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Review

Do low-calorie sweeteners promote weight gain in rodents?

John I. Glendinning

Department of Biology, Barnard College, Columbia University, 3009 Broadway, New York, NY 10027, United States

HIGHLIGHTS

- The linkage between LCS consumption and elevated body weight in rodents is examined.
- LCSs promoted weight gain when they were presented in yogurt.
- The LCS-treated yogurt formulations did not appear to taste sweet to the rats.
- The elevated weight gain could not be explained solely by increased caloric intake.
- LCS and yogurt may promote weight gain by modifying the gut microbiota.

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ABSTRACT

Low-calorie sweeteners (LCSs) are used globally to increase the palatability of foods and beverages, without the calories of sugar. Recently, however, there have been claims that LCSs promote obesity. Here, I review the literature linking LCS consumption to elevated body weight in rodents. A recent systematic review found when the LCSs were presented in water or chow, only a minority of the studies reported elevated weight gain. In contrast, when the LCSs were presented in yogurt, the majority of the studies reported elevated weight gain. This review focuses on this latter subset of studies, and asks why the combination of LCSs and yogurt promoted weight gain. First, LCSs have been hypothesized to induce metabolic derangement because they uncouple sweet taste and calories. However, the available evidence indicates that the LCS-treated yogurts did not actually taste sweet to rats in the published studies. Without a sweet taste, the concerns about uncoupling sweet taste and calories would not be relevant. Second, in several studies, the LCS-treated yogurt increased weight gain without increasing caloric intake. This indicates that caloric intake alone cannot explain the elevated weight gain. Third, there is evidence that LCSs and yogurt can each alter the gut microbiota of rodents. Given recent work indicating that changes in gut microbiota can modulate body weight, it is possible that the combination of LCS and yogurt alters the gut microbiota in ways that promote weight gain. While this hypothesis remains speculative, it is consistent with the observed rodent data. In human studies, LCSs are usually presented in beverages. Based on the rodent work, it might be worthwhile to evaluate the impact of LCS-treated yogurt in humans.

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E-mail address: jglendin@barnard.edu.

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1. Introduction

Low-calorie sweeteners (LCSs) are attractive to consumers because they make foods and beverages taste better, without the caloric or glycemic effects of sugar [8]. Despite widespread usage, LCSs remain controversial. There are persistent claims that LCSs cause adverse health effects, including cancer, neurotoxicity, allergic reactions, elevated caloric intake and obesity (review in [32, 38]). The claims of cancer, neurotoxicity and allergic reactions are contradicted, however, by a large body of empirical work (reviews in [4, 18, 23, 30, 46]) and the fact that LCSs have been approved and recommend for use by regulatory bodies (e.g., U.S. Food and Drug Administration, European Food Safety Authority, World Health Organization) and the Academy of Nutrition and Dietetics [12]. The claim that LCSs increase energy intake and body weight is based on the notion that repeated LCS use disrupts the mechanisms underlying energy regulation [16, 22, 38].

Here, I focus on empirical support for the proposed linkage between LCS consumption and weight gain in rodents. First, I discuss the specific experimental conditions under which LCS have been found to increase body weight. Second, I consider the limitations of the animal studies linking LCSs to overconsumption and weight gain. Third, I examine the extent to which results from the animal studies are relevant to humans.

2. Under what experimental conditions do LCSs increase weight gain?

To determine whether LCSs increase body weight in rodents, investigators have used several experimental approaches. In a recent systemic review of this literature, Rogers et al. [31] identified a total of 90 relevant studies, and categorized them according to one of three experimental designs. In design 1, the LCS was added to the rodents' only source of food or water (n = 47 studies). In design 2, the rodents were provided with a standard diet (chow and water) plus continuous access to an LCS-sweetened water, diet or yogurt (n = 21 studies). In design 3, the rodents were offered a standard diet plus intermittent access to an LCS-treated yogurt (n = 15 studies[1]). Only a small percentage of the studies that used design 1 (9%) or design 2 (24%) reported a significant increase in body weight [31]. In contrast, the vast majority of studies that used design 3 (87%) reported significant increases in body weight. The fact that so few of the studies that used designs 1 or 2 reported weight gain indicates that LCSs are not inherently obesogenic to rodents. Below I examine design 3 in greater detail so as to gain insight into why it was more likely to cause weight gain.

