

Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements

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The negative impact of consuming sugar-sweetened beverages on weight and other health outcomes has been increasingly recognized; therefore, many people have turned to high-intensity sweeteners like aspartame, sucralose, and saccharin as a way to reduce the risk of these consequences. However, accumulating evidence suggests that frequent consumers of these sugar substitutes may also be at increased risk of excessive weight gain, metabolic syndrome, type 2 diabetes, and cardiovascular disease. This paper discusses these findings and considers the hypothesis that consuming sweet-tasting but noncaloric or reduced-calorie food and beverages interferes with learned responses that normally contribute to glucose and energy homeostasis. Because of this interference, frequent consumption of high-intensity sweeteners may have the counterintuitive effect of inducing metabolic derangements.

Sweeteners and health

Consumption of sugar-sweetened beverages (SSB; see [Glossary](#)) has been increasingly associated with negative health outcomes such as being overweight, obesity, type 2 diabetes (T2D), and metabolic syndrome, for reviews, see [1–5]. Based largely on these associations, many researchers and healthcare practitioners have proposed that non-caloric, high-intensity sweeteners provide a beneficial alternative in foods and beverages [6–10]. There is no doubt that replacing caloric with noncaloric sweeteners reduces the energy density of foods and beverages. However, whether reducing energy density in this manner always translates into reduced energy intake, lower body weight, and improved metabolic health is much less certain. Recent reviews of studies spanning at least the past 40 years have concluded that high-intensity sweeteners are potentially helpful [11], harmful [12], or have as yet unclear effects [9,13–15] with regard to regulation of energy balance or other metabolic consequences. One purpose of this opinion paper is to summarize and evaluate recent research that is consistent with the rather counterintuitive claim that consuming high-intensity sweeteners may promote excess energy intake, increased

body weight, and other related co-morbidities. A second goal is to identify and examine the types of physiological mechanisms that could underlie such adverse health consequences. A third aim is to consider factors that can make studies into the effects of artificial sweeteners on energy and body weight regulation difficult to interpret.

Glossary

Artificially sweetened beverages (ASB): also known as ‘diet’ soft drinks, beverages manufactured with one or more high-intensity sweeteners in place of energy-yielding sugars like sucrose or high-fructose corn syrup with the purpose of reducing or eliminating calories.

Body mass index (BMI): used as an index of risk for weight-related health outcomes and is calculated as (kg/m^2) . In adults BMIs of 18.5–24.9 are considered to be within the normal range, whereas BMIs from 25 to 29.9 are classified as overweight and a BMI greater than 30 is classified as obese.

Hazard ratio (HR) and odds ratio (OR): statistical measures of how often an event occurs in one group compared to another. A HR or OR of 1 means there is no difference between the groups and an HR or OR >1 means there is an increased likelihood that the event will occur in the group of interest relative to the comparison group.

High-intensity sweeteners: also known as low-calorie sweeteners, artificial sweeteners, non-nutritive sweeteners, or noncaloric sweeteners are chemicals that produce the perception of sweet taste at very low concentrations. High-intensity sweeteners currently used commonly in foods and beverages include sucralose, aspartame, saccharin, and acesulfame potassium, as well as newly approved extracts from the plant *Stevia rebaudiana*. Although some high-intensity sweeteners can be metabolized by the body, foods and beverages typically contain them in such small quantities that even those that can be metabolized contribute minute amounts of energy to the diet.

Incretin hormones: hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that are released from L cells and K cells in the intestine, respectively, and serve to enhance the release of insulin from beta cells, slow the rate of gastric emptying, and may contribute to satiety.

Metabolic syndrome: a group of factors that occur together and contribute to increased risk for coronary artery disease, stroke, and type 2 diabetes (T2D). Typical definitions require three or more of the following: blood pressure >130/85 mmHg; fasting blood glucose >100 mg/dl; large waist circumference (men >102 cm, women >89 cm); low high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); triglycerides >150 mg/dl.

Post-prandial glucose homeostasis: following meals (post-prandial) levels of glucose in the blood are tightly regulated by the release of a variety of hormones that contribute to clearance of glucose. For example, release of insulin from the beta cells of the pancreas is required to move sugar from the blood into cells.

Sugar-sweetened beverages (SSB): also known as ‘regular’ soft drinks, manufactured with one or more caloric sweeteners such as sucrose or high-fructose corn syrup.

Thermic effect of food: increase in metabolic rate after consumption of a meal related to energy required to process and metabolize the consumed food.

Type 2 diabetes: chronic elevation of blood glucose due to insulin resistance that is also characterized by impaired incretin secretion.

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Keywords: obesity; diabetes; sweeteners.

