADI equivalents to be 18–19 cans (1 can = 12 oz, or 355 mL) of diet cola for aspartame, 9–12 packets of sweetener for saccharin, 30–32 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. Because 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. A few studies directly measured the amounts of NNS in foods, specifically in 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 because each product has different properties. Others in small selected samples have published overall NNS consumption but not the content of NNS 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 article, 2 methods were used to identify foods that contain NNS: 1) a method based on an earlier toxicity study (17) that identified aspartame-containing foods was used to locate these same foods in the US nutrient monitoring system food-composition tables and 2) keyword searches were conducted using food descriptions 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 by using the USDA food-composition table to eliminate items with names that did not match their content.

Foods were initially grouped by 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 (ie, the “soda” food group was divided into “soda, with sugar” and “soda, with nonnutritive sweetener” food groups).

An estimate of foods with NNS are shown in **Table 2**. The added foods and beverages with NS were readily measured and represent the total grams of food consumed for all Americans aged ≥ 2 on a per capita daily intake. 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. More than 66% of Americans consumed these beverages, and the mean amount (g) 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 g.

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 (Table 2). Overall, only 15.1% of all Americans indicated that they consumed any food or beverage with NNS added in 2003–2004. The amount per consumer for the beverages containing NNS was 752 g (26.2 oz) or just 120 g below that for NS beverages. Of the foods with NNS, the amount consumed per capita was 233 g. Assuming that the products containing NNS had the same level of sweetness as the products containing NS, NNS add the equivalent of $>60\%$ of the sweetening contributed by NS. This corresponds to 53 g/d (or 862 kJ/d) of sweetener for the average American aged ≥ 2 y.

The consumption trends for foods and beverages containing NNS are clearly increasing, but are different between categories. The proportion of consumers ingesting NNS in beverages remained relatively stable between 1989 and 2004 (6.9% increase), whereas the proportion of consumers of NNS in foods increased 81.2%. However, in 2004, this still represented only 5.8% of the population aged ≥ 2 y. The amount of NNS ingested in beverages and foods by consumers of NNS 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 might be overestimated. The literature shows an underestimation of less healthy, more energy-dense foods and an overestimation of healthier ones (19–22). Following this logic, it is possible that amounts per consumer are also overestimated.

ASSOCIATION BETWEEN CONSUMPTION OF NNS 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). Although these authors represent different disciplines

TABLE 2Trends in consumption of foods and beverages with either added nutritive sweeteners (NS) or nonnutritive sweeteners (NNS) among Americans aged ≥ 2 y¹

Year	Foods containing added NS ²			Foods containing NNS		
	Intake per capita	Percentage of population	Intake per consumer	Intake per capita	Percentage of population	Intake per consumer
	g	%	g	g	%	g
Beverages						
1965	190	41.1	455	10	2.5	368
1977	242	49.5	491	22	4.8	417
1989–1991	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
1989–1991	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

¹ Based on the Nationwide Food Consumption Surveys for 1965, 1977–1978, and 1989–1991 and the National Health and Nutrition Examination Survey 1999–2000, 2001–2002, and 2003–2004. The results were weighted to be nationally representative.

² NS included a wide variety of monosaccharides (glucose and fructose) and disaccharides (sucrose and saccharose) that 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.

and are supported by various funding agencies, the consistencies in their findings are striking.

NNS and appetite

Although there have been 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 postingestive hunger. However, a study of comparable design, using sodium chloride in soup replicated the findings, which suggests that 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, which indicates 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 that the 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. The

doses of aspartame were similar in trials, regardless of whether effects were observed. With the addition of this evidence, later reviews consistently concluded that NNS have little effect on appetite (26, 29, 45).

Evidence that NNS promote 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 that 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 increase in hunger. Furthermore, if an increase in hunger is elicited, the question arises as to whether this translates into increased energy intake.

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

NNS and energy intake

On the basis of 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 in energy intake. The authors noted that their findings were predicated on

substitution rather than addition of reduced carbohydrate products. Whereas controlled feeding trials, in which sugars were replaced with NNS, have yielded mixed support for the model's predictions (52, 53), a test in free-living populations has not been conducted 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 2 decades (2). Indeed, the contribution of carbohydrate as a percentage of energy intake has also increased (1, 46).