The majority of the studies that used design 3 (i.e., [5, 39, 41–43]) were conducted by a group at Purdue University. In most cases, the investigators exposed rats to one of two diets. The "sweet predictive" diet consisted of a maintenance diet (standard chow and water ad libitum) plus a 30 g supplement of low-fat yogurt per day. The yogurt was offered 6 days/week. On 3 of the days, it was sweetened with 20% glucose; and on the other 3 days, it was unsweetened. This diet was called sweet predictive because the sweet taste of the glucose predicted the presence of sugar calories in the yogurt. The "sweet non-predictive" diet was identical, except that the sweetened yogurt contained 0.3% saccharin instead of glucose. This latter diet was called sweet non-predictive because the sweet taste of the saccharin did not predict the presence of sugar calories. As compared with rats on the sweet predictive diet, those on the sweet non-predictive diet gained more weight and (in many cases) ingested slightly but significantly more calories (Fig. 1A, B). Likewise, when the maintenance diet consisted of a high-fat chow sweetened with 20% glucose [5], the rats on the sweet non-predictive diet gained more weight and ingested more kcal/week than rats on the sweet predictive diet (Fig. 1C, D). Even though the results in Fig. 1A–D have been replicated on several occasions, there are a few studies in which rats on the sweet non-predictive diet did *not* consume more calories or gain more weight than rats on the sweet predictive diet —e.g., when the maintenance diet consisted of high-fat chow (Fig. 1E and F).

A group in Brazil sought to replicate the findings reported in Fig. 1A–D. They used a similar experimental design, with a few changes: the supplemental yogurt was diluted 50% with water, and was provided continuously (5 days a week) [11, 13]. In the Feijó et al. [11] study, the sweet-non-predictive diets were supplemented with yogurt containing saccharin or aspartame, while the sweet predictive diet was supplemented with yogurt containing sucrose. They found that the rats gained significantly more weight on the sweet non-predictive diets, but consumed the same total number of calories from all three diets.

One design limitation of the study by Feijó et al. (and the studies by the Purdue University group) is that the investigators simply compared responses to different experimental diets. Without control diets, the investigators lacked a reference point against which to assess body weight changes. As a result they could not determine whether the sweet non-predictive diet increased body weight, or the sweet predictive diet decreased it. To address this concern, a second study by the Brazilian group [13] offered rats a sweet non-predictive diet (standard chow, water and a dietary supplement of 0.3% saccharin-yogurt) or a control LCS-free diet (standard chow, water and a dietary supplement of unsweetened yogurt). The rats consumed the same number of calories from both diets, but nevertheless gained more weight on the sweet non-predictive diet. Owing to the use of the control LCS-free diet, the authors were able to demonstrate that the combination of LCS and yogurt was necessary to elevate body weight.

Taken together, these studies indicate that there is something idiosyncratic about the LCS-treated yogurt, which makes it more obesogenic than the sugar-treated or unsweetened yogurt. Below, I discuss several explanations for this unexpected observation.

2.1. LCSs, sweet taste and cephalic-phase responses

Several investigators have focused on the fact that sweet tasting substances in nature (e.g., fruits and honey) typically produce a post-ingestive spike in blood nutrient levels. To minimize this spike, mammals activate variety of anticipatory (cephalic-phase) responses (or CPRs) [50]. These CPRs are elicited pregastrically by the taste, odor and visual appearance of food [24]. For instance, the sweet taste of sugars and saccharin is known to elicit at least two CPRs in rats: insulin release [3, 48, 49] and thermogenesis [34]. Whereas the cephalic-phase insulin response (CPIR) helps limit blood sugar spikes following a meal, the cephalic-phase thermogenesis helps limit the obesogenic effects of the sugars.

When humans ingest an LCS, they experience a sweet taste but no post-ingestive spike in blood nutrient levels [15, 17]. For this reason, LCSs are said to uncouple the sweet taste and post-oral nutritive effects of sugars. Because of this uncoupling, there is no obvious benefit for mammals to generate a CPIR following oral stimulation with LCSs. This reasoning has led several investigators to hypothesize that repeated dietary exposure to an LCS (e.g., in a sweet non-predictive diet) should cause the CPRs to extinguish (review in [38]). A key assumption of this hypothesis is that the LCS-treated yogurt in the sweet non-predictive diet actually elicits a sucrose-like taste sensation in rats. However, two observations are inconsistent with this assumption. First, when 0.3% saccharin was added to yogurt, it did not stimulate greater intake than unsweetened yogurt [13]. For perspective, when 0.3% saccharin is added to water, it stimulates substantially greater intake than water alone in rats [35]. The most parsimonious explanation for the lack of feeding stimulation by the saccharin-treated yogurt is that the flavor of the yogurt masked the sweet taste of the saccharin. The second observation is that rats exhibit weak to non-existent behavioral attraction to aspartame in water [6, 33]. Accordingly, if aspartame

[1] I excluded 7 studies from this analysis because they involved rats that were either ovariectomized [45] or bred for susceptibility to obesity [44].

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