1043-2760/\$ – see front matter

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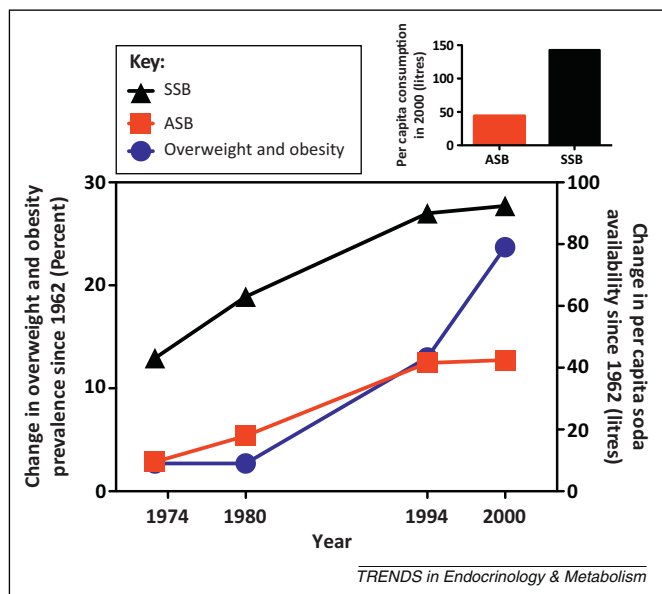


Figure 1. Beverage consumption and the prevalence of obesity. Line graph illustrates changes in *per capita* consumption of artificially sweetened beverages (ASB; red squares), sugar-sweetened beverages (SSB; black triangles), and the prevalence of obesity (blue circles) in the USA since 1962. For obesity data, years reported represent the final year of the data collection period (e.g., National Health and Nutrition Examination Survey (NHANES) II 1976–1980 shown with soda consumption data from 1980). Inset bar graph illustrates *per capita* consumption of ASB (red bar) and SSB (black bar) in the year 2000. Obesity data adapted from National Center for Health Statistics Health E-stats, September 2012: http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.pdf, accessed 28 May, 2013. Beverage data adapted from Beverages Worksheet. USDA Economic Research Service: http://www.ers.usda.gov/datafiles/Food_Availability_Per_Capita_Data_System/Food_Availability/beverage.xls, accessed 28 May, 2013.

Use of high-intensity sweeteners and artificially sweetened beverages

For the present purposes, the terms high-intensity sweeteners, low-calorie sweeteners, artificial sweeteners, and artificially sweetened beverages (ASB) have much the same meaning and are used interchangeably. Consumption and availability of artificial sweeteners have been increasing and in the USA approximately 30% of adults and 15% of children aged 2–17 years reported consumption of low-calorie sweeteners in 2007–2008 [16]. Consumption of ASB and SSB has increased between 1962 and 2000 in the USA and shows parallels with changes in the prevalence of being overweight and obesity over the same time frame (Figure 1). Consumption of ASB has also risen along with rates of obesity in Australia, whereas consumption of SSB has declined [17].

Prospective cohort studies of effects of ASB consumption

Weight gain

The San Antonio Heart Study documented weight change in men and women over a 7–8-year period. As part of that study, Fowler *et al.* [18] reported that, among participants who were normal weight or overweight at baseline, risk of weight gain and obesity were significantly greater in those consuming ASB compared with those who did not consume ASB [18] (Table 1). In a study of two adolescent cohorts, ASB intake was associated with increased body mass index (BMI) and increased body fat percentage in males and females at 2-year follow-up [19] when data were examined

cross-sectionally, but not in a longitudinal analysis. In that study, SSB intake was associated with increased BMI in males only in the longitudinal analysis, whereas there were no increased risks for increased BMI or increased body fat percentage associated with SSB in females. Differences in outcome between these adolescents and the Fowler *et al.* study could reflect smaller sample sizes, younger subjects, and/or a shorter follow-up time frame. However, neither study provided evidence that ASB consumption was associated with reduced risk for either weight gain or increased body fat percentage [18,19].

Metabolic syndrome

A number of studies have reported greater risk of metabolic syndrome for consumers of ASB across a variety of cohorts [6,20–22] (Table 1). Estimates of the size of the increase in the risk of metabolic syndrome associated with consuming ASB range from approximately 17% [hazard ratios (HRs) and odds ratios (ORs) of 1.17] to over 100% (e.g., those consuming ASB had double the risk of metabolic syndrome compared with non-consumers), with the magnitude of the risk estimate also depending on which other risk factors were taken into consideration (see below). In studies that also examined the risk of metabolic syndrome associated with SSB consumption the magnitude of the increased risk was frequently similar for SSB and ASB [20,22] (Table 1).

