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Not so Sweet Revenge: Unanticipated Consequences of High-Intensity Sweeteners

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Abstract While no single factor accounts for the significant increases in overweight and obesity that have emerged during the past several decades, evidence now suggests that sugars, in general, and sugar-sweetened beverages, in particular, may be especially problematic. One response to this concern has been an explosion in the availability and use of noncaloric sweeteners as replacements for sugar. While consumers have been led to believe that such substitutes are healthy, long-term epidemiological data in a number of cohorts have documented increased risk for negative outcomes like type 2 diabetes, heart disease, and stroke among users of artificial sweeteners. Experimental data from animals has provided several plausible mechanisms that could explain this counterintuitive relationship. In particular, my research has demonstrated that artificial sweeteners appear to interfere with basic learned, predictive relations between sweet tastes and post-ingestive consequences such as the delivery of energy. By interfering with these relations, artificial sweeteners inhibit anticipatory responses that normally serve to maintain physiological homeostasis, and over the long term, this interference could result in negative health effects like those seen in the human cohort studies. These data suggest that reducing the consumption of all sweeteners is advisable to promote better health.

Keywords Artificial sweeteners · Health · Obesity · Classical conditioning

It is becoming increasingly clear that current patterns of food and beverage intake, including overconsumption of sugar-sweetened foods, play major contributory roles in the development of overweight, obesity, and chronic diseases like diabetes, metabolic syndrome, cardiovascular disease, and hypertension. A commonsense strategy to address the role of excess sugar intake would be to replace caloric sweeteners with sweeteners that provide the same tastes but without the calories and sugar. But, common sense is not always a good guide, and scientific explanations demand data rather than intuition. And in fact, what the data show is that consumption of artificial

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sweeteners is counterintuitively associated with increased risks for the very negative health outcomes that they have been promoted to reduce. In the present paper, I discuss one hypothesis of how these unexpected outcomes could occur—that artificial sweeteners play a causal role in metabolic dysregulation because they interfere with basic learning processes that maintain homeostasis.

Obesity, Sugar, and Disease

It is now commonly recognized that rates of overweight and obesity have risen dramatically for the better part of the last three decades, both within the USA and worldwide (Flegal et al. 2012; M. Ng et al. 2014). Much effort has been directed toward understanding causes of this shift. It is critical to recognize that from a public health perspective, the primary, if not sole, concern about excess body weight is that it significantly increases the risk that people will develop a variety of chronic, debilitating, and even deadly health outcomes, including cancers, hypertension and stroke, cardiovascular disease, and diabetes (M. Ng et al. 2014). What we know about these massive and rapid changes in body weight regulation is that individuals differ in predisposition to gain weight and that there is no single factor that explains the obesity epidemic, but that changes in what we eat and drink play a large role in these recent massive increases in the prevalence of excess weight. For example, portion sizes of foods have dramatically increased along with weight changes. In 1960, the average weight of a man in the USA was 75.6 kg and the largest hamburger offered by McDonald's weighed 1.6 oz; by 2006, the largest McDonald's hamburger had increased to 8 oz and the average man's weight to 88.3 kg (McDowell et al. 2008; Ogden et al. 2004; Young and Nestle 2002, 2007).

More recently, dramatic increases in dietary sugar intake (e.g., sucrose or high-fructose corn syrup), especially sugars consumed in the form of beverages, have received particular focus (e.g., Hu 2013). Data indicate that in the USA, sugar-sweetened beverage consumption has increased by almost 20 gal per capita since 1966 and that this increased intake began prior to the remarkable 25 % increase in the prevalence of overweight and obesity over the same timeframe (Fig. 1; Swithers 2013). More importantly, intake of sugar-sweetened beverages has been closely linked to increases in the risk of developing a variety of chronic health conditions in a number of large, long-term prospective cohort studies (Fig. 2; Bernstein et al. 2012; Bhupathiraju et al. 2013; Cohen et al. 2012; de Koning et al. 2012; de Koning et al. 2011; Dhingra et al. 2007; Duffey et al. 2012; Fagherazzi et al. 2013; Fung et al. 2009; Gardener et al. 2012; Lutsey et al. 2008; Nettleton et al. 2009; Romaguera et al. 2013; Sakurai et al. 2013). In those studies, individuals were stratified based on how much sweetened beverage they reported consuming, and health outcomes were assessed over a period of time, ranging from 4 up to 28 years. The reference group comprised individuals who reported consuming no sugar-sweetened beverages, and the incidence of specific health outcomes in people who did consume sugar-sweetened beverages on a regular basis (typically one or more servings per day) was calculated relative to this nonconsuming reference group. As illustrated in Fig. 2, these cohort studies demonstrate that daily consumption of as little as one sugar-sweetened beverage predicted significant elevation of health risks. For every 100 nonconsuming individuals diagnosed with type

