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David S. Ludwig, MD, PhD

THE TASTE RECEPTOR FOR SWEETNESS, T1R2/R1R3,1 can detect sugar at a concentration as low as about 1 part in 200, whereas some bitter substances can be detected in the range of a few parts per million, perhaps explaining why most individuals prefer foods with high sugar content but little bitterness. However, this innate preference for sweetness does not necessarily lead to obesity or other diet-related diseases because sugar-containing foods in their natural form tend to be highly nutritious. For instance, an 8-oz apple contains beneficial vitamins, minerals, and phytochemicals but fewer calories than a 2-oz portion of bread. Most fruits elicit a high level of satiety relative to calories ingested due to their low-energy density, high-fiber content, and low glycemic index.2

Problems occur when sugars—chiefly sucrose and the chemically similar product, high-fructose corn syrup—are refined, concentrated, and consumed in large amounts. Without the protection conferred by an intact, natural food containing fiber and antioxidants, these refined sugars increase blood glucose and insulin levels rapidly after consumption, increasing concentrations of triglycerides, inflammatory mediators, and reactive oxygen radicals.2 In contrast to whole fruit, intake of refined carbohydrate increases risk for diabetes, cardiovascular disease, and other chronic illness.3 Sugar-sweetened beverages may have an especially adverse effect on body weight because of the exceptionally low-satiety value of sugars in liquid form.

One proposed solution to the problems caused by overconsumption of these fattening, empty calories is artificial sweeteners. Presently, 5 such products have US Food and Drug Administration (FDA) approval: saccharin, acesulfame, aspartame, neotame, and sucralose. (Stevia, a natural extract from the plant Stevia rebaudiana, received FDA approval in 2008.) These synthetic substances are hundreds to thousands of times more potent than sucrose and elicit an intense sensation of sweetness in trace concentrations.

As suggested by the term diet with which these products are marketed, foods and beverages with artificial sweeteners are intended to produce a sweet taste comparable with their sugar-containing counterparts but with fewer calories, thereby promoting weight loss when substituted for calorie-containing products. Short-term clinical trials provide some evidence for this effect. For example, obese adults who consumed an average of 600 kcal/d of sucrose, mostly in the form of beverages, for 10 weeks showed increased body weight, blood pressure, and inflammatory markers compared with a control group given artificial sweeteners.4,5

However, body weight is regulated by complex and redundant biological and behavioral pathways. Calories displaced by artificial sweeteners may be replaced over time from other sources; the nature and completeness of this compensation would therefore determine the ultimate effects on body weight and other health outcomes. In addition, overstimulation of sugar receptors by frequent consumption of hyper-intense sweeteners may cause taste preferences to remain in, or revert to, an infantile state (ie, with limited tolerance for more complex tastes). Individuals who habitually consume artificial sweeteners may find more satiating but less intensely sweet foods (eg, fruit) less appealing and unsweet foods (eg, vegetables, legumes) less palatable, reducing overall diet quality in ways that might contribute to excessive weight gain.

Diet drinks may comprise a special and particularly concerning case. Diet drinks have essentially no calories, unlike most artificially sweetened solid foods that typically contain other nutrients. Moreover, diet drinks are often consumed in the absence of other foods, producing a dissociation between sweet taste and calorie intake. One concern is that the dissociation of these physiological events might disrupt the hormonal and neurobehavioral pathways regulating hunger and satiety. In support of this possibility, Swithers and Davidson6 reported that rodents fed saccharin compared with those fed glucose showed diminished calorie compensation ability, increased calorie intake, and increased body weight. In a study of pharmacological reward, Lenoir et al7 gave rodents the mutually exclusive choice of intravenous cocaine or an oral saccharin solution. They found that most animals, including

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those with prior cocaine exposure, selected the lever that dispensed saccharin over the lever that dispensed cocaine and suggested that "[t]he absolute preference for taste sweetness may lead to a re-ordering in the hierarchy of potentially addictive stimuli, with sweetened diets . . . taking precedence over cocaine and possibly other drugs of abuse."

No long-term studies of diet drink consumption and body weight have been conducted in humans. Among observational studies, the San Antonio Heart Study found a dose-response relationship between diet drinks and measures of adiposity over a 7-year period among 5158 adults. Consuming more than 21 servings of diet drinks per week vs none was associated with a 2-fold increased risk of developing overweight or obesity. In the Multi-Ethnic Study of Atherosclerosis, daily consumption of diet drinks was associated with a 36% increased risk for metabolic syndrome and a 67% greater risk for type 2 diabetes among 6814 adults. These studies must be interpreted cautiously because excessive weight gain may prompt some individuals to increase diet drink consumption, producing reverse causation.

Artificial sweeteners have been used for a century and have received considerable scientific scrutiny. Recurring questions about cancer risk, as they relate to the 5 products with current FDA approval, have been largely dismissed. However, increasing concern about the health effects of refined sugar has driven a marked increase in the consumption of artificial sweeteners, especially in liquid form. Per capita diet drink intake has increased from less than 1 oz per day in the 1960s to about 4 oz per day this decade. Among regular consumers of diet drinks, intake now totals more than three 8-oz servings per day. If trends in consumption continue, the nation will, in effect, have embarked on a massive, uncontrolled, and inadvertent public health experiment. Although many synthetic chemicals have been added to the food supply in recent years, artificial sweeteners in beverages stand out in their ability to interact with evolutionarily ancient sensorineural pathways at remarkably high affinity.

Ultimately, high-quality, long-term clinical trials comparing all 3 beverage types are needed: sugar sweetened, artificially sweetened, and unsweetened. Even if diet drinks produce long-term weight loss when substituted for sugar-sweetened beverages, they might cause weight gain when consumed instead of unsweetened drinks. For now, diet drinks may best be considered an aid in transitioning from high-calorie beverages to traditional, minimally sweetened beverages like water, mineral waters, teas, and coffee with no more than 1 g of sugar per oz (ie, 2 teaspoons per 8-oz cup).

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