Type 2 diabetes

In the European E3N study [23] and the Health Professionals Follow-up (HPFS) [24] risk for T2D was more than doubled for participants in the highest quartile of ASB consumption compared with non-consumers, and SSB consumption was also associated with increased risk of T2D. In both these studies [23–25], comparison of the magnitude of the risk between SSB and ASB is complicated by differences in intake of the two beverage types. Data from the Nurses' Health Study (NHS) also indicated that risk for T2D was enhanced in those consuming at least one ASB or SSB per day [25]. Most recently, data from the European Prospective Investigation into Cancer and Nutrition (EPIC) has also indicated that risk for T2D was elevated in those consuming at least one ASB or SSB per day [26]. Importantly, a pronounced elevation of risk for T2D related to ASB in the EPIC study was seen even in participants who were normal weight at baseline [26].

Hypertension and cardiovascular disease

Risk for coronary heart disease (CHD) in the NHS was significantly elevated in women who consumed more than two ASB per day in age-adjusted models [27] or more than two SSB per day in fully adjusted models [27]. Similarly, in the HPFS risk of CHD was significantly elevated by ASB and SSB, but comparisons of magnitude of these effects are complicated by differences in intake [28]. In addition, consuming at least one ASB daily significantly elevated risk for hypertension for women in NHS-I and NHS-II, as well as in the HPFS [29], with the size of the effect similar to that observed for SSB in these samples. Finally, results from the Northern Manhattan Study (NMS) indicated that daily ASB consumption was associated with significantly

Table 1. Prospective cohort studies of artificially sweetened beverages (ASB) and health outcomes

Study	Sample	Length	Effect	ASB volume Risk estimate ^a	Sugar-sweetened beverage (SSB) volume Risk estimate ^a	ASB after adjustment ^b	SSB after adjustment ^b	Refs
San Antonio Heart	1250 men and women ^c	7–8 years	BMI \geq 25	<3 per week	N/A	Yes OR = 1.56	N/A	[18]
San Antonio Heart	1250 men and women ^c	7–8 years	BMI \geq 25	3–10 per week	N/A	Yes OR = 1.74	N/A	[18]
San Antonio Heart	1250 men and women ^c	7–8 years	BMI \geq 25	11–21 per week	N/A	Yes OR = 1.75	N/A	[18]
San Antonio Heart	1250 men and women ^c	7–8 years	BMI \geq 25	\geq 22 per week	N/A	Yes OR = 1.93	N/A	[18]
San Antonio Heart	2571 men and women ^d	7–8 years	BMI \geq 30	11–21 per week	N/A	Yes OR = 1.73	N/A	[18]
San Antonio Heart	2571 men and women ^d	7–8 years	BMI \geq 30	\geq 22 per week	N/A	Yes OR = 2.03	N/A	[18]
IDEA/ECHO	327 male adolescents ^e	24 months	BMI ^f	Continuous	Continuous ^g	N/A	N/A	[19]
IDEA/ECHO	339 female adolescents ^e	24 months	BMI ^f	Continuous	No	N/A	N/A	[19]
CARDIA	4161 men and women	20 years	Metabolic syndrome ^h	Any	N/A	Yes HR = 1.23	N/A	[6]
Framingham Offspring	6039 men and women	4 years	Metabolic syndrome	\geq 1 per day OR = 1.53	\geq 1 per day OR = 1.62	N/A	N/A	[20]
ARIC	9514 men and women	9 years	Metabolic syndrome	Highest tertile ⁱ HR = 1.34	Highest tertile ⁱ HR = 1.09	N/A	N/A	[21]
MESA	5011 men and women	2–5 years	Metabolic syndrome	\geq 1 per day HR = 1.31	N/A	Yes ^j HR = 1.17	N/A	[22]
MESA	5011 men and women	2–5 years	T2D ^h	\geq 1 per day HR = 1.63	N/A	Yes HR = 1.38	N/A	[22]
E3N	66 118 women	14 years	T2D	\geq 603 ml per week HR = 3.50	\geq 359 ml per week HR = 1.49	Yes HR = 1.68	Yes HR = 1.30	[23]
HPFS	40 389 men	20 years	T2D	4.5 per week to 18 per day HR = 1.91	4.5 per week to 7.5 per day HR = 1.25	No HR = 1.09	Yes HR = 1.24	[24]
HPFS	39 059 men	22 years	T2D	\geq 1 per day HR = 1.95 ^l HR = 1.87 ^m	\geq 1 per day HR = 1.57 ^l HR = 1.49 ^m	No ^k HR = 1.15 ^l HR = 1.06 ^m	Yes HR = 1.37 ^l HR = 1.33 ^m	[25]
NHS	74 749 women	24 years	T2D	\geq 1 per day HR = 1.76 ^l HR = 1.59 ^m	\geq 1 per day HR = 1.46 ^l HR = 1.74 ^m	Yes ⁿ HR = 1.09 ^l HR = 1.01 ^m	Yes HR = 1.20 ^l HR = 1.29 ^m	[25]
EPIC-InterAct	15 374 men and women	16 years	T2D	\geq 1 per day HR = 1.84	\geq 1 per day HR = 1.68	No HR = 1.13 Yes ^o HR ^o = 1.43	Yes HR = 1.29	[26]
NHS	88 520 women	24 years	CHD ^p	\geq 2 per day HR = 1.28	\geq 2 per day HR = 1.93	No ^q HR = 1.15	Yes HR = 1.35	[27]
HPFS	42 883 men	22 years	CHD ^r	4.5 per week to 18 per day HR = 1.04	4.5 per week to 7.5 per day HR = 1.21	No HR = 1.02	Yes HR = 1.20	[28]
NHS-I	88 540 women	38 years	Hypertension	\geq 1 per day HR = 1.38	\geq 1 per day HR = 1.22	Yes HR = 1.11	Yes HR = 1.12	[29]
NHS-II	97 991 women	16 years	Hypertension					[29]