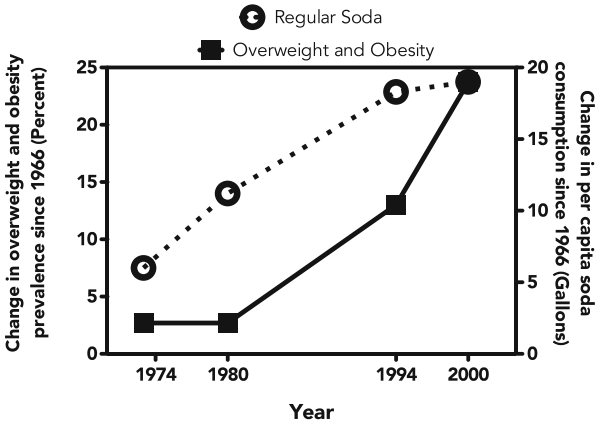

Fig. 1 Changes in the prevalence of overweight and obesity (*filled squares*) and per capita consumption of regular soda sweetened with sugars (*open circles*) in the USA since 1966. Overweight and obesity data from the National Center for Health Statistics (2012). Beverage data from USDA (2008)

2 diabetes (Fig. 2a), coronary heart disease, vascular events, high blood pressure, or stroke (Fig. 2b), between 110 and 170 sweetened beverage consumers were diagnosed with the same outcomes. In other words, daily consumers of sugar-sweetened beverages have risks that are increased by 10–70 %.

In these studies, the individual cohorts differed along a variety of factors including the length of the follow-up, exactly how sugar-sweetened beverage consumption was defined and stratified, along with the age and sex of the participants. However, the results clearly illustrate that individuals who regularly consume as little as a single sugar-sweetened beverage daily have significantly greater chances of developing type 2 diabetes, metabolic syndrome, coronary heart disease, and hypertension and stroke than those who do not consume soft drinks.

Alternative Sweeteners and Disease

One response to the increasingly well-documented negative consequences of excessive sugar intake has been to advocate the use of noncaloric sweeteners (also known as artificial sweeteners or high-intensity sweeteners; e.g., Fitch and Keim 2012; Gardner et al. 2012). These sweeteners provide a sweet taste but deliver fewer calories (or no calories) because they are not metabolized and/or because they activate sweet taste receptors at such low concentrations that minimal quantities are employed, and therefore, the energy provided is negligible. We have been led to believe that because these products deliver the sweet taste people want, but with much fewer calories, negative health outcomes like diabetes, hypertension, stroke, and cardiovascular disease will naturally be avoided. The public has embraced these beliefs, and over the past several decades, foods and beverages manufactured with one or more noncaloric sweeteners like aspartame, sucralose, saccharin, and acesulfame potassium have become increasingly popular (S. W. Ng et al. 2012; Sylvetsky et al. 2012). The consumption of the "diet" soft drinks in the USA has also risen by close to 10 gal per capita between 1962 and 2000 (Fig. 3; Swithers 2013). As seen with regular soda, the increased