There are reports from controlled trials in humans of enhanced energy intake after ingestion of a sweetened, non-energy-yielding beverage (54–57). However, the preponderance of evidence indicates that NNS exert no short-term effect on energy intake (28, 35, 58). Longer-term feeding trials generally indicate that the use of NNS results in no change or a reduction in energy intake. For example, early feeding trials conducted in a metabolic ward indicated that the substitution of NNS for NS during 3-d blocks resulted in incomplete energy compensation, as intake was 14–23% lower than baseline (59). When the sucrose-sweetened products were reintroduced, energy intake exceeded baseline by 7.4% and 5.3% in the next two 3-d trial blocks. A subsequent trial that entailed reducing the energy content of an ad libitum diet by 25% for 12 d, through the use of NNS, showed that energy intake stabilized at 85% of baseline (52). However, baseline intake in this group was ≈ 15.9 MJ/d, raising questions the ecological validity of the trial. Thus, these data suggest that the covert introduction of NNS can lead to a reduction in energy intake over days, but with uncertain sustainability. The covert manipulation and controlled test setting were appropriate for the hypotheses under study, but left unanswered questions about the 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 subsequent 3-arm crossover 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 or NNS or no soda, each for 3 wk (60). Relative to the no-soda condition, daily energy intake rose significantly with NS and declined with NNS. However, poor dietary compensation for beverages with different energy sources has been reported (61); therefore, it is not possible to attribute the effects to sweetness or to the sweetener. This concern was addressed in another crossover study that monitored the intake of 14 free-living males for two 10-d periods, during which they were provided 3 meals/d containing sucrose-sweetened beverages 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 ≈ 12.41 MJ/d. Mean dietary compensation was $\approx 42\%$, but was marked by high individual variability with responses ranging from reverse compensation to $\approx 90\%$.

A more recent trial (62) examined the effects of a 10-wk intervention in which 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; in the NNS group, the value was 80%. The diets provided 3.4 MJ sucrose/d, or 1.0 MJ of NNS products/d. Mean energy intake rose in the sucrose group by ≈ 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 in the NNS group over the trial was not statistically significant.

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

NNS AND BMI

The primary interest in the 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 2 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 1 y in 78,694 women 50–69 y of age (64). After adjustment for initial body weight, those who used NNS were significantly more likely to gain weight than were nonusers. However, the authors noted that mean weight changes differed by < 2 lb (≈ 0.9 kg) between users and nonusers, so no conclusion was actually drawn regarding the 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 (eg, the association was equally well explained by reverse causality) combined with the publication of data from shorter-term [ie, 10 d (53), 3 wk (60), 10 wk (62), 12 wk (58), and 16 wk (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-wk run-in, 16-wk intervention, 1-y maintenance, and 2-y 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 y. Whereas the reports of Stellan and Garfinkel (64) and Blackburn (67) are often cited as support for antithetical views about the role of NNS in body weight regulation; they, in fact, 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,” whereas 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 of efficacy or exacerbation of weight gain, coupled with the 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 1990s and early 2000s, attention 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 previously suggested a direct association between NNS use and body mass index (BMI; in kg/m^2) (71), noted no differences in risk of weight gain with long-term consumption of soda with NNS; those with an increased intake had a lower weight gain than did those with decreasing use. In contrast, findings from the San Antonio Heart Study indicate a direct relation. This trial recruited 5158 adults, 3682 (74%) of whom completed the study between 1979 and 1988 (72). After adjustment for baseline BMI, age, ethnicity, sex, years of education, and socioeconomic status, a dose-response relation was noted between NNS beverage consumption and the incidence of overweight or obesity among individuals with a baseline BMI <25 as well as those with a baseline BMI <30 . Significantly elevated odds ratios were noted for individuals consuming 11–21 or ≥ 22 beverages containing NNS 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 1.47 in the combined group of users of NNS and 1.01 in non-users. Use of NNS and BMI gains were higher in dieters (1.97) than in nondieters (1.26) that consumed beverages containing NNS, although the rise among nondieters was still significant. Reverse causality remains a likely explanation for a portion of the findings, but changes noted for nondieting, normal-weight individuals fit less well with this interpretation. Whether these findings hold true when total use of NNS is considered is an important question. Limiting analyses to use of beverages containing NNS may bias the data toward significant effects because 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 might. 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 methodologic difficulties in documenting associations between use of NNS, 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 CAN 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 of NNS are more reliable, which results in reduced costs and greater 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 choices to diabetic individuals attempting to moderate their ingestion of NS. They also provide options to healthy consumers interested in limiting consumption of NS for reasons unrelated to energy balance (eg, dental health, behavioral disorders), although, clearly, concerns have been voiced about the health effects of NNS as well. Perhaps the most widely recognized function of NNS in the

food supply is to help maintain the palatability of foods that are low in energy and, as a consequence, aid in weight management.