Table 1 (Continued)

Study	Sample	Length	Effect	ASB volume Risk estimate ^a	Sugar-sweetened beverage (SSB) volume Risk estimate ^a	ASB after adjustment ^b	SSB after adjustment ^b	Refs
				≥1 per day HR = 1.56	≥1 per day HR = 1.39	Yes HR = 1.12	Yes HR = 1.17	
HPFS	37 360 men	22 years	Hypertension	≥1 per day HR = 1.43	≥1 per day HR = 1.09	Yes HR = 1.20	No HR = 1.06	[29]
Northern Manhattan	2564 men and women	10 years	Vascular events ^s	≥1 per day HR = 1.66	≥1 per day HR = 1.15	Yes HR = 1.44 HR = 1.59 ^t	No HR = 1.09 HR = 1.57 ^t	[30]

^aStatistically significant increases in consumers relative to non-consumers. Hazard ratios (HR) and odds ratios (OR) listed in this column are from the least-adjusted models that did not include baseline body mass index (BMI) as a factor. Not all studies included result from models that did not adjust for BMI. The comparison group for the ratios is non-consumers of that beverage type.

^bWhether this effect was statistically significant in models that did include baseline BMI as a factor. The HR and OR listed are from models that were the most fully adjusted reported in that study for which BMI was included. Not all studies included models that adjusted for BMI.

^cNormal weight.

^dOverweight.

^eIn grades 6–11.

^fCross-sectionally but not longitudinally.

^gLongitudinally but not cross-sectionally.

^hAlso increased waist circumference.

ⁱNot otherwise defined.

^j $P = 0.06$.

^kFor caffeine-free ASB, $P = 0.06$.

^lCaffeine-free.

^mCaffeinated.

ⁿFor caffeine-free ASB but not caffeinated ASB.

^oAmong normal-weight participants but not those overweight or obese.

^pNonfatal myocardial infarction (MI) or coronary heart disease death.

^q $P = 0.07$.

^r $P = 0.05$.

^sStroke, MI, or vascular death.

^tWhen only those who had a baseline BMI <30 and no history of diabetes or metabolic syndrome were analyzed. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults; CHD, coronary heart disease; E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; IDEA and ECHO, Identifying Determinants of Eating and Activity and Etiology of Childhood Obesity; MESA, Multi-ethnic Study of Atherosclerosis; NHS, Nurses' Health Study; T2D, type 2 diabetes.

Table 2. Intervention studies of artificially sweetened beverages (ASB) and body weight

Study	Sample characteristics	Duration	Interventions	Primary outcome	Other outcomes	Refs
CHOICE	318 overweight and obese men and women	6 months	Replacement of sugar-sweetened beverages (SSB) with water Replacement of SSB with ASB Attentional control (AC) group	No differences in weight loss	↓ Fasting glucose in water and AC groups	[10]
DRINK	641 boys and girls ^a	18 months	One ASB or one SSB per day	↓ BMI z score in ASB group	SSB group had greater ↑ fat mass, skinfold thickness, and weight-to-height ratio	[31]

^aAged 4–11 years. Abbreviations: CHOICE, choose healthy options consciously every day; DRINK, double-blind, randomized intervention study in kids.

increased risk of vascular events of a magnitude similar to daily SSB consumption [30].