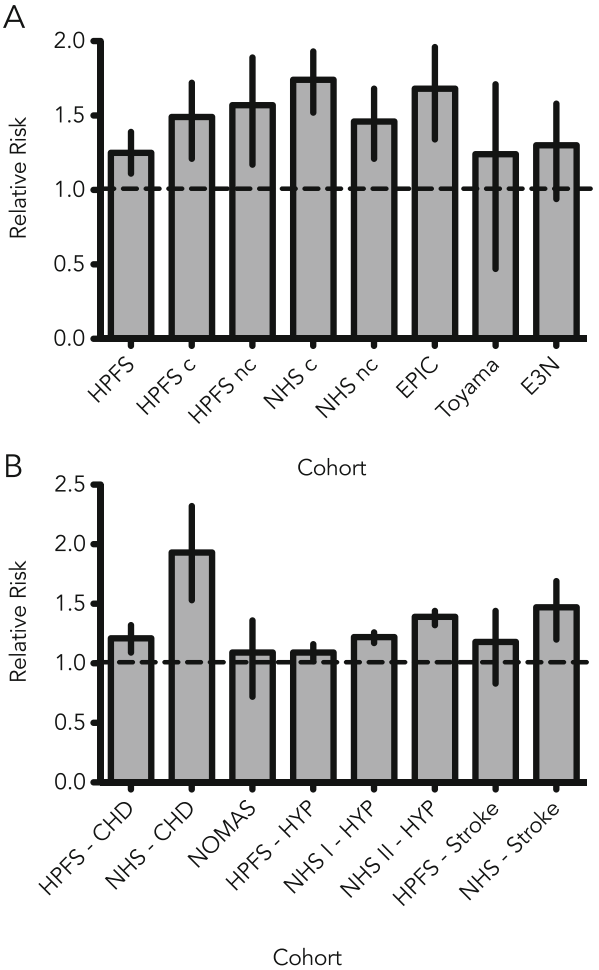

Fig. 2 Relative risk (±95 % CI) of negative health outcomes in consumers of regular soft drinks compared to nonconsumers in prospective cohort studies. Risk of 1.0 indicates no differences between consumers and nonconsumers. Risk greater than 1.0 indicates increased likelihood in consumers compared to nonconsumers. **a** Risk of type 2 diabetes. **b** Risk of cardiovascular effects. Data from Bernstein et al. (2012), Bhupathiraju et al. (2013), Cohen et al. (2012), de Koning et al. (2012), de Koning et al. (2011), Fagherazzi et al. (2013), Fung et al. (2009), Gardener et al. (2012), Romaguera et al. (2013), and Sakurai et al. 2013)

consumption of diet soda actually precedes documented increases in overweight and obesity. In 2008 alone, over 2000 new products containing artificial sweeteners were introduced (Yang 2010). Current estimates of how many people in the USA actually consume products containing artificial sweeteners are variable, with some data suggesting that approximately 15 % of the adult population (Mattes and Popkin 2009) are consumers, other results reporting 32 % of adults consume artificial sweeteners (Sylvetsky et al. 2012), and industry data suggesting that the figure is much higher with 187 million adults (approximately 80 % of the adult population) reporting use of low-calorie, sugar-free foods and beverages (Calorie Control Council 2014). Whatever the true number, millions of people have embraced the consumption of artificially

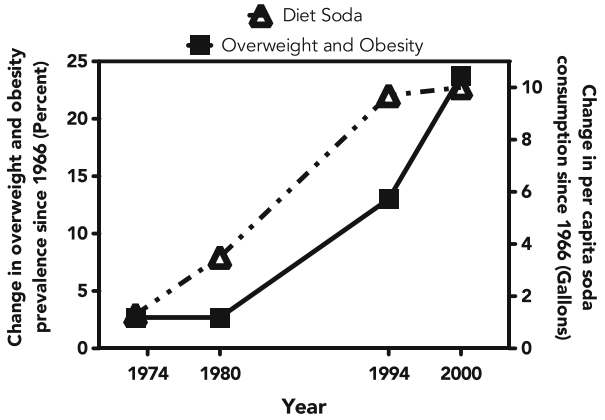

Fig. 3 Changes in the prevalence of overweight and obesity (*filled squares*) and per capita diet soda consumption (*open triangles*) in the USA since 1962. Overweight and obesity data from the National Center for Health Statistics (2012). Beverage data from USDA (2008)

sweetened products as healthy choices, expecting that use of these products will prevent the negative health outcomes so closely tied to consumption of sugars.

Unfortunately, not only do the data not support such beliefs, but they also provide evidence to the contrary. Routine consumption of diet soft drinks is linked to increases in the same risks that many seek to avoid by using artificial sweeteners—namely type 2 diabetes, metabolic syndrome heart disease, and stroke (Bhupathiraju et al. 2013; Cohen et al. 2012; de Koning et al. 2011, 2012; Dhingra et al. 2007; Duffey et al. 2012; Fagherazzi et al. 2013; Fung et al. 2009; Gardener et al. 2012; Lutsey et al. 2008; Nettleton et al. 2009; Romaguera et al. 2013; Sakurai et al. 2013). Figure 4 illustrates long-term health outcomes in the same prospective cohort studies described above; only now, the graphs demonstrate how individuals who consume diet soft drinks daily compare to those who do not drink them. For diabetes, the relative risks range from 120 consumers per 100 nonconsumers all the way up to 350 consumers for every 100 nonconsumers (Fig. 4a), and for cardiovascular disease, hypertension, and stroke, they range from 110 to 150 consumers per 100 nonconsumers (Fig. 4b). Thus, the risk of developing three of the top 7 causes of death in the USA (see Centers for Disease Control and Prevention 2014) is significantly higher not only in those who regularly consume sugar-sweetened soft drinks but also in those who have been misled to believe that diet sodas will help them avoid such outcomes because they do not provide calories.

At this point, it is important to understand what these kinds of studies can and cannot tell us about why soft drink consumption (diet or regular) is related to chronic and deadly diseases. For example, it is clear that individuals who chose to consume soft drinks differ from those who do not, and disease risk may reflect other factors rather than, or in addition to, sweetened beverage intake. In many models, factors known to contribute to health risks, such as family history, other dietary patterns, and even body mass index, are used to try to adjust for the possibility that the beverages themselves are not a contributing factor. When these factors are included, the strength of the associations is typically decreased; in a number of instances, however, diet soda intake remains a factor that significantly increases risk even after adjusting for such factors