On a metabolic level, no data indicate that the intrinsic properties of NNS modify energy balance independently of their influence on macronutrient and energy intakes. 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. Although weight loss is achievable with 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, in whom trends indicate that NNS are commonly used as dietary additions rather than as 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 physiologic 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). Some researchers hypothesize 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 an effect of NNS 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 in others (87–90). This may be due, in part, to differences in the effectiveness of sweeteners because 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 NNS does prompt an increase in insulin, it cannot be assumed that it will enhance hunger. Elevated concentrations 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 in hunger due to the stimulating effect of NNS on insulin is unlikely because CPIR moderates glucose excursions (94, 95) rather than augments swings. Moreover, other cephalic phase responses might 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 CPIR, this response may not be elicited by all sweeteners [eg, aspartame (99)]. The results combined do not show adequate 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 a 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, it is hypothesized that beverages with NNS may 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 min 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). Furthermore, nutritive effects are inconsistent. Sucrose empties from the stomach more quickly than an isoenergetic load of maltose, yet the former results in greater fullness (41). Also, an isoenergetic and iso-osmotic load of fructose empties more quickly than does 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 overridden by cognitive, sensory, metabolic, and other sources of input (116). Long-term gastrectomized individuals differ little from healthy control subjects 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 NNS to elicit the release of such peptides could theoretically result in lower satiety and augmented energy intake. Recent evidence suggests that receptors with properties similar to sweet taste receptors on the tongue are present in the gastrointestinal tract and are involved in GLP-1 release (123). 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 is also 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-energy 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 (eg, high-fiber or nutrient-fortified foods) or with desired physiologic effects (eg, 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 that 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 adjustment for intake. Studies monitoring appetitive effects beyond the meal (eg, 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 relation 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

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 use of NNS may preferentially stimulate an absolute increase in fat intake. On the basis of mathematical modeling, a 20-g reduction of NS in core foods through the substitution of NNS would shift food choice and result in an increase of 10 g fat and 6 g protein to the diet. From an energy balance perspective, this leads to little change (≈ 100 kJ), but some data suggest that the energy from isoenergetic diets that are higher in fat may be more efficiently used (134, 135). It is important to emphasize 2 points in this model: 1) NNS are substituted for NS rather than being added to the diet and 2) the substitutions are made in core foods that provide energy from fat and/or protein as well. Given that 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 directly 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 in 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, which suggests that the increment in fat would not pose a threat to weight gain. In a short-term trial in free-living adults, the substitution of NNS for NS, accounting for a 2092-kJ/d energy reduction, resulted in an 11% increase in fat intake over 10 d (53). However, mean total energy compensation was only 50%, so participants still consumed less energy than they did at 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 in dietary fat or energy intake (55, 136). A

4-wk intervention in which adults were provided supplementary beverages containing either NS or NNS showed no change in fat intake with either beverage. Additionally, use of NNS for 10 wk by free-living adults was not accompanied by significant shifts in macronutrient or energy intakes or body weight (137). Taken together, published evidence does not indicate that use of NNS leads to increased fat consumption and thus 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 OVERCOMPENSATION

Nutrient labeling allows consumers to make informed decisions about the nutritive quality of their diet, but this may be counterproductive if the information is not correctly interpreted. Labeling foods as lower in energy could lead consumers to alter their feeding behavior and paradoxically increase their 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 true 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 physiologic 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 nonsignificant, but noteworthy, increase in total daily energy intake. Compared with informed sucrose use, the increment was 937 kJ/d and with uninformed aspartame use the increment was 791 kJ/d. However, other studies failed to observe this effect (55, 141, 142). In a long-term trial in which participants were motivated to maintain weight loss, use of NNS was associated with lower weight regain. 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 because of 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 on 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 postingestive physiologic 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 foods containing NNS could lead to a noncognitive 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, which leads to greater energy consumption. This was shown in a recent trial in rats in which chow energy intake was higher after ingestion of a premeal with a flavor previously paired to a low-energy food than after ingestion of the same preload with a flavor previously paired to a comparable high-energy food (147). Preliminary data in humans have also documented this effect, albeit not solely through the 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. Furthermore, 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. 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), 2 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 in which a sweet, chocolate-flavored caloric beverage was consumed before the meal and was followed by ad libitum access to chow. Whereas intake of the sweet premeal was comparable for both groups, those that received inconsistent pairings consumed more energy from the chow than did the group receiving consistent pairings. Thus, when a sensory cue, such as sweetness, lacks predictive power, energy regulation is disrupted and is biased toward positive balance. The longer-term implications of this acute trial were shown in a subsequent 5-wk study (151). The rats receiving inconsistent training consumed more energy, gained more body weight, and gained more body fat because of a weaker dietary compensation response. It is unclear whether these findings can be extrapolated to humans who eat a more varied diet and when nonnutritively sweetened foods are ingested concurrently with high-energy foods (eg, diet soda with a hamburger, nonnutritively sweetened coffee with pie). Under such conditions, associative learning would be considerably more complicated and subtle. Will signal veracity be compromised if a meal contains 4184 kJ compared with 5021 kJ by the substitution of a beverage containing NNS for a beverage containing 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 consumption of NNS, whereas nonusers of NNS reported heightened appetite and energy intake after such stimulation. These findings indicate inconsistent exposure to NNS (paired or not paired with energy) from beverages results in blunted responses to their consumption and no elevation in risk of weight gain. However, this work explored only one source of exposure, beverages, and short-term (1 d) 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.