Interventional studies

Within the past 5 years there have been fewer interventional studies that examined the effects of ASB, compared with the number of prospective studies published. In fact, only two recent papers appear to have directly manipulated exposure to ASB as a means of assessing effects on weight gain (Table 2). In the first, de Ruyter *et al.* [31] reported that primarily normal weight children (ages 4 to 11 years) assigned to consume a single ASB daily for 18 months gained less weight, and had smaller increases in skinfold thickness, waist-to-height ratios, and fat mass compared with children assigned to consume one SSB daily. In this study, all subjects were consumers of SSB at the start of the study, but it is not clear whether the children had experience with ASB prior to the intervention. Thus, this study suggests that among children of normal weight consuming ASB may lead to reduced weight gain relative to consuming SSB. However, whether consumption of ASB is associated with differences in weight gain compared with consumption of unsweetened beverages was not assessed. In the second study, overweight and obese adults who substituted water or ASB for SSB lost no more weight at 6 months than an attentional control (AC) group [10]. Replacement of SSB with water or ASB resulted in similar changes in some metabolic outcomes, such as decreased waist circumference and decreased systolic blood pressure, compared to the AC [10]. By contrast, although AC and water groups showed improvement in fasting glucose relative to baseline the ASB group did not [10]. Thus, in this interventional trial, consuming ASB beverages did not appear to provide a significant advantage in weight or metabolic outcomes compared with water or an AC. These interventional studies suggest the possibility that ASB are linked to lower risk of weight gain than SSB in lean children. However, in overweight or obese adults ASB are not more effective than water or a simple AC at improving weight loss or metabolic outcomes over 6 months. The reason for these different outcomes is unknown, but the study populations differed across a number of variables including BMI at the outset (overweight and obese vs lean), study setting (USA vs The Netherlands), duration (6 vs 18 months), and participant age (adults vs children). Although the data could indicate that children are less sensitive to the potentially negative effects of ASB, other studies have not found such effects and, as a whole, results of trials of ASB in children appear to be mixed, for a review, see [18].

Take-home message from prospective cohort and interventional studies

Taken together, data from these recent studies suggest a link between consumption of ASB and a variety of negative health outcomes, including increased risk of being overweight and obesity, T2D, metabolic syndrome, and cardiovascular events [6,10,18–30], especially in adults. In none of these prospective studies was ASB consumption associated with significantly decreased risk; and in the adult interventional study ASB consumption was not associated with improved fasting glucose whereas water consumption was [10]. This general pattern of findings emerged across studies that varied widely in design, methodology, and population demographics. Although the models employed in most studies were adjusted for age, sex, level of physical activity, and smoking status, the methods used to specify each of these factors were variable.

Furthermore, the models employed in these studies differed with respect to the inclusion of demographic factors such as: race and/or ethnicity and education; dietary factors such as total number of calories, total amount of fat, grams of saturated fat, and fiber intake; and history of T2D or other metabolic disorders. Some models controlled for baseline BMI, but the method for controlling for this factor was not consistent across studies. Within individual studies, increased control of these types of factors tended to lower risk associated with ASB and SSB consumption. However, ASB and SSB consumption continued to be associated with significant elevations in risk even in models that attempted to control for all of these factors, including baseline BMI [6,18,22,23,25,26,29,30], with the magnitude of the effects of ASB and SSB consumption on these outcomes being generally similar when similar amounts of consumption were compared. This pattern suggests that family history, diet composition, and BMI at baseline may elevate health risks for people who consume ASB or SSB, but these factors are not sufficient to explain observed associations between consumption of ASB or SSB and negative health outcomes.

Reverse causality and cognitive influences

It has been suggested that the correlation between intake of ASB and increased incidence of negative health outcomes such as impaired energy and body weight regulation is an example of reverse causation [9], in which increasing body weight causes people to turn to the use of noncaloric sweeteners. Where reported, data from these prospective studies do indicate that those who regularly consume ASB tend to have higher BMI at baseline compared with those

who do not [18,22,24,26,28,30], but some models that adjust for this baseline difference continue to find increased risk [6,18,22,23,25,26,29,30]. In addition, studies that separately analyzed risk among individuals who were not overweight or obese at baseline showed that ASB significantly increased risks of becoming overweight or obese [18], for T2D [26], and for vascular events [30], even when baseline BMI was considered. Thus, reverse causality does not seem plausibly to account for the increased risk in all studies. In addition, some of the effects of consuming ASB on these negative health outcomes could reflect a type of cognitive process in which knowledge that an ASB that is perceived to be 'healthy' grants permission to over consume other 'non-healthy' foods [32], and the consequences of ASB could be mediated through increased energy intake due to these types of cognitive distortions.

A role for more basic learning?

The results of a number of well-controlled animal studies suggest an additional possibility. Rats and mice that have been randomly assigned to receive dietary supplements mixed with noncaloric sweeteners exhibit greater weight gain and altered physiological responses compared with animals that receive the same diets mixed with sucrose or glucose [33–36], for a review, see [37]. These alterations are attributable to reductions in energy expenditure and to a decreased ability to regulate intake of normal sweet-tasting foods that contain energy [35,38]. An associative learning account of these effects has been supported by recent data that showed that consuming saccharin reduced the ability of sweet tastes to signal the post-ingestive caloric consequences of eating sweet-tasting foods, but not foods that did not taste sweet [33]. Increased body weight gain was observed only when other foods that tasted sweet and provided energy were consumed [33]. In other words, artificial sweeteners appear to stimulate food intake by reducing the ability to compensate for energy provided by caloric sweeteners in the diet.