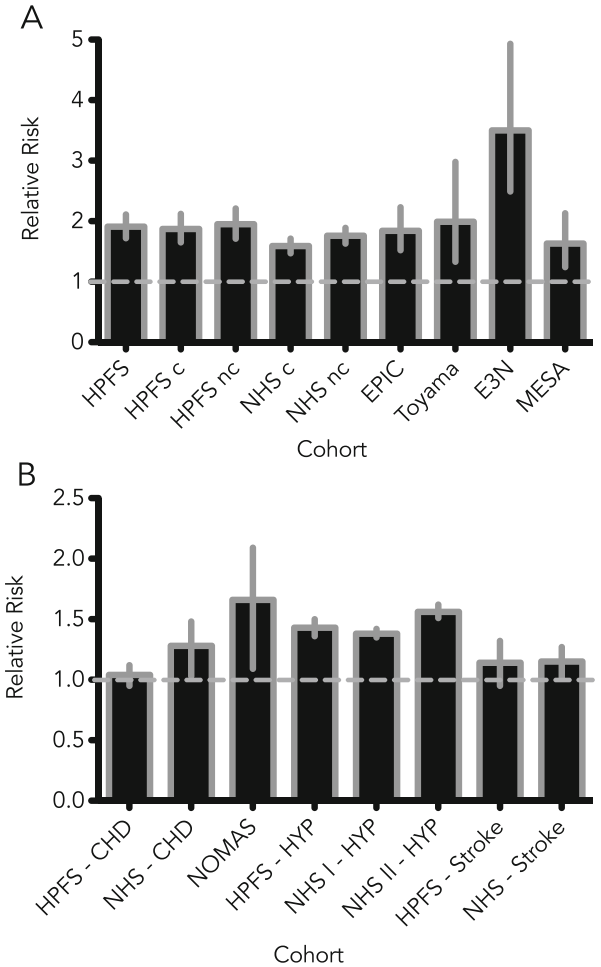

Fig. 4 Relative risk (±95 % CI) of negative health outcomes in consumers of diet soft drinks compared to nonconsumers in prospective cohort studies. Risk of 1.0 indicates no differences between consumers and nonconsumers. Risk greater than 1.0 indicates increased likelihood in consumers compared to nonconsumers. **a** Risk of type 2 diabetes. **b** Risk of cardiovascular effects. Data from Bernstein et al. (2012), Bhupathiraju et al. (2013), Cohen et al. (2012), de Koning et al. (2012), de Koning et al. (2011), Fagherazzi et al. (2013), Fung et al. (2009), Gardener et al. (2012), Romaguera et al. (2013), and Sakurai et al. (2013)

(e.g., Bernstein et al. 2012; Bhupathiraju et al. 2013; Cohen et al. 2012; Duffey et al. 2012; Fagherazzi et al. 2013; Gardener et al. 2012; Nettleton et al. 2009; Romaguera et al. 2013; Sakurai et al. 2013), and in no case, did daily consumption of a sweetened beverage (diet or regular) result in a significant decrease in risk.

In other words, the belief that artificially sweetened diet beverages reduce long-term health risks is not supported by scientific evidence, and instead, scientific data indicate that diet soft drink consumption may contribute to the very health risks people have been seeking to avoid. The importance of these relationships has typically been dismissed, with one common argument being that those who consume diet beverages in the first place are already unhealthy, and the increased risk observed is an example of "reverse causation." However, the data show that risks are increased even when

controlling for preexisting differences in known risk factors. A second common tactic used to diminish the importance of these data, especially among food industry groups, is to argue,

> "[t]here is no plausible biological explanation for this supposed correlation between soda consumption and the metabolic syndrome…. The authors provide no credible basis for believing these associations are causal, or even real, or why both regular and diet soft drinks could be implicated (American Council on Science and Health 2007)."

Experimental Evidence That Artificial Sweeteners Interfere with Learning

Despite these assertions, experimental evidence in fact supports multiple biologically plausible explanations about how the consumption of diet beverages could play a causal role in the development of negative health outcomes like metabolic syndrome, diabetes, and cardiovascular diseases. For example, work in my lab has focused on examining one of these mechanisms, which is based on the hypothesis that artificial sweeteners interfere with metabolic processes because they disrupt learned relations between the taste of sweet and the arrival of sugar and energy in the digestive tract (Davidson et al. 2011; Davidson and Swithers 2004; Swithers 2013; Swithers et al. 2006, 2009, 2010a, b, 2012a, b, 2013a, b; Swithers and Davidson 2005, 2008). Decades of work, originating with the foundational studies of Pavlov (Pavlov and Anrep 1960), have documented that learning about cues related to foods can have profound effects on digestive physiology. Pavlov's earliest studies demonstrated that physiological responses like salivation can come under the control of cues that predicted the delivery of food to the gastrointestinal tract. In the intervening years, the field has revealed how specific experiences with cues related to food not only can have profound and persistent effects on physiological responses, like the "psychic secretions" described by Pavlov, but also can significantly affect ingestive behaviors. For example, it is now well recognized that animals (including humans) will avoid flavor cues (smells and tastes) whose consumption has been followed by nausea or malaise (Garcia et al. 1955), while preferring flavors that have been followed by positive post-ingestive consequences (e.g., Sclafani 1997). Thus, the notion that learning can contribute to regulation of food intake and metabolic physiology is not particularly novel.