EFFECTS OF WATER

Given that a high proportion of NNS are consumed in beverage form (Table 2), the effects of hydration state on feeding are relevant. A reciprocal association between food and water intake is widely recognized. Animals reduce their food intake when water is restricted, and reduce their 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 relation 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 periprandial (47). Drinking may facilitate eating via 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 consumption of NNS stimulates 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 multifaceted 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 the 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 can 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, overeating can stem from a lower reward value of foods or motivation to seek them (175, 176).

Recently, it was proposed that these phenomena coexist (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). Although there is no evidence that 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 a high hedonic quality with frequent exposure (184, 185).

Individuals with heightened reward sensitivity may be at particular risk of palatability driven feeding as preliminary evidence indicates that 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 that 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 postingestive learning in the establishment of food preferences has been well documented (192) and often attributed to flavor cues. However, recent findings raise questions about a unique role of sweet taste in reward-mediated feeding. The neural substrates of rewards are also activated in sweet-blind (*trpm5*^{-/-} knockout) mice due to the energy provided by sucrose (193). In this model, NNS are not as effective at stimulating dopamine release, flavor conditioning, or promoting intake. Existing evidence does not support nor refute a role for NNS in 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 whereas there are inherently pleasant (eg, sweetness) and unpleasant (eg, 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 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 the food (201). In contrast, no hedonic shift occurs when same quantity of salt is added 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, in which 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 in the latter (206, 207). Generally, these hedonic shifts occur without changes in sensitivity to or intensity perception of the sensory qualities and typically require ≈ 8 –12 wk 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 heightened acceptance of sweetened water at 2 y of age (208). This preference is not apparent for a novel fruit-flavored beverage, which indicates that the effect is food-specific. However, ethnographic studies suggest that sweet preferences learned by children generalize, at least to other sweet beverages (209). Broader associations have also been noted between the percentage 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 sweet food intake or percentage 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 in which 59 children (mean age: 9.2 ± 0.9 y) and 46 young adults (mean age: 22 ± 2.0 y) were exposed to a sweetened orange-drink for 8 consecutive days and were 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 in the adults. Interestingly, a similar effect was not noted with a comparable manipulation of sourness. However, this may have been attributable to the short duration of exposure, because the acceptance of novel sweet items is more rapid than the acceptance of novel sour items (214).

Collectively, these observations suggest that repeated exposure to a taste or flavor leads to increased acceptance of 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. Furthermore, the sensory property may exert a stronger influence on the preferred concentration of a taste or flavor compound in a food than would 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 relation 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 subsets of the population who are

consuming energy from sweet items in excess of need for different reasons (eg, reward sensitivity, health concerns).

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 (TR1s) 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 showed that individuals who 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-physiologic factors such as food availability, health concerns, and custom (223) and, possibly, other inherited traits influencing food choice [eg, neophobia (224)].

SUMMARY

From an evolutionary perspective, NNS are a novel dietary stimulus that have been introduced into our diets in only the past few decades. Although the safety of approved NNS has been established with respect to acute toxicity and longer-term pathologies (eg, carcinogenesis), their influence on appetite feeding, energy balance, and body weight has not been fully characterized. Questions remain regarding the effects of both properties of the compounds themselves (eg, 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 as well as in products, only $\approx 15\%$ 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 NNS 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. Furthermore, it is unclear whether 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 that energy compensation is incomplete, resulting in 5–15% reductions of daily energy intake. However, evidence that use of NNS 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 that none are substantiated by the available evidence.

There is no clear evidence that NNS augment 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, although 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. Use of NNS may result in greater proportional energy contributions from fat, but work on this issue also indicates that total energy intake is moderated by NNS, and the latter is the dominant factor with respect to body weight. Knowledge of use of NNS has been shown to result in energy compensation or even overcompensation 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 using NNS; therefore, only those less susceptible to cognitive influences remain to be evaluated. The concept that use of NNS 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 beverages containing NNS and thus stimulates eating, which leads 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 use patterns of NNS, clarification of remaining potential counterproductive mechanisms, and long-term randomized, controlled trials in free-living populations.

We thank Deborah Klinger (Purdue) and Frances Dancy for administrative assistance and Phil Bardsley and Kiyah Duffey (UNC) and Bridget Cassidy, Jenny Houchins, Mary-Jon Ludy, Fiona McKiernan, and Alisa Mori (Purdue) for thoughtful assistance.

The authors' responsibilities were as follows: RDM and BMP were involved with the conceptualization of the manuscript, review of the literature, and the drafting and editing of the document. Neither author had a conflict of interest with respect to this manuscript.

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