Sweet tastes are known to evoke numerous physiological responses that help to maintain energy homeostasis by signaling the imminent arrival of nutrients in the gut and by facilitating the absorption and utilization of energy contained in food [39]. By weakening the validity of sweet taste as a signal for caloric post-ingestive outcomes, consumption of artificial sweeteners could impair energy and body weight regulation by degrading the ability of sweet taste to evoke these physiological responses when consumption of sweet tastes is followed by energy gain. This failure to anticipate calories and sugar appropriately when they do arrive could ultimately lead to the negative health consequences associated with ASB described above, by impairing the ability of sweetness to predict the arrival of energy in the gut accurately, thereby reducing the efficient utilization of that energy and perhaps weakening the cascade of events that initiate satiety. So, when consumed along with a diet high in dietary sugars, ASB might actually exacerbate the negative consequences of these dietary sugars by blunting such responses.

Physiological responses to high-intensity sweeteners

Artificial sweeteners evoke different brain responses compared with sugars

Recent studies in humans have documented that a number of metabolic and hormonal factors, typically elicited by the consumption of caloric sweeteners, either do not occur or are of reduced in magnitude following consumption of artificial sweeteners. For example, imaging studies in the human brain have indicated that sucrose, but not sucralose, activates dopaminergic midbrain areas related to reward or pleasantness, and that, compared with sucrose, sucralose results in reduced activation in other taste-related pathways [40]. Further, brain responses to sucrose differ in humans who regularly consume ASB compared with those who do not [41,42]. Patterns of brain activation differ in response to saccharin compared with sucrose in those that do not consume ASB, whereas activation patterns in brains of ASB consumers do not differentiate between saccharin and sucrose [41].

Artificial sweeteners alone do not stimulate insulin or incretin release in vivo

A common result from studies in humans has also been that acute changes in the release of a variety of hormones and markers for post-prandial glucose homeostasis [including insulin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), glucose-dependent insulinotropic peptide (GIP), and ghrelin] do not occur when artificial sweeteners are delivered directly into the stomach or intestines [43–45]. Further, release of these markers does not appear to occur following oral consumption of an unflavored sucralose solution or an ASB sweetened with aspartame [46,47] (Table 3). From another standpoint, these studies also indicated that consumption of sucralose along with maltodextrin [46] or consumption of a SSB [47] failed to elicit significant GLP-1 release, raising concerns that there was potentially low sensitivity to detect changes.

Unlike caloric sweeteners, artificial sweeteners do not augment insulin or incretin release in response to meals

Studies that measured responses to artificial sweeteners combined in various ways with nutrient signals also suggest that artificial sweeteners may not augment nutrient-dependent release of insulin or the incretins (Table 3) in the same way that caloric sugars do. For example, Anton [48] reported that glucose and insulin levels were higher after participants consumed a sucrose-sweetened premeal of tea, cream cheese, and crackers, compared with the same premeal sweetened with either aspartame or stevia, a difference that would be expected due to the additional energy and carbohydrate in the sucrose-sweetened premeal. Effects of these premeals on glucose homeostasis during lunch were also assessed, but are difficult to interpret because the volume and composition of the lunch meal was self-selected by the participant and therefore may have varied after the different premeals. As part of another study [49], subjects consumed unflavored liquid premeals sweetened with either glucose or sucralose prior to eating a potato meal fixed in volume and composition.

Table 3. Acute effects of high-intensity sweeteners on blood glucose homeostasis markers

Participant and premeal characteristics	Treatment prior to premeal	Delay between premeal and test meal	Sweetener conditions	Effects of premeal	Test meal characteristics	Effects after test meal compared to sugar-sweetened premeal	Effects after test meal compared to water premeal	Refs
One man, seven women BMI = 18.8–23.9 50 ml liquid ^a	~12 h fast	N/A	Water	N/A	N/A	N/A	N/A	[46]
			Sucralose (~41 mg) + Maltodextrin (~25 g)	↑ Glucose ^b ↑ Insulin ^b				
			Sucralose (~41 mg)	No effects ^b				
12 men, 12 women overweight and obese Mean BMI = 31.4 500 ml liquid ^c	Overnight fast ^d	N/A	Water	N/A	N/A	N/A	N/A	[47]
			Sucrose (53 g)	↓ Ghrelin ^b Smaller ↓ in GLP-1 ^b ↑ GIP ^b				
			Aspartame (~225 mg) ^e	No effects				
Seven men, three women Mean BMI = 25.5 400 ml liquid ^a premeal	~12 h fast ^d	15 min	Glucose (40 g)	N/A	65 g powdered potatoes 20 g glucose egg yolk 200 ml water	N/A	Not assessed	[49]
			Sucralose (60 mg)	↓ Glucose ^f ↓ Insulin ^f ↓ GLP-1 ^f ↓ GIP ^f				
16 lean, 12 obese men and women Mean BMI = 27.5 400 g tea with crackers and cream cheese ^g premeal	Breakfast prior to premeal ^h	20 min	Sucrose ⁱ	N/A	Sandwiches, potato chips, cookies ^j	N/A	Not assessed	[48]
			Aspartame ⁱ	↓ Glucose ^f ↓ Insulin ^f				
			Stevia ⁱ	↓ Glucose ^f ↓ Insulin ^f				
Eight women Mean BMI = 22.2 355 ml liquid ^a premeal	~10 h fast	60 min	Sucrose (50 g)	↑ Glucose ^b ↑ Insulin ^b	Fixed quantity ^k scrambled eggs with cheese orange juice buttered whole wheat toast	N/A	N/A	[50]
			Water	N/A				
			Sucralose (6 g Splenda ≈420 mg sucralose)	No effects				
			Sucrose (50 g) + Sucralose (6 g Splenda)	No effects ^f				
Ten males, 12 female ^l Mean BMI = 25.6 240 ml liquid ^m premeal	~10 h fast	10 min	Carbonated water	Not tested ⁿ	75 g glucose ^o	Not assessed	N/A	[51]
			~46 mg sucralose + ~26 mg acesulfame-K					