Nor is it surprising that sweet tastes would historically have been very strong cues of specific metabolic outcomes, namely sugar and energy. For example, mammals like humans are exposed to the sweet tastes of sugars that are prevalent in mother's milk (if not even earlier since the taste system matures prenatally in many species). The sweet taste of milk is rapidly and reliably followed by the appearance of sugar and energy in the gut. As a result of this frequent and reliable association, it is not surprising that a sweet taste in the mouth can elicit physiological responses that anticipate the arrival of sugars in a fashion akin to Pavlov's psychic secretions. Now more commonly termed "cephalic phase" responses, a variety of physiological changes related to digestion, absorption, and metabolism, are known to be subject to learned control. For example, the hormones insulin and pancreatic polypeptide, which

help maintain blood sugar levels, are released prior to the arrival of sugars in a cephalic phase fashion in humans; release of pancreatic polypeptide can be conditioned to occur in response to the taste of a flavor that has been paired with the arrival of carbohydrates in the gut (Teff 2011). Thus, even in humans, cues like flavors and tastes can serve as conditioned stimuli for the activation of physiological responses such as the release of hormones through exposure to predictive relationships. For example, the metabolism of sugars in the body reliably follows the cue produced by activation of sweet taste receptors in the mouth.

What, then, happens when artificial sweeteners strongly activate sweet taste receptors in the mouth but the anticipated metabolic consequences do not materialize? Based on principles of classical conditioning, when a predictable contingency is replaced with one in which the conditioned stimulus is no longer reliably followed by the anticipated consequence, the conditioned responses weaken (Bills et al. 2006; Calton et al. 1996). From this perspective, individuals who consume artificial sweeteners would be expected to have diminished cephalic phase responses to all sweet tastes, even those that are produced by real sugars, because their experiential histories have made it so that sweet tastes no longer reliably predict whether sugars and energy will need to be metabolized.

Behavioral Consequences of Artificial Sweeteners

To test this hypothesis, we turned to an animal model, the laboratory rat, that provided the necessary experimental control over dietary exposure to sweeteners. We conducted a series of studies to determine whether exposure to artificially sweetened foods or beverages produced metabolic derangements that might contribute to the long-term health risks observed in clinical cohorts. The general approach in these experiments was to provide animals with as much of a typical maintenance diet and water as they would consume, along with a fixed quantity of an additional food (such as yogurt) or beverage. For one group of animals, these supplemental foods or beverages were sweetened with a caloric sugar, preserving the typical predictive relation between a sweet taste in the mouth and the arrival of energy in the gut. For a separate group of animals, the supplements were sweetened with an artificial sweetener, most typically saccharin. Similar amounts of supplements were provided to both sweetener groups, and only animals that routinely consumed the supplements were included in analyses so that any differences in outcomes were due to differences in consumption of the regular diets across groups, rather than differences in the sweetened supplements.

The results of these experiments have demonstrated that rats given dietary supplements sweetened with an artificial sweetener eat more of their regular diet, gain extra weight, and are fatter than rats given dietary supplements sweetened with a caloric sugar (Davidson et al. 2011; Davidson and Swithers 2004; Swithers et al. 2009, 2010a, b; Swithers and Davidson 2008), consistent with a causal relationship between consumption of artificial sweeteners and derangement of the ability of animals to use sweet taste cues to modulate ingestive behavior.

Additional studies have tested the idea that learning is responsible for these disruptions. For example, in one set of experiments, the role of cue competition in learning preferences for flavors that predicted the delivery of calories was examined. Cue competition occurs when more than one cue predicts the same outcome. For example,

animals show a preference for an arbitrary flavor, such as grape Kool-Aid, after it has been paired with a sugar solution that delivers calories. In this case, the grape flavor competes with the caloric outcome because sweet taste itself also predicts calories. One known way to reduce cue competition is to reduce the predictive value of one of the cues by presenting it without its associated outcome (e.g., Bills et al. 2006; Calton et al. 1996), so learning about the grape flavor should be enhanced by reducing the ability of sweet tastes to predict caloric outcomes, for example by exposure to artificial sweeteners. A set of experiments confirmed this. In one, animals were first given either artificially sweetened liquids or water for several days; then, they were given one flavor (e.g., grape) that was mixed into sugar solutions and a second flavor (e.g., cherry) that was mixed into an equicaloric solution of polycose, a carbohydrate that is highly preferred by rats but that does not taste sweet. The prediction was that if artificial sweeteners reduce the associative strength of the sweet taste cue, then animals exposed to the artificial sweetener would have enhanced preference for the grape flavor paired with the sugar solution since the sweet taste no longer provided as a strong cue for the calories in this group compared to the water-exposed animals. In contrast, learning about the cherry flavor paired with the nonsweet solution should be similar across the two exposure groups because artificial sweeteners should have no impact on responses to nonsweet solutions. The results confirmed this outcome (Fig. 5; Davidson et al. 2011); animals exposed to the artificial sweetener had enhanced preferences for the flavor paired with the sweet sugar solution compared to those exposed to water, but no differences in preference for the nonsweet solution were demonstrated.