Table 3 (Continued)

Participant and premeal characteristics	Treatment prior to premeal	Delay between premeal and test meal	Sweetener conditions	Effects of premeal	Test meal characteristics	Effects after test meal compared to sugar-sweetened premeal	Effects after test meal compared to water premeal	Refs
13 male, 12 female ^l Mean BMI = 25.7	~10 h fast	10 min	Carbonated water ~46 mg sucralose + ~26 mg acesulfame-K	Not tested ⁿ	75 g glucose ^o	Not assessed	N/A	[52]
240 ml liquid ^m premeal			Not assessed			↑ GLP-1 release		
Three male, six female ^p Mean BMI = 21.7			Not assessed			N/A		
240 ml liquid ^m premeal			Not assessed			No effects ^q		
One male, nine female ^r Mean BMI = 35			Carbonated water ~46 mg sucralose + ~26 mg acesulfame-K			Not assessed	N/A	
240 ml liquid ^l premeal			Not assessed			↑ GLP-1 release ^p		

^aUnflavored.

^bCompared to premeal containing water.

^cCoca Cola or diet Coca Cola; semi-skimmed milk was also tested in this study but these results are omitted for clarity.

^dFollowing standardized evening meal.

^eAspartame concentration in diet Coca Cola was estimated based on published analysis of aspartame concentration in cola in Denmark [54].

^fCompared to premeal containing sugar (no water control included).

^gPremeal is described as 'a 400 g preload of tea and crackers with cream cheese sweetened with stevia (Whole Foods 365 brand), aspartame (equal sweetener), or sucrose'. Thus, it appears that the cream cheese was sweetened whereas the tea was not. Specific weight of the tea, cream cheese, or crackers is not reported.

^hBreakfast was standardized, but timing of breakfast relative to premeal not reported.

ⁱQuantity of sweetener was not reported.

^jSelf-selected by participants.

^kNot specified.

^lYoung healthy participants aged 12–25 years.

^mDiet rite cola or unflavored carbonated water.

ⁿData only reported for AUC of premeal and meal combined.

^oYoung participants aged 12–25 years with type 1 diabetes.

^pVolume and concentration not indicated.

^qFor blood glucose, AUC was slightly but not significantly increased after diet soda compared to carbonated water.

^rYoung participants aged 12–25 years with type 2 diabetes.

The sucralose premeal alone did not elevate glucose, insulin, GLP-1, or GIP, whereas the glucose premeal did, and after the mixed meal was consumed the sucralose premeal was associated with reduced GLP-1 release compared with the glucose premeal. As in the Anton study, the total amount of carbohydrate consumed was significantly higher after the glucose premeal compared with the sucralose premeal and thus these differences between the premeal groups would be expected. In a study that did include a control for total energy and carbohydrate intake [50], an unflavored liquid sucralose premeal had no effects on glucose and insulin levels prior to a mixed breakfast meal compared to water, whereas a sucrose premeal produced increased blood glucose and insulin levels prior to the mixed meal and decreased blood glucose after the mixed meal, compared with the water and sucralose premeals. As evidenced in Table 3, these clinical studies have been highly variable with regard to a number of procedural aspects including: length of fast prior to testing; participant demographics such as age, sex, and weight; composition, form, flavoring, and amount of premeal (e.g., liquid vs solid); delay between premeal and meal; meal composition and sweetener concentration; and comparison groups. Although this variability complicates conclusions about the effects of artificial sweeteners, the data nonetheless appear consistent with the idea that physiological responses that typically occur following consumption of caloric sweeteners are not elicited by artificial sweeteners or are of much smaller magnitude.