Further support for an influence of learning was evidenced by the fact that excess weight gain is observed only when animals need to rely on a sweet-taste cue to regulate intake of their maintenance diet. Animals given dietary supplements sweetened with sugar or with artificial sweeteners showed similar patterns of energy intake and weight

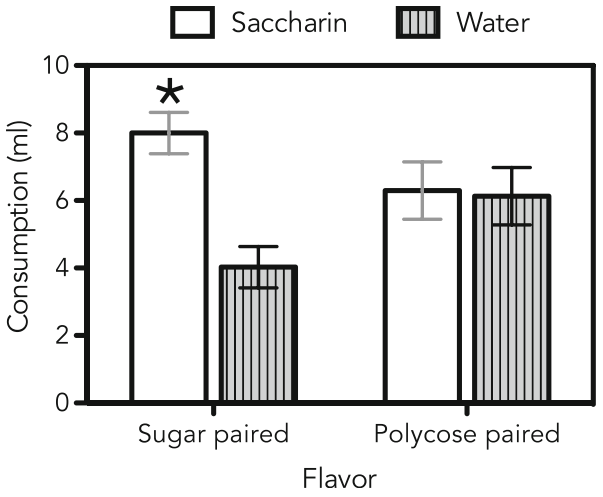

Fig. 5 Learning about a novel flavor paired with a sweet-tasting sugar (sugar paired; l*eft*) was significantly greater in animals that had been exposed to the artificial sweetener saccharin compared to animals exposed to water. There was no effect of exposure to saccharin on learning about a novel flavor paired with an equicaloric solution that did not taste sweet (polycose paired; *right*). Adapted from Davidson et al. (2011). *$p<0.05$ compared to water group

gain if their maintenance diet was high in fat and energy, but low in sugar (Fig. 6; Davidson et al. 2011). In contrast, animals given a maintenance diet high in both fat and sugar consumed significantly more energy and gained significantly more weight when given artificial sweeteners (Fig. 6). Thus, these experimental data demonstrate that in contrast to their intended outcomes, artificial sweeteners can in fact contribute to excess food intake and weight gain; similar effects have also been demonstrated experimentally with fat substitutes, which mimic the sensory properties of fats while providing little or no energy (Swithers et al. 2006, 2011).

Physiological Consequences of Artificial Sweeteners

Experimental evidence demonstrates that in contrast to their purported effects, foods and beverages manufactured with products designed to mimic the sensory properties of sweet can actually lead to overconsumption and excess weight gain when sweetened, caloric foods are consumed. These outcomes are consistent with the idea that the cues from food do not come to predict the metabolic consequences, and this dissociation impairs the animal's ability to adequately modulate food intake. But, long-term consumption of artificial sweeteners can be problematic not only because of these altered behavioral responses. Our studies have also demonstrated that consumption of artificial sweeteners causes specific alterations in physiological responses related to energy utilization and regulation of blood sugar levels. In these studies, animals were first given a training phase lasting several weeks in which they consumed fixed quantities of a food or beverage supplement that was sweetened with either sugar or an artificial sweetener (along with ad lib access to their regular food and water). Following this training phase, animals were given a test phase during which they consumed a sugar-sweetened meal to determine whether the previous exposure to the artificial sweetener had affected physiological responses to real sugar.

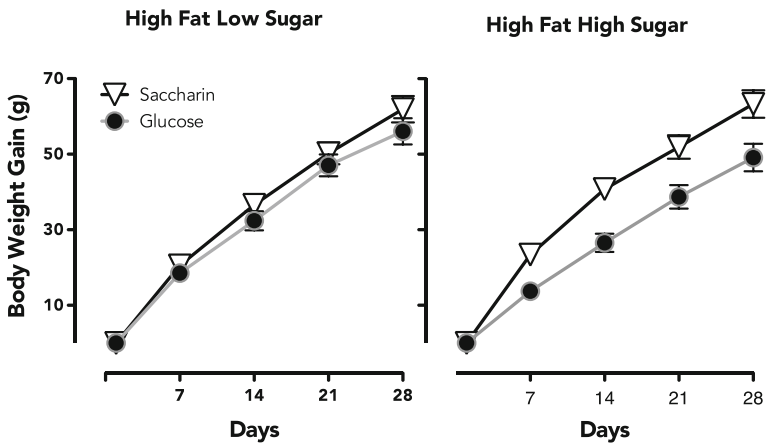

Fig. 6 Weight gain was similar in rats consuming saccharin- or glucose-sweetened dietary supplements along with a maintenance diet that was high in fat and low in sugar (*left*). In contrast, when the diet was high in fat and sugar, weight gain was significantly greater in animals consuming the saccharin-sweetened supplement compared to the glucose-sweetened supplement (*right*). Adapted from Davidson et al. (2011)

In one experiment, we used implanted transmitters to remotely measure diet-induced thermogenesis (DIT), a reflexive form of heat production that can be modulated by orosensory food cues (e.g., LeBlanc and Cabanac 1989; LeBlanc et al. 1984). The results demonstrated that DIT was significantly lower in response to a sugar-sweetened meal in animals with previous experience consuming artificial sweeteners, consistent with the idea that their history had conditioned them to expect that fewer calories were associated with the meal compared to animals accustomed to consuming sugar-sweetened diets. Thus, artificial sweeteners may contribute to excess weight gain because they promote less anticipatory heat production which requires energy use, in addition to promoting overconsumption.

While the promotion of weight gain is problematic, as described above, excess weight is concerning to the extent that it predicts negative health outcomes. More recently, our work has demonstrated additional physiological mechanisms that could explain both the short-term effects on food intake and weight seen in experimental animals and the long-term negative health outcomes observed in clinical cohorts. Namely, consumption of artificial sweeteners causes reduced release of the incretin hormone glucagon-like peptide-1 (GLP-1) in response to sugar-sweetened foods. GLP-1 is synthesized and released from L cells in the intestine in response to food intake and has been documented to slow down the rate of gastric emptying, to act in concert with insulin to suppress the release of glucagon from the liver and stimulate uptake of sugar from the blood, and to have protective effects on the cardiovascular system (for review, see Sivertsen et al. 2012). If exposure to artificial sweeteners interferes with the release of GLP-1, then short-term effects on blood glucose homeostastis and food intake would be expected, along with longer-term effects on cardiovascular function. And in fact, not only is GLP-1 release significantly lower in rats with a history of consuming artificial sweeteners, but these animals also show hyperglycemia (greater excursions in blood sugar responses; Fig. 7; Swithers et al. 2012a, b). Importantly, these effects occur only when animals actually taste the sugar solution; placing the solution directly into the stomach and bypassing the oral cavity produce similar increases in blood sugar and GLP-1 release in animals that have previously consumed artificial sweetener and those that have not (Swithers et al. 2012a, b).

Together, such results are consistent with the hypothesis that the activation of sweet taste receptors in the mouth normally triggers physiological responses that anticipate the arrival of energy and sugars in the body, including increases in heat production and the release of hormones. These anticipatory responses can contribute not only to the efficient and effective metabolism of energy, but also to reported increases in feelings of fullness and satiety in humans, to regulation of blood sugar levels, and, over the long term, to protection of the cardiovascular system. Interfering with the learned relationship between sweet taste in the mouth and the arrival of energy and sugar in the gut by consuming sweet tastes that fail to deliver these consequences reduces the magnitude of anticipatory responses. As a result, when real sugars are actually consumed, blood sugar rises higher, the thermic effect of food is not as pronounced, feelings of satiety are weakened, and animals overeat over the short term. Over the long term, the blunting of the release of hormones like GLP-1 may also lead to cardiovascular damage.

Note that it is possible, if not likely, that other mechanisms could contribute to the negative consequences of consuming artificial sweeteners. For example, several studies

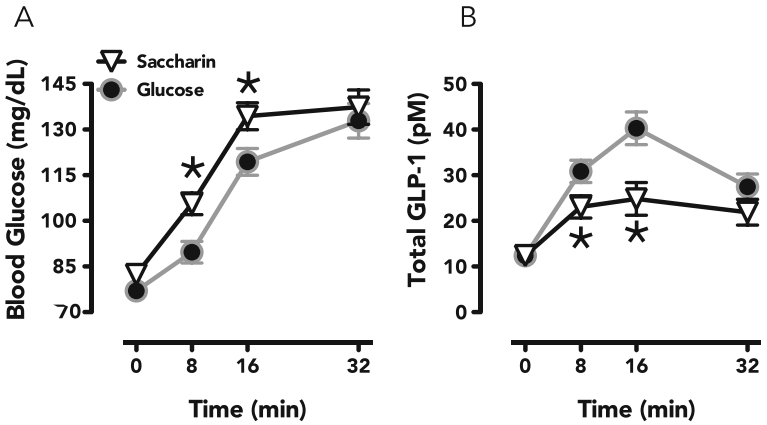

Fig. 7 Blood glucose levels (**a**) were significantly greater, and total GLP-1 levels were significantly lower (**b**) during an oral glucose tolerance test in animals who had previously consumed saccharin-sweetened dietary supplements compared to those who had previously consumed glucose-sweetened supplements. Adapted from Swithers et al. (2012a, b). *$p<0.05$ compared to saccharin-exposed animals