Artificial sweeteners may weaken learned responses

Such results have typically been interpreted as indicating that artificial sweeteners are largely inert with regard to effects on glucose homeostasis because they do not reliably elicit post-ingestive responses similar to caloric sugars. However, when considered within the framework of Pavlovian conditioning principles, experiences with noncaloric sweet tastes that are not accompanied by typical and expected post-ingestive consequences, such as post-prandial release of insulin, GLP-1, or GIP, or activation of brain regions sensitive to energy or reward, might eventually degrade or partially extinguish the capacity of caloric sweet tastes to evoke those responses. And this weakening could occur even if ASB evoke responses that are similar in direction to those evoked by caloric sweeteners but greatly reduced in magnitude. For example, Brown *et al.* [51,52] found that, compared to a carbonated water premeal, consumption of a flavored ASB premeal appeared to have no effects, but the ASB premeal did augment GLP-1 release in response to an oral glucose load in healthy subjects and subjects with type 1 diabetes, but not in those with T2D. However, the magnitude of this GLP-1 effect in response to the ASB was not compared with that evoked by a SSB; if the ASB-evoked release was of a lower magnitude than an SSB-evoked release, learned responses would be weakened. This remains to be tested. In addition, the factors that led to these studies [51,52] demonstrating a significant physiological response to an ASB compared with others that did not are not yet clear, but probably relate to the wide variability in procedural details across such studies.

Potential consequences of weakening learned responses

These data are generally consistent with the idea that ASB do not evoke responses like those evoked by caloric sweeteners. Regular consumption of ASB might thereby come to result in weaker responses to sweet tastes when they are produced by consumption of caloric sweeteners. Some evidence for this type of effect comes from recent studies in rats in which animals that had previously consumed saccharin-sweetened yogurt had a blunted thermic effect of food in response to a novel, sweet-tasting meal compared with those that had previously consumed glucose-sweetened yogurt [35]. In a second experiment, a significantly weaker GLP-1 response was shown in response to consumption of a sweet caloric solution by rats that were ASB consumers, compared with rats that did not consume ASB [36]. To date, brain-imaging studies [41,42] have provided some support for potentially similar consequences in humans, but no similar tests of physiological responses have been reported.

Concluding remarks

Recent data from humans and rodent models have provided little support for ASB in promoting weight loss or preventing negative health outcomes such as T2D, metabolic syndrome, and cardiovascular events. Instead, a number of studies suggest people who regularly consume ASB are at increased risk compared with those that do not consume ASB; with the magnitude of the increased risks similar to those associated with SSB [6,10,18–30]. In a number of cases, these effects cannot be attributed to baseline characteristics such as family history or BMI [6,18,22,23,25,26,29,30]. This somewhat counterintuitive result may reflect negative consequences of interfering with learned relationships between sweet tastes and typical post-ingestive outcomes, which may result in impaired ability to compensate for energy provided when caloric sweeteners are consumed. Paying increased attention to the ability of learning to modulate physiological and neural signals related to energy balance and metabolic regulation may improve our ability to understand circumstances under which reductions in the energy content of foods

Box 1. Outstanding questions

- Does regular consumption of high-intensity sweeteners result in changes in physiological responses to caloric sweeteners in humans? If so, what mechanisms are responsible for these changes?
- What role might differential brain responses to nutritive compared with non-nutritive sweeteners play in modulating signals related to energy balance and glucose homeostasis?
- Are sweeteners, artificial or caloric, consumed in beverage form particularly problematic? Is consumption of artificial sweeteners in other forms, with or without other foods, associated with increased, decreased, or unaltered health risks?
- Does experience with high-intensity sweeteners interfere with learning about the energetic value of nutritive sugars in people? If so, can principles of learning contribute to strategies to repair the deficits?
- Does replacement of ASB with unsweetened beverages have advantageous effects on being overweight, obesity, or other metabolic derangements?

and beverages may lead to worsened and not improved health outcomes (see also Box 1).

In addition, although consumption of ASB may contribute to being overweight, obesity, and metabolic derangements, other factors must also be in operation, particularly because not everyone consumes ASB or uses artificial sweeteners. Further, negative consequences of ASB should not be interpreted to suggest that sugars should be consumed in preference to artificial sweeteners. Instead, consumption of artificial sweeteners may exacerbate the negative effects of sugars by reducing the ability to predict the consequences of consuming sugars reliably and/or by altering cognitive processes that lead to overconsumption. Finally, most of the data documenting increased risks have come from studies of ASB; artificial sweeteners are now increasingly included in products other than beverages, often in combination with caloric sweeteners [12,16,53]. Whether such products have positive, negative, or neutral effects on body weight or other metabolic outcomes is even less clear than for ASB. However, current findings suggest that caution about the overall sweetening of the diet is warranted, regardless of whether the sweetener provides energy directly or not.

Acknowledgments

Research supported by NIH R01DK076078 and P01HD052112. The author wishes to thank Terry Davidson and three anonymous reviewers for their insightful comments.

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