in rodents have now indicated that consumption of artificial sweeteners is associated with rapid changes in gut bacteria and that these changes can contribute to impairments in the body weight regulation and the ability to regulate blood sugar levels not only in rodents, but also in humans as well (Abou-Donia et al. 2008; Palmnas et al. 2014; Suez et al. 2014). And in humans, cognitive distortions may also play an important role. For example, people underestimate the amount of calories in foods that have been labeled as "healthy" while overestimating the amount of calories in foods labeled "unhealthy" (e.g., Chandon 2012). If people believe that artificial sweeteners are healthy, then including a diet soft drink in a meal could lead to underestimating how many total calories are consumed.

Focus on Reducing Sweeteners (Real or Artificial)

In human clinical cohorts, individuals who consume diet soft drinks have been documented to be at increased risk for the very outcomes like diabetes, metabolic syndrome, and cardiovascular diseases that people seek to avoid by consuming artificial sweeteners. Whether these long-term effects in human are caused by consumption of the sweeteners, or reflect other differences among those who choose to consume diet soft drinks and those who do not, cannot be answered by correlational studies. However, studies using experimental paradigms in rodents have documented that artificially sweetened foods and beverages can and do promote excess food intake, weight gain, adiposity, and metabolic derangements including hyperglycemia. Presently, experimental studies in humans have not directly addressed the question of whether artificial sweeteners impair learned responses in humans in a fashion similar to that seen in rodent studies for a variety of reasons. First, the possibility that prior experience with artificial sweeteners could impact outcomes has typically been ignored, even though data now indicate that individuals who are habitual consumers of artificial sweeteners have been demonstrated to differ significantly from those who are

nonconsumers (e.g., Green and Murphy 2012; Rudenga and Small 2012). Second, people have difficulty accurately reporting food and beverage intake even under the best of circumstances (Livingstone and Black 2003). Noncaloric sweeteners need not be specifically identified as such on food labels. They do have to be listed as ingredients, but it is clear that even individuals who say that they seek to avoid artificial sweeteners end up choosing products that contain them (Sylvetsky et al. 2014) which results in an extra layer of complexity in accurately quantifying which individuals consume artificial sweeteners and how much they consume. This issue will likely become more problematic as more and more sweeteners become incorporated into more and more foods and beverages.

Experimental studies in animal models demonstrate multiple mechanisms by which sweet tastes without typically associated outcomes could interfere with metabolic processes. Further, long-term cohort studies in humans show that diet soft drink consumption is more closely associated with increases in health risks rather than decreases. So what does this mean from the perspective of individuals trying to mitigate health risks? Certainly, the answer is not to switch from artificially sweetened soft drinks to those sweetened with sugar. Instead, the goal should be to reduce intake of sweetened foods and beverages overall. And although it might be tempting to argue that artificial sweeteners could play a role in a transition away from excess sugar intake, data supporting that this occurs is also relatively sparse and contradicted by the results of a recent study (Piernas et al. 2013). In that work, overweight individuals who regularly consumed sugar-sweetened beverages and who were seeking to lose weight were advised to replace the sugar-sweetened beverages with either water or diet soft drinks. Over 6 months, both groups lost similar amounts of weight. Those in the diet soft drink group were consuming 917 ml (close to three cans) of diet soda daily and a total of 939 mg of low-calorie sweeteners while the water group consumed about 80 ml diet soda daily (approximately one-fourth can) and a total of 515 mg of artificial sweeteners. It is estimated that aspartame, saccharin, and acesulfame potassium are roughly 200 times sweeter than sugar, while sucralose is approximately 600 times sweeter. Thus, individuals consuming 939 mg of artificial sweetener are exposed to the sugar equivalent of over 45 teaspoons per day, while 515 mg is roughly 25 teaspoons. Despite these very large differences in artificial sweetener intake between the two groups, consumption of actual sugar was the same in both groups after the intervention—roughly 17 teaspoons. In other words, in this set of people, drinking close to a liter of diet soda every day did not lead to greater reductions in sugar intake than did drinking water. Thus, artificial sweeteners do not appear to specifically help in reducing sugar intake.

At present, little current scientific evidence supports the use of artificial sweeteners in promoting long-term positive health benefits. Accumulating evidence suggests that over the long term, regular consumption of either caloric or noncaloric sweeteners contributes to negative health effects like diabetes, cardiovascular disease, and stroke. Although a causal relationship between consuming noncaloric sweeteners and increased disease risk may at first seem implausible, experimental data now provide evidence for several specific and credible mechanisms that could this relationship. It would seem, therefore, that the most prudent public health message would be to stop promoting artificial sweeteners as healthy substitutes and, instead, encourage decreased consumption of both caloric and noncaloric sweeteners.

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